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August 10, 2008

Thomas M. Greene and Ilyas J. Rona
Greene & Hoffman
33 Broad Street, 5th Floor
Boston, MA 02109

Dear Mr. Greene and Mr. Rona,

Re: NEURONTIN – expert opinion on efficacy and effectiveness for pain

EXECUTIVE SUMMARY

Based on a thorough and scientifically valid analysis of all relevant double blind randomized clinical trials (DBRCT), Neurontin is not an effective drug for the treatment of neuropathic pain. My thorough review and meta-analysis of available published and unpublished evidence shows that Neurontin (gabapentin) has at best a clinically insignificant average effect on pain scores. The proportion of patients who recognize "improvement" on a Patient Global Impression of Change scale at the end of studies is roughly matched by the proportion of patients who experience adverse events. In the real world, to which the concept of "effectiveness" applies, patients taking Neurontin (gabapentin) should be expected to accrue less benefit and more harm. Thus, in my opinion, Neurontin (gabapentin) has not been demonstrated to be an effective treatment for pain.

Therefore, it should be obvious that it was inappropriate to recommend Neurontin (gabapentin) as "first-line" treatment for "neuropathic pain" or any other pain. In addition, my detailed review of evidence showed clearly that alternative analgesics, notably morphine, control pain better than gabapentin. Amitriptyline and other tricyclic antidepressants (TCA) appear from DBRCT comparing them with placebo to have greater benefit than gabapentin; however the direct comparison trials (against gabapentin) are too small and insufficiently well reported to prove whether TCA are better in the real world. In my opinion, the widespread "expert" recommendation of Neurontin (gabapentin) as "first-line"

treatment was based on commercial, rather than scientific or medical considerations – and derived largely from "experts" who were unaware of the full data from unpublished trials.

Finally, it is my opinion that Neurontin (gabapentin) is completely ineffective for the treatment of non-neuropathic pain. The relatively large acute pain trials I reviewed cast serious doubt on the notion that gabapentin is an efficacious analgesic, as opposed to a soporific drug.

Parke-Davis/Pfizer marketed Neurontin (gabapentin) as an effective drug for the treatment of neuropathic pain through the use of misleading, incomplete or omissive statements. The marketing transcended any reasonable bounds of evidence and succeeded principally by withholding the unpublished data which were well known to Parke-Davis/Pfizer.

Parke-Davis/Pfizer also recommended, through the use of misleading, incomplete or omissive statements, that Neurontin (gabapentin) be used as first-line treatment for neuropathic pain. Parke-Davis/Pfizer crafted an elaborate campaign to "pull the wool over the eyes" of practicing doctors, and no doubt also of patients afflicted by pain. The companies went to great lengths to ensure that their messages were not filtered through the appropriate sieves such as disinterested and competent independent peer review, for reality checking.

It was crucial for the companies to exaggerate the purported benefits of Neurontin, "push the dose", and play down Neurontin's well documented adverse effects in order to maximize off-label use for the much larger populations of patients with other chronic pain conditions who might at least purchase several months worth of the drug – even if they could not be persuaded to renew prescriptions further. It is a sad but all too common reflection on the medical profession that it collaborated so obsequiously in this endeavour.

FULL CLINICAL PHARMACOLOGIC OPINION

By letter dated March 4, 2008 and subsequent discussions both in Boston (April 1-3, 2008) and by telephone, you requested me to prepare a clinical pharmacological expert opinion on the evidence available from double blind randomized clinical trials regarding the efficacy and effectiveness of the prescription drug gabapentin when used to treat pain. You have also asked me to comment on the marketing of this drug in respect to claims you are making against the Defendant. At your request, I duly signed and returned to you a confidentiality agreement respecting documents you shared with me of which the confidentiality remains under Court protection in the United States.

With your permission, I engaged the assistance of two people to help me complete the large amount of work required to produce my opinion, within the looming deadline of August 1, 2008:

1. Vijaya Musini, M.D., M.Sc., my colleague in the University of British Columbia Department of Anesthesiology, Pharmacology and Therapeutics, is a recognized Canadian expert in critical appraisal of clinical trials and in systematic review. Dr. Musini assisted me in completing a systematic review to the standards of the Cochrane Collaboration, in particular with the meta-analysis using Cochrane RevMan software. She is an experienced member of the Cochrane Hypertension Group. Dr. Musini will send you her CV by email.

2. Kelsey Innes, B.Sc., a graduate of the University of Victoria (mathematics and statistics), who assisted in the critical appraisal and in summarizing some of the clinical trials of gabapentin for pain (mostly unpublished).

I have personally supervised and checked the work of Dr. Musini and Ms. Innes and assume responsibility for the thoroughness and accuracy of all the work reported to you as appendices, and upon which my opinion relies. Dr. Musini and Ms. Innes have each signed and returned to you by fax the confidentiality agreement with respect to documents protected by the U.S. Court.

This is my report, for which I assume full responsibility. It relies on my general scientific and medical education and background, and also on medical scientific reports which I reviewed during my own independent research, as well as on information and reports of which I am otherwise generally aware. I also reviewed specifically the materials you sent me, which are itemized in a number of Appendices at the end of this report.

I reserve the right to supplement or modify this report if new information becomes available to me, or if I have the opportunity to review further reports from published literature, unpublished studies, or other documents relevant to my opinion.

My compensation for this work is at a rate of U.S. $400/hour. I am sending you separately a CV.

The following are the law cases in which I have provided expert witness testimony at trial or during pre-trial Examination for Discovery since 2004:

1. Borglund v. Fraser Valley Health Region et al., Supreme Court of British Columbia, 2006 BCSC 1338, Registry: Vancouver (Civil)

2. Regina v. James Swanney, Supreme Court of British Columbia, 2006 BCSC 1766, Registry: New Westminster (Criminal)

For your convenience and that of the Court, I have prepared an Executive Summary attached to this report, which is based upon the full report, and which includes my answers to your specific questions. The same questions are posed and answers proposed in this complete report, in the context of the approach that I took to answering them.

I) PROFESSIONAL QUALIFICATIONS:

I graduated from the McGill University Medical School in 1978. I then took a rotating internship at Dalhousie University Medical School, and postgraduate training in Internal Medicine at the University of British Columbia. I achieved Fellowship of the Royal College of Physicians of Canada in 1985. From 1986-89, with a Fellowship from the Medical Research Council of Canada, I pursued additional subspecialty training in Clinical Pharmacology at the Karolinska Institute Department of Clinical Pharmacology in Stockholm and in the Department of Pharmacology and Therapeutics at UBC. My training focused on the metabolism of tricyclic antidepressant drugs by the liver, and on understanding how they cause the adverse effect of postural hypotension (low blood pressure) in humans.

Currently I practice hospital-based general internal medicine on the medical wards of the University Hospital and the Vancouver General Hospital, in Vancouver, British Columbia. I also teach medicine and clinical pharmacology in all four years of the undergraduate medical curriculum of the UBC Faculty of Medicine and in the General Internal Medicine postgraduate training program.

My outpatient practice is mainly with patients with high blood pressure and especially the treatment of chronic pain. I am one of relatively few physicians in B.C. who receives consultations for pain from around our province of 4 million people. I am frequently called upon to assess hospitalized patients and outpatients who are receiving complex regimens of prescription medications. Much of my daily bedside and hospital ward teaching involves helping medical students, and sometimes clinical pharmacists, to understand the practical aspects of drug actions in human beings. This includes the practical aspects of pharmacokinetics and pharmacodynamics, the understanding of when and how drugs exert their effects in individual human beings.

Like other general internists in academic practice, I am involved continuously in teaching concepts of evidence based medicine. This involves the rational application to an individual patient of the scientific knowledge gained from randomized clinical trials (experiments) conducted in large populations of patients. My work at the UBC Therapeutics Initiative (UBC TI) involves critical appraisal of such experiments in order to understand what the published results of clinical trials really mean for clinical practice. I have been privileged to work at the UBC TI amongst a group of physicians, epidemiologists, and pharmacists who have together received international stature for the meticulousness and reliability of our work, and the careful, unbiased conclusions we have drawn in our drug assessment reports to the British Columbia Ministry of Health's drug benefit program and the abbreviated versions published in our Therapeutics Letters and on our website (www.ti.ubc.ca).

I have sent you electronically a copy of my CV, including publications from the last 10 years. I do not keep track of all of my teaching and speaking engagements on my CV but could muster and report them if required.

II) QUESTIONS YOU POSED TO ME:

These are the specific questions you posed to me:

a) Science questions:

1. Based on a thorough and scientifically valid analysis of all relevant RCTs is Neurontin an effective drug for the treatment of neuropathic pain?

2. Was it appropriate to recommend Neurontin as first-line treatment for neuropathic pain?

3. Can any findings of efficacy in PHN be extrapolated to other neuropathic pain conditions?

b) Marketing questions:

1. Based on a review of their marketing documents, did Defendants market Neurontin as an effective drug for the treatment of neuropathic pain through the use of misleading, incomplete or omissive statements?

2. Based on a review of their marketing documents, did Defendants recommend through the use of misleading, incomplete or omissive statements that Neurontin be used as first-line treatment for neuropathic pain?

3. Based on a review of their marketing documents, did Defendants claim through the use of misleading, incomplete or omissive statements that findings of efficacy in PHN could be extrapolated to other neuropathic pain conditions?

I have reported my brief answers to these questions in the executive summary accompanying this detailed and comprehensive report. Below I discuss the purposes of my report in more detail, and the approach taken to answering your specific questions and the more general scientific questions that I needed to pose to myself in order to provide you with what I consider reasonable answers.

III) PURPOSE OF REPORT:

a) The main purpose of this report is to provide you with a balanced, scientifically accurate and valid assessment of the efficacy and effectiveness of gabapentin for various pain syndromes. As I explained to you when we met in Boston on April 1-3, 2008, I must base my opinion upon a detailed and thorough review of all available evidence from **double blind randomized controlled trials (DBRCT)** which compared gabapentin with placebo, “active placebo”, or with drugs known or thought to have analgesic properties. As is standard in modern medical science, evidence derived

from open label trials (where the patients and investigators are aware of each patient's treatment) may be useful to **formulate** hypotheses, but is unreliable for **testing** such hypotheses. Long experience has taught that **only DBRCT offer reliable evidence**.

However, even the interpretation of relatively high quality and difficult or expensive experiments may be fraught with various biases. Anyone who follows the media will be aware that medical conclusions and standard practice which were thought to be based on "evidence" relatively securely derived from DBRCT often turn out to be spurious, wrong, and sometimes even deliberately misleading. Throughout medical history, this has been true of most practices once thought to be "standard of care", e.g. bleeding with leeches (thought to have caused the deaths of King Charles II and President George Washington amongst many others) or the use of antimony and mercury for various ailments in the pre-scientific era. More recent examples include the utility of beta-blockers for peri-operative medicine, or the mass application of SSRI antidepressants and "atypical" (new) antipsychotic drugs to millions of people now widely recognized to have been unlikely to benefit. Selective publication of part, but not all of the evidence concerning rofecoxib (Vioxx) in the New England Journal of Medicine (NEJM) in 2000 and concerning celecoxib (Celebrex) in the Journal of the American Medical Association (JAMA) in 2000 provided a classic example of how relatively sophisticated peer reviewers, medical journal editors, and readers of journal articles may be misled - even by studies which appear to represent the highest available quality of medical research. This mis-publication fooled literally hundreds of thousands of doctors worldwide, including most academic "experts", and led to a revolution in how the best medical journals now attempt to verify the accuracy, validity and integrity of research reports submitted for publication. This "new enlightenment" has only begun and applies only to the few best medical scientific journals whereas countless others continue to apply low standards to determining whether information submitted for publication is likely to be accurate or representative of the real truth.

A series of brief articles (Therapeutics Letters) on the UBC Therapeutics Initiative website (www.ti.ubc.ca) summarized what was known about the real facts from the rofecoxib and celecoxib studies at various stages between 1999-2004. These articles demonstrate that it was possible early on to discern glimpses of the truth. Representing the work of a sophisticated team which collectively spent hundreds of hours to understand what the published rofecoxib and celecoxib trials were really reporting, the Therapeutics Letters do not even hint at the amount of intellectual work and experience necessary for an outsider (someone without access to complete privately-held data) to develop a well-informed opinion.

When you asked me to consider the Neurontin (gabapentin) case, I guessed that the academic work necessary to form an opinion would be onerous and time consuming, but I did not fully comprehend how complex this assignment would be, given the myriad ways that experiments with gabapentin were reported, and the nature and volume of the unpublished experimental reports.

My academic interest in the questions you posed derives partly from my considerable experience in the treatment of hospitalized patients and outpatients suffering from acute or chronic pain. As a specialist in general internal medicine and in pain

treatment, I have assessed clinically hundreds of patients who have taken gabapentin. Although I have occasionally prescribed gabapentin as a trial of therapy for pain, almost all of the patients I have assessed who were taking this drug were prescribed gabapentin for pain by other physicians. Gabapentin is used rarely in Canada for epilepsy.

In my daily practice of medicine in a major medical teaching centre, I utilize my specialized post-graduate training and expertise in clinical pharmacology, including my understanding of how drug kinetics and dynamics apply to individual patients. My work at the University of British Columbia medical school typically involves combining this knowledge and understanding with my academic experience in critical appraisal of clinical trial reports to formulate what I hope to be wise and rational judgments about the role of drugs in alleviating human suffering or improving health. Similarly, my clinical pharmacologic opinion in this report also applies my background knowledge and experience to questions which are critically relevant to understanding how the **average group outcomes** observed in DBRCT might be applied wisely to the rational use of a drug in clinical practice which is always directed at **individual patients**. For example, I will consider:

- the **timing of benefit and harm** experienced by patients taking gabapentin
- the **relationship between dose and therapeutic or toxic effects** (benefit and harm)
- how results might be expected to compare during **routine clinical use of gabapentin** for the same purposes or conditions for which gabapentin treatment was studied during DBRCTs – the question of "effectiveness" vs. "efficacy"

Without the prudent clinical application of such knowledge, it is difficult or impossible for a doctor to translate **efficacy** results (the ability of a drug to produce a given result during a controlled experiment under "ideal" circumstances) into clinical **effectiveness. Effectiveness** is ultimately the ability of a drug to cause more good than harm in **real life**. The prescribing physician who wants to be **effective** obviously must attempt to maximize the proportion of patients who benefit from a therapy while minimizing the proportion who suffer harm from the same therapy.

b) The second purpose of this report is to provide my opinion as to whether the intensive marketing campaign conducted on behalf of Neurontin (gabapentin) by Parke-Davis/Pfizer in the United States was **misleading, incomplete or omissive** in its depiction of the efficacy or clinical effectiveness of Neurontin (gabapentin) for the treatment of "neuropathic pain" or other pain. This question is to be considered in light of the evidence I now know, from my review of unpublished as well as published studies, was available to Parke-Davis/Pfizer at the time, as well as my review of internal marketing documents from those two companies.

I have tried to approach this question by imagining that I had been a pain specialist or any other fair-minded and intelligent physician attending one of the "advisory group" meetings, or any of the sponsored meetings where Neurontin (gabapentin) was promoted, or that I had read any of the "enduring materials" distributed

by non-academic or academic organizations entitled to provide CME credits to American physicians. I have asked myself whether the information contained in those documents, slide presentations, sponsored (non-peer reviewed) journal supplements and commercial journals and in the "advisory group" discussions:

- was generally intellectually honest;
- presented a fair balance of information on potential benefits and harms likely to arise in a patient taking gabapentin;
- conformed to professional and ordinary ethics insofar as the presentation respected an audience member's or reader's right and responsibility to be fully informed of the facts in such as way as to protect the interests of patients;
- was "ethical to patients" - that is, the presentation did not encourage the audience to recommend or prescribe gabapentin in ways that could be expected to be deleterious to patients;
- was "disinterested" – that is, the interests of patients who might be exposed to gabapentin were placed ahead of the financial interests of the manufacturer or the physicians in attendance;
- was "honest and transparent" – that is, the presentations or "enduring materials" or "infomercials" reflected appropriately full disclosure of the potential or real conflicts of interest of "experts" remunerated by the manufacturer (including but not limited to the amounts paid to such "experts" to participate in promotional advisory board meetings or presentations, and disclosure of whether the "authors" of materials circulated actually wrote those materials or disclosed "ghost authorship" when they did not write them, in such a way that an audience member could make an informed independent judgment about the overall credibility of the information presented;
- was complete insofar as all experimental evidence bearing on the efficacy or effectiveness of gabapentin was disclosed, once it was available

Note that reading documents is hardly the same as attending a live presentation. Anyone who has participated in such meetings (or who might have read the Parke-Davis/Pfizer materials I reviewed) would understand that meetings held for doctors at nice hotels in desirable locations have their own group dynamic and culture. Pharmaceutical manufacturers, or the third parties they contract to run such meetings, do not spend tens or hundreds of thousands of dollars to organize them with the expectation that the content will be purely rational. Were that their intent, they could save a great deal of money by using print media or the internet. **The emotional dimension of human contact with "experts" or "Key Opinion Leaders" is the real purpose and outcome of such meetings.**

IV) BACKGROUND – FORMULATION OF ACADEMIC QUESTIONS TO BE ADDRESSED IN ORDER TO ANSWER YOUR SCIENTIFIC QUESTIONS:

In thinking about how to approach the daunting assignment you gave me, I began with the following considerations:

a) observations and thinking about how gabapentin has been and is currently utilized for pain treatment in my local community (Vancouver and British Columbia, Canada);

b) my own experience from treating pain with prescription drugs of multiple classes (acetaminophen, NSAIDs, opioids, tricyclic antidepressants, anticonvulsants) and with teaching medical students, post-graduate trainees, and practicing doctors about effective and rational use of drugs for pain control;

c) observation of how pain is treated in the large hospitals where I work, including how nurses and doctors assess and treat pain, and discussions with doctors, nurses, and physiotherapists about the effects of gabapentin;

d) general medical literature discussion of pain treatment (journals, books, websites)

e) the Cochrane Pain Group's discussion, not limited to the Cochrane systematic review of gabapentin (see below) but also including the Oxford Pain Internet Site (http://www.jr2.ox.ac.uk/bandolier/booth/painpag/);

f) discussion with colleagues involved in systematic reviews of various drugs licensed in Canada

I derived the following key questions to guide me and my colleague Dr. Musini and assistant Ms. Innes in our systematic review of evidence about gabapentin's effects on pain in **outpatients**. I considered that gabapentin's possible effects in the immediate post-operative setting for **hospitalized patients** were not relevant to the much broader question of gabapentin use by prescription in **outpatients**. These questions are not necessarily listed in order of their clinical importance. Ultimately, for any one patient the most important question is relatively straightforward and simple: **"How will this drug help me to get on with my life in ways that are important to me?"**

Question 1a) What is the available evidence from DBRCT concerning the **average (mean) effect of gabapentin** for various painful conditions, in comparison with placebo or with active analgesic comparators?

Question 1b) What is the clinical meaning for **individual patients** of any such average (mean) effect observed for an experimental **group**?

Questions 1a and 1b are important because a valid estimate of any benefit from gabapentin can be made only by considering all available clinical trial results (to avoid publication bias by publication only of results deemed to be positive) and because effects observed in clinical trials, which may be statistically significant, are not necessarily **clinically significant**.

Question 2a) What is the available evidence from DBRCT concerning the **average (mean) toxicities (harms) of gabapentin** when used for pain, in comparison with placebo or with active analgesic comparators?

Question 2b) What is the clinical meaning **for individual patients who experience toxicity (harm)**, e.g. those who drop out early from DBRCT because of "adverse events", or who just drop out?

Questions 2a and 2b are important because any clinical benefits achieved by a drug are meaningless unless weighed against the **harms** associated with the same treatment.

Question 3a) What is the available evidence from DBRCT about the **percentage (%)** of patients who experience a **clinically meaningful benefit (to them)** from the use of gabapentin to treat pain?

Question 3b) How does this % compare with the % who experience a **clinically meaningful harm**?

Questions 3a and 3b are important because they may provide an estimate of the probability that an individual patient may realize a clinically meaningful benefit (Number Needed to Treat, NNT) or harm (Number Needed to Harm, NNH). Note that in the real world setting (outside the confines of a DBRCT with scrupulous inclusion and exclusion criteria) the NNT will generally be higher (less favourable), while the NNH will generally be lower (less favourable). The balance of benefit/harm will generally be considerably less favourable in the real world, than in a typical clinical trial run from a specialized referral base.

Question 4a) What is the available evidence from DBRCT concerning the relationship of gabapentin **dose** to clinically meaningful response (benefit)? For example, is there convincing evidence that larger doses "work better" than smaller doses (e.g. 900 mg/day vs. 300 mg/day, or 3600 mg/day vs. 900 mg/day or vs. 1800 mg/day)?

Question 4b) What is the available evidence from DBRCT concerning the relationship of gabapentin **dose** to clinically meaningful toxicity (harms)? For example, is there convincing evidence that larger doses are more likely to cause neurological adverse effects than smaller doses (e.g. 900 mg/day vs. 300 mg/day, or 3600 mg/day vs. 900 mg/day or vs. 1800 mg/day)?

Question 4c) Is any other meaningful evidence available which bears on the questions of **dose-dependence** of benefit(s) or harm(s) for gabapentin?

Questions 4a, 4b and 4c are important because "experts" who promoted use of gabapentin for pain generally advised "pushing the dose" or "titration to side effects". This encouraged a widespread belief that in an individual patient, a larger dose may be expected to "work better" than a smaller dose, whereas the same experts suggested that

many patients develop tolerance to adverse effects. General clinical pharmacologic principles and international experience with countless drugs suggest that large doses are more likely than small doses to cause significant harms. Conversely for most drugs the benefits accrue disproportionately at the lower end of the licensed human dose range (e.g. drugs for high blood pressure, drugs for stomach acid suppression, beta blockers, and most, if not all, pain drugs).

Question 5a) What is the available evidence from DBRCT concerning the relationship of **duration** of gabapentin therapy to realization of a clinically meaningful response (benefit)?

Question 5b) What is the available evidence from DBRCT concerning the relationship of **duration** of gabapentin therapy to experience of a clinically meaningful toxicity (harm)?

Question 5c) Is there any other meaningful evidence available which bears on the questions of **duration** of therapy-dependence of benefit(s) or harm(s) for gabapentin?

Questions 5a, 5b, and 5c are important because "experts" who promoted use of gabapentin for pain generally advised (by analogy to prevalent but usually non-evidence based treatment models of drug therapy for depression) that patients should be encouraged to persist with therapy despite initial therapeutic failure, in the hope that the drug may require "time to work". In contrast, some "experts" indicated at least anecdotally, and close examination of the results of DBRCT suggest that therapeutic effect or toxicity may be apparent **very early in treatment**.

Question 6: What experimental approach could clarify the most efficacious and effective drug treatment(s) for "neuropathic" pain? Why don't we have this information now?

Question 6 is important because the rational patient and/or the rational prescribing doctor might well ask,*"What is the best available treatment for my condition?"* (The New York Times of July 29, 2008 provides a striking example of how U.S. Senator Ted Kennedy used this rational approach not only to analyse therapeutic options for his malignant brain tumour, but also applied it earlier to therapeutic dilemmas affecting his children and friends. The same article points out that even many highly educated or sophisticated Americans still expect to delegate this responsibility to their physicians.) In certain circumstances, high quality scientific experimentation has provided reasonably certain answers to such questions, for example:

- thiazide diuretics, as initial treatment for high blood pressure, typically provide the best available results in prevention of premature death, ischemic heart disease, and stroke, at the lowest price and probably with the fewest adverse effects, according to multiple RCT;

- coronary bypass surgery is better than conservative medical treatment or percutaneous coronary intervention (angioplasty, coronary stenting) under specific circumstances demonstrated in RCT

Providing a rational, experimentally based answer to Question 6 would require DBRCT aimed at discovering the truth, no matter where it lies. This is the general approach taken in the Gilron study (NEJM 2005), although the crossover design becomes so complex that I found a thorough and fair interpretation to be much more difficult than it looks. Large, objective and meticulous DBRCT performed in the real world setting (effectiveness trials) could reliably answer the following questions about neuropathic or other pain treatment in various conditions, just as they have for other medical issues:

a) Which treatment (e.g. traditional opioids such as morphine, "untraditional opioids" such as methadone, gabapentin, pregabalin, carbamazepine, tricyclic antidepressants, etc.) provides the best group **mean** pain relief?

b) Which treatment provides the **fewest and least clinically significant adverse effects**?

c) Which treatment provides the **best overall functional result**? (a combination of relatively good benefit and relatively little harm, e.g. the ability to continue working or return to work, school, or important family activities)

d) What is the **probability** that an individual patient will achieve clinically or functionally meaningful benefit or harm, for each treatment? **(NNT, NNH)**

Why have such studies not been done for "neuropathic pain", with the rare exception of such innovative trials as Gilron's (NEJM 2005) or the other less prominent trials comparing active treatments? I am aware of several plausible answers, all of which are probably pertinent:

a) Regulatory bodies such as the U.S. FDA do not require evidence that a drug is superior to appropriate comparator drugs, only that it is superior to placebo. Thus the manufacturer's interest lies primarily, and often exclusively, in attempting to demonstrate superiority over placebo.

b) There is a risk to running experiments which compare active treatments. One treatment may "win", while others lose. This may complicate or torpedo the marketing of new products. It is especially risky for products which remain on patent but for which the manufacturer has only a limited interval to recoup development costs and produce profit. A trial showing disadvantage to a new product vs. an older product would effectively kill the new one. As an example, Pfizer has not to my knowledge sponsored trials comparing its formerly patent-protected product Neurontin (gabapentin) with the newly patented, licensed and anointed "successor" Lyrica (pregabalin). This is a striking omission which has not been corrected by any independent trialist, and if any studies were done by Pfizer, their results are unknown. Thus we have no idea whether pregabalin (Lyrica) is **equivalent, superior or inferior to gabapentin (Neurontin)** for any benefits or harms, whether in a clinical trial setting or in the real world. An experiment showing equivalence, let alone inferiority of pregabalin (Lyrica) to

gabapentin could be predicted to *"kill the goose that will lay the next multi-billion dollar egg"*.

c) Academically-inspired or independent DBRCT (e.g. trials sponsored by public agencies like the U.S. NIH, Veterans Administration, the United Kingdom NHS or the Canadian CIHR) are expensive and hard to organize. Although such trials were once the mainstay of medical progress, for decades they have played second fiddle to drug-company designed, organized, and managed trials for most clinical issues. Only issues judged to be of the utmost importance (e.g. some cardiovascular and cancer trials) have escaped this trend. In the 30 years I have been involved in academic medicine, the independence of medical scientific investigation has withered, in favour of industrial dominance of the questions posed, the methods used to answer them, and even the reporting of results. This is now widely recognized and lamented. (See JAMA, April 16, 2008 for articles describing how the sponsors of trials prepare the results for publication, then recruit academic "ghost authors" or "key opinion leaders"/KOL's to assume authorship - http://jama.ama-assn.org/content/vol299/issue15/index.dtl)

These are some of the reasons why we do not see major parallel group DBRCT utilizing what would likely be the optimal strategy to determine the truth, a strategy exemplified by the ALLHAT trial for treatment of high blood pressure (reported in 2002). For patients with **painful diabetic neuropathy**, for example, it would be exceedingly useful to know the results of a large real world trial, comparing not only important but highly subjective endpoints (e.g. pain scores) but also **"hard endpoints"** such as hospitalization, infections, amputations, kidney function, heart disease, and overall mortality. A rational real world DBRCT could generate meaningful and reliable answers by using some of the following strategies:

- Comparing placebo with gabapentin, and opioid (e.g. morphine), or also with a fourth arm (e.g. amitriptyline), to assess whether one treatment has overall superiority;

- Re-randomization of "therapeutic failures" randomized to one arm to an alternative drug, to learn whether patients who do not achieve good outcomes with one therapeutic option might do better with another;

- Follow-up of all patients for the most meaningful outcomes, including total mortality, total serious adverse events (SAE), specific important adverse events, functional improvement from disability, overall pain and/or goals pre-specified by the patients themselves. The latter technique for experimentation, in which the patient and/or family determine the goal(s) of therapy, has been explored in experimental studies of drug therapy in Alzheimer disease, which show that it is feasible to study in a group the same kinds of outcomes which patients and their physicians routinely seek within a therapeutic relationship.

V) BACKGROUND CONSIDERATIONS - MEDICAL TREATMENT OF PAIN:

Painful peripheral diabetic neuropathy (PDPN) and post-herpetic neuralgia (PHN), considered prototypical examples of "neuropathic" pain, were the original conditions for which gabapentin was used widely, other than for epilepsy. It is clear that Parke-Davis/Pfizer used these conditions as "levers" to expand the unapproved (off-label) prescription of Neurontin (gabapentin) for pain. Therefore, I will also use them as examples to set the background for what a competent physician and a rational patient would try to achieve in a therapeutic alliance to address the patient's clinical problem of pain.

The distinction between "somatic" or "visceral" versus "neuropathic" pain is rather arbitrary, since all pain is ultimately experienced by or through neurons in the brain. For example, pain from an inter-vertebral disc protrusion or an epidural abscess or tumour deposit could be considered "somatic" or "neuropathic", depending how one looks at it. Parke-Davis/Pfizer was quick to point out to its "advisory boards" that millions of Americans suffer from chronic back pain and headache, both conditions not traditionally designated "neuropathic". The afflicted person experiences the same suffering, regardless of how the condition is labeled by "experts". This fact is well known to anyone who has faced chronic pain. Thus, rational therapeutic principles that apply to "neuropathic" pain apply generally to any painful condition.

a) General background:

Painful diabetic peripheral neuropathy is often part of a spectrum of diabetic complications including painless neuropathy and large or small vessel arterial (or venous) disease. **These conditions pose the continuous threat of devastating local or systemic infections, especially those arising in the feet from lacerations, pressure sores or ulcers caused by the loss of sensation and impaired circulation in the toes and feet.** Any drug like gabapentin which compromises alertness or reduces sensory perception, contributes to or causes falls, or causes edema (tissue fluid collection, typically manifested mostly in the feet), holds the potential to be extremely dangerous in patients at high risk of infections arising in the diabetic foot. Double blind randomized controlled trials (DBRCT) enroll selected patients judged to be at the **least risk** for such complications (e.g. without significant kidney impairment, without significant or unstable heart disease, and able to participate and expected to survive the duration of a clinical trial), whose experience during a brief trial will almost certainly **exaggerate the apparent benefits** of drug therapy while **underestimating the harms to be expected in a more representative population.**

Postherpetic neuralgia (PHN) can disable a patient with spontaneous pain or cause an exaggerated and painful response to stimuli that are not normally painful (allodynia, dysesthesia). When it affects a limb, or if the pain is severe, PHN may also affect mobility. Often, pain disturbs sleep. **Most patients with significant pain, especially of longer duration, are elderly; many if not most of these are debilitated by other conditions.** As with PDPN, results from DBRCT enrolling patients with PHN

are virtually guaranteed to **exaggerate the benefits but minimize the harms** associated with drug therapy in this population which is mostly elderly and suffers multiple co-morbidities which increase frailty.

There is a constantly increasing pressure and tendency to polypharmacy amongst patients with diabetes, and also amongst the elderly patients most likely to suffer significant pain from a reactivation episode of *Herpes zoster* (PHN). The trend to polypharmacy intensified greatly in the 1990's, partly as a byproduct of the rise of "evidence-based medicine" and the influence of "treatment guidelines" encouraged by medical organizations, pharmaceutical manufacturers, "disease associations", and government, HMO's or other third party payers. Especially in the litigation prone United States, guidelines often assume the status of "standard of care" - even when they are clearly **not** based on good scientific evidence or obviously biased by sponsorship or conflicts of interest amongst the "consensus guideline developers".

Given this context for a typical patient consulting a doctor for relief of pain arising from either PDPN or PHN, the rational and ethical physician should consider drug treatment options with reference to the patient's other health issues, **including potential interactions of a drug which affects the central nervous system with many other drugs in simultaneous use by the same patient.**

This is obviously a totally different situation from that of a patient enrolled in a typical DBRCT, where exclusion criteria and prohibition of potentially dangerous or interacting medicines is likely to render safe outcomes more likely than in the real world. It is rather like the difference between giving a teenager the keys to the car for a driving lesson from a licensed driving school, as opposed to providing the keys to the same car for a big Saturday night on the town. The encounter with a typical pain patient in clinical practice embodies a much more complex therapeutic decision process for both patient and physician than that of most DBRCT or the typical clinical case scenario presented by a manufacturer-sponsored "pain treatment expert" during an after-dinner lecture.

b) <u>What are the goals of drug therapy for PDPN and PHN (or any other pain)?:</u>

Common sense goals for both conditions are relatively easy to define for clinical practice. The patient typically seeks a prescription for the relief of suffering. Pain inhibits her/his general enjoyment of life, and may interfere with everyday functions such as social interactions, activities of daily living (dressing, bathing, walking), or with sleep. Obvious goals of drug (or non-drug) therapy include:

1) **Preservation of general health, and avoidance of harm, including death and serious adverse effects.** Although this may not be an explicitly stated goal of therapy, it is the cardinal underlying principle of ethical medical practice since the time of Hippocrates: *"primum non nocere"*.

2) **Pain relief which the patient finds meaningful**: for example, a successfully treated patient might state at follow up: ***"I feel much better now"*** or ***"It still bothers me, but not nearly so much as before".***

3) **Restful sleep**, **when pain has disturbed sleep: this goal normally applies to the night time, and clinical utility depends critically on avoidance of daytime somnolence or potentially dangerous adverse effects such as dizziness.** Where improvement of sleep is the main goal, a relatively short-lived drug treatment may be desirable and pharmacologically rational, as opposed to an around-the-clock effect.

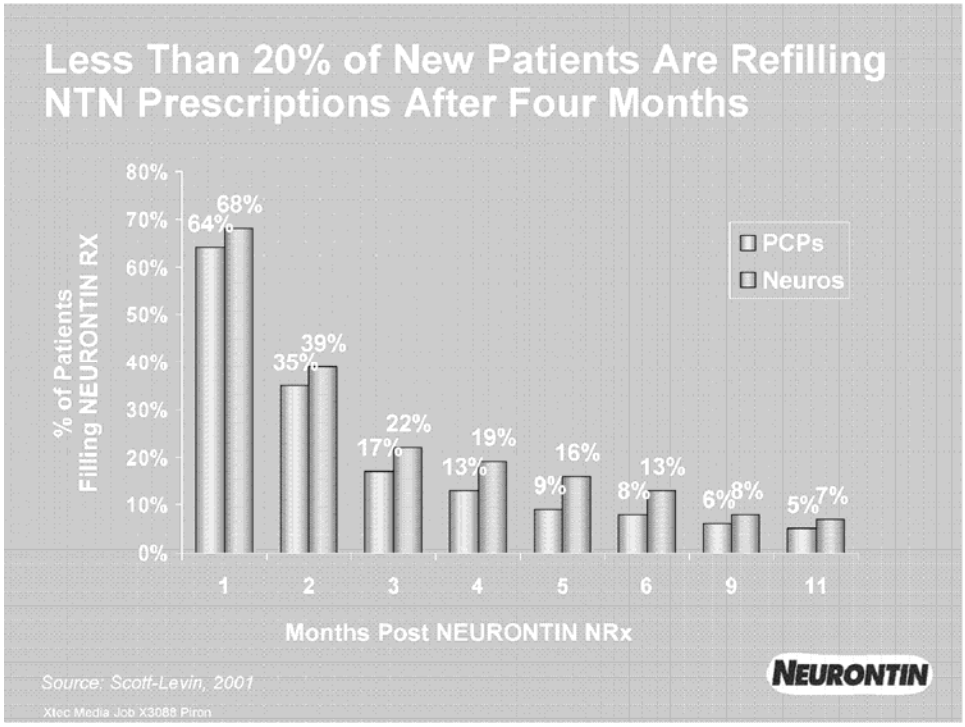
4) **Maintenance or improvement of overall function**, including the ability to read, write, perform household tasks, do routine computations (e.g. for banking or bill paying), hold conversations, and maintain physical fitness through aerobic exercise. Note that drugs which may improve sleep often impair overall function. This is one reason, for example, that benzodiazepines are not approved for long term use as hypnotics.

5) **Maintenance or restoration of happiness** (mood) in a patient in whom chronic pain has led to depression or despondency, or to relationship issues with a spouse or partner.

Note that while DBRCT of pain treatment interventions (notably drugs) often attempt to measure aspects of these **qualitative goals of therapy**, common sense suggests that achieving such qualitative or even categorical (yes/no, success/failure) goals differs markedly from recording a change on a "pain scale" or on a "SF-36 QOL" form. Measurement scales typically utilized in DBRCTs may have meaning, and may have been negotiated between manufacturers and the US FDA as surrogate endpoints considered acceptable for clinical trials. The development and popularization of such measurement scales may have generated impressive *curricula vitae* for academics and led to promotions, awards and peer recognition. But it is important to recall that the average suffering patient might be more inclined to ask in regard to a proposed new prescription**:** ***"What's in it for me?"***

One striking aspect of the promotional materials I reviewed was the graphic labeled (Pfizer_MYoder_0002511) which shows that as of 2001, "Less than 20% of New Patients Are Refilling NTN (Neurontin/gabapentin) Prescriptions After Four Months". The same graphic shows that only 35-39% or patients renewed prescriptions after the first month, although they would almost certainly have been under influence (if not frank pressure) from their physician(s) to renew and **probably to increase the dose**. **By 11 months, only 5-7% of Americans prescribed Neurontin were renewing their prescriptions.**

In 2001, most such prescriptions would have been written with the goal of pain relief. This renewal pattern obviously contrasts markedly with how highly effective analgesics, such as morphine and other opioids, are utilized by patients with chronic pain. Although neurologists may have been slightly more persuasive than primary care doctors during 2001, this graphic indicates that approximately 95% of all American patients were making their own consuming decisions, **probably because they were not achieving meaningful relief from chronic pain, or they disliked the toxicities of gabapentin.** For convenience, I have reproduced this very telling graphic below. It may have been a well known (and perhaps dreaded image) amongst Parke-Davis/Pfizer marketing staff, but I doubt that it would have featured on the "Neurontin" website, or any similar public venue.



Graphic apparently presented by Parke-Davis/Pfizer at "advisory board" meeting. (Pfizer_MYoder_0002511)

c) <u>What should a doctor strive to AVOID when treating pain?</u>

Drug (or non-drug) therapies for pain **should NOT**:

1) **Increase mortality**.

2) **Increase serious or symptomatic morbidity** (e.g. by causing visual impairment, confusion, impaired concentration or thinking, impaired balance and consequent falls, fractures or other injuries, nausea, vomiting, anorexia, or weight loss/weight gain, or exacerbation of the chronic complications of diabetes such as infection, edema and impaired wound healing, kidney dysfunction, congestive heart failure or myocardial infarction, etc.).

Both mortality and morbidity (as Serious Adverse Events/SAE) are typically recorded and measured in DBRCT, although their interpretation is contentious, since SAE as well as mortality may be difficult to relate to the experimental intervention. In general, a prudent physician should be concerned if DBRCT demonstrate higher mortality or morbidity (as total SAE or patients experiencing SAE), from an experimental intervention, even when this effect is "considered unrelated by investigators". Our academic group at the UBC Therapeutics Initiative has seen a number of examples where early signals from DBRCT regarding total mortality and total SAE turned out to be meaningful warnings that new drugs were inferior to comparators, even though these drugs cleared licensing hurdles in the United States and Canada and elsewhere (e.g. the

antibiotic grepafloxacin (Raxar) and the analgesic/anti-inflammatory rofecoxib (Vioxx) – both withdrawn from the market relatively soon after licensing/marketing).

d) <u>Timing of pain relief:</u>

Typically both patient and physician seek prompt relief of pain. In the post-anesthetic recovery room or for a surgical patient receiving "patient-controlled analgesia" (PCA) on a hospital ward, the goal is to relieve pain almost immediately. A doctor dealing with severe acute pain (e.g. migraine headache) in her/his office or a nurse treating pain in the emergency room (e.g. renal colic) typically aims for obvious benefit within 2-30 minutes. **Even a "consumer" using an over-the-counter oral analgesic such as acetaminophen, ASA, or ibuprofen expects pain relief within minutes to hours** – an expectation reinforced by countless television advertisements featuring actors posing as golfers, swimmers, Tai Chi practitioners and even dancing marionettes. While the placebo effect often has a significant role in such prompt relief, there is no clinical question that opioids and NSAIDs work promptly when they work well.

For chronic pain which is primarily "physical" in cause (as opposed to chronic psychological states), it is typically more reasonable to aim for meaningful pain relief within hours or days, and it may require a few weeks to be certain whether the benefits of any treatment outweigh its disadvantages (harms). But Franklin's motto that *"a penny saved is a penny earned"* is also not the appropriate metaphor for pain treatment. Analgesia is not like investing in education or government bonds. Both the suffering patient and the compassionate prescribing doctor seek a benefit which will not be delayed for months or years. A drug whose effect is not obvious enough to avoid the necessity for doctors to "push the dose" or to urge patients to "hang in there" is unlikely to be helpful to most people.

e) <u>Currently available drug choices for "neuropathic" pain:</u>

In principle, any drug which is a known analgesic should be considered for treatment of "neuropathic" pain, just like any other pain. The efficacy of opioids for pain was established in the Orient well before the time of Christ, and recognized by medical greats such as Thomas Sydenham and Sir William Osler as *"God's own medicine"*. Morphine and other opioids (e.g. codeine, hydrocodone, hydromorphone, oxycodone, meperidine, fentanyl, methadone) would not have acquired this reputation were it not for their almost immediate and dramatic effects on severe pain. Although they also have significant adverse effects, these are often surprisingly benign and when present (e.g. constipation) can usually be managed effectively. Thus the benefit of opioid analgesia overwhelms the harm when appropriate patients are treated, making opioids the mainstay of treatment of cancer pain because they so dramatically improve the lives of patients.

Fortunately for Americans, the attitudes of the medical establishment and the U.S. Government have mellowed from the era of near paranoia over the potential for drug dependency, diversion of opioids to non-medical uses, or "addiction". However, the lack

of pharmaceutical manufacturer interest in conventional opioids such as morphine due to their relatively low price (off-patent) may have synergized with the former establishment fear of such drugs. **This may explain the paradox that for three decades many drugs which were almost certainly less efficacious and considerably more dangerous than opioids (e.g. anticonvulsants, antidepressants, antipsychotics, anti-dysrhythmics, and topical capsaicin/pepper extract) enjoyed relatively unfettered use for off-label pain indications**.

Both the prevalent "opioid-phobia" and the perceived lack of commercial benefit to manufacturers may have limited the design of experimental studies of pain control using opioids in non-cancerous conditions such as PDPN and PHN. Unlike major cardiovascular or cancer studies, for which there is an established tradition of government-supported and academically-designed research, **virtually all large pain studies are manufacturer-funded.** With the exception of one placebo-controlled study utilizing a controlled-release formulation of oxycodone, one does not find experimental studies of opioids for "neuropathic" pain, even though this had become established practice for experienced physicians. Not until 2005 was a study comparing gabapentin with morphine published (Gilron 2005, see below). The scientific and clinical importance of an experiment **comparing gabapentin with the most efficacious known analgesic (morphine)** is attested by the publication of Dr. Gilron's study as a major article in the New England Journal of Medicine.

By 2004 opioids were officially recommended by established American medicine as one legitimate option for painful peripheral neuropathy. (Dubinsky RM et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 63: 959-65)

Tricyclic antidepressants (imipramine, amitriptyline, nortriptyline, desipramine, etc.) have shown modest efficacy (vs. placebo) for painful peripheral neuropathy and have the advantage of very low cost (off patent). Unfortunately they carry virtually inevitable anti-cholinergic and alpha-blocking adverse effects, although some patients clearly tolerate and benefit from them. It is interesting that such adverse effects were considered less important by pharmaceutical manufacturers while tricyclics were still under patent protection – for many years, tricyclics were promoted as "miracle drugs" for depression. Although there was a storm of interest in and promotion of SSRI and other new antidepressant drugs for pain, there is no conclusive evidence that they are effective for "neuropathic" or any other pain. Multiple experiments demonstrate lack of efficacy.

Anticonvulsant drugs (anti-epileptic drugs, AED) have been used with very limited success in "neuropathic" pain and have found no role in other types of pain. Typically they are at best modestly effective, and unfortunately they often produce significant adverse effects in the elderly. However, carbamazepine appears to be convincingly beneficial for some people with trigeminal neuralgia, a relatively rare condition; occasionally a dramatic benefit is observed. Unfortunately we have very little information about how the older drugs (e.g. carbamazepine, phenytoin) might compare directly with newer anticonvulsants (e.g. gabapentin, pregabalin, topiramate, lamotrigine, etc.), as manufacturers of new drugs are unlikely to sponsor, let alone design such experiments which run the risk of showing that an old (off patent) drug is superior or

equivalent to a new drug. For certain drugs which were heavily promoted for off-label (non-indicated) use in pain, e.g. topiramate (Topamax) there is abundant clinical evidence that the results are terrible for patients. Little if any analgesic benefit is achieved, but there is a wealth of sometimes frightening toxicities. Where a drug like topiramate has gained an official indication for a painful condition like migraine, a rational inspection of the evidence shows clearly that the new drug is not superior to, and likely markedly inferior to a comparator (e.g. propranolol for migraine).

Non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen, naproxen, diclofenac, ASA, "COX-2 selective inhibitors"/coxibs) and acetaminophen typically have very limited utility for "neuropathic pain", especially for PDPN or PHN, and the NSAID class (including the newer on-patent drugs) risks impairment of renal function, cardiovascular function and/or gastrointestinal bleeding. Renal and cardiovascular effects are especially problematic in diabetics given their common co-morbidities, and all NSAID toxicities are especially dangerous in old people.

In Canada and Europe, prescription of opioids for chronic non-malignant pain is increasingly common. The advantages of opioids include remarkable efficacy for moderate to severe pain, safety for the GI tract, the kidneys, the liver, the heart, and other organs, and (depending on the drug and preparation) modest cost. The disadvantages are well known, including the risk of respiratory depression, somnolence or mental impairment, constipation, and occasionally dose-limiting nausea or vomiting or confusion/delirium. Professional bodies in Canada, in deference to the significant pharmacologic advantages of opioids, officially sanctioned their use for chronic non-malignant pain in advance of their counterparts in the United States. (e.g.: Evidence-based recommendations for medical management of chronic non-malignant pain: chapter 7. Neuropathic pain, College of Physicians and Surgeons. Nov 2000. http://www.cpso.on.ca/publications/pain.PDF, accessed July 18, 2008) Hence, the most appropriate comparator drug class for clinical trials in significant pain is almost certainly the opioid class.

e) How common are PDPN and PHN?

This is a relevant question, as much of the marketing of gabapentin (Neurontin) by Parke-Davis and Pfizer tended to exaggerate (at least by implication) the prevalence of these conditions. This approach, which appears to me to have been accepted uncritically by members of "advisory boards", is hardly unique to the field of pain. Inflation of the true incidence and prevalence of depression and other conditions, is now referred to as "disease mongering". For Neurontin (gabapentin), the implication by the manufacturer, or the inference by its audiences, that PDPN and PHN represent virtual "epidemics" of inadequately treated pain may also have functioned as a "lever" to increase the use of this drug for **other purposes** for which there was no relevant experimental evidence whatsoever. Chronic back pain, for example, is so ubiquitous that "market creep" of gabapentin into this sector would have or did represent a "gold mine" for the manufacturer.

While both **painful diabetic peripheral neuropathy (painful DPN)** and **postherpetic neuralgia (PHN)** cause significant suffering, their true incidence and prevalence is not known.

1) **Painful diabetic peripheral neuropathy (PDPN):**

PDPN is a **small subset** of a much more common condition, diabetic peripheral neuropathy (DPN). Many diabetic patients experience **painless** neuropathy. Indeed, it is the inability to sense normal painful stimuli which leads to one of the most feared complications of diabetes: silent infection of the toes and feet, which can lead to chronic infection, partial limb amputation, prolonged hospital stays, high medical costs, and premature death. Estimates of the prevalence of **DPN** are irrelevant to the prevalence of **painful diabetic peripheral neuropathy (PDPN)**, for which a reliable estimate is **unavailable.** The most reasonable prevalence estimates for diabetic neuropathy sufficiently painful to warrant drug therapy ranges from 1% - 10% of chronic diabetics. (Dyck PJ et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology 1993; 43: 817-24; Boulton A. Management of Diabetic Peripheral Neuropathy. Clinical Diabetes 2005; 23: 9-15)

2) **Post-herpetic neuralgia (PHN):**

A U.S. administrative database study comprising over 2.8 million people found an overall **incidence of *Herpes zoster* infection** of 3.2/1,000 person-years. (Insinga RP et al. The incidence of herpes zoster in a United States administrative database. J of Gen Internal Medicine 2005; 20: 748-753) Of 9,152 apparent cases of *Herpes zoster*, 48% occurred in people $\geq$ age 60, and over 10% in people $\geq$ age 80. Such estimates apply to acute *Herpes zoster* reactivation, **of which only a small minority progress to PHN**. A prospective Icelandic study of 421 patients with clinically diagnosed acute *Herpes zoster* may provide a more realistic estimate of the prevalence of a persistent pain syndrome – PHN. (Helgason S et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ 2000; 321: 794-6) This experiment reflects the experience of over one third of the Icelandic population during a 5.5 year interval. In patients < 60 years old, PHN was present 3 months post-onset of acute *Herpes zoster* reactivation in only 1.8%, and was "mild" in all cases. Amongst patients aged > 60, pain persisted in 20% at 3 months, but in only 2% was pain described as "severe". At 12 month follow-up, 403/417 evaluable patients were **pain free**, whereas 14 of the original 421 patients reported mild pain (12) or moderate pain (2). No patient complained of "severe" pain at 12 month follow-up. The report concludes,***"…the risk of longstanding pain has been overemphasized in trials of drug treatments"***. A retrospective analysis of a Dutch general practice database comprising 49,000 patients suggested annual incidence of *Herpes zoster* reactivation of 3.4/1000 patients/year. Amongst such patients presenting with acute *Herpes zoster*, the overall prevalence of PHN 1 month later was 6.5%, but had declined to 2.6% by 3 months. Of 133 patients aged $\geq$ 75, the 1-month prevalence was 18%, but declined to 9% by 3 months. (Opstelten W et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract 2002; 19: 471-475) In summary, the true

prevalence of clinically significant pain from PHN is unknown, but as for PDPN, it is likely to be **much lower** than implied by the introductory or discussion sections of many research or review articles on this topic, or in the intensive marketing campaign conducted by Parke-Davis/Pfizer for Neurontin**. As noted above, the major burden of chronic pain from PHN occurs in elderly patients, who are the most vulnerable to the adverse effects of gabapentin or other analgesics.**

VI) MY APPROACH TO ANSWERING QUESTIONS TO BE ADDRESSED:

a) Initial review of available clinical trials and search for reliable systematic reviews:

You presented me in March 2008 with a massive amount of information in the form of electronic (PDF) versions of various published and unpublished reports of randomized controlled trials (both open and double blind) utilizing gabapentin for treatment of various painful conditions. These included painful diabetic peripheral neuropathy (PDPN), postherpetic neuralgia (PHN), various post-operative causes of "neuropathic pain", "neuropathic pain" associated with cancer, "neuropathic pain" associated with spinal cord injury, and pain associated with dental procedures, osteoarthritis and with orthopedic surgical operations. Some of the documentation of DBRCT experiments was in the form of detailed formal clinical trial reports compiled by the sponsoring pharmaceutical manufacturer (Parke-Davis or Pfizer), with appendices often exceeding 1300 pages – and some much longer! Most academic students of clinical trials literature, let alone practicing doctors, will not have seen this type of "in-house" report previously. I could see from differences apparent in the full PDPN 945-210 trial report(s) that it would be necessary to compare the published DBRCT reports with the original "in-house" complete trial report(s), where the latter were available.

Facing this task, as would many people experienced with reading and performing systematic reviews, I reverted to the practical approach of looking for a **Cochrane systematic review** pertaining to the use of gabapentin for pain. The most recent review, published in 2005 (Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. The Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD005452. DOI: 10.1002/14651858.CD005452) is based on a revision of an earlier review of the use of anticonvulsants to treat pain. Unfortunately, while the new version contains some additional information, it is sufficiently flawed that it did not spare me the task of performing my own systematic review, for the following reasons:

1. The Cochrane review had no access to the unpublished reports obtained by Greene & Hoffman, which contain large amounts of data and include studies which **did not find a significant benefit from gabapentin.** These studies were not submitted to, nor published in medical journals, nor made available to the general medical or scientific reader, nor even (apparently) to "medical advisory boards" which consulted for Parke-

Davis or Pfizer. (I found no evidence in the promotional materials I reviewed that the **unpublished** trial results, or even the **existence** of trials which generated negative findings, were shared with physicians and scientists who attended such "advisory board" or "CME" meetings. There must have been literally dozens, if not hundreds of opportunities for Parke-Davis/Pfizer and its medical agents (including the "clinical investigators" who participated in the unpublished trials) to share the unpublished evidence with the very doctors who were being encouraged to prescribe Neurontin. Given that no one appears to have availed him or herself of such opportunities for full disclosure, it is not surprising that academics or physicians outside what one might call the "Neurontin circle" might have been even more ignorant of what remained occult.) Hence, the Cochrane 2005 systematic review of gabapentin is **irremediably compromised by "publication bias"**, although the Cochrane reviewers at Oxford University may not have realized this. During my visit to your Boston office in April 2008, you showed me internal e-mail correspondence from Pfizer indicating that Pfizer had been in touch with Professors Wiffen and McQuay during the preparation of the 2005 updated review. Presumably Pfizer could have shared all remaining unpublished data with the Oxford pain group so as to render the updated 2005 review complete and authoritative, had the company so wished. The Cochrane 2005 review authors dealt with this question only by stating that *"Publication bias was not explored as current methods are not reliable"*. (Wiffen PJ et al. 2005. p. 3)

2. Similarly, the Cochrane reviewers did not enjoy access even to the real (unexpurgated) details of published clinical trials (e.g. Gorson 1999). The original unpublished but detailed study publications (ParkeDavis/Pfizer documents critically appraised in an Appendix to my report) show that some of the statistics utilized for the Cochrane review **do not correspond with the real data**. Notably, the denominators for the placebo and gabapentin groups are at times inappropriately recorded. Restricting the denominator to only some of the subjects (e.g. those who completed the trial) violates conventional "intention to treat (ITT)" principles, which are designed to ensure that all experimental subjects are accounted for, not just those whose outcomes please or interest the investigators. The Cochrane 2005 "methods of the review" section states explicitly that *"Intention-to-treat analysis was not carried out and patients who dropped out of studies were not included in the analysis"*. I cannot understand why this approach was taken, given the well known problems that arise in the interpretation of studies from which experimental subjects are lost to follow up.

3. Two trials included in the 2005 Cochrane review appear to be of very doubtful veracity, such that I could not myself conclude that it was reasonable to compare them in a systematic review with the other, apparently genuine trials. The Cochrane reviewers state that they confirmed from Perez 2000 that the study was randomized and double blind, but this does not seem plausible from the original study report, a < 1-page letter in the American Journal of Medicine. Similarly, the Cochrane reviewers took at face value Simpson 2001, a peculiar study published in a new and obscure journal, the purported results of which Pfizer and its expert correspondent Dr. Robert Dworkin considered highly suspicious. (Pfizer_LKnapp_0060187-91 and 0083148-50) The publication of Simpson 2001 in the Journal of Clinical Neuromuscular Disease 2001 does not meet standard reporting requirements. The Cochrane reviewers could have, but did not note

this. However, had they been aware of Pfizer's concerns about the validity (or even real existence) of this study, I wonder whether they would have chosen to include this study in their systematic review.

4. Two trials included in the Cochrane 2005 review (Dirks 2002 and Pandey 2002) are of doubtful relevance to the questions I was asked to address. Dirks 2002 relates to very brief (4 hour) post-operative assessment of surgical patients for endpoints not shared with and of very doubtful relevance to other studies, whereas Pandey 2002 relates to ventilator-dependent patients with Guillain-Barre syndrome, a very specialized situation also not relevant to the other studies or the questions I sought to answer. (I subsequently identified a large number of other surgical or peri-operative studies which are similarly irrelevant to the outpatient prescribing of gabapentin, which is evidently the basis for the lawsuit in which my opinion is sought.)

5. The Cochrane review is also technically flawed insofar as the Forrest plot figures are mislabeled. This makes it difficult to know what outcomes are being reported, and would lead the lazy or superficial reader to peruse only the Abstract and perhaps accept the conclusions at face value, without troubling to figure out what the mislabeled Forrest plots really mean. Furthermore, the numbers utilized do not always correspond from one figure to another, nor with the real figures available from the full (unpublished) trial reports. The authors conclude "enrichment bias" only for studies that specify exclusion of patients who did not achieve satisfactory pain relief on gabapentin, whereas I conclude at least potential "enrichment bias" for studies (e.g. Backonja 1998, Rowbotham 1998) which excluded patients previously treated with or "hypersensitive" to gabapentin. In my opinion, such exclusions could selectively remove from the randomized population those patients who had failed to receive benefit from, or who experienced toxicity from gabapentin, rather than fairly representing "all comers" presenting for screening. Unfortunately, despite the eminence of its authors, the Cochrane 2005 review is generally too sloppy to be considered reliable, even if one were not aware of the omitted unpublished studies which comprise a very substantial fraction of all patients experimentally exposed to gabapentin in DBRCT.

6. Additional studies have been completed and reported (relatively large unpublished reports and smaller published studies) since completion and publication of the Cochrane review.

When I looked initially at the 2005 Cochrane systematic review in your Boston offices on April 1st, you may recall that I was surprised at the mislabeling of figures and convinced that I could not be looking at the final published Cochrane systematic review. I confirmed that I was by an independent search, and notified the lead author (PJ Wiffen) by email. He subsequently confirmed by return email the mislabeling of figures and indicated his plan to correct this.

I later identified another more recent systematic review of the treatment of painful diabetic neuropathy (Wong MC, Chung JWY, and Wong TKS. Effects of treatment for symptoms of painful diabetic neuropathy: systematic review. BMJ 2007;335:87; doi:10.1136/bmj.39213.565972.AE). However this review did not obviate

the need for our own meticulous systematic review, as it only concerned one condition (PDPN) and enjoyed no access to the **unpublished** experimental data for gabapentin.

On July 29, 2008 you sent me electronically an "Expert Report of Nicholas P. Jewell, Ph.D." prepared by Dr. Jewell of the University of California School of Public Health, and bearing the same date. This document is discussed briefly later in my report.

b) Decision to undertake our own systematic review:

It thus became apparent that I would have to undertake my own systematic review involving a complete and thorough critical appraisal of all available trials (published and unpublished) and a meta-analysis of those trial outcomes which are amenable to meta-analysis (pre-defined standardized outcomes common to more than 1 DBRCT). Before proceeding to detailed evaluation of the results of individual trials, my Vancouver colleagues and I discussed and agreed on the following strategy for an independent Cochrane systematic review, utilizing the standard Cochrane hierarchy of clinical outcomes adapted to this project. We were influenced as appropriate by the principles adopted by Wiffin PJ et al in the 2005 Cochrane review of gabapentin. Note that a fundamental principle of such reviews is that the methodology should be transparent, the strategy clear, the quality of the work unimpeachable and the results **reproducible** by anyone following the same strategy. Obviously it would be desirable for the results of my systematic review to be made public at the earliest possible opportunity.

c) Strategy for independent Cochrane systematic review of gabapentin for pain

Background:

Controlled trials of gabapentin for pain use varying outcomes, some of which are incompatible for meta-analysis. There is no "consensus" on the most meaningful outcomes in acute or chronic pain. Some frequently proposed useful measures include:

- Percentage of patients achieving $\geq$ 50% reduction of individual pain scores on numerical rating scale (NRS) or visual analog scale (VAS) at pre-specified "endpoint" vs. baseline;
- Percentage of patients achieving $\geq$ 2-point reduction in a 10-point NRS (or VAS);
- Percentage of patients achieving "much" or "moderate" overall improvement, rated as either 1 or 2 on a self-rated 7-point categorical rating scale, the Patient Global Impression of Change (PGIC), or an analogous 7-point scale.

Note that the mean difference in pain scores between groups, unless dramatic, tells one almost nothing about how the individual patients have responded, or the probability that one patient treated by one doctor can expect meaningful benefit (or harm).

We considered this variability in how results of drug studies for pain are reported and interpreted. After considering how the Cochrane Pain Group (Wiffen PJ et al) chose

its hierarchy of outcome measures for the 2005 Cochrane systematic review of gabapentin, as well as other views on meaningful outcomes in pain studies and basic common sense concerning outcomes most meaningful to patients suffering from clinically significant pain, we agreed on the following outcome hierarchy before commencing our meta-analysis. The hierarchy follows the usual Cochrane practice for ordering the importance of events which occur during a DBRCT, i.e. mortality, serious adverse events, etc. – a standard of reporting common to the best modern clinical trials:

Hierarchy of outcomes adopted on July 8, 2008 for meta-analysis (all by true Intention to Treat/ITT, whereby all patients exposed to at least one dose of the study drug are accounted for).

1. Mortality (typically not expected in short term pain studies, except for cancer)

2. Serious adverse events (SAE)

3. Withdrawals due to adverse events (WDAE)

4. Total withdrawals

5. Total adverse events (AE, as patients experiencing AE and as individual most clinically relevant adverse events (where available and comparable across multiple studies)

6. Validated measures or obvious measures of improvement in global function including return to work, study, activities of daily living

7. $\geq$ 50% reduction in pain score (NRS, VRS) from baseline to endpoint (categorical variable, as used by Cochrane pain group), **where this was a pre-defined primary or secondary endpoint in a trial** (avoids post-hoc analysis; any drop out from a trial whose categorical status is not reported will be assumed **not** to have achieved the desirable outcome)

8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by true intention to treat (ITT) – **where this was the pre-defined primary endpoint in a trial** (NB: where true ITT is impossible due to missing observations, we will discuss for that trial the potential bias arising from substitution of last observation carried forward (LOCF) data, or omission of data from early drop-outs)

9. % of patients achieving "much improved" or "moderately improved" (categorical variable, as used by Cochrane pain group) on Patient Global Impression of Change (PGIC, values 1 ["much improved"] and 2 ["moderately improved"] on a 7-point ordinal scale) **where this was a pre-defined primary or secondary endpoint in a trial** (avoids post-hoc analysis; any drop out from a trial whose score is not reported will be assumed **not** to have achieved the desirable outcome)

10. Descriptive statistics:

a) Total adverse events (AE) experienced during each study which reported total AE (one patient may experience more than one AE – such statistics are not suitable for meta-analysis)

b) Summary of PGIC for all studies which reported this 7-point outcome as table and graphical (histogram) presentation (predetermined rule, July 8, 2008: presentation will be by total numerator = total N for each treatment arm for each of 7 PGIC categories [1, 2, … 7] divided by the true denominator = total N randomized to each treatment group) across all studies, for placebo, gabapentin, or other comparators)

Search strategy:

Along with my colleague Dr.Vijaya Musini, I used a variety of conventional search strategies as well as frequent Google searches and searches prompted by identification of references from research reports of RCT, reviews, systematic reviews, Parke-Davis/Pfizer promotional materials, the unpublished Parke-Davis and Pfizer documents you sent me in March 2008 as a CD, and any other source we could identify. We identified some references missed by the conventional computer-based search strategies. Some of these have also been missed by other authors of review articles and systematic reviews featuring gabapentin. We decided to exclude trials which dealt only with the peri-operative setting, on the grounds that the results are inapplicable to the outpatient setting and the methodology is typically entirely different from the outpatient trials. Dr. Musini ran several formal computerized literature searches using strategies including the following approaches. The results of these searches are widely available and therefore redundant to list in this report, but they are available upon request.

Database: EMBASE <1980 to 2008 Week 29>
Search Strategy:
---
1 gabapentin.mp. or exp GABAPENTIN/ (10805)
2 randomized clinical trial.mp. (6809)
3 randomised clinical trial.mp. (849)
4 randomized.mp. (247310)
5 randomised.mp. (33532)
6 2 or 3 or 4 or 5 (263104)
7 double blind.mp. (102116)
8 1 and 6 and 7 (365)
9 neuropathic pain.mp. or Neuropathic Pain/ (7571)
10 8 and 9 (66)
11 from 10 keep 1-66 (66)

Database: Ovid MEDLINE(R) 1950 to Present with Daily Update
Search Strategy:

---
1 gabapentin.mp. or exp GABAPENTIN/ (2667)
2 randomized clinical trial.mp. (7560)
3 randomised clinical trial.mp. (873)
4 randomized.mp. (359665)
5 randomised.mp. (35941)
6 2 or 3 or 4 or 5 (368424)
7 double blind.mp. (118040)
8 1 and 6 and 7 (229)
9 neuropathic pain.mp. or Neuropathic Pain/ (4843)
10 8 and 9 (40)
11 [from 10 keep 1-66] (0)
12 1 and 6 and 9 (88)
13 from 10 keep 1-40 (40)

Database: MEDLINE and
Database: Cochrane database of systematic reviews: Key words : gabapentin, randomized , double blind, neuropathic pain

Database: DARE

Database: Cochrane CENTRAL

Database: International Pharmaceutical Abstracts <1970 to July 2008>
Search Strategy:
---
1 gabapentin.mp. or exp GABAPENTIN/ (540)
2 randomized clinical trial.mp. (440)
3 randomised clinical trial.mp. (40)
4 randomized.mp. (20022)
5 randomised.mp. (1821)
6 2 or 3 or 4 or 5 (21582)
7 double blind.mp. (13775)
8 1 and 6 and 7 (24)
9 from 8 keep 1-24 (24)

The only DBRCTs discovered through a search independent of these techniques are apparently unreported trials, described only in press releases and brief webpage articles on the website (http://www.depomedinc.com/view.cfm/1285/Our-Pipeline) of Depomed Inc. of Menlo Park, CA. I sent e-mail requests for additional details to the company on July 27 and July 29, 2008 for additional details, but these were not responded to. The trials are described briefly below, since there is no information suitable for critical appraisal, summary, nor for meta-analysis, but the failure to publish the results may reflect information which is relevant to my overall conclusions.

List of references reviewed and critically appraised:

The Appendix labeled "APPENDIX – GABAPENTIN PROJECT Pain Studies Summary Matrix – FINAL – August 7, 2008 – Dr. Thomas L. Perry" lists the published and unpublished studies critically appraised, including the few studies which we deemed inappropriate to include in our meta-analysis. The following studies were not critically appraised: Simpson 2001 (of questionable validity, see discussion below), 1032-004/720-04481.pdf (sub-study of gastroprotection, irrelevant), McCleane 2000 (not suitable for meta-analysis due to inadequate reporting), Spira 2001 (migraine prophylaxis study, not suitable for meta-analysis). The full bibliographic references are included in the left hand columns of this matrix.

Critical appraisal of articles:

I began the critical appraisal of articles by comparing the published and unpublished reports of the Gorson and Backonja trials reporting the use of gabapentin for PDPN to identify the key issues for critical appraisal. I then constructed tables to use as templates so that we could perform a similar critical appraisal for each study we identified. What may not meet the eye is the enormous amount of work necessary to review thoroughly the unpublished reports, as well as to understand the subtle implications of omissions or varying ways of presenting data in the published reports (whether Parke-Davis/Pfizer designed trials or independently designed experiments).

The individual critical appraisal study summaries of trials are presented in an Appendix to my report designated **GABAPENTIN PROJECT Study detail summaries.** This includes:

- 25 published and unpublished study reports describing experimental use of gabapentin for chronic pain which were suitable for meta-analysis of at least some outcomes;
- 6 study reports describing use of gabapentin for acute pain which were not suitable for our meta-analysis of chronic pain outcomes;
- 2 published study reports describing use of gabapentin for chronic pain which were not suitable for meta-analysis due to reporting or study quality issues.

Due to the immense time requirement of this project, I reviewed and accepted the summaries of the 5 unpublished acute pain trials prepared by Ms. Kelsey Innes, without having attempted to review personally the hundreds or thousands of pages in the PDF versions of the trial reports. Ms. Kelsey demonstrated a meticulous mathematical approach which I checked carefully for the chronic pain studies of Gorson, Rowbotham and Rice; I am therefore confident of the accuracy of her extraction of results into the following study detail summaries: Protocol 1035-001 and Protocol 1035-001, Addendum B, both concerning pain after dental surgery; Protocol 1035-002 concerning post-operative pain after major orthopedic surgery; Protocol 1032-001 concerning post-

operative dental pain; and 1032-002/3 concerning pain from osteoarthritis (see Appendix).

These unpublished trials concern acute pain. They are not suitable for meta-analysis with the chronic pain trials. **However, they are highly relevant to the questions you posed, and fascinating insofar as they show unequivocally and repeatedly that gabapentin is not useful for a variety of types of acute pain.** It is a pity that they were not published soon after their completion and Parke-Davis/Pfizer's internal and confidential reporting of the results during the year 2000.

Presentation of evidence (Appendices):

1. Matrix of studies identified and critically appraised:

You supplied me on April 1, 2008 with a matrix of studies of which you were aware. I retained the basic structure of the matrix but modified the headings or presentation slightly so as to identify trials in the chronological order in which the trials were conducted. Because of the large numbers of electronic documents to be handled, it became impractical to renumber the studies when we identified 3 more trials on July 26-28, 2008. Therefore the final 3 trials (Study No. 23, 24, 25) in the chronic pain section of the matrix are **not** shown in the appropriate chronological order. The matrix also serves as the reference list for studies reviewed, including the unpublished Parke-Davis/Pfizer studies. **This matrix is labeled: APPENDIX - GABAPENTIN PROJECT Pain Studies Summary Matrix - FINAL – August 8, 2008, Thomas L. Perry, M.D.**

2. Detailed critical appraisal study summaries:

This Appendix, GABAPENTIN PROJECT Study detail summaries, presents the basic methodology, outcomes, and statistical or critical appraisals of each study reviewed in detail, along with my observations or conclusions particular to each study.

3. Meta-analysis summary tables:

The evidence regarding outcomes from the above hierarchy is extracted from the critical appraisal of each DBRCT (and safety outcomes as appropriate from open RCT) in the form of summary tables presented in the appendix for each study meta-analysed. These are labeled as: **APPENDIX - GABAPENTIN PROJECT Pain Studies Summary Outcomes for Meta-Analysis - FINAL – August 8, 2008 AND July 30, 2008, Thomas L. Perry, M.D.**

4. Meta-analysis Forrest plot figures:

Forrest plots, popularized by the Cochrane Collaboration, provide a simple way to summarize large amounts of data in a format that can easily be understood and

interpreted by people familiar with the format. These will be familiar to any medical scientists, physicians experienced with the modern medical scientific literature, and epidemiologists or clinical trial specialists who may look at this report. Hopefully they will also be intelligible to the Court. These are presented for the outcomes described above, using data from those studies which contribute usable data to the meta-analysis (see our pre-determined rules of July 8, 2008 above). The Forrest plots are labeled as: **APPENDIX - GABAPENTIN PROJECT Forrest plot outcomes of Meta-Analysis - FINAL – July 30, 2008, Thomas L. Perry, M.D.**

NB: The Forrest plot analyses represent results obtainable by a meticulous critical appraisal of published and unpublished reports. For some of the unpublished reports, because of the detail available to someone willing to read them meticulously, it is possible to be more certain of numerators and denominators for experimental groups (placebo, gabapentin at various doses) and for outcome measures (total AE, NRS mean pain score, PGIC, etc.) than for some of the published reports. However such analyses (Forrest plot, meta-analysis, systematic review) are still only as reliable as the data input into the statistical analysis software (Cochrane RevMan). Therefore I reserve the right to modify the Forrest plots and any other aspect of this analysis should I subsequently receive information indicating that the data inputs are incorrect in any way, or if additional data suitable for meta-analysis come to light (e.g. further unpublished trials, or published trials missed by the literature search technique). For example, I understand from you that Pfizer performed an additional post-hoc analysis of the Serpell trial of patients with “mixed neuropathic pain” (945-306). I have not seen this post-hoc analysis, but I understand that it may have been performed to segregate patients with PHN from those with PDPN or with other causes of “neuropathic pain” (e.g. CPRS, who constituted 28% of the patients in this trial). Were the results of this analysis available, it might be possible to re-analyse the data from the Serpell trial (945-306) so as to EXCLUDE data from patients with PHN and/or to analyse ONLY data from patients with PDPN, depending on how these results are presented in Pfizer documents or reports.

VII) EVIDENCE GLEANED FROM SYSTEMATIC REVIEW:

The beauty of the Forrest plot analysis is that it provides apparently simple answers to certain questions. By pooling all the available information from all relevant DBRCTs it yields, for example, the "weighted mean difference" (WMD), the apparent best estimate of the mean effect of gabapentin vs. placebo on an 11-point pain scale. For a categorical endpoint, meta-analysis yields a number needed to treat (NNT) with gabapentin (vs. placebo), e.g. for one patient to experience a $\geq$ 50% reduction in the same pain scale from baseline to study "endpoint". The results of these comparisons are presented below in the order of the outcomes hierarchy described above:

Hierarchy of outcomes:

NB: During labeling of our Forrest plots the code numbers (e.g. "Outcome 03", or "Outcome 04") may not be consistent. I have listed the "Outcomes" in the form they are shown in the Forrest plots, but ordered the English language outcomes (e.g. "Mortality", "Total Withdrawals") in the same order as in our prespecified hierarchy of outcomes.

1. Mortality, Outcome 01:

In short term studies there is **no difference** between gabapentin and placebo (RR with 95% CI = 0.92 (0.21, 3.97), and (from the few small pertinent DBRCT which are meta-analysable) **no difference** between gabapentin and active comparators.

2. Serious adverse events (SAE), Outcome 02:

In short term studies there is **no difference** between gabapentin and placebo (RR with 95% CI = 1.15 (0.74, 1.77), and **no difference** between gabapentin vs. active comparators (RR with 95% CI = 1.21 (0.47, 3.10).

3. Withdrawals due to adverse events (WDAE), Outcome 04:

In short term studies there is a **statistically significant difference** between gabapentin and placebo (RR with 95% CI = 1.36 (1.07, 1.73), **favouring placebo over gabapentin**. **Significantly more patients treated with gabapentin withdrew from trials due to adverse events, with absolute risk increase = 2.9%, NNH =35**, typically over a short period (days to a few weeks). Among the much smaller number of patients enrolled in trials of gabapentin vs. active comparators (total patients = 210, vs. total patients 2,708 for placebo-controlled trials of gabapentin for pain) **no difference** is observed between gabapentin vs. active comparators (RR with 95% CI = 1.21 (0.47, 3.10).

4. Total withdrawals, Outcome 03:

In short term studies there is **no difference** between gabapentin and placebo (RR with 95% CI = 1.06 (0.90, 1.24), and **no difference** between gabapentin vs. active comparators (RR with 95% CI = 1.04 (0.55, 1.94)

5. Total number of patients with adverse events (AE), Outcome 09:

In short term studies there is a **statistically significant difference** between gabapentin and placebo (RR with 95% CI = 1.25 (1.17, 1.34) **favouring placebo over gabapentin**. **Significantly more patients treated with gabapentin than with placebo experienced AE, with absolute risk increase = 12.4%, NNH = 8**, typically over a short period (days to weeks). In the only trial of gabapentin vs. active comparator (amitriptyline) which reports this outcome in a form suitable for meta-analysis **no difference** is observed between gabapentin vs. amitriptyline (see Forrest plot for Morello trial).

Patients treated with gabapentin experienced significantly more of the following AE's, compared with those treated with placebo (not all trials compare similar outcomes, see Forrest plot Appendix for further details):

a) **Dizziness: absolute risk increase 17.8%, NNH = 6**
b) **Somnolence: absolute risk increase 15.3%, NNH = 7**
c) **Confusion: absolute risk increase 10.1%, NNH = 10**
d) **Ataxia: absolute risk increase 10.1%, NNH = 10**
e) **Lethargy: absolute risk increase 10.1%, NNH = 10**
f) **Aesthenia: absolute risk increase 4%, NNH = 25**
g) **Lightheadedness: absolute risk increase 13.4%, NNH = 7.5**
h) **All CNS events: absolute risk increase 12.5%, NNH = 8**
i) **Edema: absolute risk increase 8.9%, NNH = 11**

This shows that the chance that highly selected patients (with lower than average risk for adverse events and higher than average expectation of benefit) would experience an adverse event during gabapentin short term therapy (vs. placebo) was approximately the same as the chance that they would perceive a benefit (see below).

6. Validated measures or obvious measures of improvement in global function including return to work, study, activities of daily living:

No trials reported this outcome. No relevant information is available as the scores utilized in various trials do not report hard outcomes such as the above.

7. $\geq$ 50% reduction in pain score (NRS, VRS) from baseline to endpoint, Outcome 07:

In short term studies there is a **statistically significant difference** between gabapentin and placebo (RR with 95% CI = 1.72 (1.36, 2.17) **favouring gabapentin over placebo**. **Significantly more patients treated with gabapentin than with placebo rated their pain as reduced by $\geq$ 50%, with absolute difference = 13%, NNT = 8**, at the end of study. However, the definition of such "responders" in most studies appears to include people who dropped out early, almost certainly including some who dropped out because of adverse effects. Thus the benefit may not be unmitigated. In the only trial of gabapentin vs. active comparator (nortriptyline) which reports this outcome in a form

suitable for meta-analysis **no difference** is observed between gabapentin vs. amitriptyline (see Forrest plot for Chandra trial).

8. Mean change from baseline in NRS/VAS pain score, Outcome 06:

In short term studies there is a **statistically significant difference** between gabapentin and placebo (WMD with 95% CI = -0.78 (-0.99, -0.58) **favouring gabapentin over placebo**. **Gabapentin was associated with a weighted mean difference by the end of study (LOCF) of –0.78, vs. placebo, on an 11-point scale.** No trial of gabapentin vs. active comparator reports this outcome in a form suitable for meta-analysis.

9. PGIC "moderately or much improved" as % of patients, Outcome 05:

In short term studies there is a **statistically significant difference** between gabapentin and placebo (RR with 95% CI = 1.78 (1.53, 2.07) **favouring gabapentin over placebo**. **Significantly more patients treated with gabapentin than with placebo rated themselves "moderately or much improved", with absolute difference = 17.2%, NNT = 6.** No trial of gabapentin vs. active comparator reports this outcome in a form suitable for meta-analysis.

10. Descriptive statistics:

Total adverse events (AE) are reported by study in the **APPENDIX –GABAPENTIN PROJECT – Summary tables for Forrest plot analysis.** They are not amenable to analysis since they have no appropriate denominators (one patient may have more than one AE). Histograms of outcomes on PGIC have been included in some of the study detailed summary reports, and an overall histogram is also presented.

What does this all mean?

It is important not to "lose sight of the forest for the trees". Overall, this analysis shows that for the available published and unpublished studies of gabapentin for chronic pain:

a) The average apparent benefit on an 11-point pain score over a number of weeks, compared with placebo, was less than 1 point (best estimate: 0.78 point, range of statistically valid estimate: about 0.6 to 1 point on an 11-point scale). This overall best estimate of the "benefit" of gabapentin is essentially clinically meaningless. It is substantially less than the estimate of the effect of this "primary outcome" obtained from the published trials which formed the basis for the aggressive marketing of Neurontin by Parke-Davis/Pfizer and its medical allies.

b) The probability that a patient might achieve a more clinically meaningful benefit, expressed as the chance of achieving a $\geq$ 50% reduction in the same pain score from start to finish of the clinical trial (or withdrawal from it) looks on the surface

to be somewhat more interesting: one of eight patients taking gabapentin rather than placebo might expect this outcome; NNT = 8.

c) Similarly, one in six patients taking gabapentin rather than placebo could expect to achieve "moderate or much improvement" on end of study PGIC, NNT = 6.

In return, about one in thirty-five people taking gabapentin rather than placebo could expect to be forced out of a short term study, due to gabapentin's adverse effects, NNH = 35. Similarly, one in eight patients taking gabapentin rather than placebo could expect an adverse effect such as dizziness, somnolence, impaired thinking (confusion), lack of energy (lethargy, asthenia), or edema.

Unfortunately, even the most intensive analysis of study reports provides little real understanding of what this all really means. **The patients do not truly speak to us through the publications, whether to describe their experience of adverse effects (harms) or of benefits.** And real understanding of the clinical significance of these results is not quite so simple for the following crucial reasons:

a) The clinical trials typically recruited only the healthiest available patients, taking the fewest interacting drugs, and with the fewest risk factors predictive of trouble with gabapentin, such as impaired kidney function, impaired mental or cognitive status, etc. This concern relates to the question of effectiveness, since harms from gabapentin are virtually certain to be higher in the real world than in the "glass fishbowl" environment of a DBRCT.

b) The trials mostly did not enroll patients previously exposed to gabapentin, or who had experienced untoward effects or no benefit from gabapentin. This "enriched" the study populations so as to artificially favour gabapentin, and one would not expect these results to reflect subsequent real world experience. This also relates to the question of effectiveness, since it is reasonable to expect that the DBRCT exaggerated any apparent benefits of gabapentin, compared with the real world.

c) An outcome such as the $\geq$ 50% reduction in pain appears superficially to be rather attractive. Yet it has no known meaning in real life – for example, it is not known whether a patient experiencing a 50%, or even a 75% reduction on a pain scale might return to work, sporting activities, or escape seclusion to resume an active social life. Furthermore, the design of some major trials appears to have allowed patients who **dropped out of the trials** because of adverse events to count as "responders" (pain score reduction $\geq$ 50%), even if they were burdened by side effects. This makes no clinical sense, as it would be equivalent in some ways to an inebriated person who is "feeling no pain".

d) The unblinding effect referred to below must almost certainly have exaggerated the apparent benefits of gabapentin. Most patients who enroll in clinical trials do so in the hope of a personal benefit. Those who enroll them seldom reflect in person the supposed "equipoise" (uncertainty as to whether a drug will "work")

reflected in submissions to ethics committees – they are inevitably enthusiasts for the new treatment. Thus patients who suspect they are taking the active drug are more likely to experience "benefit" than those who suspect they are taking the placebo. It is clear from several experiments that formally tested blinding that it is hard to keep people blinded when they take gabapentin, and this is also suggested by Professor Jewell's analysis.

Sensitivity analyses:

Professor Nicholas P. Jewell's report dated July 29, 2008 raises the specific question of whether the Backonja 1998 trial results favouring gabapentin over placebo for change in mean NRS pain scores over 8 weeks may be **mostly or completely related to unblinding**, and indeed may not represent a true analgesic effect of gabapentin. Note that the same criticism likely applies to many or all of the other studies we meta-analysed, and some of them frankly disclose unblinding due to the toxicity of gabapentin (notably van de Vusse 2004).

Although unblinding may inject a systemic bias into all trials of gabapentin, we repeated the Forrest plot meta-analysis after extracting **only the data from the Backonja 1998 trial in PDPN**. Similarly because PHN has an obviously different pathophysiology and clinical character from PDPN or other pain syndromes, and because gabapentin holds US FDA approval for this indication, **we also repeated the same analysis after extracting only the data from the two trials of gabapentin for treatment of PHN (Rowbotham 1998 and Rice 2001).** The results of these sensitivity analyses are as follows.

a) All pain trials of gabapentin vs. placebo EXCEPT Backonja 1998:

The weighted mean difference (WMD) in pain score declines trivially from – 0.78 to –0.74, still favouring gabapentin. (Sensitivity Analysis No. 1, p.12, vs. p.7 of the Forrest plot Appendix for gabapentin vs. placebo) There is little difference because the number of patients in the Backonja trial is small, compared with all other trials. There is a much larger difference between the point estimate for the Backonja trial and the other 3 trials in PDPN seen in the full data Forrest plot (Forrest plot Appendix for gabapentin vs. placebo, p.7). Similarly, removing the Backonja trial data does not change the estimate of NNT for PGIC from 6 (Forrest plot Appendix for gabapentin vs. placebo, p.13).

b) All pain trials of gabapentin vs. placebo EXCEPT PHN trials:

This sensitivity analysis reveals a more interesting result, at least for the mean difference in pain score, which shrinks (with extraction of the PHN data) to a point estimate of – 0.36 which is now barely statistically significant (95% CI, - 0.63, -0.09) almost touching the vertical line of equivalence on the Forrest plot (Forrest plot Appendix for gabapentin vs. placebo, p.15). Similarly, with the PHN trial data extracted, the chance of "moderate or much improvement" on PGIC is slightly less favourable to gabapentin, increasing

from NNT = 6 to NNT = 6.7 (Appendix, p. 14), while the probability of achieving a ≥ 50% reduction in pain score during the trial declines commensurately from NNT = 8 to NNT = 9 (Appendix, p. 16).

These results give us the best available summary of the effects of gabapentin vs. placebo in DBRCT. However, they still omit information from additional unpublished trials such as those performed on behalf of Depomed Inc. using a slow release formulation of gabapentin vs. placebo for PDPN and for PHN. It is possible that inclusion of data from these and any other unreported trials still unknown to me might further refine the estimate of gabapentin effects from meta-analysis.

How should Dr. N.P. Jewell's report affect interpretation of this meta-analysis?

This is a crucial point. After re-analysing the individual patient data from the 165 patients randomized in the Backonja 1998 study of gabapentin for PDPN, Dr. Jewell concluded that unblinding of the gabapentin recipients by adverse effects inescapably altered the results so as to create artificially the statistical impression of an analgesic effect. The final sentence at page 14/15 in Dr. Jewell's report is telling: ***"It is my view that my new, more thorough, analysis completely undermines the claims of treatment efficacy made in Backonja et al."***

Although I have read and comprehend Dr. Jewell's report, I defer to his statistical expertise and acumen in a specialty different from my own. However, it should obviously be unsettling to anyone who wants to seek truth from the clinical trial data. **The same concerns had troubled me as I read the scientific reports of clinical trials.** Well before I was aware of Dr. Jewell's interest in this matter, let alone his opinion, it struck me as obvious in many of the DBRCT reports (both published and unpublished) that early adverse effects must unblind the patients, and often the examiners. In the Backonja trial, for example, 3 of 84 patients randomized to gabapentin withdrew during the first 7 days (at days 2, 5, and 7) and were dropped from the analysis. My detailed reading of the full unpublished trial report left me wondering about the same question as that ultimately addressed statistically by Professor Jewell. See my detailed 6-page critical appraisal study summary in the Appendix, which was virtually complete on April 7, 2008, long before I saw Dr. Jewell's opinion on July 29, 2008. Van de Vusse 2004, who may have looked most scrupulously for this effect, found that **unblinding of both patients and doctors** was obvious and significant, because the toxicity of gabapentin was so apparent to those taking it. (See also this study detailed summary in Appendix.)

Let me re-emphasize that when patients expect more benefit from a new drug to which they gain privileged access in a clinical trial, unblinding should be **expected** to increase the apparent effect of the drug in a way which might not occur under routine use, when expectations are inevitably lower.

There is no reason to think that the other large DBRCT were exempt from the effect observed by Dr. Jewell in the Backonja trial. This convinces me that even our

meta-analysis of gabapentin vs. placebo **significantly exaggerates the apparent analgesic effects of the drug. Since these are small to negligible to begin with, Dr. Jewell's re-interpretation of the Backonja trial to the effect that gabapentin has essentially no analgesic effect is perfectly consistent with our results.**

May additional evidence from unpublished DBRCT yet come to light?

It may. Indeed it probably will in the "fullness of time". While double checking on July 26-28, 2008 via a Google internet search for any additional studies we might have missed inadvertently, I was able to identify the following:

a) Additional information regarding dose-effect relationships:

Rowbotham MC, Diamond C et al. Gabapentin for painful HIV neuropathy blinded, randomized trial comparing high and low doses. (Abstract, 10th World Pain Conference 2002) – found at http://www.painstudy.ru/10wcp/anticonvulsants.htm. I could not find any formal publication of this study, which was sponsored by an external research grant from Parke-Davis/Pharmaceuticals/Pfizer Inc. Dr. Rowbotham acknowledged that he had been a consultant to and received grant support from the sponsor. This study compared gabapentin at 900 mg/d with gabapentin at 3600 mg/d, but the abstract does not suggest that there was any placebo group. The abstract results and conclusions read as follows:

"RESULTS: Sixty-five subjects formed the ITT sample. Subjects on low dose GBP reported a 28% reduction in pain compared to 41% reduction with high dose GBP (p=.12). In the EE sample (n=58), pain declined by 30% with low dose GBP and 46% with high dose GBP (p=.04). Secondary measures showed numerical advantages with high dose GBP, but none reached statistical significance.
"CONCLUSIONS: Pain declined during 4 weeks of gabapentin therapy at both 900 and 3600 mg/day. Secondary measures also favored high dose gabapentin, but more subjects discontinued the study due to adverse effects…"

When I asked Mr. Rona of Greene & Hoffman by telephone whether he was aware of this study or any further publication, he replied that he had information describing significant costs absorbed by Parke-Davis/Pfizer to finance the study. **Why was this study of Professor Rowbotham's never published? The obvious explanation is that publication or release of the complete study results would have provided additional evidence that the overall effects of larger doses of gabapentin were undesirable.**

b) Evidence that additional trials were performed:

At (http://www.clinicalstudyresults.org/documents/company-study_1926_0.pdf) I found a 6-page PDF document identified as (01000006060590\1.1\Approved\20-Sep-2006 11:36) and also identified as (PhRMA Clinical Study Synopsis Protocol A9451004 06

September 2006 Final). This is a report of a "Phase 4" (post-marketing) 11-week open-label multicenter study of gabapentin titrated to a clinical effect, or to 3600 mg/d in 10 study centers in Brazil. This study was initiated in 2003 and completed in August 2004. I cannot tell whether the results may have been published or utilized in some other standard "published" format I could not locate, whether in Brazil or elsewhere. However, like the Rowbotham study noted immediately above, this Pfizer document may hint that other studies of gabapentin for pain were performed under Parke-Davis/Pfizer sponsorship, some of which might provide scientifically useful information which has not yet been revealed. Since Parke-Davis and Pfizer had no compunction about republication of studies in multiple formats and venues, it is unlikely that any conclusive positive study results would have been kept secret.

As an open-label study, the only contribution this Brazilian study (A9451004) can make to my understanding of gabapentin is its report that only 74/95 patients completed the trial (21 discontinued), 8/95 discontinued to adverse events, and that the proportion of patients experiencing adverse events was at the higher end of the range found in other studies, e.g.:

- somnolence 32/95 (34%)
- dizziness 28/95 (30%)
- edema 14/95 (15%)

While Brazilians are recognized internationally for many things, somnolence is not one of their defining national characteristics. This study may inadvertently have provided further evidence that the CNS toxicity (neurotoxicity) of gabapentin is dose-dependent but the presentation of results does not make this clear.

c) Additional DBRCT of gabapentin for PDPN and PHN with unavailable results:

The most intriguing finding I made was by looking for additional gabapentin trials by searching various on-line clinical trial registries. This led me on July 26, 2008 to the website of Depomed, a California pharmaceutical company developing slow or controlled release formulations of off-patent drugs, including gabapentin. The Depomed website (http://www.depomedinc.com/view.cfm/1285/Our-Pipeline) includes press releases and very brief summaries of several DBRCT of gabapentin whose results could add to our understanding of this drug (in the setting of DBRCT) but are not available. I attempted to obtain more detailed results from the company by e-mails on July 27 and July 28, 2008 but obtained only an auto-acknowledgement from Mr. Thadd Vargas of Depomed indicating that my e-mail had been received and read on July 30, 2008. This is what can be learned from the company website:

i. PDPN: A multicenter, 4-week, double-blind, placebo-controlled Phase II clinical trial randomized 147 patients to 3 treatment groups – Gabapentin GR (slow release) 3000 mg/d as a once daily dose, Gabapentin GR (slow release) 3000 mg/d divided as a twice daily dose, or placebo. A Depomed press release dated December 12, 2006 suggests that the combined gabapentin groups achieved a mean difference of -1.19 on an 11-point NRS

(Likert) pain scale compared with placebo, and suggests this was statistically significant ("p = 0.002"). **However, it also suggests that this effect may have been seen predominantly in the once daily dose of 3000 mg, as opposed to the divided dose group (still 3000 mg/d), where the difference was -0.49 points, "p=0.190".** While Depomed's CEO John W. Fara, Ph.D. (himself a former Pfizer senior executive) indicated in the press release that *"We are enthusiastic about sharing these data with companies that have expressed an interest in partnering Gabapentin GR with us …"*, he may not have been quite so enthusiastic as he sounded on paper, as the results do not seem to have been published. Neither has the slow release formulation of gabapentin been brought to market. This suggests to me that a more thorough analysis of the data might leave a disinterested observer less "enthusiastic". It is intriguing that Dr. Sherwyn Schwartz, a co-author of the Backonja 1998 JAMA report on gabapentin for DPN, is cited in this press release as favouring the nocturnal effects of Gabapentin GR. It would be interesting to know Dr. Schwartz' full interpretation of these same data.

ii. PHN: A multi-centre, 10-week, double-blind, placebo-controlled "Phase 3" clinical trial randomized 407 patients to 3 treatment groups – Gabapentin GR 1800 mg/d as a once daily dose (presumably also in the evening), Gabapentin GR 1800 mg/d divided as a twice daily dose, or placebo. **The press release dated July 10, 2007 indicates that at the 10-week study endpoint, the primary outcome of mean reduction in 11-point NRS pain score was 1.83 for once daily Gabapentin GR, 1.72 for twice daily Gabapentin GR at the same total daily dose of 1800 mg/d, but 1.43 for placebo. The difference (-0.40 or –0.29, depending on the group) was not statistically significant.** As in so many of the previously reported (or unpublished) trials of gabapentin, the reporting of secondary outcomes in this press release suggests that gabapentin has a pronounced sedative effect. The same press release indicates that Depomed CEO Dr. Fara regarded the results as *"…very surprising and disappointing to us…"* and a later article on the Depomed website indicates that a further Phase 3 trial involving approximately 450 PHN patients was initiated in March 2008, comparing Gabapentin GR once/day at 1800 mg/d with placebo, again over a 10-week period.

Presumably it has not been possible for Depomed to gain licensure for Gabapentin GR, or interest from commercial partners, on the basis of the negative results obtained from the Phase 3 study described above. From the brief description available on the company website, this appears to be the largest single DBRCT of gabapentin vs. placebo for any variety of pain.

One cannot help but note that this large DBRCT in PHN (N = 407) achieved a mean separation of about –0.29 to –0.40 vs. placebo on the 11-point NRS pain scale, a result strikingly similar to that found in the unpublished Pfizer 945-1008 study of PDPN, which was conducted on 389 patients during 2002-2003. Full access to the results of the above-referenced Depomed trial in PHN, might cast into doubt the efficacy of gabapentin even for the specific and approved indication of PHN.

Taken together, the above information about studies whose results have not been fully disclosed suggests that there may be <u>yet more information hidden from</u>

the public eye. If disclosed, as it ought to have been, the real facts might fundamentally alter the results of our meta-analysis – and force "expert" medical perceptions of gabapentin to align themselves more closely with reality.

Evidence gleaned directly from the individual trial reports:

Just as one should not "lose sight of the forest for the trees", a meta-analysis is not intended to obscure the "trees" (real facts) from view. Meta-analysis should help in the search for truth, not hide it. One would be **obtuse** to ignore important information obtained from a careful review of the available trial reports which relates to the rational clinical questions I proposed earlier in this report. Before re-approaching these questions, consider some examples of what can be learned from detailed scrutiny of the individual trials:

a) The following example from a large unpublished trial of gabapentin for PDPN conducted in Europe from 1999-2000 (Reckless 2000) casts a very different light on the question of whether gabapentin has any mean efficacy for pain. The first figure, excerpted from the unpublished final study report, shows the trial design.

Parke-Davis 945-224 – European Multinational trial of gabapentin for PDPN, 1998-99 (Reckless) – UNPUBLISHED FINAL STUDY REPORT dated February 7, 2000, p. 43/3214

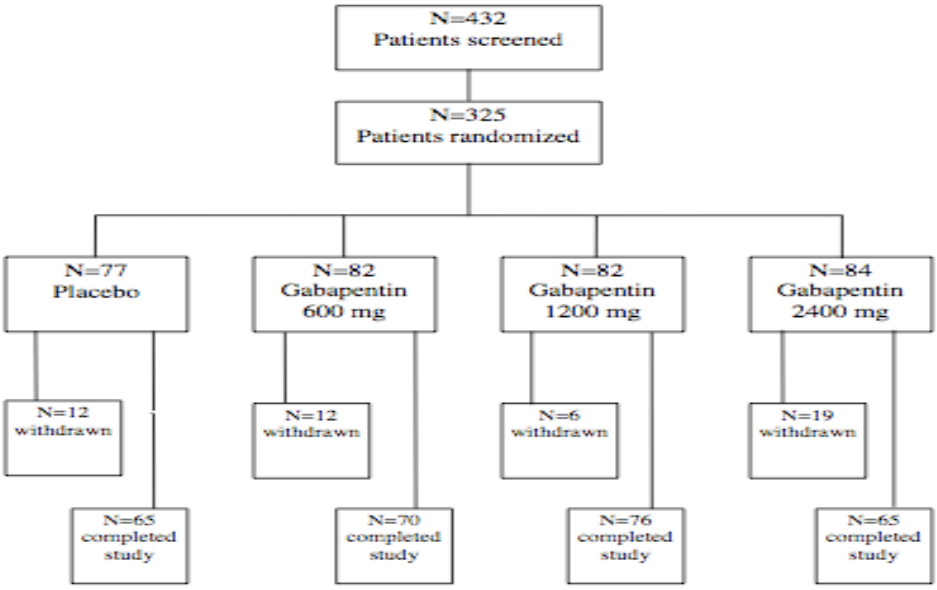


FIGURE 2. Number of Patients in the Course of the Study (Screening and Double-Blind Phase)

The graph on this page is excerpted from the same report, showing the observed pain score changes over time. **Need one point out that this graph did not achieve wide circulation amongst the Parke-Davis/Pfizer advisory boards, let alone the general medical world? How many people outside of these two companies have seen this graph?**

Parke-Davis 945-224 (Reckless) – European multinational study, UNPUBLISHED from page 53/3214, final study report dated February 7, 2000 plus appendices.

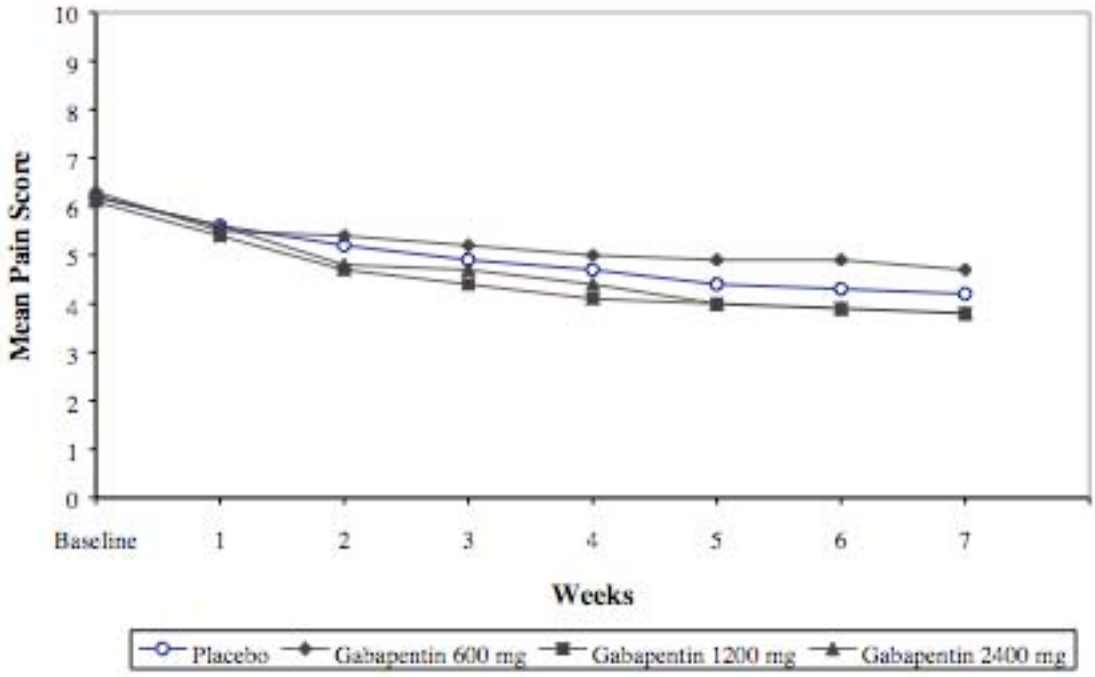


FIGURE 3: Weekly Mean Pain Score (Double-Blind Phase, ITT Population)

In the same study, even a post-hoc "Responder Analysis" looking for patients who had achieved ≥ 50% reduction in pain score, found no difference:

Parke-Davis 945-224 (Reckless) – European multinational study, UNPUBLISHED
(from 945-224 Final Study Report, p. 57/3214)

In an additional analysis responders were evaluated. Responders were defined as patients with at least 50% reduction in pain score from baseline to Week 7/Termination, who did not withdraw from the study due to lack of efficacy and did not take any forbidden medication during the study days included in the endpoint calculation. Seven patients with at least 50% reduction in pain were defined as non-responders because they took forbidden medication during the days included in the calculation (placebo: pat. no. 8908; 600 mg gabapentin: 1513, 7209; 1200 mg gabapentin: 5701, 5804, 7905, 8102). Table 15 displays the responders in the treatment groups.

TABLE 15. Responders/Non-responders (ITT Population)

	Treatment Group			
	Placebo N = 77	Gabapentin 600 mg N = 82	Gabapentin 1200 mg N = 82	Gabapentin 2400 mg N = 83
Responders, N (%)	19 (24.7)	13 (15.9)	33 (40.2)	25 (30.1)
Non-Responders, N (%)	58 (75.3)	69 (84.1)	49 (59.8)	58 (69.9)
Total, N (%)	77 (100.0)	82 (100.0)	82 (100.0)	83 (100.0)

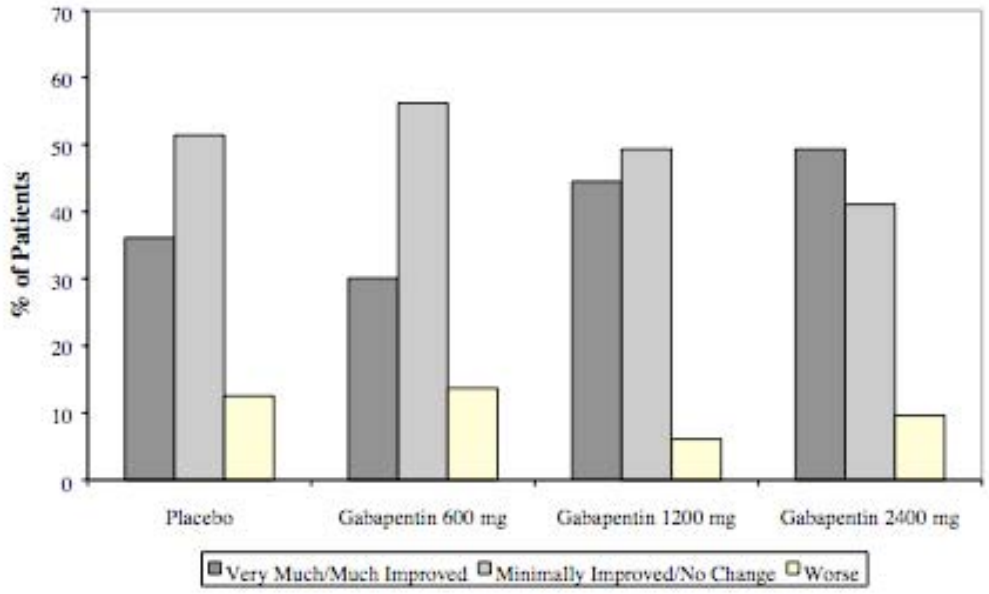


FIGURE 9: PGIC Score (Double-Blind Phase, ITT Population)

At the end of the double-blind treatment phase in all treatment groups a substantial number of patients assessed their own status as very much or much improved. The percentage of patients with this positive evaluation was higher in the 1200 and 2400 mg gabapentin group than in the placebo or 600 mg gabapentin group. Correspondingly, the number of patients who felt no change or a deterioration of the status was lower in the 1200 and 2400 mg gabapentin group than in the placebo or 600 mg gabapentin group.

A statistical test did not show a statistically significant difference between the gabapentin groups and the placebo group concerning PGIC ($p>0.05$, ANOVA).

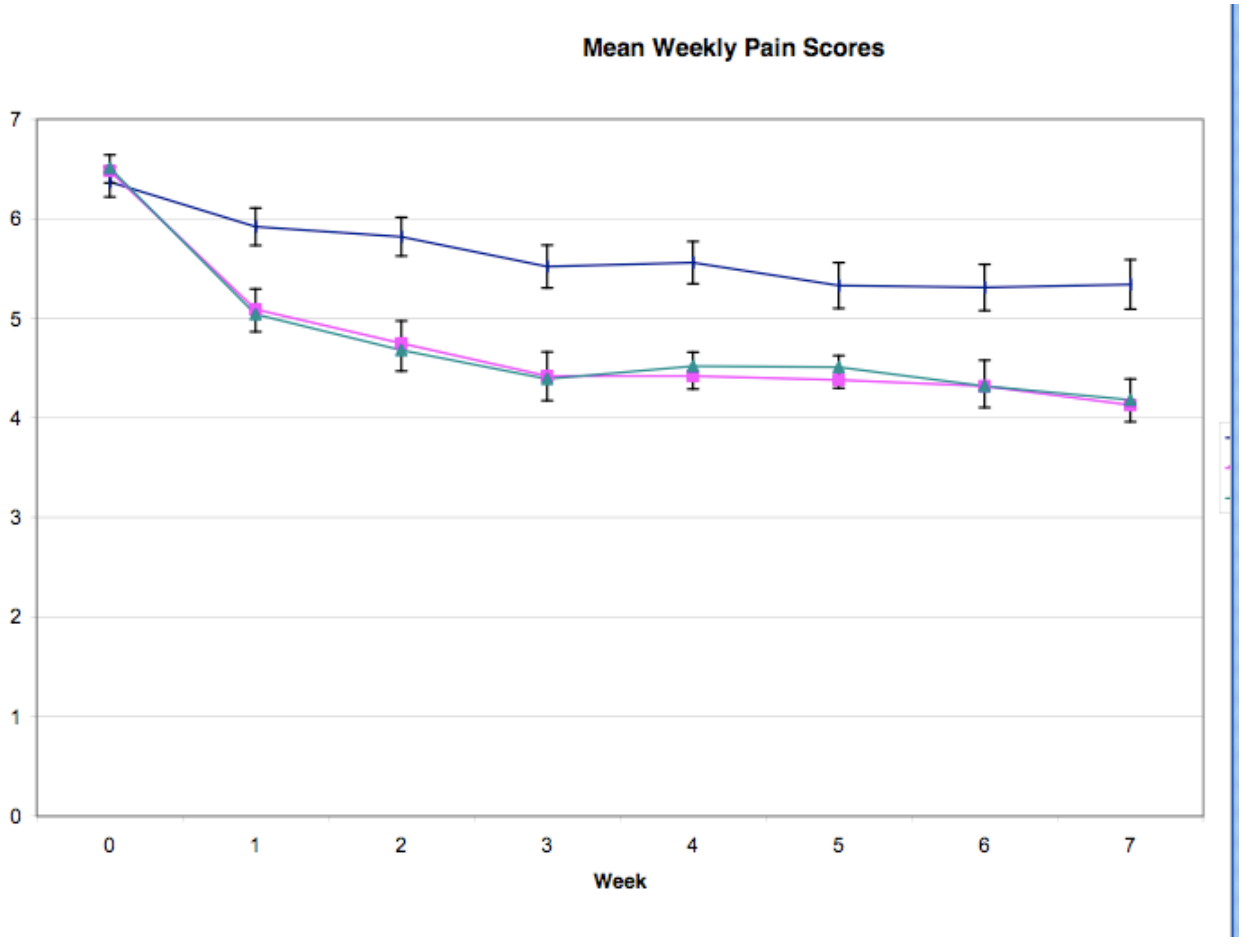
(945-224 PDPN – summary of PGIC from p. 72/3214 in final report February 6, 2000)

The above histogram from the same study (Reckless 2000, unpublished) shows no improvement from gabapentin on PGIC and indicates that the effect is not dose-dependent. It is little wonder that this study was so effectively buried, and Parke-Davis/Pfizer did not make the mistake of replicating it.

Looking **very closely at another study (Rice 2001)** is also revealing. Consider the example of time course of NRS pain score during treatment with G=1800 mg/d or G=2400 mg/d vs. placebo. Unfortunately in copying this from a PDF of the original document I have **lost the symbol key**, but the upper line in this case is the placebo, while the lower two lines represent G=1800 mg/d or G=2400 mg/d.

NB: the curves separate by 1 week (at 1200 mg/d during titration) but <u>do not separate further</u>. This may be analogous to the early adverse effect-associated difference in group mean pain scores discerned by Professor Jewell. It is not clear if this analysis is true ITT, ITT-LOCF, or if some dropouts are not included in pain scores, which may further bias the interpretation of this study (in favour of gabapentin).

From: Rice et al (published 2001) – April 3, 2000; final study report 945-430-295 appendices, p. 181/1357.



Looking at the details in a critical appraisal of the detailed unpublished report of the same study (Rice, published 2001) turned up another surprise. **Could differences in pain, including "responders" or favourable comparison on PGIC possibly relate to more frequent use of amitriptyline in the gabapentin groups?** (The Table on the next page is copied from Appendix C.2, p. 183/1357 but **abbreviated** for space reasons by

omitting drugs which alphabetically follow “dihydrocodeine”. Apart from amitriptyline, I could discern no numerically apparent differences between the groups of patients taking gabapentin vs. placebo. **However, amitriptyline, which is known to reduce pain in PHN, was more often used by the patients taking gabapentin in both arms of the Rice study than by the placebo group**.)

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Appendix C.2
Neuropathic Pain Medications

	Number of patients		
	Study drug		
	gaba 1800	gaba 2400	placebo
Generic name			
ACETYLSALICYLIC ACID	0	0	1
AMITRIPTYLINE	31	32	22
ANADIN /UNK/	0	0	2
APOREX	14	16	11
BENZYDAMINE HYDROCHLORIDE	0	0	1
CAPSAICIN	0	1	0
CARBAMAZEPINE	0	1	2
CODEINE PHOSPHATE	0	1	3
DIAMORPHINE	0	1	0
DICLOFENAC	0	0	2
DIHYDROCODEINE	3	3	1

From: Rice et al (published 2002) – April 3, 2000; unpublished final study report for 945-430-295 appendices, p. 183/1357.

Amitriptyline was more often used by the patients taking gabapentin in both arms of the Rice study (N=115 randomized for G1800, N=108 randomized for G2400) than by the placebo group (N=111). Could this influence the pain score results, and other results which depend on it (including sleep)?

Here is another example of why **looking at the details of studies is so crucially important.** The **unpublished final study report** of Rice et al (published 2002) in appendices at page 197/1357 suggests that the 50% "responder" analysis counts withdrawals due to lack of efficacy as failures, **but allows other withdrawals (e.g. WDAE) to be counted using the patient's final week's pain scores (LOCF). Thus, "responders" may include people who have to withdraw from the experiment due to toxicity. This does not appear to make clinical sense.** By analogy a patient taking morphine who experiences dangerous respiratory depression or disturbing mental status changes would not be considered a clinical success or a "responder", even though pain is almost inevitably suppressed in the presence of significant CNS toxicity from opioids.

7.2 Secondary Analyses

7.2.1 Objective B

Patients achieving a 50% or greater reduction in mean pain scores between baseline and end of treatment will be described as responders. Where the baseline and end of treatment mean pain scores are defined as described above. Comparison the percentage of patients responding to gabapentin 1800mg and placebo will be compared using Cochran Mantel-Haenszel Chi-Square procedures, stratifying by cluster in the model. The procedure will be repeated to compare gabapentin 2400mg and placebo. Patients withdrawing due to lack of efficacy will be regarded as treatment failure irrespective of the pain reduction experienced. All other withdrawals will be assessed using the final week's pain scores as defined in the primary objective.

7.2.2 Objective C

Protocol 945-295 IAP
Page 6 of 11
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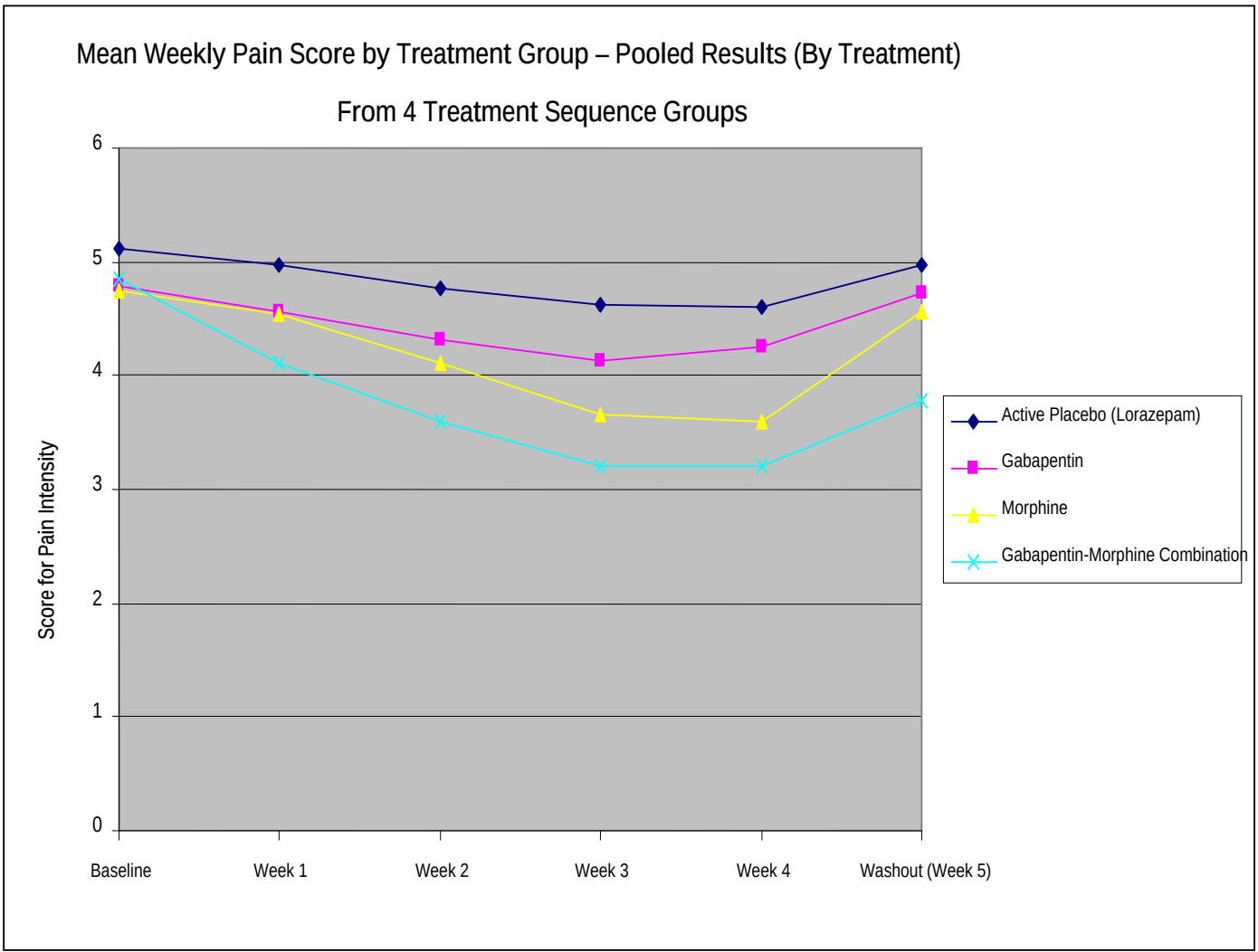
Excerpt of Protocol 945-295 taken from unpublished final study report of Rice et al (published 2002) in appendices at page 197/1357. Patients who withdraw due to adverse events are defined as eligible to be counted as "responders" (successes).

What can be learned from the very interesting experiment of Dr. Ian Gilron, the first and still the only known experiment comparing gabapentin with a strong opioid in a chronic pain model? (Gilron I, Bailey JM et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005; 352: 1324-34.) This a complicated multiple-crossover experiment which is difficult to understand (see Study No. 15 study detail summary in appendices). Looking carefully at the original Figure 2A from the publication, gabapentin appears to "work" in 2/4 periods, but "not to work" in the other 2/4 periods. The group numbers are small, and a significant portion of the patients did not complete the trial or even complete 2 periods (allowing at least 1 comparison between at least 2 of 4 possible treatments). Below is our presentation of the same data, re-formatted to make it easier to compare the individual treatments (active "placebo"/lorazepam; gabapentin; morphine; morphine plus gabapentin). Because of how the data are presented in the publication, we have had to make some interpolations to derive data for the graph below (see details in Study No. 15 study detail summary, appendix).

This figure suggests that in an experiment with patients suffering pain from PHN or PDPN, gabapentin has virtually no effect, compared with active placebo (lorazepam), considering that the gabapentin group starts from a somewhat lower baseline pain score. The curves on the graph are parallel.

From Study No. 15 study detail summary, p. 14/14 – Appendix to this report



As a final but interesting example of what can be learned from a close reading of even the published reports, consider a relatively early report from a single pain clinic in Northern Ireland, published in an obscure journal. (McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain ? A randomized, double-blind, placebo controlled study. The Pain Clinic 2001;13:103 – see Study number 23 in APPENDIX – GABAPENTIN PROJECT Pain Studies Summary Matrix – FINAL – August 8, 2008, Thomas L. Perry, M.D.) This is an interesting if little known study report, which unlike the study of Simpson 2001, has the ring of truth to it. It is worth thinking about what a single experienced and observant physician in one pain clinic with access to many patients and no axe to grind may be able to teach us about the use of gabapentin for back pain in the real world of clinical practice.

In this DBRCT completed in 2000 or earlier (dates not specified, published 2001) 80 typical outpatients were randomized to take either gabapentin titrated to 1200 mg/d (N = 40) or placebo (N = 40) in a 6 week parallel group design. The exclusion of patients who had previously taken gabapentin "or were known to be sensitive to it" is likely to have "enriched" the study population so as to favour gabapentin. Even so, only 31/40 patients randomized to gabapentin completed the trial, vs. 34/40 taking placebo. Adverse effects were numerically greater in the gabapentin group than in the placebo group. The meta-analysable data are included in our meta-analysis.

Here is what I find most interesting about this low profile study, which may give us a much more realistic picture of how well gabapentin "works" in real life:

a) of 40 patients exposed to gabapentin 1200 mg/d for up to 6 weeks, only 13 wished to continue it at the end of the trial;

b) of these 13/40, only 5 wished to continue gabapentin 2 months later, after having the opportunity to titrate the dose further up to 3600 mg/d.

c) the gabapentin patients' consumption of other analgesics declined only negligibly;

d) the overall effect reported for back pain at rest (probably the closest equivalent to an average NRS/VAS weekly pain score, since most patients with back pain tend to be sedentary) was not significantly different for gabapentin vs. placebo (We used this outcome statistic as the closest equivalent to the primary outcomes of other trials in our meta-analysis).

Dr. McCleane, an experienced Northern Irish specialist who may have personally assessed the patients (and may himself not have been effectively blinded) commented dryly that:

"The results of this study suggest that gabapentin has some effect on movement pain and referred pain, but that this effect is small. Furthermore, the benefit of a small reduction in these pains gained by taking four gabapentin capsules with no improvement in mobility and only a marginal reduction in concomitant analgesic consumption is open to question. Two months after the end of the study, only 5 of the 40 patients originally

receiving gabapentin judged the benefit to be sufficient to warrant continued treatment with the drug…It is our experience of many hundreds of patients treated with gabapentin that individuals from this part of the world do not tolerate the doses used by others (here he references the Backonja and Rowbotham 1998 JAMA publications) *and that, when greater doses are used, the side-effects outweigh any analgesic benefit."*

This is certainly a different conclusion than obtains from the more enthusiastic published clinical trials, but might be close to the true thoughts of participants (whether clinical investigators or their experimental subjects/patients) who participated in the negative unpublished trials. I say it has the ring of truth, because it reminds me strongly of the Parke-Davis/Pfizer market research graphic which presented virtually the same message, couched in terms of the troubling economic implications for the manufacturer, at about the same time (2001) as Dr. McCleane published his article!

What can be learned from the unpublished acute pain studies?

The unpublished acute pain studies constitute another important data set that was not suitable for meta-analysis with studies of gabapentin for chronic pain. These results, accessible to me only because of the Neurontin litigation, add a crucial dimension to understanding the whole body of evidence as to whether gabapentin is an efficacious or effective analgesic. The total enrolment was 1171 patients, who mostly received a single dose of gabapentin or the alternative study drugs, including placebo.

Fortunately I can review this evidence succinctly, since the conclusions are so obvious. See the Appendices to my report for the 5 study detail summary documents prepared by my junior but meticulous colleague Kelsey Innes, B.Sc. These summarize unpublished Parke-Davis trials conducted in the United States during 1999 and early 2000. All trials were completed and reported on in formal Parke-Davis/Pfizer unpublished research reports by 2000. The co-investigators ought to have been aware of the results, as access to results and intent to publish them would normally be requirements for approval of a clinical trial by a research ethics board.

These trials show uniformly and conclusively that gabapentin is not efficacious for acute pain, whether it is acute pain experienced after a dental operation, acute pain experienced after major orthopedic surgery, or acute pain from osteoarthritis, including pain extending for up to 28 days. The osteoarthritis experiment suggests that even at a very low dose of 250 mg/d taken for up to 28 days, gabapentin caused the typical adverse events of edema, dizziness, somnolence and asthenia.

In contrast, the same studies demonstrated that acetaminophen, naproxen, and hydrocodone all worked relatively well for pain, and that the experimental model could easily separate their effects from placebo with statistical significance.

Put simply, acetaminophen (Tylenol and other brands) at 1000 mg single dose, naproxen at 250-550 mg single dose, and hydrocodone at 5-10 mg single dose all worked for pain. Gabapentin did not.

It is sad but not surprising that these studies were never published. They could have been expected to decimate the market for gabapentin. The evidence from the osteoarthritis experiment (study 1031-002; research report 720-04479) demonstrating numerically increased incidence of typical adverse events, but at rates substantially lower than when larger doses of gabapentin were used, might have been especially dangerous, had it surfaced in the year 2000 or soon thereafter. It would be logical to expect this evidence to undermine (perhaps fatally) the widespread contention that adverse effects of gabapentin were not dose-dependent.

The interesting experiment of Berry 2005 in acute herpes zoster (shingles) might be interpreted as inconsistent with the above. However, pain from herpes zoster is a markedly different phenomenon from virtually any other type of pain, with the possible exception of trigeminal neuralgia. This experiment did not compare gabapentin with an active comparator such as hydrocodone, naproxen, amitriptyline, or even acetaminophen. Therefore, it is impossible to tell whether the effect of gabapentin for acute shingles pain is equivalent to, better than, or inferior to established analgesics for acute pain from shingles.

IX) Answers to my own clinically relevant questions:

I posed these questions near the beginning of this opinion to provide a reader open to a rational consideration of the evidence available from DBRCT with a framework for a clinically meaningful interpretation of that evidence. Let me now reiterate those questions and provide the answers which strike me as reasonable after more than four months of intensive study and thought.

Question 1a) What is the available evidence from DBRCT concerning the average (mean) effect of gabapentin for various painful conditions, in comparison with placebo or with active analgesic comparators?

Answer 1a) For chronic pain, the average (mean) effect of gabapentin, in comparison with placebo, is probably almost zero (no effect). It may exceed zero slightly in the artificial setting of DBRCT. However, the overall 0.78 point change favouring gabapentin over placebo on an 11-point pain scale resulting from our meta-analysis almost certainly exaggerates the true effect obtainable in the real world. There is no evidence that gabapentin is superior to established analgesic drugs (opioids, TCA's, etc.) for any painful condition.

For acute pain, the answer is even simpler. Gabapentin has no beneficial effect whatsoever, and is clearly inferior to acetaminophen, naproxen, or hydrocodone.

Question 1b) What is the clinical meaning for individual patients of any such average (mean) effect observed for an experimental group?

Answer 1b) For chronic pain, the meta-analysis suggests that at best 1 in every 6-8 patients might achieve a clinically meaningful benefit. However this apparent "benefit" observed in DBRCTs ignores the roughly equal proportion of patients who would be harmed by the same treatment. In the real world the balance of harms is likely to exceed the benefits of gabapentin. For acute pain there is no benefit whatsoever from gabapentin, only harm.

Question 2a) What is the available evidence from DBRCT concerning the average (mean) toxicities (harms) of gabapentin when used for pain, in comparison with placebo or with active analgesic comparators?

Answer 2a) Gabapentin can be expected to harm about 1 in 8 relatively healthy people who are unlikely to be representative of the patients typically most exposed to this drug. In real life, I would expect the toxicity of gabapentin to be much higher. For example, it is almost certain that in the real world of medical practice and prescribing in North America, far more than 1 in 6-7 people experience "dizziness" or "lightheadedness" or "ataxia" (balance disturbance) or "somnolence" or "impaired thinking or concentration" or other CNS adverse effects from gabapentin.

Question 2b) What is the clinical meaning for individual patients who experience toxicity (harm), e.g. those who drop out early from DBRCT because of "adverse events", or who just drop out?

Answer 2b) This is where the DBRCT fail to give any true impression of how gabapentin likely affects people in the real world. It is rational to expect that older patients, and especially frail elderly who are vulnerable to polypharmacy, infections, the adverse effects of edema (including infection risk and the chance of being misdiagnosed with kidney disease, venous or lymphatic obstruction, or heart failure) suffer adverse effects of gabapentin much more frequently and seriously than the controlled trials imply, for example as gabapentin-related:

- **falls and fractures**
- **mental impairment (which often leads to the prescription of more drugs and may lead to inappropriate diagnosis of "dementia" or "cognitive impairment")**
- **motor vehicle accidents caused by or involving drivers taking gabapentin**
- **over sedation and sedentarism with all its long term implications**
- **impaired wound healing of foot or leg ulcers leading to additional treatment costs and/or delay in recovery or worse**

Note that consequences of such adverse events may be long term or even permanent (e.g. disability or death from falls and fractures), something not reflected in the clinical trial reports from populations of less vulnerable experimental subjects.

Question 3a) What is the available evidence from DBRCT about the percentage (%) of patients who experience a clinically meaningful benefit (to them) from the use of gabapentin to treat pain?

Question 3b) How does this % compare with the % who experience a clinically meaningful harm?

Answers 3a and 3b) I have dealt with these questions in my answers above. For chronic pain it is likely that at least as many people are harmed by gabapentin as might benefit from it in some way. For acute pain there is nothing but harm.

Question 4a) What is the available evidence from DBRCT concerning the relationship of gabapentin dose to clinically meaningful response (benefit)? For example, is there convincing evidence that larger doses "work better" than smaller doses (e.g. 900 mg/day vs. 300 mg/day, or 3600 mg/day vs. 900 mg/day or vs. 1800 mg/day)?

Question 4b) What is the available evidence from DBRCT concerning the relationship of gabapentin dose to clinically meaningful toxicity (harms)? For example, is there convincing evidence that larger doses are more likely to cause neurological adverse effects than smaller doses (e.g. 900 mg/day vs. 300 mg/day, or 3600 mg/day vs. 900 mg/day or vs. 1800 mg/day)?

Question 4c) Is any other meaningful evidence available which bears on the questions of dose-dependence of benefit(s) or harm(s) for gabapentin?

Answers 4a, 4b and 4c) Interpreted in the light of general clinical pharmacological principles and common sense, I found no evidence from DBRCT for <u>dose-dependence</u> of benefit from gabapentin. On the other hand, it is apparent that larger doses of gabapentin cause more frequent adverse effects. (I have not discussed these issues in detail in the text of this opinion, but I have considered dose-effect relationships in the critical appraisal of each individual published and unpublished trial – see appendix.)

Gabapentin would truly have to be a "wonder drug" dissimilar to virtually all other drugs known to affect the brain, were it not to cause more neurotoxicity at higher doses or concentrations. It may be spared some toxicity by dose-dependent absorption kinetics (the absorbed dose and the plasma or brain concentrations of gabapentin may not rise proportionately to the ingested dose), but those who "push the dose" of gabapentin in ignorance of such basic pharmacologic principles and the evidence available from DBRCT and clinical experience do so at the expense of their patients.

Question 5a) What is the available evidence from DBRCT concerning the relationship of duration of gabapentin therapy to realization of a clinically meaningful response (benefit)?

Question 5b) What is the available evidence from DBRCT concerning the relationship of duration of gabapentin therapy to experience of a clinically meaningful toxicity (harm)?

Question 5c) Is any other meaningful evidence available which bears on the questions of duration of therapy-dependence of benefit(s) or harm(s) for gabapentin?

Answers 5a, 5b and 5c) If there were a benefit from gabapentin, it would accrue early in treatment. The experiment of Berry 2005 in acute herpes zoster (shingles) suggests that healthy patients can discern the effect of a 900 mg dose of gabapentin within 1.5 hours (or less), although the unpublished experiments for acute dental and joint or post-operative pain show that the results are not generalizable. The chronic pain studies all show that any observed separation of gabapentin from placebo groups (even if it was due to unblinding caused by the adverse effects of gabapentin) also occurs early, typically by the first observation visit after baseline. If observations had been scheduled before 2 weeks, any clinically discernable effect (whether good or bad) might well have been evident by then. Although many "experts" retained by Parke-Davis/Pfizer to market gabapentin (see below) asserted frequently that patients adjust to the adverse effects of gabapentin, I did not find any convincing evidence of this in the clinical trials, and many suggestions to the contrary. That is consistent with my own clinical experience with patients who have taken or take gabapentin.

Question 6) What experimental approach could clarify the most efficacious and effective drug treatment(s) for "neuropathic" pain? Why don't we have this information now?

Answer 6) I have alluded above to an experimental approach that might answer this question, and to the reasons why pharmaceutical companies will not design nor sponsor such experiments. The independent experiment of Gilron does show that it is possible to answer such questions. He found that morphine was more efficacious than gabapentin for neuropathic pain from PDPN and PHN, but suggested that gabapentin seemed to add some additional effect. I am not convinced that this is the correct interpretation of his experiment, which presents an extremely challenging intellectual exercise. Please see the detailed summary prepared by Ms. Innes and me in the appendix. One of the clearest insights into the real meaning of this study came from our reconstruction of a graph summarizing the results by drug, reproduced earlier in this opinion as well as in the appendix.

X) Comparison of my expert clinical pharmacologic opinion with the expert opinion of Dr. Shawn Bird (neurologist, University of Pennsylvania) dated November 29, 2006:

You provided me with a copy of this opinion. The opinion is brief (6 pages, plus 5 pages of references), whereas Dr. Bird's CV is long (17 pages). It is obvious that my opinions about the evidence concerning the efficacy of Neurontin (gabapentin) in DBRCT, let alone its clinical effectiveness (extrapolation of such trials to the general population of potential patients and) or its real utility in clinical practice (medical judgment based on real life experience) are much more conservative than those of Dr. Bird. Whence arises this difference of opinion? I see a number of reasons why we may have arrived at different conclusions:

1. Dr. Bird's literature review includes uncontrolled experiments and case reports which do not provide the same quality of scientific evidence as properly performed and reported DBRCT. It also refers to and appears to depend at least partially upon DBRCT pertaining to situations **not relevant** to the questions you are asking. For example, very brief studies in post-operative patients in a hospital nursing setting, which study primarily the consumption of opioid analgesic in patients recovering from general anesthesia, are not relevant to the outpatient setting where patients receive gabapentin from a pharmacy under prescription. Although I found Dr. Bird's report helpful in drawing my attention to certain studies that I had previously missed (e.g. van de Vusse 2004), I note that Dr. Bird also missed certain studies that I was able to uncover with the help of Dr. Musini's computerized literature search. (e.g. McCleane 2001)

2. Dr. Bird relied upon the Cochrane 2005 systematic review (Wiffen PJ, McQuay H et al) as the "highest level of evidence". Perhaps he was unaware that the Cochrane review included some studies which may not have been genuine (Simpson 2001) or which are unlikely to have been genuinely double-blind and were inadequately reported (Perez 2000). He does not refer to the mis-labeling of the Forrest plots in the Cochrane 2005 review, and may not have read this report carefully or completely. Many busy physicians rely on abstracts to obtain their impressions of complex reports. Were Dr. Bird to repeat the exercise I have performed in the last few months, he might be less sanguine about the conclusions of the 2005 Cochrane systematic review.

3. Dr. Bird may have been unaware of the major **unpublished** studies of gabapentin vs. placebo for chronic "neuropathic" pain (945-224 Reckless 2000 for PDPN; 945-271 Gordh 2003 for POPP; 945-1008 Parsons 2005 for PDPN) which had long since been completed and reported internally, but not publicly disclosed by Parke-Davis/Pfizer. Similarly, Dr. Bird's report shows no sign that he was aware of the **unpublished acute pain studies** completed by Parke-Davis/Pfizer in 1999-2000, all of which had been reported internally by 2000. Had he been aware of these data, I think his opinion must obligatorily have been tempered, if not different; and he should have disclosed and referred to these results in his opinion. I would be most interested to learn Dr. Bird's interpretation of the detailed experimental results of unpublished studies summarized in the Appendices to this report, should he be allowed to read it. When Dr. Bird completed

his report on November 29, 2006, he would presumably not have been aware of the Depomed trials of Gabapentin GR, of which the results (as incompletely reported subsequently on the manufacturer's website) would also oblige any independent medical scientist to reassess one's understanding of the evidence.

4. I consider it unlikely that Dr. Bird reviewed the published or unpublished DBRCT of gabapentin as **meticulously** as did I and my colleagues Dr. Musini and Ms. Innes. Without doing so, it is really impossible to understand accurately the numbers of patients, the incomplete or misleading reporting of outcomes, and the complex issues of statistical analysis raised – let alone face the issues of unblinding discussed in Professor Jewell's report.

5. Dr. Bird does not deal with the question of what drugs are **suitable comparators** for gabapentin for active treatment experiments (e.g. morphinan opioids, methadone, tricyclic antidepressants, carbamazepine). All of these have at least some putative clinical trial evidence for efficacy in neuropathic pain, and morphine is clearly demonstrated by the Gilron 2005 experiment to have efficacy markedly superior to gabapentin.

XI) How did Parke-Davis/Pfizer market Neurontin so successfully?

The following is a general itemized summary of the information I reviewed, by year, starting with the calendar year 1995. I have summarized as succinctly as possible my impression of the content, apparent intent, and potential import of statements, positions, opinions, events, or planned actions referred to in documents I reviewed. I have referenced such items to the "Bates number" of key pages, for easy identification of the relevant sources. I will refer to Neurontin and gabapentin interchangeably, since patent protection ensured that Neurontin was the only brand of gabapentin available in the United States during these years.

1995:

1. A document entitled "Marketing Assessments Neurontin in Neuropathic Pain and Spasticity" dated July 31, 1995 shows that Parke-Davis had developed a strategic plan to expand the utilization of Neurontin (gabapentin) well before it commenced to design and sponsor randomized clinical trials. (WLC_Franklin_0000166608 et seq.) This was an international effort, involving company staff from Holland and Germany, as well as the United States. Page 1 of the letter from Olivier Brandicourt of Parke-Davis Product Planning in Morris Plains, NJ accompanying distribution of this document within Parke-Davis is telling:

"The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published …"

The main document shows that Parke-Davis' principal interest was what it saw as a large and lucrative market for Neurontin in pain therapy, as opposed to the relatively limited market which might be available for spasticity, e.g. from multiple sclerosis. Preliminary contacts with physicians at various pain management centres had allowed Parke-Davis to come up with a list of potential investigators, including Dr. Gorson who later became the first that we are aware of to complete a DBRCT with Neurontin for PDPN. The potential market for PDPN was thought to be "moderate in size", at about $200 million U.S. per annum in 1995. I find it intriguing that a table on page 11 of this document refers to the efficacy of acetaminophen with codeine (e.g. Tylenol #3) for "neuropathic pain" as clearly superior ("+++" vs. "+") to that of amitriptyline, which it termed the "gold standard" of therapy. The same table categorized the analgesic efficacy of gabapentin as unknown.

Amongst "opportunities" this document states with respect to "neuropathic pain" (NP) at page 14: *"The NP market is undervalued due to the inexpensive cost per day of therapy associated with generic antidepressants, and generic narcotic and nonnarcotic analgesics."* Page 15 proposed that "Neurontin Development" could begin by pooling open label data from several centers known to be experimenting informally with Neurontin for pain, and by arranging for *"investigators* (to) *present this data at neurology and pain conferences"*. This could be followed by partial funding and drug supply for "exploratory" trials in several U.S. pain management centres using identical protocols, from which data might later be pooled for publication. *"This will facilitate a rapid completion of studies which could be rapidly highlighted at the neurology and pain congresses in 1996/1997."*

Page 1 of the document (WLC_Franklin_0000166608 et seq.) reveals that the urgency to get such trials under way promptly and to disseminate any "positive" results (covering letter) derived from the expected expiry of the patent extension in 1999. To use a Canadian metaphor, if there were going to be a Klondike gold rush, it was essential to get on the first boat to Skagway and over the Chilkoot Pass before winter closed the window of opportunity. It was, so to speak, "North to Alaska and full steam ahead!"

1996:

2. An article appears by Dr. Rudolph H. de Jong of the University of South Carolina School of Medicine (de Jong RH. Neurontin: Pie in the Sky or Pie on the Plate? Pain Digest 1996; 6:143-4) labeled as a "Guest Editorial". (MDL_Vendors_086685-6) A Google search (July 29, 2008) suggests that this article was rather widely cited thereafter, even though it appeared in an obscure new journal (Volume 6). Interestingly Dr. de Jong's editorial indicates that he had been using gabapentin off-label for various pain syndromes but typically at relatively low doses: ***"From 600 to 900 mg per day, given in three divided doses of 200 or 300-mg tablets – after initial up titration – is a good target for gauging analgesic effectiveness. If inadequate or no relief is obtained from 1200 mg gabapentin per day, little is likely to be gained from further dose escalation."*** (emphasis added) Although Dr. de Jong acknowledged the potential of larger doses, he also pointed out that ***"Since pain patients, by the very nature of their symptoms, are heavy consumers of analgesics and coanalgesics with potential CNS-depressant effect, it stands to reason that gabapentin be prescribed with circumspection."*** (emphasis

added) This relatively conservative **early message** about the off-label use of gabapentin is scarcely echoed in the marketing campaign of subsequent years (see below).

1997:

3. As early as June 6, 1997 Parke-Davis sponsored a series of "continuing medical education" fora, initially entitled "Emerging Concepts on the Use of Anticonvulsants". (WLC_FRANKLIN_0000066844, et seq). These were used to introduce the concept of "Treating the Neuropathic Pain Syndromes". Different speakers were invited to present what appear to have been similar materials and ideas, e.g. Dr. David R. Longmire on May 10, 1997 (Saratoga Springs NY), Dr. Charles E. Argoff on May 16, 2997 (Rye Brook, NY), Dr. Alexander Mauskrop on May 30, 1997 (Newport RI), and again Dr. Longmire on June 7, 1997 (Rochester, NY). The speakers' titles suggest that the doctors delivering the speeches were interchangeable. I presume they were members of a paid "speakers bureau" for Parke-Davis, and may indeed have been interchangeable, insofar as they may have undergone similar training regarding the materials and/or slides to be presented, notably a set of "Key Presentation Slides" of the same name (WLC_CBU_180737). Dr. Ahmad Beydoun also lectured during two of the above May 1997 sessions, on "Current Decisions in Treatment Options: Finding a Place for Newer AEDs". Many presentations of a similar nature followed. The presenters had no evidence from DBRCT of gabapentin for pain, as there was no such evidence until the Gorson trial was completed (at about the same time, mid-1997). This did not stop presenters from making standardized favourable references to anecdotal clinical evidence (WLC_CBU_180753 et seq). **The common themes of these presentations appear to me to have been to:**

a) Introduce Neurontin (gabapentin) **favourably** to a broad audience;

b) Introduce the notion that gabapentin might have efficacy for non-approved uses outside the field of epilepsy (for which Neurontin was licensed but little used) – a hypothesis for which there was **no scientific evidence**;

c) Encourage the notions that **larger doses** of gabapentin might be better tolerated than the audience knew or suspected to be the case, and that **larger doses were more likely to be efficacious** for some medical purpose(s) – an idea for which there was **no evidence and indeed evidence to the contrary** from the monotherapy clinical trials in epilepsy;

d) Stimulate a **good feeling or "buzz"** about Neurontin as an up-and-coming drug of the future – in the **absence of evidence** that it was efficacious or effective outside of the approved but little used indication for epilepsy.

Reading the electronic or paper records some 11 years later strains the eyes and leaves one little inspired. However, I can well imagine from personal experience of similar marketing events in nice hotels (typically presented as "CME" and eligible for maintenance of competence CME credits) that the "buzz" created by these presentations was **real and exciting** for those in attendance. I see no indication from the materials I reviewed that realistic Conflict of Interest (COI) declarations were made to the audiences. Even recent history in a time of greater scrutiny suggests that meaningful COI declarations would have been highly unlikely.

4. A "continuing medical education" program sponsored by Louisiana State University Medical Center-Shreveport entitled "Managing the pain of diabetic neuropathy" commenced in November 1997. One of the first pages of the "enduring materials" document (WLC_Franklin_00080453) provides typically non-informative "declarations" by "faculty" of "no significant conflict of interest disclosed". In my general medical and academic medical experience this is a **meaningless statement**. As a former legislator and member of the Executive Council (provincial Cabinet) in British Columbia who was subject to meaningful and enforced Conflict of Interest legislation, I find such declarations non-credible or even pathetic, rather than laughable. Again the gist of these "CME" presentations was to promote pharmacotherapy generally, and gabapentin specifically. For example:

a) Dr. Roger E. Kelley (WLC_FRANKLIN_0000080457) promoted the notion that **cost should not stop patients from taking a drug**, arguing that *"…When cost is an issue, patients are likely to give up on a medication much sooner,* ***… For example, someone may say a medication is 'intolerable' when, in reality, side effects are mild."*** (emphasis added) This may be a peculiarity of the United States. I have never in my career heard any patient confuse cost with clinical tolerability. I think most intelligent patients would be offended by the above remark.

b) Dr. Gloria M. Galloway (WLC_FRANKLIN_0000080462 et seq) promoted the notion of using gabapentin at doses of 1800-3600 mg/day. At this time, there was no clinical trial evidence supporting the use of gabapentin for this purpose, and Parke-Davis was well aware that 1 trial (Gorson) had been completed and produced negative results in PDPN at 900 mg/day. I have no way of knowing whether Dr. Galloway was aware of Dr. Gorson's results.

c) A "post-test" component designed ostensibly to provide CME credit for doctors can more realistically be construed as a promotion for **"non-evidence based medicine"** (WLC_FRANKLIN_0000080472) insofar as it promoted the "advantages to the use of gabapentin in the management of painful diabetic neuropathy" in the absence of any real evidence.

1998:

4. The Cleveland Clinic Foundation also participated in this process, via a "closed symposium" held on July 24, 1998. This was presumably intended not only to maintain the "buzz" but to be disseminated as "Proceedings" in the Cleveland Clinic Journal of Medicine (Supplement 1 to Volume 65, 1998). The technique of supplement publication avoids peer review, but allows publication in what appear to most relatively naïve doctors to be highly prestigious and presumably reliable medical journals. The acknowledgement of "an educational grant from Parke-Davis" is less prominent and typically such acknowledgements appear on an inside page of the original journal or reprint. (Pfizer_TMartin_0001739) A presentation by Dr. Harold H. Morris of the Cleveland Clinic promoted the concept that because gabapentin does not require liver metabolism, it might be **safer** than alternative anticonvulsant drugs and states that *"…The most common adverse effects of gabapentin are somnolence, ataxia, dizziness, and fatigue. Significant side effects, however, are uncommon and rarely necessitate withdrawal of the drug."*

(Pfizer_TMartin_0001754) This statement strikes me as calculated to encourage use of Neurontin with relatively little regard for its pharmacodynamics, including its interactions with other drugs affecting the brain, commonly taken by patients who might use gabapentin. A presentation by Dr. Edward Covington alluded to the Backonja 1998 JAMA study as "in press", although Dr. Covington was not a co-author of that study, which was not to be published until December 2, 1998. (Pfizer_TMartin_0001762) It is interesting that Dr. Covington pointed out the **sedative effects of gabapentin**, which he felt might be useful for sedative drug withdrawal syndromes. He described an almost immediate effect from his own observations, something that contrasts with the general push for long periods of treatment (weeks to months) and gradual dose escalation (see below).

5. A series of Parke-Davis documents (WLC_CBU_000222 et seq) contain a vivid "play by play" description starting on October 1, 1998 of how Parke-Davis planned the "launch" of the JAMA reports of DBRCT of gabapentin for PHN and PDPN. This included such strategies as:

a) a multi-pronged launch of the scientific publications on December 2, 1998 to be coordinated if possible with the institutional bases (universities) of the principal authors Backonja and Rowbotham, the JAMA itself, and relevant "disease organizations" – Drs. Backonja and Rowbotham were to figure prominently in this campaign;

b) an attempt to develop a **"consensus conference"** for the use of antiepileptic drugs (AED) for pain at the Curacao Southern Clinical CME Event in January 1999 (presumably a highly desirable destination at that time of year for "consensus developers");

c) a wide range of meetings of **"Neuropathic Pain Advisory Boards"** composed of neurologists, anesthetists, pain specialists, and primary care physicians (estimated cost about $2,000 per physician attending), and a wide series of "CME Dinner Meeting Series" on "New advances in pain management" featuring doctors **trained at a cost of about $2,000 per trainee** who would be provided with "slide kits"; (WLC-CBU_000229);

d) A highly sophisticated news and **"infomercial"** (my terminology) campaign extending to the use of video "infomercials" to **"captive" airplane audiences and a "blast e-mail"** to physicians and infiltration of internet "bulletin boards" devoted to pain treatment (WLC-CBU_000232-238 et seq)

One important strategic plank in this campaign appears to have been to systematically exaggerate the prevalence of painful diabetic neuropathy and post-herpetic neuropathy. This is borne out in the "Neurontin Studies/JAMA Video News Release/B-Roll" designed by Makovsky & Company of New York City for Parke-Davis. (WLC-CBU_123550 et seq) Note the "Suggested Studio Lead-In": *"There's encouraging news today for **millions of Americans** who suffer from an unrelenting condition called chronic neuropathic pain…"* (emphasis added) It must have been encouraging indeed for bored passengers to view such good news, presented by confident white-coated doctors and a

mellifluent voiceover announcer, especially after wedging themselves into the cramped quarters of a trans-continental airplane.

Although it was not unusual at the time (and remains unfortunately common in 2008), it is noteworthy that the putative beneficial effects of Neurontin were couched in these "infomercials" in **relative, rather than absolute terms**, e.g. for PHN, "*importantly, almost twice as many patients treated with Neurontin (16%) were pain-free versus those treated with placebo (8.8%) at the end of the trial"* (WLC-CBU_123550). Would the "buzz" have been quite so vibrant if Parke-Davis or its medical allies had stated that of all patients treated with gabapentin for PHN, about 7% of patients similar to those enrolled in the Rowbotham trial might expect to be "pain-free" at the end of 8 weeks, thanks to the treatment? I doubt it. **The latter way of explaining clinical trial results reflects more accurately the real benefit of the treatment.** But it is obviously **much less attractive** to the average person to present a number needed to treat (NNT) of 14, which can be expressed in plain English by saying: "If you and fourteen of your peers take this drug, one of you will really like it." No wonder drug companies and others promoting medical treatments still prefer to advertise **relative, as opposed to absolute** changes – the relative approach sells much better.

Apparently, Parke-Davis marketers hoped this campaign might produce a sales increase in the range of $46 to $70 million in the first year. (WLC-CBU_000261)

6. (WLC_CBU_028473) gives a simple example of how Parke-Davis utilized a third party, the seemingly independent "Institute for Continuing Healthcare Education" (Philadelphia, PA) to deliver its message as a 1 hour "audioconference" delivered by Dr. Ahmad Beydoun of the University of Michigan Medical School (second author of Backonja 1998). While labeled (or disguised) as "Continuing Medical Education", and made eligible for official CME credit, this program was available 24 hours a day through a toll-free long distance telephone number: 1-888-836-2764. This was obviously not a 2-way exchange between a university faculty member and an inquiring audience. I would suspect it was more likely to appeal to a physician desperately seeking to meet a "CME quota" before the end of the calendar year 1998 to prepare for re-licensure or hospital privileging. An objective observer from outside of the medical world might recognize this sort of presentation as "propaganda".

7. (Pfizer_LeslieTive_0002824 et seq.) demonstrates how these messages were converted into slide kit presentations which could be made available directly to doctors, presumably the various local "Key Opinion Leaders" favoured by Parke-Davis. (I have not recently been offered this sort of slide set by a pharmaceutical company, although I would find a few examples handy for teaching my medical students and postgraduate medical trainees about how marketing influences distort the interpretation of clinical trial results.) The *"Commentary"* sections beneath the bottom of some slide sets appear to be suggestions as to what the speaker using the slide set might say when making a standardized presentation which he/she had not personally prepared. Is it likely that such medical "experts" or "KOL's" disclosed to their audience: "*By the way, I didn't prepare these slides – they were made by Parke-Davis who paid me to learn how to present them to you"*? I doubt it. I have seen many academic physicians sneak such slides into their "grand medical rounds" or similar ostensibly academic presentations. Sometimes they

flaunt their dependence on external coaches or purveyors of packaged content. Often the more inexperienced members of the audience, even in a university teaching hospital, cannot tell the difference between genuine academic content and "infomercial". That is why such approaches work so well. Much more money is expended in North America on pharmaceutical advertising to physicians than on real medical education because the advertising, in all its forms, works.

Again, one can scarcely perceive in these dry paper or electronic files the full impact achievable in a live presentation through the personal warmth, self-deprecating humour, and sense of confidence which a good medical "expert" can inspire when performing before a willing medical audience. Physicians are no more immune than anyone else to seduction by power and perception. But even the paper materials reveal Parke-Davis/Pfizer's systematic effort to **exaggerate the prevalence of painful diabetic neuropathy** - as opposed to all diabetic neuropathy, which is typically **not** painful but causes reduced sensation. (Pfizer_LeslieTive_0002865 et seq.) The general technique of the slide sets is to mix **what appears to be "science"** (e.g. "basic pharmacology of gabapentin" or "pathophysiology of diabetic neuropathy") with marketing in such a way as to give the **illusion of education while steering the audience in a very specific direction.** W. B. Yeats' famous quotation, *"Education is not the filling of a pail, but the lighting of a fire***"** did not apply in these sessions. Physicians in attendance at such sessions were having their "pails filled". It was Neurontin's "fire" that was to be lit.

For example, the suggested slide commentary describing the change in mean pain scores for PDPN (Backonja 1998) reads *"Mean pain scores were significantly lower in patients receiving gabapentin compared with those receiving placebo at weeks 2 through 8."* (Pfizer_LeslieTive_0002897) A more thorough, accurate, and balanced description of the same data would have presented the numbers of patients still present at each observation point (to adequately reflect drop outs from the experimental groups). An objective presenter would have pointed out that the modest difference in mean pain score between the gabapentin group and the placebo group was observed at a dose of 1800 mg/d by week 2, that any such difference may well have been present earlier, and that the difference between groups **did not increase as the dose was later increased to 2400 mg/d and then to 3600 mg/d.** Unfortunately, I found **no balanced interpretation of the data** in any of the slide presentations I reviewed. Similarly, a slide for the PHN study (Rowbotham 1998) fails to point out that higher doses after week 2 of the trial produced no further separation of the gabapentin group from the placebo group for mean pain scores, but it is unlikely that this was emphasized by presenters. (Pfizer_LeslieTive_0002929)

Rare moments of candour can be found in the slide sets. A slide entitled "Overview of Adverse Events" discloses that in the PHN study (Rowbotham 1998) the gabapentin group experienced almost twice as many adverse events (278 total AE vs. 151 for the placebo group), a statistic not reported in the JAMA article and not otherwise knowable without access to the confidential final study report. (Pfizer_LeslieTive_0002942) Whether this slide (which is reproduced incompletely) was utilized in what must already have been long-winded presentations, I cannot tell. But a closely following slide (Pfizer_LeslieTive_0002944) again underplays the significance of neurological adverse

effects from gabapentin, and the *"Commentary"* suggests blithely that *"Despite doses of gabapentin up to 3600 mg/day in a population with an average age of 73 years, no serious drug-related adverse events were reported"*. Given what was already known clearly from clinical trial experiments about the incidence of somnolence, dizziness, "asthenia", ataxia and edema caused by gabapentin, it strikes me that this was an open invitation for doctors in the audience to prescribe or precipitate neurotoxicity. Although the slide sets typically presented the study inclusion and exclusion criteria, how many doctors in the audience would recall by the end of the presentation that these strict inclusion and exclusion limits for participation in the DBRCTs virtually guaranteed that the results would **not** be applicable to the real world? That is the difference between true continuing medical education and advertising or propaganda. **Education fosters inquiry and reflection; advertising (propaganda) smothers both.**

1999:

8. The Institute for Continuing Health Care Education of 210 West Washington Square in Philadelphia, PA revealed its hand in a letter dated February 2, 1999 addressed to David Simpson, DO of Farmington Hills, Michigan. The labeling on this paper document (VOX027405 at the bottom right corner) is somewhat different from other "Bates numbers". Just above that it also bears the numbers CCI 06087. Either way it is a revealing insight into the Institute. Here are some tantalizing excerpts:

"February 2, 1999

"David Simpson, DO
2859 Orchard Lake Road
Suite 200
Farmington Hills, Michigan 48334

"Dear Dr. Simpson:

"The Institute for Continuing Health Care Education invites you to become a faculty member for a series of Continuing Medical Education programs supported by an educational grant from Parke-Davis. These CME programs will consist of dinner programs, grand rounds and telephone conferences X (sic) *all to be conducted throughout 1999. The program is one of several nationwide efforts in continuing medical education known as the* ***National Initiatives in Continuing Medical Education****. The current program is entitled,* ***Reevaluating Neuropathic Pain Treatment Algorithms: New Data in the Management of Diabetic Peripheral Neuropathy and Postherpetic Neuralgia****…* (emphasis in original)

"Qualified speakers will be entitled to conduct CME-certified presentations. These presentations will reevaluate the role of anticonvulsants in the treatment algorithm of both diabetic peripheral neuropathy and postherpetic neuralgia in the light of new data. You will be provided with a lecture curriculum to complement your personal slides for your presentations.

*"**For faculty training, we ask that you listen to a taped CME telephone presentation delivered by program chair, Ahmad Beydoun, M.D…. Please dial 1-888-836-2764 at your convenience …*** (emphasis in original)

"! An honorarium will be provided for each lecture that you deliver.
"! Travel and accommodation expenses related to your participation will be fully reimbursed according to normal guidelines on such expenses…"

(exclamation marks in original, as shown). The letter was signed by Theresa Gaulthier of the **"National Initiatives"** staff.

I find this one of the most intriguing of all the documents I perused, because there are subsequent intimations (see calendar year **2003** below) that the same Dr. David Simpson later appears to have come under suspicion by senior Pfizer staff of having made mischievous use of the slide sets. Pfizer staff became aware of this possibility when Dr. Robert Dworkin (an eminent academic pain specialist with a real research record) drew to their attention in 2003 his concerns about Dr. Simpson's unusual publication in a 2001 edition of the obscure Journal of Clinical Neuromuscular Disease of an article with purported methodology and results strikingly similar to that of the Backonja 1998 trial. Dr. Simpson's 2001 article itself states that an earlier partial version of his apparent study of gabapentin and venlafaxine for DPN had been presented at the 23rd Annual Electrodiagnostic Medicine Course in September 2000. Whether Parke-Davis ever knew about Dr. Simpson's real or non-existent clinical trial in 1999 or later is unclear to me. However, the observed similarities between Dr. Simpson's 2001 publication and the 1999 Parke-Davis slide sets suggest that Parke-Davis and its agent the Institute for Continuing Health Care Education later achieved a significant if unintended "spin-off" from their wide duplication and circulation of the Neurontin slide sets to "faculty members".

9. The full frontal promotion of Neurontin continued as planned the previous October by Parke-Davis. A beautiful example is what appears superficially to be a new "medical journal", labeled "Progress in Neurology Volume 1, Number 1 March 1999". (WLC-CBU_079302) The use of another third party, the "Dannemiller Memorial Educational Foundation", may have side-stepped more traditional and appropriate academic requirements for certification of CME, and the "Faculty Disclosure" is superficial and given little prominence in small print. Although the materials are clearly labeled as "supported by an educational grant from Parke-Davis", they do not even hint at Parke-Davis' ambitious marketing plan (described in the documents referred to above) to use Dannemiller as what might be termed an "external validator". The use of a medical journal format might be expected to mislead the reader into believing that the content was subjected to an external peer review. This is obviously not the case. The overall structure is designed to make advertising look like continuing medical education.

The aggressive "roll-out" of Neurontin after the JAMA publications was continued by Dr. Michael J. McLean, speaking at "Treating the Aging – New Options for Pain, Psychiatry, Epilepsy, Stroke", an event held at the Marriott Marquis hotel in Atlanta,GA. Dr. McLean couched gabapentin (Neurontin) as *"the new"*, contrasted with other

anticonvulsant drugs (antiepileptic, AED) such as carbamazepine, which *"will represent the old"*. (MDL_Vendors_085847) This is out and out attention-seeking marketing language, not scientific or medical language. It is comparable to how self-promoting biologists refer to their discovery of a "new" yet ancient biological species, or how anthropologists may describe an isolated Brazilian aboriginal tribe as "new". Both carbamazepine and gabapentin are artificial chemical compounds which are latecomers to the human environment, both were discovered within 1-2 decades; thus if one is "new" then so is the other. The context of Dr. McClean's remarks must have been to raise excitement about a drug largely because it was "new", rather than because of its own merits, relative to other treatment options (drug or non-drug). This is how all newly licensed drugs are sold. Only the most experienced physicians and the most discerning of patients prefer "old drugs" to "new ones"! The latter class of physicians are the old hands who joke to their students: *"I always try to prescribe a lot of the new drugs during their first six months on the market, while they still work!"* This is of course intended to be facetious, although in my experience some medical students are already so socialized to believe that "new" = "better" that they miss the joke.

10. By November 1999 Dr. Ahmad Beydoun continued promotion of Neurontin in another Parke-Davis/Dannemiller Memorial Education Foundation product, "New Pharmacologic Options for the Management of Neuropathic Pain – A Practical Treatment Guide", also designated for official CME credit. (SH_0044640 et seq). As in other such documents, the discussion of "Diabetic Neuropathy" appears calculated to exaggerate the prevalence of painful diabetic peripheral neuropathy (PDPN). **No specific claim for the prevalence of PDPN is made**. **Instead, estimates of prevalence for all diabetic neuropathy (most of which is not painful) are presented and highlighted.** For example, a sidebar emphasizes in bold type that ***"… In another study …neuropathy was diagnosed in 61% of patients with diabetes."*** (emphasis in original, SH_0044654)

Similarly, the cited prevalence of ongoing pain from post-herpetic neuralgia (PHN) strikes me as grossly exaggerated, compared with more reliable published estimates (see my discussion earlier in this report). The article attributed to Dr. Beydoun trumpets, ***"Pain lasting more than one year is estimated to occur in 22% of PHN patients over 55 years of age and in 48% of patients over 70 years of age."*** (SH_0044654-7)

Dr. Beydoun's discussion of alternatives for treating pain in PDPN and PHN, such as opioid analgesics, was brief, superficial, and unbalanced. He noted that in one small study comparing oxycodone with placebo for PHN, *"… 75% of patients treated with oxycodone reported adverse events that included constipation ,nausea, and sedation"*, but not whether in clinical experience patients adjust to such adverse effects, as they were purported to adjust to the adverse effects of gabapentin. (SH_0044664) The highlighted comment ***"Opioid narcotics are rarely used for the treatment of neuropathic pain and should be reserved for patients who have failed other treatment modalities"*** (emphasis in original) constitutes pure opinion, and is contrary to the view expressed in 1995 by Parke-Davis' own marketing department (see paragraph 1, **1995** in this section).

This article may not even have been written by Dr. Beydoun - it would be unusual for an academic physician to use the redundant phrase ***"Opioid narcotics".*** In this document the discussion of gabapentin's safety is somewhat more balanced than elsewhere, noting:

"The side effects most commonly associated with gabapentin include somnolence, dizziness, and generalized fatigue. However, most of the side effects typically subside within 2 weeks. Some patients might develop nystagmus, ataxia, or weight gain. A nonpitting peripheral edema is dose related and age related; it is most commonly experienced by elderly patients treated with high doses…" (SH_0044664) Similarly, Dr. Beydoun notes that *"… some patients respond to daily doses as low as 100 mg…"*

However, while the assertion that adverse effects of gabapentin "typically subside within 2 weeks" might conceivably be correct, I have been unable to find anything in the clinical trial or unpublished reports that supports this. Repetition of this mantra by "experts" is not supported by the experimental evidence, such as it is, even from open trials like the Brazilian trial A945-1004 referenced above. It flies in the face of clinical experience and comments made by various doctors who participated in "advisory boards".

Gabapentin was now being promoted as "First-Line Therapy" (as an alternative to tricyclic antidepressants) for painful neuropathies other than trigeminal neuralgia, **with opioids relegated to "Fourth-Line Therapy"** behind strange choices (already or later proven to have no useful clinical value for pain) such as mexilitine, SSRI antidepressants, phenytoin, and lamotrigine! The sponsor (Parke-Davis) and unidentified formulators of these materials protected themselves from chastisement by the US FDA by placing small asterisks indicating that virtually all such uses were "not approved for this indication". (SH_0044684-5)

11. There is **still no mention in these materials** of the less favourable results from other trials, already known or likely to have been known to Parke-Davis, if not Dr. Beydoun, by this time, i.e.:

- Gorson (trial completed by 1997, results known to Parke-Davis by August 23, 1997
- Reckless (trial completed September 1999, blind broken by Parke-Davis statisticians October 26, 1999)

12. As **1999** came to a close, the "roll-out" planned in October 1998 continued to reach a broad audience via additional non peer-reviewed publications, e.g. "Supplement to Clinical Geriatrics The Clinical Authority in the Care of the Mature Patient" (CDM 0022270) The ultimate message attributed to Dr. Keith R. Edwards was simple: *"The statement that amitriptyline is the 'gold standard' for treatment of painful diabetic neuropathy or postherpetic neuralgia is probably outdated, given the comparable efficacy of gabapentin with a greater safety profile."* (CDM 0022270)

13. Parke-Davis ended **1999** with the Neurontin wind full in its sails. (WLC_CBU_175636 et seq) strikes me as a good example of how the "Neurontin Advisory Board" meetings were used by Parke-Davis, assisted by "IntraMed Educational Group", to utilize or manipulate physicians for the promotion of Neurontin (gabapentin). In this case, Texan doctors in the Houston area convened at the Omni Hotel in Houston on December 1, 1999 to listen to Dr. Ahmad Beydoun and for "dialogue". The meeting summary prepared by Alissa Sklaver of IntraMed and addressed to Cyndy Phillips of

Parke-Davis on December 13, 1999, shows that *"Parke-Davis's goal for the meeting was to gain information from the attendees on how they can better market Neurontin in the future, and how their current marketing strategies are working and being perceived."* (sic) Ms. Phillips presented images of new 600 and 800 mg tablets of Neurontin. Dr. Beydoun referred not only to the Backonja (945-210) and Rowbotham (945-211) trials, but also to a migraine prophylaxis protocol (945-220). I am not familiar with this protocol, which did not show up during my review of pain, unless it is the Australian study (Spira 2003), which its authors describe in Neurology 2003 as "investigator-initiated" but supported by Parke-Davis. Dr. Beydoun again comes across in the written notes as somewhat more conservative in his views about gabapentin dost-titration than Parke-Davis. The notes suggest there was a lot of speculation amongst attendees about various potential uses for gabapentin, something presumably intended by Parke-Davis to maintain the Neurontin "buzz".

14. (WLC_CBU_072249 et seq) shows that by December 21, 1999 Parke-Davis had also involved Medscape, another internet-based commercial source of "CME" for physicians, through an "educational grant", now involving Dr. Gary Bennett (Ph.D.), Dr. Robert Dworkin (Ph.D.) and Dr. Bruce Nicholson in a program entitled "Anticonvulsant Therapy in the Treatment of Neuropathic Pain". Parke-Davis was concerned about rivalry from two other drugs (topiramate/Topamax and lamotrigine/Lamictal) approved in the USA only as anticonvulsants but rapidly gaining market share for off-label uses. (Both of these drugs have subsequently been demonstrated to be very toxic, especially topiramate, and virtually useless for pain.)

2000:

15. The "Neurontin fever" (my term) continued to mount. If none of the speakers' bureau members literally headed "North to Alaska", that may be because the population of Alaska was too small to bother with or because Alaskans, like extreme northern Canadians, do not feel pain. (WLC_CBU_164409 et seq) shows that in January 2000 similar "Speakers Bureau" presentations continued virtually everywhere in the "lower 48". For example "Advanced Perspectives in the Management of Neurological Disorders", a large conference held in Scottsdale, AZ attracted not only 8 "Marketing Managers", "Area Business Managers" or "Territory Managers" and 1 "Medical Liaison" from Parke-Davis as well as 5 prominent members of the "Speakers Bureau" or "Faculty", but 98 "South Central Region" U.S. physicians and 38 "West Region" physicians. Judging by the addresses, these were primarily community (non-academic) physicians. Notes from this meeting labeled "Lecture Summaries and Panel Discussions" suggest that the lead "Faculty" member, Dr. Martha J. Norrell of Columbia University, promoted the concept that (at least for epilepsy) **gabapentin up-titration was remarkably safe**: *"The data on tolerability suggests that patient tolerability not lost as titrate upwards. Tolerability issues will be apparent with initiation but not with titration. The only side effect emergency with higher dosage was somnolence."* (sic) (WLC_CBU_164418) Intriguingly, Dr. Beydoun is cited as suggesting with respect to treatment of PDPN with gabapentin (from study 945-210, JAMA 1998) that: *"As early as week 2, there was significant improvement that was maintained.* ***If there will be a***

response, it will appear early. No high doses needed. *Placebo data exhibited a bell shaped curve while the gabapentin group shifted to the left with the majority being improved and pain free…"* (emphasis added) (WLC_CBU_164423) Dr. Beydoun's relatively conservative message that a patient should be able to tell early in treatment whether gabapentin could provide any useful balance of benefit vs. harm, and his suggestion that this was usually ascertainable at low doses, seems to have been **buried in these minutes**, compared with the dominant message to **"push the dose"**, or that the "majority" of gabapentin-treated patients were pain free (something clearly not in accordance with the evidence, compared with placebo). Sample comments excerpted on the last page of this internal report document how the meeting psychology worked as intended, e.g. the comment of one attendee: *"My utilization for Neurontin was rapidly falling down in direct relationship to a rapid climb for my utilization of Topiramate. Thanks to current information learned on this meeting I will reverse that trend."* (sic) (WLC_CBU_164432)

16. (WLC_CBU_076620 et seq) gives a clear example of the dominant **"push the dose"** message, now incorporated by Dr. Charles E. Argoff in "Management of Neuropathic Pain Syndromes – A Supplement to Neurology Reviews, Clinical Trends & News in Neurology, March 2000". What appears superficially to be a "medical journal" is in fact a publication of "Partners in Medical Communications", made possible through an "unrestricted educational grant from Parke-Davis". All but one of the speakers (including Dr. Miroslav M. Bakonja) disclosed in fine print at page 2 associations (grants, Speaker's bureau, consultant) with Parke-Davis and other pharmaceutical companies. Although this material was "designated" for 2 hours official CME, like similar documents referred to above (and below), this description is by any reasonable standard a euphemism for "infomercial advertising". Dr. Argoff of the "Pain Management Centre", Syosset, NY emphasized: *"**It is important not to underdose gabapentin** when managing PHN; the average maximally effective dose in the recently published controlled trial was 3,600 mg (with an average participant age of over 70). In practice, I have seen many patients who were told to stop gabapentin due to apparent lack of efficacy at doses of 1,800 mg or less. The available data strongly suggest that this is not appropriate, absent significant side effects. (63)"* (emphasis added,WLC_CBU_076638) The reference (63) is to the Rowbotham 1998 trial of gabapentin for PHN, which used a forced titration schedule to 3,600 mg/day, **but this trial does NOT show greater efficacy for higher doses.** This trial also excluded patients who had previously taken gabapentin, and may have thereby artificially reduced the apparent toxicity of gabapentin. Dr. Argoff's message in print is an obvious **misunderstanding, distortion, or misrepresentation of the experimental evidence**, and is inconsistent with what can be discerned from a careful examination of all trial data. Interestingly, the sentence cited above **does not state** that increasing the gabapentin dose above 1,800 mg/d improves results, **although it is obviously crafted to encourage doctors to use higher gabapentin doses!** Did Dr. Argoff in fact write this article published via "Partners in Medical Communications"?

17. (WLC_CBU_164379) refers to a presentation at the Westin Hotel in Denver, CO by Dr. Beydoun, who was now suggesting that for **epilepsy**, dose titration of gabapentin beyond 1800 mg/d to 3600 mg/d or even 4800 mg/d *"… indicated that the side effect profile was very similar at 3600 mg as compared to the profile at 1800 mg … The*

investigators found dissociation between the dose and side effect profile …" This remark relates to **epilepsy**, and I do not know whether the published or unpublished data confirm this claim, which lay outside of my mandate to review gabapentin for pain treatment. In response to a questioner identified only as "Phillips", Dr. Beydoun responded that in treatment of epilepsy *"If they do experience adverse events, they'll tell you right away. If they tolerate the drug, they will tolerate it early on."* (WLC_CBU_164380) I find this response more consistent with my own clinical experience with gabapentin and with other drugs acting on the central nervous system. It would be a very unusual drug indeed for which increasing doses did not increase adverse effects. Dr. Beydoun again insisted that most side effects of gabapentin are transient, e.g. *"… It's important to let the patients know that there is a 1 in 5 chance of developing side effects and they will lessen after 10 days…"* I could find no evidence from the clinical trial reports satisfying me that this is correct, although it would not be unprecedented for patients to accommodate to adverse effects, just as many accommodate to pain. Had I been an attendee at these presentations, it might have been easier for me to discern whether Parke-Davis' real strategy was to encourage the use of high doses of Neurontin in epilepsy to pave the way for "dose-creep" in pain. From a strictly commercial point of view, if Parke-Davis could persuade doctors that they were "underdosing" their patients, at least another few weeks or months of Neurontin sales could be racked up for each sufficiently gullible or desperate patient. This reminds me of the Las Vegas approach to separating gamblers from their money: if you haven't won yet at the slots, the big payoff is probably "right around the corner". Many gamblers have believed this over the years; few have been right.

18. Dr. Michael McClean of the Vanderbilt University School of Medicine was at full throttle by April 13, 2000 when he appeared for a meeting of the "Parke-Davis Advisory Board on Neurontin" at the Adam's Mark Hotel in St. Louis, MO on April 13, 2000. (MDL_Vendors_057668 et seq). After what I would consider a pseudoscientific prelude (How many practicing doctors who attend pharmaceutical "advisory board" meetings recall or care what a "zwitterion" is, amusing as it may be to pronounce this word in German?), Dr. McClean turned up the heat, arguing that Neurontin had *"…no interactions with other drugs… therapeutic efficacy skyrockets when you increase the dosage… The therapeutic index is 4-20. It means that there is a wide range of doses to try and you won't compromise tolerability when you're trying to reach efficacy. The useful dose range is about 900-4800 mg/day…"* In this presentation he was talking about treatment of epilepsy, but while I agree with him that gabapentin may be safer or easier to eliminate (through two healthy kidneys) than some other CNS-active drugs, I consider these comments both rash and at times incomprehensible. I can not imagine what he meant by a "therapeutic index of 4-20", as it is clear that some people experience marked neurotoxicity at doses as low as 100 mg/day, whereas others tolerate 4800 mg/day with no apparent effect, either beneficial or harmful. Dr. McClean's presentation suggests to me that he was more familiar with gabapentin data than most other "faculty" at meetings of this nature, perhaps from epilepsy studies which I have not reviewed. For example at (MDL_Vendors_057671) he pointed out that about 10% of patients (presumably those treated for epilepsy) may gain 5-10 pounds, within minutes of dismissing gabapentin-induced edema in elderly patients as "reversible". Overall, this presentation strikes me as less than appropriately cautious or restrained for a faculty member at a leading medical school noted for its program in clinical pharmacology. **An unidentified physician in the**

audience, responding to a question from Parke-Davis Area Business Manager Steve Goodrum at (MDL_Vendors_057673) **seems to have provided a reality check** by stating: ***"The only people I use it on complain about side effects at low doses. The more I use it, they worsen. I've taken them off before they reach adequate doses."*** This message does not seem to have left the room, let alone appear in subsequent Neurontin advertising. A little later during the same meeting, Parke-Davis Medical Liason Dan Thomson helped answer an attendee's question about using Neurontin on fibromyalgia patients: *"The literature background for Neurontin is overwhelming. We would be happy to send you all the information about these cases."* I wonder what he was referring to – presumably anecdotal case reports of which Parke-Davis was aware. Would Mr. Thomson have been equally enthusiastic to distribute the reported comments of the previous questioner?

I think that most ethical physicians would recognize this level of hucksterism as fraudulent, but the ratings indicate that the attendees (specifically selected because they were already generous prescribers of Neurontin and known to be friendly to Parke-Davis) saw it differently **–** see the enthusiastic if not rapturous responses excerpted at (MDL_Vendors_057667).

18. Dr. McClean made similar presentations espousing generous doses of Neurontin for neuropathic pain, for example at a similar meeting at the Jefferson Hotel in Richmond, VA. (MDL_Vendors_056840 et seq.) Had I attended one of these meetings and listened to an apparently eminent academic physician from a major medical school, I think I might have expected Dr. McClean to alert me if there were contradictory evidence from any studies other than those he cited in his 3 references to gabapentin (one of them an editorial). (MDL_Vendors_056847). By now, the Morello trial comparing gabapentin with amitriptyline for PDPN had been published (1999), and the Reckless (945-224) trial report had been finalized by Parke-Davis. Recall that the unpublished but now completed Reckless trial showed no dose-dependent efficacy for gabapentin (indeed no efficacy whatsoever for the primary outcome) but at least a strong suggestion of dose-dependent toxicity. It was a much larger trial than that of Backonja and therefore more definitive. Similarly, Gorson's negative trial at 900 mg/d had been published, albeit selectively and incompletely so as to paint a better picture than the reality of the trial. Why are these not mentioned? What of the four large trials in acute pain, none of which had shown any analgesic benefit from gabapentin and all of which had been completed, analysed and reported within Parke-Davis by early 2000? **Was Dr. McClean really unaware of this information? If so, he was effectively duped. If he had been aware of it, then his audience was duped, and he should have been ashamed to present a slide set without so much as a pro forma conflict of interest declaration. I wonder what the Vanderbilt University School of Medicine would think of this now? Note that Dr. McClean was not alone. The same observations could be made about any other physicians with close ties to Parke-Davis, who by 2000 ought to have surmised or inquired about the possibility of negative trials.**

19. Excerpts from a Parke-Davis Neurontin Advisory Board Meeting held on June 20, 2000 in Alabama afford additional fascinating but disturbing insights into how Parke-Davis utilized what are now called local "Key Opinion Leaders" (KOL's) to get its

message across. (Pfizer_TMartin_0002200 et seq) These KOL's were also useful to help Parke-Davis understand what forces were determining Neurontin's market share for epilepsy and off-label uses. The "Attendee List" shows what appear to be neurologists and/or psychiatrists from small and large towns throughout the southeastern USA. The "advisory board" was clearly **advisory to Parke-Davis for marketing, not for medical issues.** Members advised that to gain more market, *"Neurontin just needs to emphasize off-label indications."* (Pfizer_TMartin_0002205) Doctors present were impressed that Neurontin was in fact a *"…model to get indication for one thing* (epilepsy) *and then use it for everything else"*. (Pfizer_TMartin_0002205) It is also apparent that Parke-Davis was keen to see specialists push the Neurontin dose. Tammy Martin, CNS Area Business Manager for Parke-Davis Southeast CBU: *"How many of you have patients who come to you and say that they have tried the drug and it didn't work? Are they willing to try it again"?* Responding "attendee": ***"They didn't try enough. They were lowballing the dose. It takes effort to get them to retry it."*** (emphasis added) (Pfizer_TMartin_0002207)

Again, Dr. Ahmad Beydoun, co-author of the Backonja 1998 trial in PDPN, pointed out that when gabapentin was used for PHN (Rowbotham 1998) an effect on pain scores appeared as early as week 2, the first assessment date after baseline. (Pfizer_TMartin_0002211) Once more, Dr. Beydoun was more conservative in his dosing recommendations than other Parke-Davis spokesmen like Dr. Michael J. McClean, stating that *"for new patients, most do well on 9(00)-1200 mg (per day)"*. (Pfizer_TMartin_0002211) However, Dr. Beydoun's relative restraint may have been useful primarily to temper audience perceptions about Parke-Davis' control of the agenda, as his conservatism was not the overall message, which clearly favoured **much higher doses**. Dr. Jeff Robinson (PhD) of Parke-Davis Medical Affairs is cited as having remarked that *"Gabapentin is an amino acid and thus is a safe product."* (Pfizer_TMartin_0002212) This obviously incorrect statement gives some flavour of the "scientific" tenor of such meetings. Their real purpose is betrayed by the comments from "attendees" on the final page of the meeting summary, e.g. ***"I would like to have stock options in your company as an advisor" or "The comment by Jeff that it (gabapentin) is the same as an amino acid will be a great selling point."*** (emphasis added) (Pfizer_TMartin_0002216)

20. Dr. Misha-Miroslav Backonja was now also into the act. He is listed for example as a speaker at a similar event held on June 10, 2000 at the Westin William Penn Hotel in Pittsburgh, PA, although no content appears under his name in this document. (SH_0064559.0076474) I cannot tell from this what Dr. Backonja had to say, I would be curious to know and also to learn whether he disclosed to his audiences a reasonable conflict of interest declaration. (I noted serendipitously that Dr. Backonja may not always have been scrupulous with conflict declarations. Via the on-line access to the publication history of the van de Vusse 2004 study on use of gabapentin for CPRS-1 [see appendix, Study No. 7] I learned that Dr. Backonja was a peer reviewer for that publication. This information is freely available on the BMC Neurology website linked automatically to the web reference I have listed in the appendix. The other reviewer for the van de Vusse paper, Dr. Wouter W.A. Zuurmond, completed a "Declaration of competing interests" by disclosing *"yes, I have performed a lecture for Pfizer and*

received a fee for it". In contrast, Dr. Backonja responded on May 24, 2004 to the same question with the answer *"none"*. This seems unlikely to have been a reasonable answer, although it is possible that by 2004 Dr. Backonja had severed all ties with Parke-Davis/Pfizer.) As of June 2000, financial connections between Dr. Backonja and Parke-Davis were certainly extant, and one would suspect that Dr. Backonja, (like Dr. McClean and Dr. Beydoun) might have been amongst the most likely people outside of Parke-Davis/Pfizer to have known the results of the unpublished trials available by mid-2000. **What did he say about them, and to whom?**

21. Yet another meeting in San Francisco on July 20, 2000 now involved Dr. Edgar Ross, Director of the Pain Management Centre at the prestigious Brigham and Women's Hospital of Boston, MA in sharing the glad tidings about Neurontin. (Pfizer_JMarino_0002191) Dr. Ross' slides appear different from the other slide sets and are more idiosyncratic. He was still referring to only two trials of gabapentin for PDPN (PDN) and PHN, although he also made a point of referring to *"8 patients* (who) *had advanced HIV"* in whom he appears to suggest that gabapentin was *"very effective"*. I could not tell what study he may have been referring to. The last slide in the set (Pfizer_JMarino_0002192) is enigmatic. A "seeing-eye" dog is about to fail its final test by leading a blind man directly into a jet engine. **Could this be a reference to the "blind leading the blind" with respect to Neurontin? Perhaps Dr. Ross was indeed unaware of the unpublished results on which Parke-Davis had now been sitting for months.**

22. Even Professor Robert Dworkin, who later documents show enjoyed a close working relationship with Parke-Davis/Pfizer for many years, made no allusion to the unpublished trials at the same "Worldwide Pain Conference". (Pfizer_JMarino_0002198) Although Professor Dworkin's remarks are sufficiently carefully written that they remain technically accurate, he too gave the "Worldwide" conference no hint that there was more to the story than he was saying. Why did he not refer to the Gorson study, which had failed to show benefit of gabapentin in PDPN, or Morello which the independent VA investigators interpreted as evidence to continue choosing TCA as "first-line" therapy? Professor Dworkin already had ties to Parke-Davis, and had published sub-analyses of the Backonja 1998 study. **Could he too have been kept outside the "Parke-Davis/Pfizer" circle of knowledge? Was Parke-Davis deceptive with Dr. Dworkin, or was Dr. Dworkin deceptive to his audience in San Francisco and elsewhere about the real facts? One cannot have it both ways.** Given the later record showing that Dr. Dworkin was keen to check the authenticity of what he considered the highly suspicious 2001 report of Dr. Simpson, I wonder whether Dr. Dworkin was kept in the dark like the rest of the world. **If so, how must he have felt when he eventually learned about the unpublished gabapentin studies in September 2001?** (see below)

23. In September 2000 the parade was joined by publication of yet another supplement "supported by an educational grant from Parke-Davis", this time in the Clinical Journal of Pain (another relatively minor journal of which Dr. Dworkin was an Associate Editor), reporting "Proceedings of a Symposium" held on August 23, 1999 in Vienna, Austria. (Pfizer_AFannon_0008126 et seq.) Here, Dr. Nadine Attal of Boulogne, France

presented a table labeled "Placebo-controlled studies in neuropathic pain …" which purported to show that only 1 trial had been conducted with gabapentin for PDPN, and 1 trial for PHN, both "positive". (Pfizer_AFannon _0008138). **This is not only incorrect, but frankly misleading or deceptive.** We now know that by the time this publication appeared, the much larger Reckless 945-224 trial had been completed and reported on. Dr. Attal mentioned and cited the 1997 Gorson trial (published 1999) but did not include it in the table as a negative trial. Even the Perez trial from Monterrey, Mexico (which I have considered insufficiently reported to include in meta-analysis) had at least been published. One could criticize Dr. Attal for incompleteness, inadvertent ignorance of the unpublished Reckless trial, or sloppiness, but where were the supplement editor and the company that supported publication with an "educational grant" when it came to full disclosure? What was the **educational** point of publishing incorrect and misleading information?

24. I found similar evidence of sloppiness, or perhaps "ghost writing", in a document of whose title the first word "Interface" has a rather disturbing Rorschach-like quality. It is otherwise entitled "Neurology & Psychiatry Diagnostic and Treatment Issues EME Enduring Manual Monograph based on proceedings of symposia held January 16, 1999; February 12, 2000 …" (SH_0044769) This document is labeled as sponsored by the Albert Einstein College of Medicine and "made possible through an unrestricted educational grant from Pfizer Inc." but I suspect that Einstein would have been disappointed to see his name associated with it. The document is labeled "CONFIDENTIAL" on every page, but appears to have been intended for release in October 2000. A chapter attributed to Dr. Michael J. McClean incorrectly cites the numbers of patients assigned to the gabapentin arms in the Backonja 1998 and Rowbotham 1998 clinical trials. (SH_0044844) While this is a trivial error easily correctable by the reader by a look at the original publications, it makes one wonder how closely Dr. McClean was involved in the authorship. Who might have read this monograph, and what was its real intended purpose?

2001:

25. Perhaps the most telling of all the documents I reviewed is that labeled (Pfizer_MYoder_0002511). I have reproduced and discussed this earlier in this report, but I cannot tell when it was produced – only that it refers to disappointing prescription renewals for Neurontin during 2001. Parke-Davis/Pfizer had clearly realized by now that there was much less money to be made if people stopped using their product after only a month or two.

26. Dr. Roy Freeman of the Harvard Medical School now joined the fray with what strikes me as a **specific mission to encourage doctors to "push the dose"** of Neurontin. (SH_0064559.0093275 et seq.) From this mysterious document , also stamped "CONFIDENTIAL" on every page, we learn something about the price Pfizer was willing to pay for a "hired gun". A letter from John Christensen, Faculty Liason for IntraMed Educational Group (a contractor to Pfizer under yet another "educational

grant") apparently wrote to Dr. Freeman on January 18, 2001 proposing an honorarium of **$2,000 per program ("Clinical Success Factors in Managing Neuropathic Pain")** which was to be "given to you on the day of the program". (SH_0064559.0093292) Naturally, expenses were also covered or reimbursed. Dr. Freeman was scheduled to deliver three such lectures out of a total of 10 scheduled for the period March-June 2001. The key message in Dr. Freeman's talk seems to have been the idea that ***"Therapeutic actions for neuropathic pain typically require doses of around 2400 mg, however, anecdotally, doses up to 4 Gm/day* (4000 mg/d) *have been used."*** (emphasis added) (SH_0064559.0093282) **This message was not supported by any evidence, contradicted the frequent more conservative advice offered to other company-sponsored fora by Dr. Beydoun, and is not referenced in the article. It is frankly deceptive, in my opinion.** Dr. Freeman was also long out of date when he wrote that *"Although no head to head trials of gabapentin versus a tricyclic antidepressant or a standard anti-convulsant such as carbamazepine have been reported, many pain specialists are now using gabapentin as a first line drug for neuropathic pain …"* Dr. Freeman's chapter seems to be undated, so I cannot tell when he wrote this presentation (if it was indeed his primary work), but the reference list shows reports through 2000, whereas Morello's study of gabapentin vs. amitriptyline for PDPN was published in 1999, indexed by PubMed and MEDLINE, and certainly known to me by the year 2000. Needless to say, there is no indication that Dr. Freeman informed his audience of the results of the Reckless trial.

27. Dr. Ahmad Beydoun may have been more cautious in how he appears to have presented his opinions about Neurontin (at least to the extent one can judge from printed documents as opposed to the live performance, which surely must have been more entertaining), yet he too must have been on the gravy train. For example, he appeared on June 2, 2001 at the Hyatt Regency Coral Gables in Coral Gables, FL. A table from his presentation (MDL_Vendors_094818) still referred only to the Backonja and Rowbotham studies, although it was now over 3 years since initiation and about 2 years since completion of the larger European PDPN trial (Reckless 945-224), and over a year since the final trial report had been completed and signed off at Parke-Davis. Neither was the Gorson trial mentioned. The Serpell study of mixed neuropathic pain (945-306) had been completed in the U.K. and the internal research report was finished. Even the reasonably large Nordic study (Gordh, 945-271) was nearing completion. Had Dr. Beydoun been aware of the negative acute pain trials of gabapentin, he might have considered them irrelevant to neuropathic pain, but I think an academically honest presentation would have had to mention such results to the audiences, let alone some of the bad news for Neurontin that had already emerged, or was continuing to emerge from the chronic pain clinical trials.

In light of what I <u>now</u> know, I find the table referenced above to be clearly misleading, omissive, and/or deceptive. In Dr. Beydoun's defence, I must state that he appears to have "stuck to his guns" (even if hired) in continuing **not to recommend the huge doses of gabapentin** that others like Dr. Freeman and Dr. McClean were now espousing. (MDL_Vendors_094823) Perhaps Pfizer felt it could overcome any of Dr. Beydoun's reticence about "mega-dosing" (my term) by massaging (figuratively) the

attendees in the hotel corridors. Like others in the Pfizer stable of speakers, Dr. Beydoun was quick to apply the term "first-line therapy" to gabapentin for neuropathic pain (along with TCAs). I still see no thoughtful, let alone scientifically based discussion of oral opioids as alternative "first-line treatment" for serious pain, although Pfizer now knew conclusively from the 1999-2000 acute pain experiments that opioids and naproxen were efficacious for acute pain of various types, whereas **gabapentin was not.**
The use of the term **"first-line"** appears to me to be a political or marketing term, not a medical or scientific one. To understand this better, see my long discussion of the goals of pain treatment, earlier in this report.

28. Not long after this, on September 6, 2001, Pfizer convened a meeting of very senior academic experts on pain research at the Crowne Plaza Hotel in Ann Arbor, MI, to review the possibility of a New Drug Application to the U.S. FDA seeking an indication for Neurontin (gabapentin) for PHN and DPN. (Pfizer_LeslieTive_0013555). Presumably the outside experts (Dr. Mitchell Max of NIH, Professor Robert Dworkin and Dr. Gary Bennett and Paul Leber) were put under confidentiality agreements which would have precluded them from later disclosing what they learned from Pfizer in order to prepare for this meeting.

The results of the Reckless (945-224), Serpell (945-306) and Nordic (945-371, Gordh) studies were now revealed to the outside experts. According to the available notes (Pfizer_LeslieTive_0013556), Dr. Max was as authoritative as he was succinct: *"You're done."* Although Dr. Dworkin was not quoted verbatim, the notes show on the same page that he found the (Reckless, 945-224) *"… large placebo-controlled negative dose-response (600, 1200, 2400 mg/d) study, in which 2400 mg appeared worse than 1200 mg, striking"*. Apparently he advised that another positive, well controlled study would be needed to "overcome this study" (note taker's words, not Dr. Dworkin's). Amongst other things, there was consensus that, "Importantly, gabapentin is not effective in non-neuropathic models of pain." Presumably this conclusion was based on the Nordic (945-371, Gordh) study, as I saw no indication that the acute pain study results were revealed to the outside experts in preparation for or during the September 6, 2001 meeting.

The cat was out of the bag, but the room was sealed, so to speak. Unlike the royal chamber at Elsinore, the walls did not "have ears". The seal was highly effective.

I can now answer some of the questions I posed in paragraph 22 above. There can be little doubt that even Dr. Dworkin had been kept in the dark about the emerging negative results for Neurontin. Consider the year 2001. Pharmacia (now Pfizer) had similarly controlled access to the real data about celecoxib (Celebrex) in order to fool the Journal of the American Medical Association into publishing an inaccurate, misleading, deceptive, and ultimately fraudulent account of the "CLASS Study" only one year earlier. (JAMA. 2000;284:1247-1255) The editorialist who endorsed celecoxib in the same issue of JAMA later complained to the media that he would not have done so, had he know the real facts, although an astute and meticulous reader could have discerned that there was something wrong with the JAMA report about Celebrex. (See our series of Therapeutics Letters on celecoxib at www.ti.ubc.ca, which

made our University of British Columbia academic group, the UBC Therapeutics Initiative, very unpopular at the time. Our analysis was ultimately vindicated and has strengthened our reputation for academic honesty.)

Dr. Dworkin would have been well aware of this scandal, which brought international attention to the need to reform medical journal standards and practices. I wonder whether he was feeling that he too had been bamboozled. But Dr. Dworkin and the other outside experts consulted by Pfizer in September 2001 may now have been muzzled by a Pfizer confidentiality agreement. Dr. Dworkin apparently remained happy to maintain a cordial relationship with the company. (see below)

29. Nothing stopped Pfizer from proceeding apace with its indoctrination of a "Primary Care and Neurology Advisory Board" on November 8, 2001. (Pfizer_RGlantzman_0049084 et seq.) Low back pain was now to be considered a "condition associated with neuropathic pain" (Pfizer_RGlantzman_0049091) with a prevalence 3-4 times greater than that attributed to diabetic neuropathy, which itself was probably exaggerated (as all diabetic neuropathy, not PDPN). Backonja's and Rowbotham's studies were again presented *ad nauseam* and even Serpell's study (945-430) was now introduced into "evidence" (Pfizer_RGlantzman_0049119 et seq.).

Slides apparently prepared for or by Suzanne Doft, Director, Neurontin US Marketing Team (identified at: Pfizer_LeslieTive_0074392) are labeled in their left lower corner "Xtec Media Job X2855 Doft". There is a clue at (Pfizer_RGlantzman_0049119) that the slides had been in preparation for some time, since the reference for a description of 945-430 was given as "Source: Serpell, MG, Pain 2000 (Submitted)". The published version of Serpell's study (Serpell, MG, Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Pain 2002; 99: 557-66) indicates that the article was not submitted to Pain until April 10, 2001, which implies that it may have had an interesting "prepublication history". Parke-Davis/Pfizer of course had not only enjoyed access to the study results since it's completion in February 2000, but had been responsible for their analysis. Dr. Serpell, after all, was merely a consultant paid for his "independent help and advice on this project". (Pain 2000, p 565) The slide set notes beginning at (Pfizer_RGlantzman_0049120) suggest that this version was prepared for presentation by Dr. Serpell *"…as you will see when Dr. Serpell goes through the patient population."*

Did Parke-Davis/Pfizer succeed with the mischievous, if not devious interpretation of the study data suggested in the bottom notes at (Pfizer_RGlantzman_0049121)? Here I note what appears to be a **prompt**, suggesting that the presenter (Dr. Serpell himself, if possible) introduce the slide to an audience with the commentary that *"It would be interpreted from this graph that there are no benefits to be gained from prescribing 2400 mg, **however, when we consider the response in relation to duration of disease there is a distinction between the 1800 and 2400 mg dosage groups.**"* (emphasis added) If this were not "torturing the data until they speak the desired words", then it would surely have amounted to putting the desired words into the speaker's mouth!

I have no knowledge of what manuscript Dr. M.G. Serpell and colleagues may have submitted to the journal Pain on April 10, 2001 (shown as the submission date in the 2002 published article), a manuscript virtually certainly prepared by Parke-Davis/Pfizer for the "ghost authorship" of Dr. Serpell. **However, Serpell and the "Neuropathic Pain Study Group" certainly made no such claim in the final Pain article reporting on 945-430 (Serpell, Pain 2002). On the contrary, the authors were at pains to suggest in their discussion that the purported clinical benefits of treatment were apparent <u>early</u>, and Figure 3 of the published report claimed statistical significance at 1-4 weeks, <u>before any patient had reached 2400 mg/d</u>**.

Anyone who reads Serpell 2002 (Pain) or my detailed study summary (Appendix), let alone anyone who digests the information available in the full unpublished study report from Parke-Davis dated May 5, 2002 will see that the above interpretation of 945-330, purporting a greater benefit at higher doses, is a totally fallacious and frankly duplicitous perversion of what the study showed. A follow-on slide strikes me as intended to rub in the message by labeling with the title "Neuropathic Pain – Efficacy Summary" a slide which shows only the titration schedule of the published (or soon to be published) U.S. and U.K. studies, and which properly should have been entitled "Titration Schedules". (Pfizer_RGlantzman_0049122)

The only possible interpretation I can make of this slide set is that it was a bold-faced attempt to manipulate physicians into prescribing larger doses of gabapentin than they might otherwise have chosen – by flying in the face of the truth! But the audience could scarcely have realized in a matter of a few minutes or hours what has taken me months of thinking and hard work to discern. **Of course, Pfizer would have known that. There is no mistaking that Pfizer used this to its advantage.**

30. The same documents, beginning at (Pfizer_RGlantzman_0049128 et seq.) show that Pfizer was now moving to follow the advice received barely two months earlier in Ann Arbor. New multi-centre trials were now planned for the European Union and the United States, presumably to "overcome" the Reckless (945-224) trial, which was starting to live fully up to its name! Pfizer was again going to push the dose of gabapentin towards a target of 3600 mg/d. The United States trial appears to have unfolded as what became 945-1008, for which the original protocol is dated December 4, 2001 although the first patient was not enrolled until April 4, 2002. (See detailed summary report in my Appendix.) Unlabelled Pfizer documents which I reviewed indicate that by May 2003 the proposed new European trial had already been cancelled. It appears to have been labeled as "945-1007". Another trial was proposed, apparently for Japan, Australia, and perhaps Latin America ("JAALA", 945-1009) and at one point planning for an investigator meeting was underway for early 2003. (Pfizer, also an unnumbered document)

There seems to have been a virtually frantic attempt to use the notion of these newly proposed or planned trials to encourage more prescribing of Neurontin, utilizing the "advisory boards" or "KOL's" as their main "change agents". (see for example:

Pfizer_LeslieTive_0042341 et seq.; Pfizer_RGlantzman_0053265 et seq.; Pfizer_RGlantzman_0059497 et seq.)

I find the latter document (Pfizer_RGlantzman_0059497 et seq.) **particularly unsettling,** because a Pfizer "Neuropathic Pain Advisory Board Focus on the Specialist" meeting, or a series of such meetings (dates are not clear to me) was **moderated and introduced by Dr. Roland W. Moskowitz**, Professor of Medicine and Director of the Arthritis Research Centre at Case Western Reserve University School of Medicine in Cleveland, OH. The slide sets for these sessions are replete with recitations of Pfizer's noble mission as well as its global economic power, although (perhaps fortuitously, to spare me from choking) the ellipse labeled "Values" is not legible in the version I reviewed of a slide labeled "Pfizer Mission: Purpose, Mission, Values" (Pfizer_RGlantzman_0059500 et seq.)

What disturbs me about Dr. Moskowitz' involvement is that as a principal investigator in the 1999-2000 short term trial of gabapentin for pain in osteoarthritis, he was in a privileged position to know that gabapentin was not efficacious for acute pain, and that the company had not revealed the results of its multiple experiments to the world. Effectively the trust of patients who participated in trials approved by ethics boards had been breached. An ethical ethics review board normally will insist that trial results must not be hidden from the public. Did Dr. Moskowitz share what he knew about these acute pain trials with the "attendees" at any session which he may have proceeded to moderate?

31. At (Pfizer_RGlantzman_0059500 et seq.) it becomes apparent that Pfizer had carefully studied the attitudes of neurologists, pain specialists and primary care doctors to learn as much as it could about the psychology of how they titrated Neurontin for patients in pain. The "Research Conclusion" (Pfizer_RGlantzman_0059595 et seq.) is that "Few physicians are titrating up to the maximum dose of 3600 mg, as outlined in the new product profile."

The use of the word "Pivotal Studies" in a graph designed to show how specialists and particularly generalists were deficient in their "dosing and titration behaviours" is striking. (Pfizer_RGlantzman_0059598) **"Pivotal studies" were those that Pfizer liked, not those which it disliked and whose results it kept hidden** (e.g. 1032-002 in osteoarthritis for which Dr. Moskowitz was a principal investigator, or the much-feared Reckless 945-224 trial, or the soon-to-be completed 945-1008). It is important to understand that the term "pivotal" has no scientific meaning, but it definitely has a psychological and political meaning: **in this sense "pivotal" means the information or disinformation required to cause doctors to pivot toward their prescription pads.**

The next slide in the sequence (Pfizer_RGlantzman_0059599 et seq.) suggests to me that doctors invited to such meetings by Pfizer were being "pivoted" into the belief that they were contributing in some way based on their clinical expertise to "research", when in point of fact they were really experimental subjects in a marketing exercise. Where this extends to "workshops" intended to help specialist doctors develop the language

appropriate to use in consultation reports as a "one-paragraph response persuading your colleague to prescribe Neurontin", the border between "research" and manipulation has clearly been transgressed. This reminds me somehow of the "re-education camps" of the old Chinese communist regime during the Cultural Revolution which most Westerners considered intellectually and ethically repugnant.

What would have been going through the minds of physicians who might put themselves into the position of attending such workshops? Did such "workshops" really proceed with physicians as participants, or were they only figments of someone's fevered imagination in the marketing departments at Pfizer? What would their patients have thought, had any such physicians disclosed their recent indoctrination whilst writing out a prescription for Neurontin? Astute patients sometimes draw their own conclusions from inspection of their doctors' office walls, their desks, their apparel, and even by noticing from the patient waiting area any delicious lunchtime deliveries to doctors' receptionists.

2002: (some of the above documents are undated, but may be from 2002)

32. There was now a "full court press" to bring the Neurontin glad tidings to managed care organizations, for example at a meeting held on March 3-4, 2002 at the Disney BoardWalk Resort in Orlando, FL.(Pfizer_LeslieTive_0074344 et seq.) This was for the "PBM Managed Care Advisory Board" and attended by senior managers and executives of organizations such as Merck-Medco, Caremark, Walgreens Health Initiative, and VAMC Denver. A phalanx of Pfizer marketing staff including Suzanne Doft (Director, US Neurontin Marketing Team), Valerie Flapan (Corporate Counsel) and Dr. Leslie Tive (Medical Director/Team Leader) were joined by three "Health Strategies Group" attendees whose role I cannot imagine. (Pfizer_LeslieTive_0074381)

The slide set for this presentation appears to have been more colourful than what was typically used for doctors. I was impressed by the striking photograph of Dr. Silas Weir Mitchell, Civil War surgeon, accompanying his vivid and excruciating description of "causalgia", a particularly venal prototype of neuropathic pain. (Pfizer_LeslieTive_0074344 et seq.) I wonder whether the PBM managers were fooled as easily as the physicians by presentation of many of the same slides, e.g. the now-outdated Serpell figure, which still bore the legend "Source: Serpell, MG, Pain 2000 (Submitted)" even though the 2002 Pain article's publication history shows that the manuscript was still undergoing prolonged revision at this time. (Pfizer_LeslieTive_0074378)

Was the audienc impressed by the presentation of "SF-36 Results: NEURONTIN in Painful DPN" which might strike a neutral observer as showing nothing? (Pfizer_LeslieTive_0074381) Pfizer was still touting the coming "US/EU Study of NEURONTIN in Painful Diabetic Neuropathy" (the unpublished/suppressed 945-1008 and the later-cancelled 945-1007) and the "JAALA Study of NEURONTIN in Painful Diabetic Neuropathy" as well as a new "Chronic Pain Screener" test to identify more

patients - perhaps those too "patient" to complain that they needed Neurontin, so to speak. (Pfizer_LeslieTive_0074383)

Presumably this presentation left the impression with PBM managers that there was and ongoing active research program to better characterize the optimum (large) Neurontin doses. It must certainly have been calculated to ensure that the institutional buyers of Neurontin would not discover the results of the Reckless trial, let alone the findings from 945-271 (Nordic Trial, Gordh) which were now known (completed 2001) or those later compiled from 945-1008. What would the same managers now think?

33. A similar presentation (Pfizer_RGlantzman_0149235 et seq.) was made by Pfizer on June 24, 2002 to its "Managed Care and Long Term Care Neuropathic Pain Advisory Board", although the slides pertaining to the Serpell study were now labeled: "Source: Serpell, MG, Pain 2000 (Submitted)". **Were there any question that Pfizer's manipulation of the results and implications of the Serpell trial was accidental, this presentation clarifies that the real lessons of this study were still being distorted – deliberately and <u>systematically</u>.** (Pfizer_RGlantzman_0149269 et seq.)

34. Pfizer convened another meeting at its offices in Sandwich, England on July 2, 2002, to which it invited Dr. Andrew Rice of the Pain Research Group, Department of Anesthesetics, Imperial College School of Medicine (and lead author of the second published trial in PHN, Rice 2002) as well as Professor Martin Koltzenburg of the Institute of Child Health & Neurology at the National Hospital for Neurology & Neurosurgery, University College London. Important Pfizer managers from England, Ann Arbor, New York, and Groton (England) attended. (Pfizer_LKnapp_0070537 et seq.) The Englishmen were less than impressed with the American approach to pain quantification and wanted to see outcomes that were clearly meaningful for patients. They wanted to see original data published, and felt that the Pfizer data bases might contain meaningful answers to many important questions. For example, *"Does the degree of pain relief correspond with the number of side effects …?"* In the clinic, they were concerned that *"…the most important side effects of gabapentin are dizziness and somnolence with oedema also significant in the elderly…"* They perceived amitriptyline as more effective than gabapentin ($\geq$ 50% reduction of pain score in 50% of patients vs. 34% of patients for gabapentin). As the note taker recorded dryly, *"This needs improvement."*

Pfizer executives, notably Larry Alphs of Ann Arbor (Pfizer_LKnapp_007056), were alarmed at the first paragraph of the minutes (Pfizer_LKnapp_0070539) which read: *"Current treatment options are limited. In the clinic most patients are not on single therapies. This may be due to the inadequacy of individual treatments, …* ***The success of gabapentin is not due to its efficacy, it is less efficacious than Tricyclic antidepressants (TCA), but is due to a more acceptable side effect profile…"*** (emphasis added) From their point of view, Neurontin was now the "meat in the Sandwich", so to speak.

It strikes me that in their hearts and minds, Pfizer staff had already realized that Neurontin's days were numbered, partly because it now required an increasingly hard flogging to induce doctors to write long and high dose prescriptions for Neurontin or to convince patients to renew them. Even more important may have been the looming patent expiry for Neurontin. Pfizer may have needed to concentrate its corporate energies on learning from the Neurontin experience before the imminent launch of Lyrica, its heir apparent.

What conclusions can be drawn from this chronology?

1. It was crucial for Parke-Davis/Pfizer to exaggerate the purported benefits of Neurontin, "push the dose", and play down Neurontin's well documented adverse effects in order to maximize off-label use. If doctors' attention could be attracted through the selective use of data from the published PHN and PDPN trials, it would be possible to expand the prescription of Neurontin to the much larger patient populations affected by other chronic painful conditions (e.g. chronic back pain or "fibromyalgia"). **In a demographic this large, the purchase of several months' worth of Neurontin would be lucrative for Pfizer – even if the patients stopped taking it and could not be persuaded to renew such prescriptions.**

2. Parke-Davis/Pfizer could not afford for the truth to surface from studies which produced unfavourable results. It must have realized even before completion of the large unpublished United States primary care study in PDPN (945-1008, Parsons, unpublished report dated March 24, 2005) **that there was little point pursuing further studies of Neurontin when a new drug was coming fast down their "pipeline". It would have been imperative to begin marketing pregabalin (Lyrica) before its patent cycle also began to wind down. It was better to keep repeating the mantra of the Backonja and Rowbotham studies, distort the basically negative results from 945-271 (Serpell) and hope that Serpell's published report would be little noticed and less carefully read, and ensure that doctors would forget or never learn about Gorson's trial and the small independent trials (e.g. McCleane 2001, van de Vusse 2004). After all, these more independently published trial results basically supported the English experts' take on Neurontin at Sandwich: gabapentin was not an impressive drug and the small Morello 1999 trial had already suggested that for most patients amitriptyline was a more practical option.**

3. When it came to disclosure, neither Parke-Davis/Pfizer nor its "hired guns" acquitted themselves honestly. The records I reviewed showed example after example of distortion of the evidence by doctors who ought to have known better. This was amplified by the creative "spin" of the marketing personnel who were

ubiquitous at "continuing medical education events" and used Parke-Davis/Pfizer's ample resources to ensure that their message was tightly controlled, and that their Key Opinion Leaders (KOL's) stayed "on message".

4. It is a sad but all too common reflection on my own profession and on the state of academic medicine that so many physicians, including prominent university based clinical and basic "investigators", collaborated so obsequiously in this endeavour.

In Middlemarch, George Eliot's penultimate novel, Dr. Tertius Lydgate is heroic partly because he has turned his back on medical hucksterism. He is the prototype reformer who recognizes that a doctor cannot both prescribe and dispense medicines without an inherent conflict of interest. The author Mary Anne Evans (George Eliot) was aware that British physicians influenced by the Nineteenth Century's exciting new scientific influence on medicine were beginning to realize the prescribing/dispensing conflict. Like the fictional Dr. Lydgate, they were starting to eschew the dispensing of drugs and limit themselves to prescription.

This hard-won and courageous separation of physicians' prescribing decisions from the economic returns that accompany dispensing was not inevitable. After all, naturopaths, pharmacists, veterinarians, optometrists, and other professionals or quasi-professionals recommend (prescribe) and sell drugs, vitamins and other "supplements" or "health foods" from which they derive a significant part of their income. The decision to avoid conflict of interest was a major ethical step for physicians, and it represented a potential triumph for patient interests over those of the health service provider. It is iniquitous that pharmaceutical manufacturers have since undermined this ethical accomplishment so systematically and with such nearly ubiquitous success.

In the case of Neurontin, documents I reviewed provide so many examples of misleading, incomplete or omissive statements by physicians, marketing representatives, or even by key "investigators" that one becomes depressed in thinking about how easily human beings can be manipulated. But as Abraham Lincoln is said to have stated: "You can fool some of the people all of the time, and all of the people some of the time, but you can not fool all of the people all of the time." Neurontin (gabapentin) is probably a drug whose time is nearly up.

Preparing this opinion required substantially more work, thought, and time than I had initially imagined, but I have learned a great deal from this review. I hope my report and its Appendices also provide you and the Court with additional insight into the matters to be considered at litigation. Perhaps my observations will also assist anyone interested in understanding what it would take to reform our system of drug licensing, marketing, and medical education so as to foster the interests of patients' above all others. This is

important not only in the United States but in any other countries whose governments believe that the interests of their citizens should come first.

I thank again my colleagues Dr. Vijaya Musini and Ms. Kelsey Innes for their hard work in assisting me to meet the Court's deadline for submission of this report. However I am solely responsible for its content.

Sincerely,

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List of Documents Reviewed

Documents

1. CDM0022270
2. MDL_VENDORS_046284
3. MDL_VENDORS_056827
4. MDL_VENDORS_057666
5. MDL_VENDORS_085846
6. MDL_VENDORS_085867
7. MDL_VENDORS_086643
8. MDL_VENDORS_094765
9. PFIZER_AFANNON_0008126
10. PFIZER_BPARSONS_0000073
11. PFIZER_BPARSONS_0001128
12. PFIZER_JMARINO_0002157
13. PFIZER_JMARINO_0002191
14. PFIZER_LCASTRO_0027113
15. PFIZER_LCASTRO_0043325
16. PFIZER_LESLIETIVE_0002581
17. PFIZER_LESLIETIVE_0002824
18. PFIZER_LESLIETIVE_0013555
19. PFIZER_LESLIETIVE_0034253
20. PFIZER_LESLIETIVE_0042341
21. PFIZER_LESLIETIVE_0049975
22. PFIZER_LESLIETIVE_0074344
23. PFIZER_LKNAPP_0006623
24. PFIZER_LKNAPP_0009569
25. PFIZER_LKNAPP_0009830

26. PFIZER_LKNAPP_0013491
27. PFIZER_LKNAPP_0024958
28. PFIZER_LKNAPP_0050385
29. PFIZER_LKNAPP_0055357
30. PFIZER_LKNAPP_0060187
31. PFIZER_LKNAPP_0070537
32. PFIZER_LKNAPP_0070545
33. PFIZER_LKNAPP_0070547
34. PFIZER_LKNAPP_0083148
35. PFIZER_MYODER_0002471
36. PFIZER_NMANCINI_0024603
37. PFIZER_RGLANZMAN_0049084
38. PFIZER_RGLANZMAN_0053265
39. PFIZER_RGLANZMAN_0059497
40. PFIZER_RGLANZMAN_0149235
41. PFIZER_TMARTIN_0001736
42. PFIZER_TMARTIN_0002022
43. PFIZER_TMARTIN_0002200
44. SH_0006934
45. SH_0012453
46. SH_0030111
47. SH_0036543
48. SH_0044640
49. SH_0044769
50. SH_0045500
51. SH_0064559.0072317
52. SH_0064559.0076474
53. SH_0064559.0093275

54. SH_0064559.0093290
55. SH_0064559.0096673
56. SH_0064559.0096785
57. WLC_CBU_000221
58. WLC_CBU_013197
59. WLC_CBU_028461
60. WLC_CBU_028473
61. WLC_CBU_072249
62. WLC_CBU_076620
63. WLC_CBU_079302
64. WLC_CBU_092879
65. WLC_CBU_093708
66. WLC_CBU_123550
67. WLC_CBU_164376
68. WLC_CBU_164409
69. WLC_CBU_175636
70. WLC_CBU_180727
71. WLC_CBU_180735
72. WLC_FRANKLIN_0000015522
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79. WLC_FRANKLIN_0000050304
80. WLC_FRANKLIN_0000066844
81. WLC_FRANKLIN_0000073645

82. WLC_FRANKLIN_0000080451

83. WLC_FRANKLIN_0000082494

84. WLC_FRANKLIN_0000090053

85. WLC_FRANKLIN_0000090214

86. WLC_FRANKLIN_0000090215

87. WLC_FRANKLIN_0000090220

88. WLC_FRANKLIN_0000092698

89. WLC_FRANKLIN_0000098315

90. WLC_FRANKLIN_0000098352

91. WLC_FRANKLIN_0000100273

92. WLC_FRANKLIN_0000166608

93. WLC_FRANKLIN_0000199743

94. WLC_FRANKLIN_0000199997

95. VOX027405

96. Additionally, please the documents referred to in the Report and Appendices

Publications

1. Catherine Arnst, "Conquering Pain: New Discoveries and Treatments Offer Hope", Business Week, March 1, 1999.

2. Dubinsky RM et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 63: 959-65.

3. Dyck PJ et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology 1993; 43: 817-24; Boulton A. Management of Diabetic Peripheral Neuropathy. Clinical Diabetes 2005; 23: 9-15

4. Helgason S et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ 2000; 321: 794-6

5. Opstelten W et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract 2002; 19: 471-475

6. Wong MC, Chung JWY, and Wong TKS. Effects of treatment for symptoms of painful diabetic neuropathy: systematic review. BMJ 2007;335:87

7. McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain? A randomized, double-blind, placebo controlled study. The Pain Clinic 2001;13:103

8. de Jong RH. Neurontin: Pie in the Sky or Pie on the Plate? Pain Digest 1996; 6:143-4

9. Additionally, please see the references to published articles in the Report and Appendices

Websites

1. Evidence-based recommendations for medical management of chronic non-malignant pain: chapter 7. Neuropathic pain, College of Physicians and Surgeons. Nov 2000. http://www.cpso.on.ca/publications/pain.PDF, accessed July 18, 2008.

2. http://www.depomedinc.com/view.cfm/1285/Our-Pipeline

3. http://www.painstudy.ru/10wcp/anticonvulsants.htm

4. http://www.clinicalstudyresults.org/documents/company-study_1926_0.pdf

5. Additionally, please see the websites referred to in the Report and Appendices

Research Reports

1. 430-00124

2. 430-00125

3. 720-03908

4. 720-04130

5. 720-04378

6. 720-04455

7. 720-04471

8. 720-04479

9. 720-04481

10. 720-04483

11. 720-30044

12. 720-30049

13. 744-00664
14. 744-00669
15. 995-00070
16. Research Report for Study 945-210
17. Research Report for Study 945-211
18. Research Report for Study 945-220
19. Research Report for Study 945-224
20. Research Report for Study 945-224
21. Research Report for Study 945-306
22. Research Report for Study 945-306
23. Research Report for Study 945-371
24. Research Report for Study 945-430
25. Additionally, please the research reports referred to in the Report and Appendices

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT Pain Studies Summary Matrix
FINAL – August 8, 2008 - Dr. Thomas L. Perry

Thomas L. Perry M.D.

Thomas L. Perry, M.D., FRCPC

APPENDIX - GABAPENTIN PROJECT Pain Studies Summary Matrix - FINAL – August 8, 2008, Thomas L. Perry, M.D.

CHRONIC PAIN

TRIALS SUITABLE FOR DETAILED REVIEW AND META-ANALYSIS (SEE NOTES AT END OF TABLE)

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
1) 1997 Gorson PDPN WLC_FRANKLIN_0000100272 WLC_FRANKLIN_0000100273 WLC_FRANKLIN_0000088375.pdf Gorson KG, Schott C et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. (letter) J Neurol Neurosurg Psychiatry 1999; 66:251-2	**Gorson J Neurol Neurosurg Psychiatry 1999**	**PDPN**	**Study Size:** 126 screened, and 53 were randomized (crossover design), however, the published letter to the editor makes no mention of the 13 who dropped and says N = 40. **Treatment Duration:** 6 weeks. **Dose:** 900 mg / day	No	Letter to the editor	**Detailed summary table analysis completed & checked, July 22, 2008**
2) 1997 Morello Independent study, US VA system Morello CM, Leckband SG et al. Randomized Double-blind Study Comparing the Efficacy of Gabapentin With Amitriptyline on Diabetic Peripheral Neuropathy Pain. Arch Intern Med 1999; 159: 1931-7	**Morello Arch Intern Med 1999**	**PDPN**	**Double Blind** **Study Size:** 28 were screened, 25 were randomized – 12 to Gabapentin-Amitriptyline arm, and 13 to Amitriptyline-Gabapentin arm (crossover design) **Treatment Duration:** 6 weeks for each treatment **Dose:** 900 – 1800 mg/day Gabapentin or 25 – 75 mg/day Amitriptyline.	No	Comparator Study v. Amitriptyline	**Detailed summary table analysis completed & checked, July 27, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
3) 1997 Backonja PDPN **945-210** 720-03908_Vol_1.pdf 720-03908_Vol_2.pdf 720-03908_Vol_3.pdf Backonja M, Beydoun A et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with Diabetes Mellitus. JAMA 1998; 280: 1831-6	**Backonja** **JAMA 1998**	**PDPN**	**Study Size:** 232 screened, 165 enrolled - 84 were randomized to Gabapentin, 81 randomized to placebo (parallel design) **Treatment Duration:** 8 weeks. **Dose:** Titrated from 900 mg – 3600 mg per day or maximum tolerated dosage.	Yes	JAMA article; forced titration	**Detailed summary table analysis completed & checked, July 22, 2008**
4) 1997 Rowbotham PHN **945-211** 995-00070_945-211_(Part_I).pdf 995-00070_945-211_(Part_II).pdf 995-00070_945-211_(Part_III).pdf Rowbotham M, Harden N et al. Gabapentin for the Treatment of Postherpetic Neuralgia. JAMA 1998; 280: 1837-42.	**Rowbotham** **JAMA 1998**	**PHN**	**Study Size:** 292 screened, 229 randomized, 113 received Gabapentin, 116 received placebo (parallel design). **Treatment Duration:** 8 weeks. **Dose:** Titrated to a maximum of 3600 mg/day or maximum tolerated dose.	Yes	JAMA article; forced titration	**Detailed summary table analysis completed & checked, July 22, 2008**
5) 1997 Dallochio Parke-Davis, Italy (4th author) Dallocchio D, Buffa C et al. Gabapentin vs. Amitriptyline in Painful Diabetic Neuropathy: An Open-Label Pilot Study. J. Pain and Symptom Management 2000; 20: 280-3. **OPEN LABEL**	**Dallocchio** **J. Pain and Symptom Management 2000**	**PDPN**	**Open label (? Marketing trial - Parke-Davis co-authored)** **Study Size:** 25 enrolled, 13 were treated with Gabapentin while 12 were treated with Amitriptyline. **Treatment Duration:** 12 weeks for each treatment **Dose:** Titrated to a maximum dosage of 2400 mg/day of Gabapentin or 90 mg/day of Amitriptyline.	No	**Open label** comparator Study v. Amitriptyline **Not suitable for meta-analysis of any outcomes.**	**Detailed summary table analysis completed July 23, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
6) 1998 Reckless PDPN **945-224** 720-04130.pdf **1998 Reckless PDPN (continued)** **945-224** 720-04130.pdf	**Reckless** **Unpublished** 1998-1999 study, final report 2000. (Summarized favourably in: Backonja M, Glanzman RL. Gabapendin Dosing for Neuropathic Pain: Evidence from Randomized, Placebo-Controlled Clinical Trials. Clinical Therapeutics 2003; 25: 81-104)	**PDPN**	**Study Size:** 432 screened, 325 randomized, 77 randomized to placebo group, 82 randomized to 600 mg/day Gabapentin, 82 randomized to 1200 mg/day Gabapentin, 84 randomized to 2400 mg/day Gabapentin (parallel design) **Treatment Duration:** 7 week treatment period (double blind) after which a subset of patients could enter a 4-month open label extension phase. **Dose:** 600 mg/day, 1200 mg/day, or 2400 mg/day.	Yes	Fixed dose study; not published as standalone article. Reference to results in Backonja M, Glantzman RL 2003 is an incomplete reporting.††	**Detailed summary table analysis completed & checked, July 22, 2008**
7) 1998-1999 van de Vusse van de Vusse AC Stomp-van den Berg SGM, et al., Randomized controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 (ISRCTN84121379). BMC Neurology 2004; 4: 13 (9 pages)	**van de Vusse** **BMC Neurology 2004**	**CPRS type 1**	**Study size:** Crossover study of gabapentin vs. placebo for 2 x 3-week periods, separated by 2-week washout. N=58 patients P first (29) or to G first (29); 12/58 excluded from analysis **Treatment Duration:** each treatment was given for 3 weeks **Dose:** targe tdose G=1800 mg/d	No	††	**Detailed summary table analysis completed & checked, July 24, 2008**
8) 1998-2001 Gordh, Nordic Study **945-271** PFIZER_LCASTRO_0043325.pdf PFIZER_LCASTRO_0027113.pdf	**Gordh et al (Nordic study)** **Unpublished** Final study report 2003	**POPP NeP**	**Study Size:** 159 screened, 120 randomized – 61 to Gabapentin-Placebo arm, 59 to placebo-Gabapentin arm (crossover design) **Treatment Duration:** 5 weeks **Dose:** Titrated to 2400 mg/day or maximum tolerated dosage.	No	**Unpublished** Scandinavian study of postoperative and posttraumatic neuropathic pain††	**Detailed summary table analysis completed & checked, July 22, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
9) 1999 Rice **945-295** 430-00124.pdf Rice ASC, Maton S, Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomized, double-blind, placebo controlled study. Pain 2001; 94: 215-224	**Rice** **Pain 2001**	**PHN**	**Study Size:** 411 screened, 334 randomized – 115 to Gabapentin 1800 mg/day, 108 to Gabapentin 2400 mg/day, and 111 to placebo (parallel design, if unable to tolerate dose pt. was pulled from study) **Treatment Duration:** 7 weeks **Dose:** Either 1800 mg/day or 2400 mg/day	Yes	Fixed dose study**	**Detailed summary table analysis completed & checked, July 22, 2008**
10) 1999-2000, Serpell **945-306** 430-00125.pdf 430-00125_Correction_Memo_1.pdf 430-00125_Correction_Memo_2.pdf Serpell MG, Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Pain 2002; 99: 557-66.	**Serpell** **Pain 2002**	**Mixed NeP**	**Study Size:** 351 screened, 307 randomized – 153 to Gabapentin, 152 to placebo (parallel design) **Treatment Duration:** 8 weeks **Dose:** Initially titrated to 900 mg/day. Patients who did not show at least 50% pain reduction were increased to 1800 mg/day and then if necessary again to 2400 mg/day.	Yes	Study involving neuropathic pain symptoms from a variety of different etiologies**	**Detailed summary table analysis completed & checked, July 22, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
11) 1999-2000 Bone Bone M, Critchley P, Buggy DJ. Gabapentin in Postamputation Phantom Limb Pain: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study. Reg Anesth Pain Med 2002; 27: 481-6	**Bone Reg Anesth Pain Med 2002**	**Post-amputation phantom limb pain**	**Single centre English DBR crossover trial** **Study Size: 33 screened, 19 randomized** after 1 week screening/washout phase to: placebo (9) or gabapentin (10) as first treatment, then crossover to alternative treatment Treatment Duration: 6 weeks, with 1 week intervening washout Dose: gabapentin titrated from 300 mg/d to maximum of 2400 mg/d			**Detailed summary table analysis completed & checked, July 23, 2008**
12) 1999-2002 Caraceni 945-420-276 PFIZER_LCASTRO_0026332 Caraceni A, Zecca E, et al. Gabapentin for Neuropathic Cancer Pain - A Randomized Controlled Trial from the Gabapentin Cancer Pain Study Group. J. Clin Oncology 2004; 22: 2909-17	**Caraceni J. Clin Oncology 2004**	**Neuropathic Cancer pain**	**Multicentre Italian/Spanish DBRCT** **Study Size: 691 patients screened, 121 patients randomized to** Gabapentin 80 (79 received drug) vs. 41 placebo, in addition to stable opioid dose and additional opioid as needed **Treatment Duration:** ten days **Dose:** Gabapentin was titrated from 600 mg/day – 1800 mg / day		Not meta-analysable other than safety outcomes, as the outcomes are not similar to any other study..	**Detailed summary table analysis completed & checked, July 26, 2008**
13) 2000-2001 Gomez Perez LADPN 945-411 PFIZER_LKNAPP_0006623 Gomez-Perez FJ, Perez-Monteverde A et al. Gabapentin for the treatment of painful diabetic neuropathy: dosing to achieve optimal clinical response. Br. J. Diabetes Vasc. Dis. 2004; 4: 173-8 **OPEN LABEL**	**Gomez-Perez Br. J. Diabetes Vasc. Dis. 2004**	**PDPN**	**Study Size:** 421 screened, 339 randomized – 170 to Gabapentin fixed dose, 160 to Gabapentin titration dose. **Treatment Duration:** 7 weeks **(open label)** **Dose:** fixed dose of 900 mg/day or titrated to a maximum of 3600 mg/day	No	**Open label Latin American study (LADPN) ††** **Unsuitable for meta-analysis, as there is no placebo group. May provide some insight into dose-dependent toxicity.**	**Detailed summary table analysis completed & checked, July 22, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
14) ? 2002 Levendoglu Levendoglu F, Ogun CO., et al. Gabapentin Is A First Line Drug for the Treatment of Neuropathic Pain in Spinal Cord Injury. Spine 2004; 743-751.	**Levendoglu Spine 2004**	**NeP after spinal cord injury**			††	**Detailed summary table analysis completed & checked, July 26, 2008**
15) 2001-2003 Gilron Gilron I, Bailey JM et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005; 352:1324 – 34.	**Gilron N Engl J Med 2005**	**PHN and PDPN**	**Study Size:** A four-period crossover trial for which 86 patients were screened, 57 were randomized to one of four treatment sequences which included Gabapentin, Morphine, Placebo (active, lorazepam), and Gabapentin-Morphine combination. **Treatment Duration:** Each treatment was given for 5 weeks. **Dose:** Target daily dose ceilings were 120 mg/day for morphine treatment, 2400 mg/day Gabapentin and 60 mg/day morphine for Gabapentin-Morphine combination, 3200 mg/day Gabapentin for Gabapentin treatment, and 1.6 mg/day lorazepam for placebo.		Comparator Study v. Morphine and lorazepam as active placebo	**Detailed summary table analysis completed & checked, July 22, 2008**
16) 2002-2003 Parsons 945-1008 PFIZER – PhrmaWebSynopsis-Final-2 June 2005 and PFIZER – Bruce Parsons, Guy Cohen-24 March 2005	**Unpublished** – not on CD (available as paper copy of final report), no appendices available … found by Greene & Hoffman … "Phase 4" of development	**PDPN**	**Study Size:** 724 screened, 389 randomized – 189 to P, 200 to G **Treatment Duration**: 2 weeks titration, 12 weeks fixed dose (14 weeks total after 1 week run-in) **Dose:** Titrated to 3600 mg/day or maximum tolerated dose (at least 1800 mg/day)	?	Unpublished USA study in 43 primary care "centres" – referred to obliquely during Pfizer marketing efforts for Neurontin - ? marketing study††	**Detailed summary table analysis completed & checked, July 22, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
17) 2002-2005 Chandra (partially Pfizer supported) Chandra K, Shafiq N et al. Gabapentin versus Nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial – The GONIP trial. International Journal of Clinical Pharmacology & Therapeutics 2006; 44: 358-63	**Chandra International Journal of Clinical Pharmacology & Therapeutics 2006**	**PHN**	**Study Size:** 110 screened, 76 randomized: NT=38, G=38 **Treatment Duration:** 1 week run-in, 8 weeks parallel group study **Dose**: titrated to NT = 150 mg/d; G= 2700 mg/d		No placebo group.††	**Detailed summary table analysis completed & checked, July 22, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
18) 2002-2003 Rao Rao RD, Michalak JC et al. Efficacy of Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy: A Phase 3 Randomized, Double-Blind, Placebo-controlled, Crossocver Trial (N00C3) Cancer 2007; 110: 2110-18	**Rao Cancer 2007**	**Cancer chemotherapy-induced peripheral neuropathy**	**DBR crossover trial (independent, supported by North Central Cancer Treatment Group and Mayo Clinic and US Public Health Service grants) – gabapentin vs. placebo** **Study size:** 115 eligible patients screened, 115 randomized between March 2002 and December 2003 to placebo = 58, gabapentin = 57 **Study duration**: 2 x 6 weeks, 2-week washout between periods **Dose:** titration to target of 2700 mg/day over 3 weeks		**Very complex and unusual statistical analysis with few completers. Most outcomes not suitable for meta-analysis.††**	**Detailed summary table analysis completed & checked, July 22, 2008**
19) 2001-2004 Rintala Rintala DH, Holmes SA et al. Comparison of the Effectiveness of Amitriptyline and Gabapentin on Chronic Neuropathic Pain in Persons with Spinal Cord Injury. Arch Phys Med Rehabil 2007; 88: 1547-60	**Rintala Arch Phys Med Rehabil 2007**	**Chronic neuropathic pain after spinal cord injury**	**DBR triple crossover trial (independent, supported by US Department of Veterans Affairs, VHARRDS grant) – gabapentin vs. amitriptyline vs. diphendydramine a(s active placebo), plus oxycodone 5 mg/acetaminophen 325 mg up to 8 tablets/day for "breakthrough pain"** **Study size:** screened 50, randomized 38 to 6 groups taking 3 drugs in different sequences **Study duration:** 3 x 9 weeks, titrated to maximum dose, then tapered down, then 1 week washout between periods **Dose:** gabapentin to maximum of 3600 mg/day, amitriptyline to maximum of 150 mg/day, diphenhydramine at 75 mg/day after titration		**Very complex and unusual statistical analysis with few completers. Many outcomes not suitable for meta-analysis ††**	**Detailed summary table analysis completed & checked, July 23, 2008**
20) ? 2003 Hahn Pfizer 0945-00S-P02 Hahn K, Arendt G, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J. Neurol 2004; 251 : 1260-6	**Hahn J Neurol 2004**	**HIV-associated distal-symmetric polyneuropathy**	**DBRCT (supported and apparently designed by Pfizer as 0945-00S-P02)** **Study size:** screened ?, randomized 26 to P=11, G=15 **Study duration:** 4 weeks, titrated to maximum dose **Dose:** gabapentin to maximum of 2400 mg/d		**Small trial which reports median (rather than mean) pain scores. Submitted in 2003 but dates of study not shown. ††**	**Detailed summary table analysis completed & checked, July 27, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
21) 2003-2006 Arnold Arnold LM, Goldengerg DL et al. Gabapentin in the Treatment of Fibromyalgia : A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial. Arthritis & Rheumatism. 2007 ; 56 : 1336-44	**Arnold Arthritis & Rheumatism 2007**	**Fibromyalgia**	**DBRCT (supported by U.S. NIH grant)** **Study size:** screened 252, randomized 150 to P=75; G=75 **Study duration:** 12 weeks, titrated to maximum tolerated dose **Dose:** gabapentin to maximum of 2400 mg/d		††	**Detailed summary table analysis completed & checked, July 27, 2008**
22) 2006 (or earlier) Kimos Kimos P, Biggs C et al. Analgesic action of gabapentin on chronic pain in the masticatory muscles : A randomized controlled trial. Pain 2007; 107: 151-60	**Kimos Pain 2007**	**Chronic masticatory myalgia (CMM)**	**DBRCT (supported by University of Alberta, gabapentin provided by Pharmascience Inc.)** **Study size:** screened 79, randomized 50 to P=25; G=25 **Study duration:** 12 weeks **Dose:** gabapentin to maximum of 4200 mg/d		††	**Detailed summary table analysis completed & checked, July 27, 2008**
Trials added late in review, NOT numbered consecutively by date of performance						
23) ? 2000 (or earlier) McCleane McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain ? A randomized, double-blind, placebo controlled study. The Pain Clinic 2001; 13: 103-7	**McCleane The Pain Clinic 2001**	**Low back pain**	**DBRCT (no support identified, appears independent Northern Ireland hospital-based)** **Study size:** screened ?, randomized 80 (P=40, G=40) **Study duration:** 2 week run-in to baseline, then 6 weeks **Dose:** titration to G=1200 mg/d		††	**Detailed summary table analysis completed & checked, August 6, 2008**
24) 1999-2003 Smith Smith DG, Ehde DM et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. JRRD (Journal of Rehabilitation Research & Development) 2005; 42: 645-54	**Smith JRRD 2005**	**Phantom limb/residual limb post-amputation pain**	**DBR crossover trial (supported by private donor grant to Harbourview Medical Centre for Limb Loss Research and US National Institute of Child Health and Human Development and National Institute of Neurological Disorders and Stroke grant PO1 HD/NS33988)** **Study size:** screened 78, randomized 24 to P/G=13, G/P=11 **Study duration:** total 17 weeks - 6 weeks for each active treatment, 5 week washout **Dose:** titration to maximum of G=3600 mg/d		††	**Detailed summary table analysis completed & checked, August 7, 2008**

Study Number, Date of study Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
25) 2002-2005 Nikolajsen Nikolajsen L, Finnerup N et al. A Randomized Study of the Effects of Gabapentin on Postamputation Pain. Anesthesiology 2006; 105: 1008-15	**Nikolajsen Anesthesiology 2005**	**Postamputation pain (prophylaxis and treatment)**	**DBRCT parallel (supported by a grant from Pfizer Denmark)** **Study size: screened ?, randomized 46; P=23, G=23, "completed" 41** **Study duration:** 30 days treatment to pre-specified primary outcome, then follow-up to 6 months post-amputation **Dose:** titration to G=1200 mg/d or G=2400 mg/d depending on kidney function		††	**Detailed summary table analysis completed & checked, August 6, 2008.**

†† denotes studies not contained in the Cochrane Systematic Review 2005
Indications: PDPN: painful diabetic peripheral neuropathy; PHN: post-herpetic neuralgia; NeP: 'neuropathic pain'; POPP: 'post-operative pain'; SCP: "spinal cord pain" after traumatic spinal cord injury; CIPN: cancer chemotherapy-induced peripheral neuropathy
NB: Numbering of studies is consecutive for this matrix by apparent chronology of study performance (except for final trials identified after others had been labeled)

GABAPENTIN PROJECT PAIN STUDIES SUMMARY MATRIX – FINAL – AUGUST 8, 2008, THOMAS L. PERRY, M.D.

ACUTE PAIN

TRIALS SUITABLE FOR DETAILED REVIEW BUT NOT FOR META-ANALYSIS

N.B. – MANY DIFFERENT OUTCOMES, VARYING DURATION OF THERAPY (SEE INDIVIDUAL TRIAL SUMMARY TABLES)

(SEE NOTES AT END OF TABLE)

Study Number Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
Acute 1) 1999 Scirex 1032-001 720-04378.pdf 720-04378_Correction_Memo.pdf	**Scirex Corporation, Austin, Texas**	**Postoperative Dental Pain**	**Study Size:** Parallel design to evaluate Gabapentin vs. or in combination with Naproxen. 563 screened, 483 randomized to one of the following combinations: 1. Placebo: n=52 2. Gabapentin 250 mg: n = 50 3. Gabapentin 125 mg and Naproxen Sodium 125 mg: n = 50 4. Gabapentin 250 mg and Naproxen Sodium 125 mg: n = 52 5. Gabapentin 125 mg and Naproxen Sodium 250 mg n=50 6. Gabapentin 250 mg and Naproxen Sodium 250 mg. n = 50 7. Naproxen Sodium 125 mg – n=50 8. Naproxen Sodium 250 mg- n=50 9. Naproxen Sodium 550 mg – n=79 **Treatment Duration**: **patients received 1 dose of study medication** **Dose:** See above.	No	Combination product, "CI-1032" (gabapentin + naproxen combination) for nociceptive pain††	**Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry.** **Reviewed July 30, 2008.**

<table>
<tr><th>Study Number
Document Number</th><th>Lead Investigator
Publication Name</th><th>Indication</th><th>Details</th><th>Results Submitted to the FDA</th><th>Comment</th><th>Study Detail Summary Completed</th></tr>
<tr>
<td>Acute 2) 1999-2000 Moskowitz, Sunshine, Schnitzer et al

1032-002
720-04479.pdf</td>
<td>Moskowitz, Sunshine, Schnitzer et al</td>
<td>Acute Osteoarthritis Pain of the Knee</td>
<td>Study Size: 441 patients were screened 262 patients were randomized to receive:
<table>
<tr><th>Phase 1 (Day 1)</th><th>Phase 2 (Day 2–28)</th><th>N randomized to this group</th></tr>
<tr><td>Placebo</td><td>Placebo BID</td><td>53</td></tr>
<tr><td>G – 125 mg
NS – 250 mg</td><td>G – 125 mg
NS – 250 mg
BID</td><td>52</td></tr>
<tr><td>G – 125 mg</td><td>G – 125 mg
NS – 250 mg
BID</td><td>51</td></tr>
<tr><td>NS – 250 mg</td><td>G – 125 mg
NS – 250 mg
BID</td><td>54</td></tr>
<tr><td>NS – 550 mg</td><td>NS – 550 mg
BID</td><td>52</td></tr>
</table>
Treatment Duration: 4 weeks
Dose: See above.</td>
<td>No</td>
<td>Combination product; “CI-1032” (gabapentin + naproxen combination) for nociceptive pain††</td>
<td>Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry.
Reviewed July 30, 2008.</td>
</tr>
<tr>
<td>Acute 3) 2000 Moskowitz, Sunshine, Schnitzer et al
1032-003
720-30044_(Official).pdf

OPEN LABEL CONTINUATION STUDY</td>
<td>Moskowitz, Sunshine, Schnitzer et al</td>
<td>Osteoarthritis of knee</td>
<td>Study Size: N = 212 for this open label study continuing from above (002).
• 169 continued from 002 study,
• 43 screen fails from 002/completed 002 addendum A/de novo patients.
Treatment Duration: No minimum time.
Dose: Either (Gabapentin 125 mg in combination with Naproxen Sodium 250 mg) BID or (Gabapentin 250 mg in combination with Naproxen Sodium 500 mg) BID.</td>
<td>No</td>
<td>Combination product; “CI-1032” (gabapentin + naproxen combination) for nociceptive pain††</td>
<td>Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry.
Reviewed July 30, 2008.</td>
</tr>
<tr>
<td>Acute 4) Scirex Corporation 1035-001 Addendum B, RR 720-04455
720-04455.pdf
720-04483_(Official).pdf

NB: Official study report uses different numbers from original study report.</td>
<td>Scirex Corporation, Austin, Texas</td>
<td>Postoperative Dental Pain</td>
<td>Study Size: 375 patients screened, 325 patients randomly assigned to
1. Placebo: n=51
2. Gabapentin 250 mg/hydrocodone 10mg: n=75
3. Gabapentin 250 mg: n=77
4. Hydrocodone 10 mg: n=76
5. Acetaminophen 1000 mg/hydrocodone 10 mg: n=46
Treatment Duration: Single dose
Dose: See above.</td>
<td>No</td>
<td>Combination product; “CI-1035” (gabapentin + hydrocodone) for nociceptive pain††

? different numbers in original and official study reports?</td>
<td>Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry.
Reviewed July 30, 2008.</td>
</tr>
</table>

Study Number Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
Acute 4b) Scirex Corporation 1035-001 Addendum B, RR 720-04483 720-04455.pdf 720-04483_(Official).pdf NB: Official study report uses different numbers from original study report.	**Scirex Corporation, Austin, Texas**	**Postoperative Dental Pain**	**Study Size:** 140 patients screened, 101 patients randomly assigned to 6. Placebo: n=20 7. Gabapentin 250/hydrocodone 5mg: n = 20 patients. 8. Gabapentin 125 mg/hydrocodone 10 mg: n = 20 9. Gabapentin 500 mg/hydrocodone 10 mg: n = 20 10. Gabapentin 500 mg: n= 21 **Treatment Duration:** Single dose **Dose:** See above.	No	Combination product; "CI-1035" (gabapentin + hydrocodone) for nociceptive pain†† ? different numbers in original and official study reports?	**Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry. Reviewed July 30, 2008.**
Acute 5) 1999-2000 Sunshine A, Katz JA 1035-002 720-04471.pdf	**Sunshine A, Katz JA Unpublished**	**Postoperative Pain Following Major Orthopedic Surgery**	**Study Size:** patients assigned to 1 of four treatment groups 1. Placebo: n = 49 2. Gabapentin 250 mg, Hydrocodone 10 mg: n = 51 3. Gabapentin 250 mg: n = 50 4. Hydrocodone 10 mg: n = 50 **Treatment Duration:** Single Dose **Dose:** See above.	No	Combination product; "CI-1035" (gabapentin + hydrocodone) for nociceptive pain††	**Not suitable for meta-analysis – outcomes not comparable. Summary tables prepared by K. Innes, checked by Dr. T. Perry. Reviewed July 30, 2008..**
Acute 6) 2002-2003 Berry Berry JD, Peterson KL. A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. Neurology 2005; 65: 444-447	**Berry Neurology 2005**	Acute herpes zoster	**DBR crossover trial (independent, supported by investigator-initiated grant from Pfizer, no Pfizer involvement in study according to report) – gabapentin vs. placebo** **Study size:** 26 patients enrolled November 2002-December 2003 **Study duration**: single dose on two occasions separated by at least 24 hours **Dose:** 900 mg single dose		Interesting study but medians, not means are reported, and only applies to 6 hours after single dose. ††	**Not suitable for meta-analysis. Outcomes not comparable. Detailed summary table analysis completed & checked, July 27, 2008**

†† denotes studies not contained in the Cochrane Review

Indications: PDPN: painful diabetic peripheral neuropathy; PHN: post-herpetic neuralgia; NeP: 'neuropathic pain'; POPP: 'post-operative pain'; SCP: "spinal cord pain" after traumatic spinal cord injury; CIPN: cancer chemotherapy-induced peripheral neuropathy

NB: Numbering of studies is consecutive for this matrix by apparent chronology of study performance.

Notes: Acute pain trials cannot be meta-analysed with chronic pain. The above are all outpatient trials or include a significant post-operative component which is likely to be relevant to outpatient practice and/or understanding of role of gapapentin in typical outpatient-treated pain . There are various published trials (and ? unpublished, not available trials) describing use of gabapentin vs. placebo for pre-operative and post-operative use in the hospital setting, typically for up to a few hours after general anesthesia. These may be relevant to hospital care, but are not relevant to outpatient treatment of pain. Typically these studies measure total opioid consumption and/or short term pain and cannot rationally be compared with the above studies. They are also even more difficult to interpret (see McQuay, HJ, Poon KH et al. Acute pain: combination treatments and how we measure their efficacy. Br. J. Anesthesia 2008; 101: 69-76), and typically do not consider hard outcomes (mortality, SAE, length of hospital stay, etc.) relevant to the situation.

GABAPENTIN PROJECT PAIN STUDIES SUMMARY MATRIX – FINAL – AUGUST 8, 2008, THOMAS L. PERRY, M.D.

CHRONIC PAIN (AND ACUTE PAIN, #4)

TRIALS REVIEWED IN DETAIL BUT EXCLUDED FROM META-ANALYTIS BECAUSE OF POOR METHODOLOGY, QUESTIONABLE VALIDITY, OR MISCELLANEOUS REASONS (see comments) - (SEE NOTES AT END OF TABLE)

Study Number Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
Excluded 1) ? 2001 Tai Tai, Q, Kirshblum S, et al. Gabapentin in the Treatment of Neuropathic Pain after Spinal Cord Injury: A Prospective, Randomized, Double-blind, Crossover Trial. J. Spinal Cord Med 2002; 25; 100-5	**Tai** **J Spinal Cord Med 2002**	Traumatic spinal cord injury	**DBR crossover trial (independent, supported by American Academy of Physical Medicine and Rehabilitation research award and Eastern Paralyzed Veterans Association) – gabapentin vs. placebo** **Study size:** 7 patients **Study duration**: 2 x 4 weeks, 2 week washout between periods **Dose:** titration from 600-1800 mg/day		Only 7 patients crossed over. Results are not suitable for meta-analysis and are of questionable validity.	**Not suitable for meta-analysis. Summary analysis completed and reviewed July 22, 2008. Co-reviewers agree we should not include this trial in meta-analysis because it is too seriously flawed to draw any reasonable conclusions.**
Excluded 2) ? 2000 Perez (HE) No sponsorship indicated Perez HE, Sanchez GF. Gabapentin Therapy for Diabetic Neuropathic Pain (letter). American J Medicine 2000; 108: 689	**Perez HE, Sanchez GF** **Am. J. Medicine 2000**	**PDPN**	**Reported as DBRCT** (apparently independent, no description) **Study size:** 32 patients; P=15, G=17, parallel design **Treatment Duration**: 3 months (reported as 1 month) **Dose:** titrated to pain relief or 1200 mg/day	?	< 1 page letter to the editor, unreliable study. Although this was accepted for meta-analysis by Wiffen et al (2005), we do not feel this is a credible trial, given reporting at 1 month and absence of any detailed methodology including description of randomization/blinding.	**Not suitable for meta-analysis. Detailed summary table analysis completed and reviewed, July 22, 2008. Co-reviewers agree we should not include this trial in meta-analysis because we cannot be certain that methodology and results are reliable.**

Study Number Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
Excluded 3) ? performed at all (? 2000 or earlier) Simpson Simpson DA. Gabapentin and Venlafaxine for the treatment of painful diabetic neuropathy. J. Clin Neuromuscular Dis 2001; 3: 53-62	**Simpson** **J. Clin Neuromuscular Dis 2001**	**PHN**	**See original publication**	See original publication and Pfizer e-correspondene with Dr. R. Dworkind, Rochester, N.Y.	This study may never have existed. Dr. Dworkind had serious concerns that the trial could not have been performed as reported.	**Not suitable for meta-analysis. We cannot confirm that this is a genuine study. No detailed study summary prepared – see Pfizer emails with Prof. R. Dworkin.**
Excluded 4) 1032-004 720-04481.pdf	**Unpublished**	**Gastroprotection**	**Study Size: Sub-study of 002**. After 1-week of treatment, patients underwent endoscopy to see whether or not Gabapentin protected against Naproxen damage. **Treatment Duration:** 1 week. **Dose:** See data from 002.	No	Combination product; "CI-1032" (gabapentin + naproxen combination) for nociceptive pain††	**Not suitable for meta-analysis – sub study irrelevant to analgesic effect of gabapentin. No detailed study summary necessary.**
Excluded 5) ? 1999 (or earlier) McCleane McCleane GJ. Gabapentin reduces chronic benign nociceptive pain : a double-blind, placebo-controlled cross-over study. The Pain Clinic 2000; 12: 81-5	**McCleane** **The Pain Clinic 2000**	**Mid-line lumbar back pain with local tenderness**	**DBR crossover trial of gabapentin vs. placebo (appears independent from 1 Northern Ireland hospital clinic, no discussion of sponsorship, trial design)** **Study size:** screened ?, randomized 30 (no further description of numbers Randomized to P/G vs. G/P, 24 apparently completed **Study duration**: 6 week treatments interrupted by 1 week washout **Dose:** G titrated to ≤ 15 mg/kg (maximum 1800 mg/d)		Reporting is too incomplete to trace patients and thus data cannot be used. ††	**Not suitable for meta-analysis. Insufficiently reported to use data. No detailed summary table prepared due to lack of time, July 28, 2008.**
Excluded 6) ? 2001 Spira Spira PJ, Beran RG et al. Gabapentin in the prophylaxis of chronic daily headache. A randomized, placebo-controlled study. Neurology 2003; 61: 1753-9	**Spira** **Neurology 2003**	**Chronic daily headache prophylaxis**	**DBR crossover trial of gabapentin vs. placebo from 12 headache clinics in Australia (Parke-Davis support for investigator-initiated study)** **Study size:** screened ?, randomized 133 (P/G=65, G/P=68 in first phase; after washout patients continuing = P/G=52, G/P=56 for second phase **Study duration:** 8 weeks per phase, as 2 weeks dose titration and 6 weeks stable dose, with 1 week intervening washout **Dose:** titration to target dose of G=2400 mg/d		Study of gabapentin for prophylaxis; outcomes differ from other studies (e.g. headache-free days) and are not meta-analysable. There are many dropouts complicating analysis. WDAE and AE are similar to other studies.††	**Not suitable for meta-analysis. No detailed summary table prepared due to lack of time, July 28, 2008.**

†† denotes studies not contained in the Cochrane Review

Indications: PDPN: painful diabetic peripheral neuropathy; PHN: post-herpetic neuralgia; NeP: 'neuropathic pain'; POPP: 'post-operative pain'; SCP: "spinal cord pain" after traumatic spinal cord injury; CIPN: cancer chemotherapy-induced peripheral neuropathy

NB: Numbering of studies is consecutive for this matrix by apparent chronology of study performance.

ADDITIONAL ARTICLES REVIEWED BUT NOT SUITABLE FOR META-ANALYSIS

Study Number Document Number	**Lead Investigator** Publication Name	**Indication**	**Details**	**Results Submitted to the FDA**	**Comment**	**Study Detail Summary Completed**
	Backonja & Glanzman PFIZER_LESLIETIVE_00038508	--	A review of previously published studies – refers to Reckless as unpublished but implies it would be published soon, gives hint of results.		Backonja, Glanzman Clinical Therapeutics Dosing Article	**We have used the complete reports, including unpublished Reckless report 945-224**
	Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain (Review). The Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD005452. DOI: 10.1002/14651858.CD005482 Gabapentin for acute and chronic pain.pdf	--	The Cochrane report.		Cochrane Review	**To be discussed in Dr. Perry's clinical pharmacologic opinion report.**

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT Study detail summaries

Contents:

- **Chronic pain studies Numbers 1-25 – (suitable for meta-analysis)**
- **Acute pain studies Numbers 1-6 – (not suitable for meta-analysis with chronic pain)**
- **Excluded studies Numbers 1-2 - (not suitable for meta-analysis, or low quality, or of questionable validity)**

completed on various dates, 2008
Dr. Thomas L. Perry

Thomas L. Perry M.D.

Thomas L. Perry, M.D., FRCPC

Study No. 1 - Gorson 1997 - Study Detail Summary and Analysis – Final, July 27, 2008

There are four separate reports analyzed within this document:

1. the initial report sent to Phil Magistro at Parke-Davis Pharmaceuticals by Kenneth Gorson, M.D., on August 23rd, 1997 (hereinafter referred to as the August '97 report)
2. an updated / altered version of the initial report distributed as a Parke Davis memorandum dated January 7th, 1998 (hereinafter referred to as the January '98 report)
3. an abstract which was published in the April 1998 issue of *Neurology (*Volume 50, supplement 4, hereinafter referred to as the abstract)
4. a letter to the editor from Gorson et. Al published in February 1999 in *The Journal of Neurology, Neurosurgery, and Psychiatry* (Volume 66, number 2, hereinafter referred to as the letter to the editor).

Both the August 1997 and January 1998 reports clearly state that 53 patients were randomized; however, the later reports state that 19 patients were randomized to the active drug and 21 to placebo during first treatment period for a total of 40 patients. Furthermore, both the abstract and the letter to the editor use the number 40, not 53, when referring to the number of patients in this study and neither make any reference to the thirteen patients who withdrew at various intervals in the study. These thirteen withdrawals do not seem to have been included in any analyses. The patient flow diagram has been obscured in the PDF version (contents of boxes not viewable) and it is difficult to assemble much information with regard to time point and reason for withdrawal. This is problematic as it indicates that no ITT analysis was performed and also two patients dropped out in phase II meaning that they completed 6 weeks on either placebo or Gabapentin (impossible to tell which), and their results have not been incorporated into the data. The Cochrane 2005 review did not have access to the true ITT numbers.

In general patient flow for this trial is unclear. This is, in part, due to the fact that Table 1, reporting the flow of participants contained in the January 1998 report, is obscured. However, what can be seen of this table does not appear to be in the correct format for a crossover trial. We are told that 126 patients were screened, 53 were randomized and 13 dropped out, while 40 completed the trial. It is also reported that 11 patients withdrew in phase I, and two more in phase II; eight patients withdrew due to adverse effects, four while taking Gabapentin and four while taking placebo. However, it is impossible to discern when which patients withdrew. For example, it is not stated whether the patients who withdrew while receiving placebo withdrew in phase I before having received active drug, or in phase II after having taken Gabapentin.

The reporting of adverse effects as is also unclear. For example, the letter to the editor states that 12 in the Gabapentin group and one in the placebo group suffered adverse effects. The earlier reports (August 1997 and January 1998) state that 16 in the Gabapentin group and 5 in the placebo group suffered adverse effects. These earlier reports also state that, as previously mentioned, eight patients withdrew due to adverse effects, but do not say when, or which adverse effects were suffered, by whom. It can be inferred that whatever the effects, they are not properly detailed in the earlier reports as the letter to the editor makes no mention of the eight who withdrew but gives the same numbers as the earlier reports for those who suffered drowsiness (6), fatigue (4) and imbalance (3). Furthermore, different tests were used to assess the incidence of adverse effects with Gabapentin and placebo. The earlier reports used Fisher's exact test, while the letter to the editor references McNemar's test. The reason for this is not clear.

The August 1997 report, states in Statistical Analysis on page 6 "*Because of multiple comparisons, we used the Bonferroni correction and a p-value of < 0.01 was considered statistically significant".* The Statistical Analysis section of the January 1998 report, and for that matter the letter to the editor and the abstract, make no mention of the use of the Bonferroni correction or any other method which can be used to correct for multiple dependant comparisons. Although some might argue that Bonferroni's rule is too conservative, there are clearly multiple, dependant comparisons being performed in this trial (i.e. multiple pain scales analyzed), and therefore, the corresponding p-values should be corrected by some method to account for this. It would also be useful to obtain the initial statistical analysis plan to determine whether or not it was the pre-set plan to use a Bonferroni correction; it would seem safe to assume that it was. The failure to correct for multiple comparisons might seem like a minor detail, however, the p-value for the comparison between Gabapentin and Placebo for the difference in the reduction of the McGill Pain Questionnaire Score (MPQ) was 0.03. With the Bonferronni correction, this p-value is insignificant and the study fails to demonstrate the efficacy of Gabapentin with all three of the pain scales employed (PPI, MPQ, and VAS). However, without correcting for multiple comparisons, the p-value appears significant as it is less than 0.05. It is possible that the sentence in Dr. Gorson's initial August 1997 study report, referring to the Bonferroni correction, was removed in order to demonstrate Gabapentin effectiveness on the MPQ scale. This assumption is supported by the observation that most of the conclusions made in subsequent reports which support the effectiveness of Gabapentin are based on how MPQ decreased "significantly" more for those in the Gabapentin group.

The study protocol, signed by Kenneth Gorson, states that "*Subjects will be assessed every 3 weeks for efficacy, safety, and compliance.*" However, the January 1998 report reads "*Patients were contacted every week by phone to insure adequate dose titration and to assess compliance and adverse effects. Compliance was monitored by pill counting at the end of each treatment period.*" The Aug 1997 report is similar to the Jan 1998 report; therefore, there is a clear discrepancy between what was planned and what took place. Additionally, no definition of what, for this study, constituted compliance versus non-compliance; the details and data surrounding compliance are not reported anywhere in the reports except to say that five people withdrew due to non-compliance or personal/other reasons.

Narcotics, specifically codeine, were permitted throughout this trial. Specifically ten patients continued to use them throughout. It would seem that no calculations were done to account for the possibility of interaction (either additive or synergistic) between the Gabapentin and the narcotics. This is worrisome as according to an article published by Gilron et. al. in 2005 in the New England Journal of Medicine, Gabapentin may be more effective when combined with morphine and therefore it is possible that narcotic use throughout this trial may have increased the apparent effectiveness of Gabapentin.

The protocol implies that pain intensity measured on a Visual Analogue Scale (VAS pain intensity) is the primary variable. Furthermore, the protocol stated that a VAS of pain intensity and a VAS of pain relief would be recorded daily by subjects in a diary and a weekly mean score for each VAS would be calculated for each week of the treatment period. The August 1997 report states that "*At the beginning and end of each treatment period, patients rated their typical level of pain over the preceding week on a 10 cm visual analog pain scale (VAS) ...A composite VAS score was determined by averaging the daily VAS scores in the first and last week of each treatment period."* The January 1998 report states *"At the beginning and end of each treatment period, patients rated their level of pain over the preceding 24 hours on a 10 cm visual analog pain scale (VAS)"* This report makes no mention of how the composite score was calculated. Therefore, not only are the August 1997 and the January 1998 reports themselves different, but neither make any mention of a VAS pain relief score or about calculating VAS each week.

Crossover designs often have greater power than parallel group designs with more patients so long as withdrawal rates are not too high, the underlying disease is not rapidly changing, and the washout period is adequate. The dropout rate in this study does not seem unreasonably high, in comparison with other crossover trials. PDPN is not rapidly changing and other crossover designs have been employed in clinical trials involving PDPN. Therefore, the main issue to be addressed is whether or not the washout was adequate. The January 1998 report, the August 1997 report, and the letter to the editor all state that the MPQ and VAS scores did not return to baseline after the washout period for those who received the active drug in phase I. The January 1998 report uses this supposed inadequate washout as evidence that a parallel study might have detected more benefit in Gabapentin group (see page 8, discussion). However, the baseline MPQ fell from 36.0 (SD = 16.8) to 33.1 (SD = 13.9). The baseline VAS scores fell from 6.5 (SD = 2.4) to 6.3 (SD = 2.2). No standard deviation for the differences is given so a paired T-test is not possible without more information; however, since it is not stated that the difference from baseline was statistically significant it seems safe to assume that it most likely wasn't, inspection of the results don't indicate a large difference. Furthermore, given the short half-life of Gabapentin and the small difference between the baseline values it is safe to assume that the washout was indeed adequate. Therefore, a crossover design was probably sufficient to detect benefit; especially given the power of the study was predetermined to be 80% (using VAS pain intensity) so long as 40 people completed the study, which they did. Consequently there was a low probability of not detecting a benefit when one is present. Additionally, several crossover studies involving Gabapentin have employed washout periods of three weeks or less (Gilron, Nordic Study) and did not site inadequate washouts.

According to page 7 of the January 1997 report, there was a treatment order effect for the Present Pain Intensity Score (PPI). It is not stated what this effect was or whether or not it was statistically significant but that fact that it's statistical significance is not included would seem to point to insignificance. If in fact there was a failure to return to baseline for the MPQ / VAS scores for those given the active drug in phase 1, and there was a significant order effect for PPI, it could be due to the fact that an inactive placebo was used which lead to unblinding. According to all the reports, a significantly higher proportion of patients suffered adverse effects on Gabapentin than on the placebo. Although the reports were unclear as to the adverse effects suffered by those on placebo, it would seem that those not in common with placebo included drowsiness, fatigue, and imbalance. Therefore, it is probable that certain patients, as well as their assessing physicians, were able to determine in which phase they were on the active drug which could easily have affected baseline scores and order effects.

One final point, the table included in the letter to the editor is analogous to Table 3 in the August 1997 report (Table 4 in the January 1998 report). However the "standard deviations" listed in the letter to the editor do not match those in the earlier reports and have in fact, been divided by square root of 40, the sample size after withdrawals. Therefore, the values in this table, although falsely labelled, are the standard error of their corresponding estimates. It should be noted that it is preferable and conventional to report a mean with it's standard deviation, not it's standard error.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Kelsey Innes
Study No. 1 Kenneth C. Gorson, M.D. PDPN Study Design: Prospective, randomized, double-blind, two-period, crossover trial. Study Duration: 6 weeks Gabapentin/placebo, 3 week washout period, and 6 weeks placebo/Gabapentin WLC_FRANKLIN_0000100272 WLC_FRANKLIN_0000100273 WLC_FRANKLIN_0000088375 Protocol approved by the Institutional Review Board at St. Elizabeth's Medical Center. Parke-Davis CBU Phase IV Protocol signed January 15th 1996 by Gorson and February 2, 1996 by Magistro. The document was also signed by Ropper but no date is given.	Painful diabetic neuropathy. <u>Inclusion Criteria:</u> • Age between 18 and 85 • Diabetes for at least 6 months on a stable dosage of insulin or oral hypoglycemic agent • A distal symmetrical sensorimotor neuropathy as demonstrated by impaired pin prick, temperature, or vibration sensation in both feet or absent or reduced ankle reflexes. • All patients had daily pain in the acral extremities of at least moderate severity for greater than three months that interfered with daily activity or sleep and could be attributed to the neuropathy <u>Exclusion Criteria:</u> • Presence of another painful condition	<u>Study Design:</u> Phase I (6 weeks): Patients randomly assigned to Gabapentin (300 mg capsules initially) Or Placebo Washout (3 weeks): Phase I followed by 3-week washout period. Phase II (6 weeks): Crossover. The dose of Gabapentin or placebo was increased by one capsule every three days to a stable dosage of one capsule, three times daily (900 mg/day) which was maintained through the remainder of the treatment period	<u>Predefined Outcomes:</u> Predefined outcomes were 1. MPQ 2. VAS Pain Intensity 3. PPI scores 4. Global assessment of pain relief (none, mild, moderate, or excellent or 0 = no pain relief, 1 = slight improvement, 2 = moderate improvement, 3 = complete pain relief, depending on the protocol or the report) None of the reports explicitly state which was the primary outcome. The reports, seem to focus on MPQ as this score changed the most significantly with Gabapentin treatment. The protocol seems to imply that VAS is the primary outcome as the sample size required was determined with VRS and VAS in mind (page 8 of protocol). NB: The 10 point (1-10) Visual Analog Scale (VAS) is the closest equivalent to the 11-point (0-10,	<u>1. Mortality</u> Although none of the reports specifically mention mortality, the reports state that there were no serious adverse effects (p. 7 of '98 report, p. 8 or '97 report, ¶ 5 of letter to editor) P = 0/53, G = 0/53 <u>2. Serious Adverse Events</u> See above P = 0/53, G = 0/53 <u>3. Withdrawals Due to Adverse Events:</u> G = 4/53, P = 4/53 Denominators not apparent, as no version of report shows how many patients were randomized to P or G in "phase 1" vs. "phase 2" of crossover.	1. This study reports NO DIFFERENCE in the pre-defined primary endpoint (change from baseline to study endpoint in VAS 10-point pain scale): P=1.4 (0.3), G=1.8 (1.4), difference = -0.4 (0.6) favouring G; p=0.42. It does not account adequately for early dropouts and it is NOT an ITT nor even an ITT-LOCF study. The AE clearly suggest unblinding of the Gabapentin groups, but are incompletely reported such that the figures reported are at least somewhat unreliable. TLP thinks that it is reasonable to use the following in meta-analysis, on conservative grounds that a negative study should not be excluded from meta-analysis where it can still contribute some useful data: • WDAE can be reported as 4/53 and 4/53 for want of denominator for each group; • AE total can be included by using the denominator 40, as Gabapentin AE would otherwise be significantly larger if remaining 13 patients had completed; • Specific AE similar to AE reported in other studies can be included by using denominator 40, as above; • VAS pain score mean difference from baseline to "endpoint" and between-group difference may be reported using

The specific time frame of the study (i.e., date of first patient randomized, date that last patient took study medication) are unclear; however, the protocol states that 40 subjects will be randomized to either placebo or treatment groups. As is stated by both the Jan '98 and the Aug '97 reports, 53 patients were initially randomized, which makes one wonder whether or not this protocol was approved after the completion of the study or if this 40 is given as it is the sample size required to achieve 80% power.

Date of Study: ?
Study completed by Spring 1997.
Blind broken: ?

Initial report sent to Phil Magistro at Parke-Davis Pharmaceuticals August 23rd, 1997.

Updated / altered report sent as Parke Davis memorandum January 7th,

- Cognitive or language impairment that precluded accurate assessment
- A history of alcohol or substance abuse, depression, or other cause for painful polyneuropathy

*Note that the protocol, pages 4-5, is much more specific with regard to the inclusion and exclusion criteria

Patients taking tricyclic antidepressants, anticonvulsants, capsaicin cream, benzodiazepines, and mexiletine discontinued these medications three weeks before study entry.

NSAIDS and narcotics (see protocol page 5 for specific list) were allowed but the dosage was kept unchanged during the treatment periods.

Baseline Characteristics*:
*values according to Table 4 of Jan '98 report. Table 2 of August '97 report was to contain baseline characteristics but is absent. The other two articles do not list baseline characteristics, only mean change in pain scores.

Flow of Participants:
The table to contain the flow of participants (table 1 in Jan '98 report) is obscured.
126 patients screened.
53 fulfilled entry criteria and were randomized.
13 dropped out

- 11 in phase I, 2 in phase II
- 8 WDAE (4 P, 4 G)
- 5 withdrew due to personal reasons/non-compliance (note original report lists personal reasons as a reason for dropout, in Jan '98 *personal reasons* changed to *other reasons*)

Other info regarding dropouts? How come not included in statistical analysis? No intention to treat analysis → bias.

According to the Aug '97, the Jan '98 reports and the letter to the editor, 19 patients were randomized to active drug and 21 to placebo in phase 1. The letter to the editor published in Neurology makes no mention of the 13 patients who dropped

Likert) Numerical Rating Scale (NRS) used in most Gabapentin (DBRCT). Since it is slightly compressed, (10 vs. 11 points) a 1 point difference should theoretically be acceptable as roughly equivalent to a 1-point difference on the NRS.

MPQ:

Gabapentin Group
Baseline: 36.0 (SD = 16.8)
Week Six: 27.1 (SD = 15.5)
P-value < 0.005.

Placebo Group
Baseline: 33.1 (SD = 13.9)
Week Six: 31.0 (15.3)
P-value: 0.33

Change in MPQ:
Gabapentin: 8.9 (SD = 14.5)
Placebo: 2.2 (SD = 13.8)*
p-value: 0.03
*the mean change for this scale does not reflect differences between baseline and week 6 from table 2 due to statistical corrections for order and washout effects

Notes

According to the letter to the editor, MPQ were recorded at the initial and final visits of each treatment period. This is also implied in both the Aug

According to p. 6 of the Aug '97 report "one hundred and twenty six patients were screened and 53 fulfilled the entry criteria and were randomized…8 patients withdrew due to adverse effects (four on placebo, four on active drug) and five due to non-compliance or personal reasons." P. 4 of the Jan '98 report is similar but states that "…five due to non-compliance or other reasons". Why the change? Also, one wonders what these personal reasons were.

The JNNP article makes no mention of the 13 who withdrew and states only "we recruited 40 patients".

The abstract also makes no mention of the 13 who withdrew.

4. Total Withdrawals:

There were 13 total withdrawals:

- 8 WDAE (4 while on placebo, 4 while on Gabapentin)
- 5 withdrew due to person reasons or non-compliance but none of the reports specify in which group each of these 5 dropped out.

5. Total Adverse Events:

denominator 40, because it is impossible to know any other denominators from this report.

2. Both the Aug '97 and Jan '98 reports clearly state that 53 patients were randomized. Further on the reports, however, it is stated that 19 patients were randomized to the active drug and 21 to placebo during first treatment period. And, the abstract / letter to the editor say 40, never 53. The thirteen who withdrew do not seem to be included in any analyses, especially since two dropped out in phase II meaning that at least two completed 6 weeks on either placebo or Gabapentin (although it does not state which). It is impossible to discern who withdrew, when, and why. This information should have been provided
3. Narcotics were allowed throughout this trial (10 patients continued to use throughout the trial) and no apparent calculations to account for the possible interaction between narcotics and Gabapentin. According to NEJM study by Gilron, Gabapentin + Morphine more effective than Gabapentin or Morphine alone, therefore, use of narcotics (codeine) could have potentially increased Gabapentin's apparent effectiveness.
4. The conclusion in the abstract of the Aug '97 report states "Gabapentin, at a dose of 900 mg/day, is probably no more effective than placebo in the treatment of painful diabetic neuropathy". The conclusion in the abstract of the Jan '98 report states "Gabapentin may be effective in the treatment of painful diabetic

1998. Published as: Abstract published in *Neurology*, April 1998 (Volume 50(4) Supplement 4) Gorson KG, Schott C et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. (letter). J Neurol Neurosurg Psychiatry 1999; 66: 251-2	MPQ (McGill Pain Questionnaire): P: 33.1 (SD=13.9) G: 36.0 (SD=16.8) VAS (Visual Analog Scale): P: 6.3 (SD=2.2) G: 6.5 (SD=2.4) PPI (Present Pain Intensity): P: 4.1 (SD=3.0) G: 4.6 (SD=2.8) Notes What are the different numbers for each group (i.e., it says 53 were randomized, 13 dropped out, 11 in phase I, 2 in phase II, and 8 WDAE and 5 due to non-compliance or personal reasons)? The report also states that 19 were randomized to active drug while 21 to placebo in phase one, what about the other 13? With regard to baseline characteristics, The protocol states that "*The subjects will also provide a verbal rating scale of global assessment of pain at baseline and every 2 weeks during the*	out whatsoever.	'97 and Jan '98 reports. MPQ data collection is not detailed in the protocol. Note: for those who received active drug in Phase 1 MPQ score did not return to baseline after washout. This fact is mentioned twice in the Jan '98 report, no note as to whether or not this failure to return to baseline was statistically significant which leads me to believe it may not have been. The p-value of 0.03 for the change in mean change in MPQ appears significant at first, however, with the Bonferroni correction used to analyse the statistics, as mentioned in the Aug '97 report, it is in fact not significant, as the Jan '98 report, which makes no mention of this correction, would have you believe. <u>VAS</u> Gabapentin Group Baseline: 6.5 (SD = 2.4) Week Six: 4.7 (SD = 2.8) P-value: 0.001. Placebo Group Baseline: 6.3 (SD = 2.2) Week Six: 5.0 (2.5) P-value < 0.005	Comment: Because we cannot trace the 13/53 patients who are not reported on, we cannot adequately assess the total number of Adverse events for the whole trial. Total Patients with Adverse Events: According to Aug '97/Jan '98 report (p. 7) G = 16, P = 5, p-value = 0.01 with Fisher's exact test According to letter to the editor G = 12, P = 1, p-value < 0.001 with McNemar's test. Therefore, assume that G = 16/53, P = 5/53 (including the 13 withdrawals) or G = 12 / 40, P = 1 / 40 (not including the non-completers / the 13 who withdrew) Both McNemar's test and Fisher's test seem appropriate, however, it seems odd that they have been switched, should have used one or the other. <u>Because we cannot trace the 13/53 patients who are not reported on, we cannot adequately assess total patients with AE for the whole trial. If we use the following in meta-</u>	neuropathy. Our results suggest that further studies evaluating higher dosages of Gabapentin are warranted." 5. The protocol states that "*Subjects will be assessed every 3 weeks for efficacy, safety, and compliance.*" However, the Jan '98 report reads "*Patients were contacted every week by phone to insure adequate dose titration and to assess compliance and adverse effects. Compliance was monitored by pill counting at the end of each treatment period.*" The Aug 97's report is similar to the Jan '98 report. Discrepancy. Also, compliance is not reported anywhere in the reports except to say that 5 people withdrew due to non-compliance or personal/other reasons. No definition of what would have constituted non-compliance is given. 6. With regard to baseline VAS: the protocol stated that a VAS of pain intensity and a VAS of pain relief would be recorded daily by subjects in a diary and a weekly mean score for each VAS would be calculated for each week of the treatment period. The Aug '97 report states that "*At the beginning and end of each treatment period, patients rated their typical level of pain over the preceding week on a 10 cm visual analog pain scale (VAS) ...A composite VAS score was determined by averaging the daily VAS scores in the first and last week of each treatment period."* The Jan '98 report states *"At the beginning and end of each treatment period, patients rated their level of pain over the preceding 24 hours on a*

	treatment period as follows: 0 = no pain relief, 1 = slight improvement…etc" The Aug '97 report states that *"at the end of each treatment period patients provided a global assessment of pain relief: none, mild, moderate, or excellent, as compared to the baseline level of pain preceding the trial"*. The updated/altered report states *"At the end of each treatment period patients provided a global assessment of pain relief: none, mild, moderate, or excellent, as compared to the level of pain preceding each pain period."* Which is it?? It would seem that the actual study deviated from the protocol here. With regard to baseline VAS: Page 5 of the protocol stated that a VAS of pain intensity and a VAS of pain relief would be recorded daily by subjects in a diary and a weekly mean score for each VAS would be calculated for each week of the treatment period. The Aug '97 report states that "*At the beginning and end of*		Change in VAS: Gabapentin: 1.8 (SD = 3.1) Placebo: 1.4 (SD = 2.1) P-value = 0.42 Notes There are discrepancies between the protocol and reports of the study with regard to VAS data collection and analysis. See notes in Inclusion Criteria / Baseline Characteristics column Note: for those who received active drug in Phase 1 VAS score did not return to baseline after washout. This fact is mentioned twice in the Jan '98 report, no note as to whether or not this failure to return to baseline was statistically significant which leads me to believe it may not have been. As stated in both the Aug '97 and the Jan '98 reports, the significant improvement in the mean VAS with placebo underscores the importance of the placebo response in treating painful diabetic neuropathy. PPI Gabapentin Group	analysis, I suggest the only appropriate denominator is 40, but this will omit the WDAE patients from the total AE. Specific AE's: Note that here the denominator is unknown, presumable 40; number of patients for placebo, for drowsiness, fatigue, and imbalance inferred as 0 as they are not mentioned in contrast with reporting for other specific AE: Drowsiness: G = 6* Fatigue: G = 4 Imbalance: G = 3 The numbers for drowsiness, fatigue and imbalance are the same in the letter to the editor and in the Aug '97, Jan'98, therefore, assume, but cannot say for sure that they are 6/40, 4/40, 3/40 respectively. Since these effects are detailed in the letter to the editor, which makes no mention of the 13 subjects who withdrew, one can only assume these do not include the patients who	*10 cm visual analog pain scale (VAS)"* This report makes no mention of how the composite score was calculated. Neither the Aug '97 nor the Jan '98 reports say anything about a VAS pain relief score or about calculating VAS each week. 7. The protocol states that "*The subjects will also provide a verbal rating scale of global assessment of pain at baseline and every 2 weeks during the treatment period as follows: 0 = no pain relief, 1 = slight improvement…etc"*. The Aug '97 report states "*At the end of each treatment period patients provided a global assessment of pain relief: none, mild, moderate, or excellent, as compared to the baseline level of pain preceding the trial".* The Jan '98 report states "*At the end of each treatment period patients provided a global assessment of pain relief: none, mild, moderate, or excellent, as compared to the level of pain preceding each treatment period".* Which is it? 8. Also with regard to the Global Assessment of Pain Relief, patients rated their improvement as none, mild, moderate, or excellent. None and mild were then grouped as were moderate / excellent. What was the reason for this? Was this the plan always? 9. On page 6 of the Aug '97 report, a phrase in Statistical Analysis section reads "*The p-values presented are two-sided. Because of multiple comparisons, we used the Bonferroni correction and a p-value of < 0.01 was considered statistically significant".* The

	each treatment period, patients rated their typical level of pain over the preceding week on a 10 cm visual analog pain scale (VAS) ...A composite VAS score was determined by averaging the daily VAS scores in the first and last week of each treatment period." The Jan '98 report states *"At the beginning and end of each treatment period, patients rated their level of pain over the preceding 24 hours on a 10 cm visual analog pain scale (VAS)"* This report makes no mention of how the composite score was calculated. Neither the Aug '97 nor the Jan '98 reports say anything about a VAS pain relief score or about calculating VAS each week. Again the reports differ from the protocol. Even though MPQ is heavily focussed on in the study reports, the Protocol makes no mention of the MPQ unless this is part B. of the Data acquisition on page 6.		Baseline: 4.6 (SD = 2.8) Week Six: 3.4 (SD = 3.2) P-value: 0.008 Placebo Group Baseline: 4.1 (SD = 3.0) Week Six: 3.8 (SD = 2.9) P-value: 0.62 Change in PPI Gabapentin: 1.2 (SD = 2.7) Placebo: 0.3 (SD = 3.1)* P-value: 0.2 *see above starred notes. According to the Aug '97 and Jan '98 reports, the standard deviations for the change in MPQ/VAS/PPI are as above. The letter to the editor has divided all of these SDs by √(40) to yield the standard error of the estimates for mean change, this is why there is the discrepancy. <u>Global Assessment of Pain Relief:</u> None / Mild Pain Relief: Gabapentin 23, Placebo 31 Moderate / Excellent Pain Relief: Gabapentin 17, Placebo 9 The p-value for above table is 0.11 (using McNemar's test).	withdrew. Diarrhea, tremulousness, ankle swelling, and cramps G = 2, P = 2 (Assume this is what is meant by "…were reported by two patients each" – p. 7) Dizziness, slurred speech, nausea, and impaired memory. G = 1, P = 1 (Assume this is what is meant by "One patient each reported…" None of the reports specify the adverse effects suffered by the 8 who withdrew due to adverse effects. None of the reports clearly detail the adverse effects suffered by those on placebo. According to the Aug '97 / Jan ' 98 reports, 5 on placebo suffered adverse effects but can account for a max of three (two with diarrhea etc, and one with dizziness etc,). The above makes it very likely that many patients taking Gabapentin were unblinded. <u>6. Validated measures of improvement in global function</u>	Statistical Analysis section of the Jan'98 report makes no mention of two-sided p-values or the use of the Bonferroni correction. As multiple, dependant comparisons are being performed, the p-value should be corrected to some degree, some say Bonferroni's rule is too conservative but still. In my opinion, the Bonferroni correction was removed as, without it, the p-value for the difference in MPQ score reduction between placebo and Gabapentin groups (P = 0.03) becomes significant, a fact upon which most of the conclusions which support the effectiveness of Gabapentin is based in this report. With the correction, this p-value is insignificant. 10. The reporting of adverse effects is very unclear. For example, the letter to the editor states that 12 in the Gabapentin group and 1 in the placebo group suffered adverse effects. The earlier reports (Aug'97, Jan '98) state that 16 in the Gabapentin group and 5 in the placebo group suffered adverse effects. These earlier reports also state that 8 WDAE, but does not say when, or which adverse effects were suffered, however, it can be inferred that whatever the effects, they are not mentioned in the earlier reports as the letter to the editor makes no mention of the 8 who withdrew but gives the same numbers for those who suffered drowsiness (6), fatigue (4) and imbalance (3). Furthermore, different tests were used to assess the incidence of adverse effects with Gabapentin and placebo. The earlier reports used Fisher's exact test,

			Let G be the event "Moderate / Excellent pain relief with Gabapentin" Let P be the event "Moderate / Excellent pain relief with placebo"  Discrepancy into how patients specified global pain relief and how often. See notes in Inclusion Criteria / Baseline Characteristics column. Although the data for this indicator was not significant, one wonders about post-hoc analysis, i.e. why was none group combined with mild$ group and why was moderate grouped with excellent. This doesn't seem to have been the initial plan (initially power of study was calculated in order to have the ability to detect a 1 grade difference on the VRS from 0 – 3), and none of the numbers were given for the individual groups.	<u>including return to work, study, activities of daily living:</u> • None reported for this study. <u>7. Greater than 50% reduction in pain score (NRS, VAS) from baseline to endpoint where this was a pre-defined primary or secondary endpoint in a trial:</u> • Not a predefined outcome for this trial. <u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by true intention to treat (ITT) where this was the pre-defined primary endpoint in a trial:</u> • None of the papers explicitly what the primary endpoint was however, according to page 8 of the protocol, the sample size required for this study was calculated to detect a difference of 1 grade on the verbal rating scale (global assessment of pain relief) at 6 weeks of a mean difference of at least 2 points between treatment and placebo in the 6 week VAS score.	while the letter to the editor references McNemar's test. This seems to indicate post-hock analysis. 11. In general patient flow is unclear as Table 1 in the Jan\98 report is obscured. We know 126 patients were screened, 53 were randomized and 13 dropped out, while 40 completed the trial. • 11 dropped in phase I, 2 in phase II (page 5 of Jan '98 report / p 6 of Aug '97 report) • 8 WDAE 4 in placebo, 4 Gabapentin but we don't know when. % withdrew due to non-compliance or personal/other reasons depending on the report. • The earlier reports state later that 19 were randomized to the active drug and 21 to placebo in the first treatment period; however, this is clearly not the case since 53 were randomized. 12. Also with regard to adverse effects, the letter to the editor states that *"all adverse effects resolved promptly after discontinuation of the drug"*, does not state whether or not this was the case for the ITT population…was there any follow up there? 13. Crossover designs often have greater power than parallel group designs with more patients so long as withdrawal rates are not too high, the underlying disease is not rapidly changing, and the washout period is adequate. The dropout rate in this study seems adequately low, PDN is not rapidly changing as crossover designs are popular in assessing treatment of

				○ Since no data on VRS are reported, it was inferred that VAS was the primary endpoint. ○ Note that page 5 of the January '98 report states that the power calculations were done to detect a 20% reduction in MPQ and VAS; however, this is not what the protocol says. Assume this was placed in later as MPQ was the only variable to show any significance. • Additionally this is the closest outcome to the NRS (11-Point Likert) scale used in most other studies. <u>VAS Outcome (endpoint):</u> Placebo N: not listed, assume 40 Endpoint: 5.0 (SD = 2.5) P-value: < 0.005 Range: Not listed Mean Reduction: 1.4 (SD = 2.1, SE = 0.3) Gabapentin N = not listed, assume 40 Endpoint: 4.7 (SD = 2.8)	PDN, so that leaves the washout. The earlier studies, as well as the letter to the editor all state that the MPQ and VAS scores did not return to baseline after the washout period for those who received the active drug in phase I and the Jan '98 report uses this fact as evidence that a parallel study might have detected more benefit in Gabapentin group (see page 8). However, it is never stated how far/close to baseline the VASMPQ scores were. No numbers are given and it is never stated whether or not this deviation from baseline is statistically significant, my feeling is that if it were significant, than this would have been stated. Therefore, a crossover design was probably adequate to detect benefit; especially given the power of the study was predetermined to be 80% (for VAS) so long as 40 people completed the study, which they did. Consequently there was a low probability of not detecting a benefit when one is present. 14. If besides the failure of the MPQ / VAS scores to return to baseline for the group who received Gabapentin in Phase 1, it is also mentioned on page 7 of the Jan '97 report that there was a treatment order effect for the PPI score, but again it doesn't give any value for this effect or for its significant. The fact that it is not stated makes me think it wasn't significant and therefore, it is unfair to attribute the lack of improvement in VAS/PPI scores to this and an inadequate washout. 15. If in fact the failure to return to baseline for the MPQ / VAS scores for those given the active

				P-Value: 0.001 Range: not listed Mean Reduction: 1.8 (SD = 3.1, SE = 0.5) <u>9. % of Patients achieving "much improved" or "moderately improved" on Patient Global Impression of Change</u> <u>Global Assessment of Pain Relief:</u> • Note that scale used was not a 7-point scale, but was 0= no pain relief; 1 = slight improvement, 2= moderate improvement, 3=complete pain relief (according to page 5 of the study protocol) • According to p. 5 of the August 1997 report, the scale was none, mild, moderate, or excellent. Placebo: Number of patients reporting moderate or excellent pain relief: 9/53 Gabapentin: Number of patients reporting moderate or excellent pain relief: 17/53 It would seem that the numbers above are all out of 40, which implies	drug in phase 1, and the order effect were in fact significant, it could be due to the fact that the use of an inactive placebo caused unblinding. Although the reports state that a stable low-dose of Gabapentin was used to avoid unblinding, unblinding is likely. According to all the reports, a significantly higher proportion of patients suffered adverse effects on Gabapentin than on the placebo. Although the reports were unclear as to the adverse effects suffered by those on placebo, it would seem that those not in common with placebo included drowsiness, fatigue, and imbalance. Therefore, it is probable that certain patients, as well as their assessing physicians, were able to determine in which phase they were on the active drug which could easily have affected baseline scores and order effects. 16. Although various numbers are given for the mean reduction in MPQ/ VAS/PPI scores, the MCID values for these scores are not given; it would be interesting to check. 17. P-values were checked and seem accurate. 18. Of those who completed the study, 31 were men and 9 were women. One wonders whether or not, the significantly higher proportion of men might affect results at all. 19. The table included in the letter is analogous to Table 3 in the Aug '97 report (table 4 in the Jan '98 report). However the "standard deviations" listed do not match those in the earlier reports. After investigation, it was found that the SD's from the earlier reports

				that there was no ITT analysis done. Furthermore, there is no mention in the reports of any ITT analysis being done. <u>10. Histogram presentation of all PGIC 7-Point Results, where ported:</u> 1. Not applicable, PGIC was on a 4-point, not 7-point scale.	have been divided by square root of 40, the sample size after withdrawals, and are therefore the STANDARD ERROR of those estimates, which is different. 20. The protocol is different from what was reported in many ways (see notes throughout document).

Study No. 2 – GABAPENTIN vs. AMITRIPTYLINE FOR PDPN – DBR CROSSOVER TRIAL (published) – FINAL **– July 27, 2008**

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 2 Morello CM, Leckband SG et al. Randomized Double-blind Study Comparing the Efficacy of Gabapentin With Amitriptyline on Diabetic Peripheral Neuropathy Pain. Arch Intern Med 1999; 159: 1931-7 **Support**: U.S. Veterans Affairs San Diego Health Care System **Dates**: Patients enrolled and completed between March 1997 – December 1997 **Trial design:** Independent. DBR Crossover Trial, 13 weeks after 2 week washout to baseline, including 2 treatment periods of 6 weeks separated by 1 week washout, comparing gabapentin (G) to maximum dose of G=1800 mg/d with amitriptyline (A) to	PDPN Inclusion: • ≥ 18 years • diabetics with chronic daily pain > months consistent with PDPN • creatinine clearance ≥ 30 mL/min Exclusion: • worse "non-DPN pain" • allergy or adverse reaction to gabapentin or amitriptyline • previous dose of gabapentin or amitriptyline exceeded 1800 mg/d or 75 mg/d • postural hypotension with	**Study design:** 15 week double blind crossover RCT comparing G with A after 2 week washout of prior drugs to baseline as 2 arms: G/A x 6 weeks with 1 week washout between treatments vs. A/G with 1 week washout between treatments. **Patient flow** (Fig 1, p 1934): • Sceened: 28 • Excluded: 3 • Randomized: 25 as G/A = 12 A/G = 13 • **Completed both arms of crossover: 19/25** (76%) as G/A=9/12 (75%), A/G=10/13 (77%) • **Exposed to drug** (completers + withdrawals for each drug): G=23; A=24 • **Exposed to both G and A: 21** • Completed assigned treatments: G=10/23; A=20/24 • Withdrawn from treatments: G=3/23; A=4/24	**Predefined outcomes:** **NB: results are not ITT, as they are reported for completers after excluding data from patients who did not complete both arms.** **Primary:** "Pain Scale Rating System" with conversion of subjective ratings on a "scale of 13 words" to numbers (? Post-hoc – not specified in report) **Secondary:** "Global Rating Scale" to measure pain relief, scored by a neurologist who evaluated	**Mortality:** Not reported **Serious Adverse Events:** Not reported **Withdrawal Due to Adverse Events:** interpreted for this table as total from each sequence including early crossers-over (by treatment) over total exposed): G=3/23; A=3/24 These appear suitable for meta-analysis **Total withdrawals:** G=3/23; A=4/24 **Total patients with AE's:** (Table 6, p. 1936) G total = 18/23 (78%) A total = 17/24 (71%) These appear suitable for meta-analysis	1. This early study generally appears to show slightly less efficacy, and greater neurological toxicity from gabapentin than from amitriptyline in this model. It is virtually certain that patients would be unblended, and the analysis is not ITT and excludes some patients for efficacy assessments. 2. The authors conclude that *"Although gabapentin provides pain relief in patients with DPN pain, it should be reserved as an alternative to patients in whom a less costly agent fails, such as amitriptyline, or for whom tricyclic antidepressants are*

maximum dose of 75 mg/d Concealment: identical capsules Randomization: *"randomized by the VASDHS clinical research pharmacist, the only unblended investigator for the stuey, to receive either gabapentin or amitripytyline in a double-blind design per protocol..."* (p. 1932)	cardiovascular symptoms • severe depression or treatment for seizures • creatinine clearance < 30 mL/min Allowable drugs: previous analgesics discontinued for 2 weeks, but allowed acetaminophen 325 mg up to 4 times/day Baseline characteristics: Mean age: 60 22/25 Type 2 DM vs 3/25 Type 1 DM Mean creatinine clearance 76 mL/min 14/25 had received amitriptyline and 1/25 nortriptyline previously, and 9/25 were taking amitriptyline at recruitment (required	Drug doses/titration (p. 1353): Titration according to pain from G=300 mg/d on day 1 to 600 mg/d on day 2 to 900-1800 mg/d final dose thereafter; titration from G=12.5 mg/d on day 1 to 25 mg/d on day 2 to 25-75 mg final dose thereafter. Gabapentin was divided into 3 doses/day vs. amitriptyline given only as evening dose. Statistical Analysis: (p. 1933) Conversion of verbal descriptors in pain diary to numerical equivalents using Pain Scale Rating System. Comparison of mean pain scores in each final treatment week by paired 2-tailed t test, with examination for period and sequence effects ty t-test. Global rating scale scores analysied with paired, 2-tailed Wilcoxon signed rank test. …	patients at baseline and end of each treatment where patients were asked to make a global rating of overall pain relief on a 6-point scale ("complete relief", "a lot", "moderate", "slight", "none", or "pain worse"). This appears to be close to PGIC used elsewhere but not comparable as a 6-point vs. 7-point scale and terminology is different, e.g. "slight" vs. "minimal" for PGIC. NB: neither of these scores is comparable with any other commonly used scales. Test of blinding:	Most important AE's: Table 6, p. 1936) Reporting is somewhat different from other studies. TLP has combined ["dizziness" + "postural hypotension"] and reported the totals as dizziness comparable to other studies, "sedation" = somnolence, "lethargy" = asthenia. Dizziness: G=13/23 (57%); A=7/24 (29%) Somnolence: G=12/23 (52%); A=6/24 (25%) Lethargy: G=4/23 (17%); A=5/24 (21%) Ataxia: G=5/23 (22%); A=2/24 (8%) These appear suitable for meta-analysis. Total AE's (patients may have > 1 as total exceeds total patients with AE): Not reported Disability: not reported > 50% reduction in NRS pain score at endpoint vs. baseline: not reported (not an outcome) Primary outcome "Pain Scale Rating System" converted to a numerical score: NB: NOT ITT analysis (completers only) See Figures 2 and 3 in publication. The scores are different from all other studies because the numerical scale is totally different, and not comparable. Not suitable for meta-analysis as not comparable to	*contraindicated..."."* 3. Outcomes other than safety are not suitable for meta-analysis. .

	washout). 1/25 was taking gabapentin at recruitment and required washout.		Not described but 15/25 patients were familiar with amitriptyline (14) or nortriptyline (1) and would have been familiar with its AE, 9/25 presumably tolerated amitriptyline; 1/25 was familiar with gabapentin and presumably tolerated it. This makes it virtually impossible that patients remained blinded.	other studies. Secondary outcome "Global Rating of Pain Relief" (6-point scale analogous to PGIC): (NB: NOT ITT; interpolated from Table 5, p. 1935 which reports results as percentages of 21 patients who were exposed to both G and A) Pain relief (categorical): "Complete": G=1/21; A=1/21 "A lot": G=5/21; A=4/21 "Moderate": G=5/21; A=9/21 "Slight": G=3/21; A=4/21 "None": G=6/21; A=3/21 "Worse": G=1/21; A=0/21 Because they use a 6-point, rather than 7-point scale, these are not meta-analysable with other studies. PGIC: not reported	

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 3 Backonja, PD 945-210 8-week DBRCT July 2, 1996 – March 20, 1997 Investigators meeting March 22-23, 1996 17 USA, 3 Canadian sites Final protocol approved April 24, 1996; "Inferential Analysis Plan" approved by company statisticians April 11-12, 1997 – AFTER completion of study but BEFORE breaking blind (Appendix D.1, p. 275). Blind broken April 22, 1997. Submitted to JAMA, March 25, 1998 (with Rowbotham, 945-210; see Parke-Davis	Painful diabetic peripheral neuropathy (PDPN): Inclusion/exclusion: • No prior treatment with gabapentin (potential "enrichment bias" by exclusion of non-responders or non-tolerators) • No chronic kidney disease (Cr clearance ≥ 60 mL/min predicted • Pain score (Likert) ≥4 on daily pain diary before randomization • Pain score (VAS) ≥ 4 at screening and randomization (SF-MPS) NB: A few patients sneaked through screening without meeting criteria	Placebo vs. forced titration gabapentin from 900 mg/d (wk 1), 1800 mg/d (wk 2), 2400 mg/d (wk 3), 3600 mg/d (wk 4), to maximum tolerated "regardless of any efficacy achieved at lower dosages", then reduced 1 dose step "if intolerable adverse reactions occurred", then 4 weeks steady dose. *see figure from protocol in research report at end of this table (59/84 patients in G group reached 3600 mg/day for at least 1 day – p. 24/69 of final report; 10/84 patients in G group received 0 mg/day for up to 9 days – p. 24/69,	Predefined outcomes: Primary: • Pain (Likert 0-10 score) as group mean of last 7 available scores while on study medication from daily diary records of previous 24 hours (LOCF for noncompleters) – see p. 14, 20 of full report, p. 1833 of JAMA report – NB this is LOCF, therefore does not appear to represent the true group mean for ITT populations at 8 weeks post-randomization NB: In this study, by definition "baseline" = "last 7 available scores during the screening phase", including Day 0 (Visit 2) … i.e. patients were asked to rate pain daily by Likert, as part of screening, and only those with mean pain ≥4 (last 7 scores) were to be randomized, so all patients should have started at pain score ≥ 4. Close reading of p. 10, 14 of full report shows "end of screening" = "screening" = "baseline" = beginning of Day 0-1 of Week 0-1 = Visit 2. The comparable 945-224 study	Mortality: P = 0/81; G = 0/84 (p 51, full report) Serious Adverse Events: P = 2; G = 3 (p. 51, full report, Appendix B gives details) (SAE do not appear related to gabapentin's expected toxicities.) Withdrawals Due to Adverse Events: P = 5/81; G = 7/84 (p. 51, full report, Appendix B for details) Total Withdrawals: P=16/81; G=14/84 Adverse events: Total patients with AE: P=54/81; G = 70/84 Total patients with "associated" AE: P=21/81; G=52/84 (p. 48, appendices) Nervous system AE's most prominent, e.g. (# of patients): Dizziness: P = 4/81; G = 20/84 Somnolence: P = 5/81; G = 19/84 Confusion: P = 1/81; G = 7/84 These are similar to all other studies of gabapentin. Median time of onset and median duration adverse events (Table 27, pp. 50-51 of Final Report) NB: Median time to onset of most AE from G was in the range 2-3 weeks, associated with G dose of 1800-2400 mg/day, indicating that toxicity is dose-dependent. Median duration of AE for G (e.g.	1. Incomplete follow-up of (unbalanced) early withdrawals may influence materially the final conclusions of study. 2. Potentially "enriched" study did not include any patients previously treated with gabapentin (would tend to exclude preferentially "gabapentin failures" but not include "gabapentin successes", who have no incentive to participate in trial. 3. Prominent neurologic AE's appear inseparable from analgesic effect and contribute partly to it in post-hoc exploratory analysis.NB: Median time to onset of most AE from G was in the range 2-3 weeks, associated with G dose of 1800-2400 mg/day, indicating that toxicity is

memorandum March 30, 1998, WLC_CBU_093708) Published in JAMA December 2, 1998 as Backonja M, Beydoun A, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with Diabetes Mellitus. JAMA 1998; 280: 1831-6 (prior publication abstract or meeting presentation?) Final study report December 30, 1998	Baseline characteristics: Mean pain score (Likert NRS, 0-10): P (N=81/81): 6.5 (SD 1.5) Range: 4 - 10 G (N=83/84): 6.4 (SD 1.5) Range: 4 – 10 – 1 had no baseline score? Page 27 of final report (Table 9) shows ranges as P: 4.0-9.9; G: 3.9-10.0. Groups appear generally similar.	unexplained) P = 81 randomized (81 reported for safety, 80 for efficacy – unexplained in JAMA report); 65 completed 8 weeks; G = 84 randomized (84 reported for safety, 82 for efficacy – unexplained); 70 completed 8 weeks NB: P = 16/81 noncompleters; G = 14/80 non-completers	reports non-integer means of pain scores at baseline, in contrast with this study, which appears to "round them". NB: At p. 283 of report (Vol 1) reasons for exclusion of patients from evaluation are provided for 5 patients. By comparison with Appendix E.4 (pp 264, 298, 299, 306, 308) it is possible to identify the experimental groups to which these patients belonged: Pt. 4003 – placebo (quit Day 8) Pt. 4008 – gabapentin (quit Day 21) Pt. 4021 – gabapentin (quit Day 7) Pt. 6002 – gabapentin (quit Day 5) Pt. 7002 – gabapentin (quit Day 2) All 4 of the censored gabapentin treated patients experienced adverse events, but not the placebo treated patient. (Appendix E.6) The first 3 of these (4003, 4008, 4021) are also censored from ITT analysis because they recorded no pain diaries – unclear whether they are included in PGIC or CGIC impression of change statistics. Secondary: NB: all secondary outcomes are <u>dependent,</u> not independent of primary	dizziness: "10.8" days, somnolence 16 days, confusion: 15 days) SHOULD NOT BE INTERPRETED (as it is later by various Parke-Davis-associated and Pfizer-associated speakers) as indicating that patients accommodate to the adverse event – it is logically more reasonable that the median duration divides patients into those who reduced dose or stopped taking G earlier than the median, vs. those whose AE symptoms continued for longer than the median. Weight gain from screening to study termination (Appendix C.41, p. 267): P (N=76): 0.56 kg G (N=80): 1.61 kg Weight gain > 7% of initial weight (8 weeks maximum!): P =1, G =3 No statistical analysis is reported on this observation. <u>Primary outcome (endpoint):</u> P (N=80): 5.1 (SD 2.2); range 1.0 – 10.0, mean change -1.4 (SD 1.7) G (N=82): 3.8 (SD 2.5); range 0.0 – 9.1, mean change -2.6 (SD 2.5) p. 27 of study report, Table 9 "Mean Pain Scores: Descriptive Statistics" – <u>no statistical test is made, no difference claimed</u>. Note this is subtly different from p. 27 Table 10: <u>"Endpoint Mean Pain Scores: Results of Analysis of Covariance", which reports P (N=80): 5.13, G (N=82): 3.88, difference = -1.25; p = 0.0004.</u> Appendix D.1 at p. 275 et seq of report describes "Inferential	dose-dependent. Median duration of AE for G (e.g. dizziness: "10.8" days, somnolence 16 days, confusion: 15 days) SHOULD <u>NOT</u> BE INTERPRETED (as it is later by various Parke-Davis-associated and Pfizer-associated speakers) as indicating that patients <u>accommodate</u> to the adverse event – it is logically more reasonable that the median duration divides patients into those who reduced dose or stopped taking G earlier than the median, vs. those whose AE symptoms continued for longer than the median. 4. Statistical interpretation (ANCOVA and "Inferential Analysis") is very difficult to understand (e.g. adjustments for multiple centres). The group mean differences do not appear different from the "descriptive statistics",

			outcome, as they all measure various aspects of the same thing (pain relief). • Pain reduction evaluated by comparison with baseline pain score - unclear from full report (p. 19-20) whether comparisons by ANCOVA are individual pairwise comparisons (e.g. patient "x", mean of 7 diary Likert scores which must ≥ 4 at baseline vs. mean of 7 diary Likert scores during last week achieved of treament (weeks 1-8, LOCF) or comparisons of group means • Weekly mean pain score from daily diaries • Sleep interference by pain ("how pain interfered with sleep") • Short form McGill Pain Questionnaire (SF-MPQ): pain descriptors, visual analog scale (VAS), present pain intensity (PPI) • Patient and physician global impression of change (includes LOCF, therefore unblindedas it will include people who dropped out due to "intolerability", etc.) • Profile of Mood States (POMS) • SF-36 Quality of Life Questionnaire (SF-36 QOL)	Analysis Plan" approved by Parke-Davis April 11-12, 1997, 1 year after the initial protocol was filed and after March 20, 1997 completion of study 945-210, but just prior to April 22, 1997 breaking of blind "after all decisions regarding evaluability have been made". This plan limited "evaluable" patients to those with ≥4 days of pain diary during screening AND≥ 7 days of drug therapy. Anyone who dropped out during first week would not be evaluated, but plan was to repeat analysis for ITT population. At page 278: "preliminary analyses will be performed in order to aid in strategic planning". It is not clear what this means. Exploratory analysis of effects of dizziness or somnolence (most common AE which predominate in G > P groups) on primary efficacy variable (NRS pain score) is shown at p. 49 of report and Appendices D.80, D. 81, pp. 234-9 of Volume 2. Numbers of patients do not match exactly (P: 81-5 for somnolence should = 76, but shown as 75; G: 84 or 83 – 19 for somnolence = 65 or 64, shown as 64; P 81-4 for dizziness should = 77, shown as 76; G: 84 or 83 – 20 for dizziness should = 64 or 63, shown as 62). The effect of this analysis is to reduce baseline-endpoint differences from "statistically significant" group mean difference of -1.25 favouringgabapentin to -0.89 with data from patients reporting somnolence excluded, or to -1.2 when patients reporting dizziness were excluded. The discussion in report (p. 49) differs from JAMA (p. 1835) by citing different p values and omitting the magnitude of change, which is reduced when the patients reporting somnolence are excluded. Exploratory (post-hoc) "responder" analysis: Final report includes (p. 30)post-hoc "responder" analysis not pre-specified in protocol, suggesting a discrimination between patients who experienced a change from baseline to endpoint of ≥50% (P=16/80; G = 39/82) or who experienced any increase in pain (P=15/80; G=10/82),	especially when non-evaluable patients are considered. 5. Secondary outcome measures are not independent of primary measure; repeated statistical tests are not convincing that these outcomes add additional information. 6. Patient and Clinician global impression of change groupings are post-hoc. Better to display all data, along with distribution of all pain score changes at "endpoint", in graphs which show original values. 7. Blinding undoubtedly broken due to prominent neurological effects of gabapentin – many patients and clinicians could have been unblended even if patient did not describe "adverse event", e.g. somnolence might be "favourable event" for those disturbed by sleep. Gabapentin effect on "sleep

				claiming statistical significance for the difference between responders (p=0.001, CMH test). This claim is not made in the JAMA paper, presumably because it is a post-hoc analysis which cannot be interpreted for statistical significance. The same "responder" analysis suggests that P=15/80 [19%] vs. G=10/82 [12%] of patients had "increased" pain at endpoint. (I have maintained denominators of P=80 and G=82 from final report as a conservative assumption, since early dropouts would not have been eligible to "worsen".) TLP: this is not a pre-specified analysis, and therefore cannot be used in the meta-analysis. Secondary outcomes (endpoint and various weeks): Multiple secondary outcomes are claimed to favour G > P despite disclaimer in "Inferential Analysis Plan" that multiple comparisons will generate some falsely "statistically significant" findings, and lack of correction for multiple comparisons. More important, the secondary outcomes are not independent of the primary, since they all appear to rely on pain as the main factor assessed, or its influence on sleep ("sleep interference") – a drug which causes somnolence may tend to improve "sleep interference" over placebo, regardless of analgesic effect. Weekly mean pain score (Figure 2, p. 1834 in JAMA, Figure 3, p. 29 and Figure 8 pertaining to patients taking protocol-specified G dose, p. 41 in final report) do not show any increase of effect beyond 2	disturbance" could be sedative, as opposed to primarily analgesic. If so, any benefit obtainable for "sleep disturbance" might be best obtained by a single bedtime dose, as opposed to continuous exposure. 8. Information available from 945-224, e.g. consumption of analgesics by group (acetaminophen) is not available for this study other than the comparable number of patients in each group using acetaminophen (P=22/81, G= 23/84) (Appendix C.8, p. 211, Volume 1) – no information on mean consumption is not provided. 10. It is not possible from the data provided to tell whether patients who escalated their dose according to forced titration protocol did "better" or "worse" than they would have if they had continued at a lower dose. 11. Claim of more

				weeks, i.e at doses > 1800 mg/day. Some secondary outcomes are surprising, e.g. at Volume 2, p. 395, Appendix D.6, "Present pain rating" at LOCF endpoint shows little difference between groups and still fails to account for 5 patients: P (N=79/81): 1.83 (present pain rating) G (N = 81/84): 1.23 (present pain rating) Difference = 0.6; p =0.0004 according to p. 396 Patient Global Impression of Change (PGIC) might be best measure of overall improvement in some respects (although not blinded). The analysis at p. 429 claims a 1-point difference between groups favouringgabapentin by ANCOVA (p=0.0001). The following scores can be summed from the raw data starting at page 419 for P (N=76/81 randomized) and G (N=79/84 randomized), where 1 = much improved, 2 = moderately improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = moderately worse, 7 = much worse: Category 1: P = 12, G = 33 Category 2: P = 13, G = 14 Category 3: P = 13, G = 12 Category 4: P = 25, G = 18 Category 5: P = 5, G = 1 Category 6: P = 6, G = 1 Category 7: P = 2, G = 0 The study publication and report group these into categories 1&2, 3&4, 5,6&7. If one adds to the gabapentin group the early WDAE not counted in primary outcome analysis (non-evaluables), Category 7 for G could = 4.	"responders" in gabapentin group does not seem to fit clinically with more early dropouts and fewer completers. 12. Backonja et al subsequently suggest that a > 50% reduction in NRS pain score is a "somewhat artificial study goal" (Backonja&Glantzman, ClinTher, 2003)

RK 720-03908

Protocol 945-210
Final, April 24, 1996
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APPENDIX A.3

DOSING TITRATION SCHEDULE

Number of Study Medication Capsules[a]

Week	Days							Target Dose
	0[b]	1	2	3	4	5	6	
1	1	1-3	1-3	1-3	3	3	3	900
2	3-6	3-6	3-6	3-6	6	6	6	1800
3	6-8	6-8	6-8	6-8	8	8	8	2400
4	8-12	8-12	8-12	8-12	12	12	12	3600 (maximum)
5-8	Fixed-Dose Weeks 5-8							

[a] One capsule = Gabapentin 300 mg or placebo.
[b] First dose will be taken in the evening of Visit 2/Randomization (designated as Day 0)

*

STUDY NO. 4 - DETAILED SUMMARY AND ANALYSIS: ROWBOTHAM 1998
PARKE-DAVIS 945-211 – POST HERPETIC NEURALGIA

Summary:

Information taken from:
a) Rowbotham M, Harden N, et al. Gabapentin for the Treatment of Postherpetic Neuralgia. JAMA 1998; 280: 1837-42 (December 2, 2008), referred to as the **JAMA report**
b) Parke-Davis research report number RR-995-00070 dated December 29, 1998, referred to as the **unpublished report**. The unpublished report is dated **later** than the report published in JAMA.

Enrichment bias: Patients who had previously taken gabapentin were excluded from this trial as were patients with a "hypersensitivity" to the drug This causes "enrichment bias" favouring gabapentin by excluding patients who may have been likely to experience adverse events, or who may have previously "failed" gabapentin therapy.

Serious adverse events (SAE) and adverse events (AE):
p.1840 of the JAMA report states that "*Minor adverse events that were deemed associated with the study medication were reported in a total of 62 subjects (54.9%) receiving Gabapentin and 32 subjects (27.6%) receiving placebo"* and *"No serious adverse events that were determined by the investigator to be related to Gabapentin were reported."*By deferring to the investigators' opinion about causation of SAE, the JAMA report implies that no serious adverse events (SAEs) were associated with gabapentin use, whereas Table 35 on p. 143 of the unpublished report shows that:

- P = 5/116 patients experienced 5SAE (1 fatal, 4 non-fatal)
- G = 10/113 patients experienced 17 SAE (all non-fatal)

The JAMA report also does not provide the total number of adverse events experienced by each group whereas the unpublished report specifies:

- P = 151 AE (total)
- G = 278 AE (total)

Withdrawals due to adverse events (WDAE):
The JAMA report is again inconsistent with the unpublished report. JAMA report states at p. 1840, by qualifing for WDAE "described as related to the study medication":

- P = 11/116 (9.5%) WDAE
- G = 15/113 (13.3%) WDAE

However, both Figure 1 (p. 1839) of JAMA report and pp.149-150 of the unpublished report indicate:

- P = 14/116 (12%) WDAE
- G = 21/113 (19%) WDAE

In the safety reporting at p. 1840 the JAMA report accounts only for withdrawals that the investigator(s) deemed as related to the study drug, whereas the complete WDAE shown above should be used.

Estimation of NNT (number needed to treat), NNH (number needed to harm):
At p. 1842 of the JAMA report, a paragraph in the conclusion reads "*From the data in Figure 4 and the text, the NNT for benefit is 3.2, the NNT (NNH) for minor adverse events is 3.7, and the NNT (NNH) for adverse events leading to study withdrawal is 25".* Independent calculations performed for NNT benefit using the data in figure 4 yield 3.77. Calculations of NNH for minor adverse events yield 3.7 when using the numbers reported in the published report, however the real NNH for minor adverse events must be lower as certain adverse events deemed by the investigators not associated with study drug were excluded. While the total numbers of adverse events are provided for each study group in the unpublished report, the number of patients suffering total AE are not. Finally, the correct NNH for adverse events leading to study withdrawal is much lower, 15.3, when the correct numbers for WDAE are used.

Probable unblinding:
The larger total number of AE in the gabapentin group, as well as the nature of AE which are more common with gabapentin than placebo (somnolence, 27.4% vs. 5.2%, dizziness 23.9% vs. 5.2%, ataxia 7.1% vs. 0%, all from JAMA report) are likely to have caused unblinding. Neither the JAMA nor the unpublished report discuss this issue, nor make any corrections for unblinding.

Failure to account for multiple comparisons:
P. 1839 of JAMA report states that *"no adjustments were made for multiple comparisons."* Both the JAMA report and the unpublished report make several dependent comparisons and therefore, a multiple comparisons procedure (e.g., Bernoulli's correction, Fisher's LSD method) should have been performed; specifically, the alpha level should have been adjusted.

"ITT" population improperly defined, missing data not explained or accounted for:
P. 1838 of the JAMA report defines the intent-to-treat (ITT) population as patients who, once randomized, had evidence of taking at least one dose of study medication and provided at least 1 follow-up efficacy assessment. This sacrifices 4 early dropout patients from gabapentin group, but 0 patients from placebo group. The JAMA report does not specify how data from dropouts were handed. However, the unpublished report, on page 228, states that last-observation-carried-forward (LOCF) was applied to any missing post-baseline value. That is, any missing post-baseline value was replaced with the last available post-baseline observation regardless of the assessment date. The LOCF method is biased and assumes no within-patient variability, and still fails to account for the 4 early dropouts from gabapentin group, since a more conservative assumption, e.g. baseline observation carried forward (BOCF) was not applied to these subjects.

For most of the efficacy results, the sample size for the ITT gabapentingroup is reported as N=109, whereas for the safety analyses the size of the gabapentingroup is N=113, the same as the number of patients randomized to the gabapentin group. Even the unpublished report does notexplain why 4 subjects randomized to gabapentin were not included in the efficacy analyses but were included in the safety analyses. Pages 25 and 26 of the unpublished report state criteria for assignment to each group. To be included in the safety analysis, patients had to have had evidence of taking at least one dose of the study medication and had **at least one follow-up assessment at which adverse events could be reported**. In order to be included in the ITT population, patients had to have had evidence of taking at least one dose of the study medication

and have had one post-baseline efficacy assessment. **It is curious and unexplained that 4 patients in the gabapentin group had a post-baseline follow-up assessment during which adverse events could have been reported but yet had no post-baseline assessment in which efficacy was reported.**

Misleading reporting of secondary efficacy variable (MPQ PPI – present pain intensity at study endpoint):

For the secondary efficacy variable, McGill Pain Questionnaire (MPQ) Present Pain Intensity (PPI), the JAMA report indicates that at study endpoint (final week) there was a rating of "no pain" for:

- P = 8.8% of patients
- G = 16.0% of patients

This is misleading for several reasons. P. 26 of the unpublished report states that PPI is a 5-point scale (although it is in fact a 6-point scale ranging from 0=no pain to 5=excruciating pain); this isnot described nor referenced in the JAMA report, such that a reader cannot interpret the results without searching for the score's meaning. The JAMA report does not provide numerators/denominators, standard deviations, nor results for any of the other categories of the PPI scale (i.e. mild, discomforting, etc.), yet states (p. 1840) that these results were *"statistically significantly improved among subjects treated with gabapentin(P < 0.01)"*. Theunpublished report indicates that the significant difference in PPI is from baseline to endpoint, and that there was a significant difference not only for the gabapentin group, but for the placebo group as well (P<0.01). However, neither report provides the statistical significance for the most important indicator, namely the difference for PPI between the placebo vs. gabapentingroups at endpoint (if any). As standard deviations are not presented, it is impossible to independently assess statistical significance.

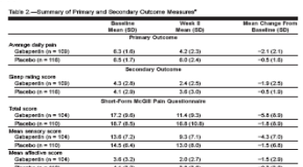
With regard to the secondary efficacy variables Subject's Global Impression of Change (SGIC) and Clinical Global Impression of Change (CGIC), the JAMA report does not specify that these outcomes were rated on a 7-point categorical scale and does not report results for each of the 7 categories, as does the unpublished report. Instead, the percentages for certain categories are grouped together without an explanation as to whether this was a pre-specified outcome comparison. Furthermore, graphs are provided for these results but no test of statistical significance is provided, and no reason is provided for the absence of 14 evaluations from the placebo group and 15 from the gabapentin group. The results of categorical variables should be expressed as percentages of the true ITT N's (P=116, G=113).

The PGIC is specified in the protocol (Appendix 3). Page 9 of the protocol clearly states that on the final visit (week 8) investigators and patients will complete a Global Impression of change. Page 16 of the protocol also lists PGIC as a secondary efficacy variable (letter a in the list). Page nine of the protocol does refer to Appendix C after it mentions Patient Global Impression of Change, which does in fact contain the familiar 7-point Global Impression of Change scale. Additionally, (Global Impression of Change, Patient and Investigator Assessments) contains the raw data for this variable. The main inconsistency is that page 18 of the protocol states that "The proportion of patients with at least 'much improved' for their global impressions of change (physician and subject)along with 95% confidence intervals will be calculated." This "at least" does not make sense as much improved is the highest category of pain relief on their scale, and as is clear in the JAMA report, much improved moderately improved were grouped .

With regard to the secondary efficacy variable SF-36 quality of life, the unpublished report shows different sample sizes for each subsection (e.g. P=99, G = 89 for health transition but P=101, G= 92 for physical functioning). Independent calculations show that the average number of patients in the placebo group who filled out each section of the SF-36 was 100.1 (the ITT sample size of the placebo group was 116) with a standard deviation of 1.4. The average number of patients in the gabapentin group to fill out this survey was 91.4 with a standard deviation of 2.7 (the ITT sample size of the gabapentin group was 109). It is unexplained why a lower proportion of gabapentin patients completed this questionnaire but also why there was twice the variability in the number of patients who completed each section. Both JAMA and the unpublished reports state that 1 questionnaire used to assess quality of life, the SF-36, was completed once at baseline and once at the week eight efficacy assessment, so the reason for these discrepancies is not apparent.

Inadequate reporting of compliance with dosing schedule:

Pp. 20-21 of the unpublished report present specific criteria for determination of patient compliance with medication in this study. In the JAMA report, rates of compliance for the placebo and gabapentin groups are not reported. However, by looking at the appendices of the unpublished report , specifically appendix E.6 (Study Medication: Based on Dispensing Record) it is possible to determine compliance by looking at the number of capsules returned vs. capsules dispensed for each patient. Appendix A.9 includes major protocol violations (e.g. not reaching minimum dose). I still cannot seem to locate a general statistic for overall compliance.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Kelsey Innes
Study No. 4 **Rowbotham M**, Harden N, et al. Gabapentin for the Treatment of Postherpetic Neuralgia. JAMA 1998; 280: 1837-42 (December 2, 2008 **Study Number:** 945-211 **Study Design:** Multicenter, randomized, double-blind, placebo-controlled, parallel design **Study Duration:** 8 weeks **Patients Randomized:** 229 **Randomization Procedure:** see page 1838 of published report **Number of Study Centers:** 16	**Post Herpetic Neuralgia** **Inclusion Criteria:** • At least 18 years of age • Pain present for more than three months after healing of a herpes zoster skin rash • A pain-intensity score of at least 40 mm on the 100-mm VAS on the SF-MPG at screening and at randomization • Average daily diary pain score of at least 4 on a scale of 1-10 during the baseline week • Discontinuance of muscle relaxants, anticonvulsants, mexiletine, topical analgesics, and antiviral agents beginning at least 2 weeks prior to screening	**Study Power:** • Given the assumption that the SD for this parameter would be 3.4, a sample size of 80 evaluable patients in each treatment was required to provide 80% power to detect a difference of 1.5 on the Likert scale (11 point scale) with a 5% error rate for a 2-sided test. According to page 1841, the actual power approached 100%. • All p-values were 2-sided and no adjustments were made for multiple comparisons **ANCOVA** • All of the between treatment comparisons for the change from baseline parameters were accomplished by ANCOVA • Including fixed terms of treatment, centre, treatment by center interaction, and baseline scoring. **Study Populations:** According to p. 1838 of published report. • "ITT" population included those subjects who, once randomized to treatment had evidence of taking at least 1 dose of study medication and provided at least 1 follow-up efficacy	**Primary Efficacy Measure:** • Change in average daily pain score based on an 11-point Likert scale (0 = no pain, 10 = worst pain ever), calculated as difference for each patient between mean of NRS pain score at baseline vs "endpoint" – means of differences for each group were compared, as well as NRS pain score group means at baseline and "endpoint". **Secondary Outcome Measures:** • Average daily sleep scores • Short-Form McGill Pain Questionnaire (SF-MPQ) • Subject Global Impression of Change (SGIC) • Investigator-rated Clinical Global Impression of Change (CGIC) • Short-Form 36 Quality of Life Questionnaire (SF-36) • Profile of Mood States (POMS) The results presented below and in JAMA report Table 2 – Summary of Primary and Secondary Outcome Measures (p. 1840) are for the "ITT" population. 	**<u>1. Mortality (p. 1840):</u>** **P = 1 / 116** **G = 0 / 113** **<u>2. Serious Adverse Events (p. 1840):</u>** • JAMA reportstates that *"No serious adverse events that were determined by the investigator to be related to Gabapentin were reported."*This is problematic, see comments. • Unpublished report (p. 143, table 35) however gives the following results for SAEs **P: 5/116 patients experienced 5 adverse events (1 fatal, 4 non-fatal)** **G: 10 patients experienced 17 SAEs none of which were fatal. For details about each of these serious adverse events see table 35 on the page 144 of the unpublished report** **<u>3. Withdrawals Due to Adverse</u>**	1. The study was published in JAMA on December 2, 1998 and the research report is dated December 29th, 1998. Shouldn't the research report have been finished first? 2. Patients who had previously taken gabapentin were excluded from this trial as were patients with a hypersensitivity to the drug, however, what would constitute hypersensitivity is not stated. This may introduce enrichment bias. 3. The doses of narcotics or other supplementary drugs are reported in the unpublished report – See Appendix E.8 (Prior and Concomitant Medications) 4. On page 1839 of the published report it states that "no adjustments were made for multiple comparisons", in this study we have several dependant variables and some form of adjustment should have been made on the p-values for this reason. 5. Dropouts were handled with LOCF – see page 28 of research report, this is not specified in published report.

Study Dates: 8/26/96 – 7/14/97

Study Protocol: April 22, 1996 (pp. 206-207/1194)

PUBLISHED:
Rowbotham M, Harden N, et al. Gabapentin for the Treatment of Postherpetic Neuralgia. JAMA 1998; 280: 1837-42 (December 2, 2008)

Final study report (unpublished):
RR995-00070
Magnus-Miller L, Podolnick P.
December 29, 1998

Exclusion Criteria:

- Prior treatment with gabapentin or demonstrated hypersensitivity to the drug or its ingredients
- Neurolytic or neurosurgical therapy for PHN
- Immunocompromised state
- Significant hepatic or renal insufficiency
- Significant haematological disease
- Severe pain other than that caused by PHN
- Use of experimental drugs or participation in a clinical study within 2 months of screening
- A history of illicit drug or alcohol abuse within the last year
- Any serious or unstable medical or psychological condition.

Allowed Medications:

- Previously prescribed TCAs and/or

assessment (p. 1838)

- The efficacy-evaluable population consisted of those subjects who, in addition to meeting the criteria required for the ITT population met strict protocol-specific criteria regarding study medication compliance, use of concomitant medications, and number of diaries returned.

The research report gives similar criteria but provides slightly more detail on pp.25-6 of the research report.

Dose Schedule:

- 1-week baseline
- 4 week titration up to maximum tolerated dose or target ceiling of 3600 mg/day (minimum dose of 1200 mg/day was allowed)
- 4 week stable dosing period
- See page 1838 for details of titration/dosing etc.

Patient Flow:

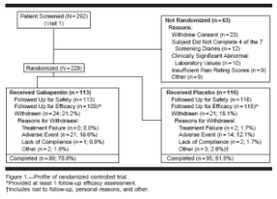


Figure 1.—Profile of randomized controlled trial.
*Provided at least 1 follow-up efficacy assessment.
†Includes lost to follow-up, personal reasons, and other.

- The above is figure 1 – profile of randomized controlled trial (p. 1839

Change in Average Daily Pain: (pp.1839-40)

- Measured by the difference in average daily pain during baseline week and average daily pain score in the final study week
  - Evaluated from daily pain diaries
  - Minimum treatment group difference in chance from baseline that was considered clinically meaningful was 1.5 points

The following compare the JAMA report with unpublished report results:

Placebo (n = 116/116)
Baseline: 6.5 (SD = 1.7)
Week 8 (LOCF): 6.0 (SD = 2.4)
Mean Change from Baseline: -0.5 (SD = 1.6)
Percent Change: 7.7%
P-value (p. 83 of unpublished report) < 0.005

Gabapentin (n = 109/113)
Baseline: 6.3 (SD = 1.6), SD = 1.7 in unpublished report
Week 8 (LOCF): 4.2 (SD = 2.3)
Mean Change from Baseline: -2.1 (SD = 2.1)
Percent Change: 33.3%
P-value (p. 83 of unpublished report) < 0.001

P-value for the difference between placebo and gabapentin is < 0.001

Figure 2 (below) from page 1840 shows the change from baseline in average daily pain score. According to figure reduction was established at week 2, but figure does not indicate p<0.005 for

Events (WDAE), JAMA p. 1840):

According to the JAMA report:

P = 11 / 116 (9.5%)
G = 15 / 113 (13.3%)

- 6 / 15 on Gabapentin withdrew due to dizziness
- 5 / 15 on Gabapentin withdrew due to somnolence
- 2 / 11 on placebo withdrew due to somnolence and 0/11 on placebo withdrew due to dizziness

According to the unpublished report (p.149):

P = 14 / 116 (12.1%)
G = 21 / 113 (18.6%)

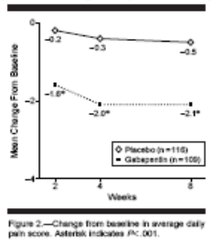
We will use these for Cochrane systematic review.

Most common reasons for withdrawal:

Placebo :
Peripheral Edema: n=2
Depression: n=2
Somnolence: n = 2

Gabapentin:
Dizziness: n=6

6. The results reported for the primary efficacy variable for Gabapentin say n = 109 but 113 were randomized to the gabapentin group - why are the missing 4 not reported as LOCF?
7. The only results given for MPQ PPI were that there was a rating of "no pain" in final week for 16.0% of patients on gabapentincompared with 8.8% of patients treated with placebo. JAMA report states that these results were "statistically significantly improved among subjects treated with gabapentin(P < 0.01)" however it does not give standard deviations, or sample sizes for the gabapentin and placebo groups, omits statistically significant p-value for placebo group, and does not give a p-value for the comparison of gabapentinand placebo.
8. No accounting for unblinding.
9. No p-values or significance listed for SGIC / CGIC in JAMA report, presumably as this is a post-hoc analysis.
10. JAMa p. 1840 states that "*Minor adverse events that were deemed associated with the study medication were reported in a total of 62 subjects (54.9%) receiving Gabapentin and 32*

	narcotics could be continued if therapy was stabilized prior to study entry and remained constant throughout the study.	of final report) **Patients Screened:** 292 **Patients Randomized:** 229 **Received Gabapentin:** 113 **Completed Gabapentin Treatment:** 89/113 (78.8%) **Received Placebo:** 116 **Completed Placebo Treatment:** 95/116 (81.9%) **Completed Study:** 184 (80.3%) • The two treatments were comparable with regard to the proportion of patients who WDAE (P = 0.2) and the proportion who completed the study (P = 0.62)	placebo group at endpoint (see above).  Figure 2.—Change from baseline in average daily pain score. Asterisk indicates P< .001. **Average Daily Sleep Scores (p. 1840)** • Measured similar to primary efficacy variable, change in average daily pain. **Placebo (n = 116/116)** Baseline: 4.1 (SD = 2.9) Week 8 (LOCF): 3.6 (SD = 3.0) Mean Change from Baseline: -0.5 (SD = 1.9) **Gabapentin (n = 109/113)** Baseline: 4.3 (SD = 2.8), Week 8 (LOCF): 2.4 (SD = 2.5) Mean Change from Baseline: -1.9 (SD = 2.5) P< 0.001 favouring gabapentin; this is not an independent outcome from the primary outcome (less pain = more sleep, or more sleepiness = less pain) **Short-Form McGill Pain Questionnaire (SF-MPQ) (p. 1840 of JAMA report, p. 95 of unpublished report)** • Completed after initial screening (week -1), at baseline (week 0), and at weeks 2, 4, and 8. Also not an independent outcome.	Somnolence: n=5 Ataxia: n=2 Nausea: n=2 Vomiting: n=2 • For rest see table 37 of unpublished report • p = 0.013 for withdrawal due to dizziness fromgabapentin vs. placebo **<u>4. Total Withdrawals (p. 1839 of published report)</u>** **Gabapentin (n=113):** Total Withdrawals: 24 / 113 Reason for Withdrawal: • Treatment failure: 0 / 113 • Adverse Event: 21/113 • Lack of Compliance: 1/113 • Other: 2/113 **Placebo (n = 116)** Total Withdrawals = 21 Reasons for Withdrawal: • Treatment Failure: 2/116 • Adverse Event: 14/116 • Lack of compliance: 2/116 Other: 3/116 **<u>5. Total Adverse Events:</u>** According to JAMA report, the following adverse effects occurred among the gabapentin group at	*subjects (27.6%) receiving placebo." Authors cannot decide whether or not minor adverse events are associated with the study, if an adverse even occurs we mu*st assume it is associated with the study drug. The passage also states, *"No serious adverse events that were determined by the investigator to be related to Gabapentin were reported."* This is *problematic for the same reasons.* 11. *No p-values / significance given for adverse events, why?* 12. *For WDA*E, the descriptionaccounts for 11 / 15 Gabapentin withdrawals (6 for dizziness, 5 for somnolence) but does not account for the other 4. The JAMAreport accounts for 2 of the placebo withdrawals (somnolence) but not for the other 9. Also, other withdrawals are not accounted for in this section. WDAE numbers do not match between the unpublishedreport and the JAMAreport; according to the unpublished report the numbers stated in the JAMAreport for WDAE are the treatment associated withdrawals – **this is an inappropriate distinction!**The reporting of SAE also differs between JAMA and

Placebo (n = 110/116)
Baseline: 18.7 (SD = 8.5)
Week 8 (LOCF): 16.8 (SD = 10.8)
Mean Change from Baseline: -1.8 (SD = 8.9)

Gabapentin (n = 104/113)
Baseline: 17.2 (SD = 9.6)
Week 8 (LOCF): 11.4 (SD = 9.3)
Mean Change from Baseline: -5.8 (SD = 8.9)
P-Value < 0.001

Additional non-independent secondary endpoints:

Sensory Pain (1st component of SF-MPQ)

Placebo (n = 110/116)
Baseline: 14.5 (SD= 6.4)
Week 8 (LOCF): 13.0 (SD = 8.0)
Mean Change from Baseline: -1.5 (SD = 6.8)

Gabapentin (n = 104/113)
Baseline: 13.6 (SD = 7.2)
Week 8 (LOCF): 9.3 (SD = 7.1)
Mean Change from Baseline: -4.3 (SD = 7.0)
P-Value < 0.001

Affective Pain (2nd component of SF-MPQ)

Placebo (n = 110/116)
Baseline: 4.1 (SD = 3.2)
Week 8 (LOCF): 3.8 (SD = 3.6)
Mean Change from Baseline: -0.3 (SD = 3.0)

higher incidences than those in the placebo group:
*note that the results were reported in percentages so calculations were performed to determine actual numbers

- Somnolence
  - P = 6/116 (5.2%)
  - G = 31/113 (27.4%)
- Dizziness
  - P = 6 / 116 (5.2%)
  - G = 27 / 113 (23.9%)
- Ataxia
  - P = 0 / 116 (0.0%)
  - G = 8 / 113 (7.1%)
- Peripheral Edema
  - P = 4 / 116 (3.4%)
  - G = 11 / 113 (9.7%)
- Infection
  - P = 3 / 116 (2.6%)
  - G = 9 / 113 (8.0%)

- In the placebo group 12/116 (10.3%) reported pain compared with 5/113 (4.4%) in the Gabapentin group

According to the unpublished report (Table 31, p.120)

	P (n=116)	G (n=113)
Patients with AE	60/116 (53.1%)	84/113 (74.3%)
Number of AE (total)	151	278
Number of mild AE	70	113
Number of moderate AE	57	105

unpublished report.

13. The JAMA report conclusion states on page 1842 "*From the data in Figure 4 and the text, the NNT for benefit is 3.2, the NNT for minor adverse events is 3.7, and the NNT for adverse events leading to study withdrawal is 25".*Independent calculation for NNT = 3.77. For NNH calculation is similar (NNH=3.7) to JAMA report, but this must underestimate true NNH for adverse events because certain adverse events that were deemed not associated with the drug were excluded. Duration of harm is unknown.
14. The quality of life gives different sample sizes for each subsection (e.g. G = 89, P = 99 for health transition but g = 92, and p = 101 for physical functioning). I can see any reason for this. Also I can't understand why, in general significantly more people on placebo filled out the QoL (e.g. average sample size for placebo group on the SF-36 was 100.2, SD = 1.39, and for Gabapentin it was 91.4, SD = 2.7) i.e. lots of variability in the number of people who completed the Gabapentin survey.
15. Note that page 143 of the research report states that *"In*

			Gabapentin (n = 104/113) Baseline: 3.6 (SD = 3.2) Week 8 (LOCF): 2.0 (SD = 2.7) Mean Change from Baseline: -1.5 (2.9) *note that this is stated as -1.5 but clearly 2.0 – 3.6 = -1.6 P-Value < 0.001 **MPQ Ratings of Present Pain Intensity (PPI)** • Unclear what this means in JAMA report; Table 26 on p. 101 of unpublished report clarifies that MPQ-PPI is a "5-point" scale of present pain intensity (0 = no pain, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, 5 = excruciating) – this is in fact a 6-point scale. • The only results presented in JAMA report (p. 1840) were that there was a rating of "no pain" in final week for 16.0% of patients on Gabapentin compared with 8.8% of patients treated with placebo. • The report states that these results were "statistically significantly improved among subjects treated with Gabapentin (P < 0.01)" however it does not give standard deviations, or sample sizes for the gabapentin and placebo groups and implies that the cited p-value (<0.01) is for the comparison of gabapentinvs.placebo (not correct) • The unpublished report states that the results were significant for both placebo and gabapentin (P < 0.01) however no p-value is provided for the comparison gabapentin vs. placebo - with the data provided it in unpublished report, it is not possible to calculate this independently.	<table><tr><td>Number of Severe AE</td><td>15</td><td>30</td></tr><tr><td>Deaths</td><td>1/116</td><td>0/113</td></tr><tr><td>Patients with Serious non-fatal AE</td><td>4</td><td>10</td></tr><tr><td>WDAE</td><td>14</td><td>21</td></tr></table> • Note that page 143 of the research report states that *"In the placebo group, 5 patients (4%) experienced 5 serious adverse events (1 fatal and one non-fatal); in the Neurontin® group 10 patients (9%) experienced 17 serious adverse events, none of which were fatal."* However, according to Table 31 of page 120 of the research report, there were 30 severe adverse events. This difference between total "serious adverse events" (P=5, G=17) vs. "severe adverse events" (P=15, G=30) is not explained. **6. Validated measures of improvement in global function including return to work, study, activities of daily living** • No efficacy variable of this nature was included in the reports. **7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint**	*the placebo group, 5 patients (4%) experienced 5 serious adverse events (1 fatal and one non-fatal); in the Neurontin® group 10 patients (9%) experienced 17 serious adverse events, none of which were fatal."* However, according to Table 31 of page 120 of the research report, there were 30 severe adverse events. What is the difference? 16. Compliance is defined very specifically on pages 20-21 of the research report but compliance rates in the placebo and gabapentin groups are not reported.

The unpublished report presents the following results (NB "Week 8" are LOCF).
These would be better expressed by using the true ITT denominator (113) for the gabapentin group, as for the placebo group (116) – see comments page before table.

Placebo (n = 116)

Pain Rating	Baseline	Week 8
0	3 / 116	10 / 116
1	15 / 116	29 / 116
2	46 / 116	38 / 116
3	34 / 116	27 / 116
4	9 / 116	4 / 116
5	6 / 116	5 / 116
Missing	3 / 116	3 / 116

Gabapentin (n = 109/113)

Pain Rating	Baseline	Week 8
0	2/ 109	17 / 109
1	15 / 109	34 / 109
2	48 / 109	40 / 109
3	27 / 109	8 /109
4	9 / 109	4 /109
5	5 / 109	3 /109
Missing	3 / 109	3/ 109

Subject's Global Impression of Change (SGIC) – not independent of primary outcome

- Subjects completed SGIC at final visit, week 8
- The JAMA report implies that the SGIC was either a 5 point scale (Moderately Improved, Much Improved, Minimally Improved, No change, Worse) where Moderately/Much Improved were pooled post-hoc,**or** a 4 point scale

The unpublished report clarifies that SGIC is a 7-point categorical scale (1= much improved,

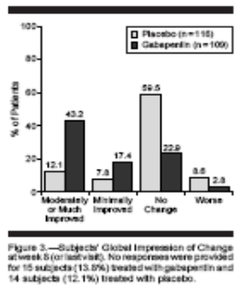
- No efficacy variable of this nature was included in the reports.

8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by true intention to treat (ITT) –where this was the pre-defined primary endpoint in a trial

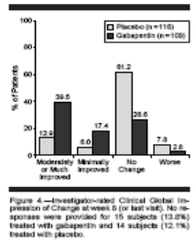
- Measured by the difference in average daily pain during baseline week and average daily pain score in the final study week on the Likert scale
  - Evaluated from daily pain diaries
  - Minimum treatment group difference in chance from baseline that was considered clinically meaningful was 1.5 points

The following compare the JAMA report with unpublished report results:

Placebo (n = 116/116)
Baseline: 6.5 (SD = 1.7)
Week 8 (LOCF): 6.0 (SD = 2.4)
Mean Change from Baseline: -0.5 (SD = 1.6)
Percent Change: 7.7%
P-value (p. 83 of unpublished report) < 0.005

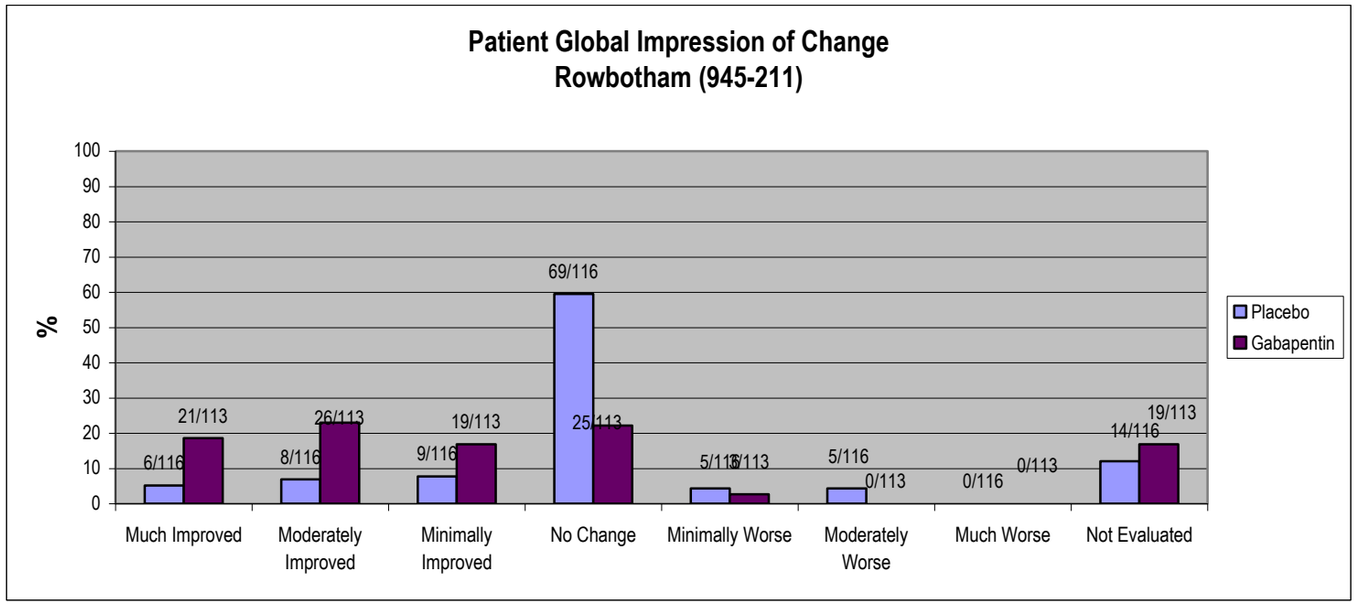
			2=moderately improved, 3=minimally improved, 4= no chance, 5= minimally worse, 6=moderately worse, 7=much worse). Furthermore, some data are missing.
			• See JAMA report Figure 3 – Subjects' Global Impression of Change at week 8 (page 1840)
			 
			
			Figure 3.—Subjects' Global Impression of Change at week 8 (or last visit). No responses were provided for 16 subjects (13.8%) treated with gabapentin and 14 subjects (12.1%) treated with placebo.
			
			According to the JAMA report:
			
			Placebo (n = 116/116)
			***note that these results were provided in percentages so we have made calculations to discern N's for each category for each group:**
			
			Moderately or Much Improved: 14/116(12.1%)
			Minimally Improved: 9 / 116 (7.8%)
			No Change: 69 / 116(59.5%)
			Worse: 10 / 116 (8.6%)
			No Response: 14 / 116 (12.1%)
			
			Gabapentin (n = 109/113)
			***note that these results were provided in percentages so we have made calculations to discern N's for each category for each group: Results should be expressed for categorical variables as % of the true ITT N (113)**
			
			Moderately or Much Improved: 47/109 (43.1%) (42/113 = 42%), etc.
			Minimally Improved: 19/109 (17.4%)
				Gabapentin (n = 109/113)
				Baseline: 6.3 (SD = 1.6), SD = 1.7 in unpublished report
				Week 8 (LOCF): 4.2 (SD = 2.3)
				Mean Change from Baseline: -2.1 (SD = 2.1)
				Percent Change: 33.3%
				P-value (p. 83 of unpublished report) < 0.001
				
				The mean between group difference between change in pain score is estimated by change in Gabapentin pain score – change in placebo pain score = (-2.1) – (-0.5) = -1.6
				
				p-value < 0.001
				
				<u>9. % of patients achieving "much improved" or "moderately improved"</u>
				
				• Percentage of patients achieving much improved was
				  ○ Study reports Gabapetin : 47 / 109, 43.1% but should be 47 / 113, 41.6%
				  ○ Placebo: 14/116 or 12.1%
				  ○ A between groups p-value was not calculated here.
				  ○ Note we have not decided what to do about missing values (i.e. 14 observations missing in placebo group and 15 missing in Gabapentin	

			No Change: 25/109 ((22.9%) Worse: 3/109 ((2.8%) No Response: 15/109 (13.8%) **According to the unpublished report at p. 89:** **(Results should be expressed for categorical variables as % of the true ITT N (113)** **Placebo (n = 116/116)** 1. Much Improved: 6 /116 (5.2%) 2. Moderately Improved: 8 /116 (6.9%) 3. Minimally Improved: 9/116 (7.8%) 4. No Change: 69/116 (59.5%) 5. Minimally Worse: 5/116 (4.3%) 6. Moderately Worse: 5/116 (4.3%) 7. Much Worse: 0/116 (4.3%) 8. Missing: 14/116 (4.3%) **Gabapentin (n = 109/113)** 1. Much Improved: 21 / 109 (19.3%) e.g. 21/113 = 19%, etc. 2. Moderately Improved: 26/109 (23.9%) 3. Minimally Improved: 19 / 109 (17.4%) 4. No Change: 25/109 (22.9%) 5. Minimally Worse: 3/109 (2.8%) 6. Moderately Worse: 0 / 109 (0%) 7. Much Worse: 0 / 109 (0%) 8. Missing: 19 / 109 (13.8%) **Investigator-rated Clinical Global Impression of Change (CGIC) – not independent of primary outcome**	group) **10. Histogram presentation of all PGIC 7-point results** • See histograms included at end of table.	

			• Clinicians completed questionnaires at end of treatment (week 8) • Similar to above, seems like a 4 or 5 point scale in published report but is clearly a 7 point scale in the research report. • JAMA Figure 4: Investigator-rated Clinical Global Impression of Change at week 8 (p. 1841)  Figure 4.—Investigator-rated Clinical Global Impression of Change at week 8 (or last visit). No responses were provided for 15 subjects (13.0%) treated with gabapentin and 14 subjects (12.1%) treated with placebo. **JAMA Report:** **Placebo (n = 116)** ***note that these results were provided in percentages so calculations were done do discern sample sizes.** Moderately or Much Improved: 15 / 116 (12.9%) Minimally Improved: 7 / 116 (6.0%) No Change: 71 / 116 (61.2%) Worse: 9 / 116 (7.8%) No Response: 14 / 116 (12.1%) **Gabapentin (n = 109/113)** ***note that these results were provided in percentages so calculations were done do discern sample sizes. Results should be expressed for categorical variables as % of the true ITT N (113)** Moderately or Much Improved: 43/109 (39.5%) e.g. 43/113 = 38%, etc. Minimally Improved: 19/109 (17.4%) No Change: 29 / 109 (26.6%) Worse: 3 / 109 (2.8%)		

			No Response: 15 / 109 (13.8%) **Unpublished Report:** **Results should be expressed for categorical variables as % of the true ITT N (113)** **Placebo (n=116)** 1. Much Improved: 3/116 (2.6%) 2. Moderately Improved: 12/116 (10.3%) 3. Minimally Improved: 7/116 (6.0%) 4. No Change: 71/116 (61.2%) 5. Minimally Worse: 7 /116 (6.0%) 6. Moderately Worse: 2/116 (1.7%) 7. Much Worse: 0/116 (0%) 8. Missing: 14/116 (12.1%) **Gabapentin (n = 109/113)** 1. Much Improved: 17/109 (15.6%) e.g. 17/113 = 15% 2. Moderately Improved: 26/109 (23.9%) 3. Minimally Improved: 19/109 (17.4%) 4. No Change: 29/109 (26.6%) 5. Minimally Worse: 2 /109 (1.8%) 6. Moderately Worse: 0 /109 (0%) 7. Much Worse: 1/109 (0.9%) 8. Missing: 15/109 (13.8%) **Short-Form 36 Quality of Life Questionnaire (SF-36) – not independent of primary outcome** • Completed at week 0 and again at week 8 at the final visit • According to P. 1840 of JAMA report, the SF-36 measures of physical functioning, role-physical, bodily pain, vitality, and mental		

			health all showed Gabapentin to be superior to placebo (P < 0.01; table 3) • Table 3 (JAMA report, p. 1841) was too large for this column and is therefore not included here. • Table 28 of the unpublished report (p. 107) shows the same results as Table 3. **Profile of Mood States (POMS) – not independent of primary outcome** • Completed at week 0 and again at week 8 at the final visit • According to page 1840 of JAMA report, patients treated with gabapentin showed significantly greater improvement than subjects treated with placebo in the POMS assessments of depression-dejection, anger-hostility, fatigue-inertia and confusion-bewilderment, as well as in total mood disturbance (P ≤ 0.01) • Results also in table 3 on page 1841 (see end of document) • Results in table 30 on page 115 of unpublished report match results in published report.		


Patient Global Impression of Change
Rowbotham (945-211)
%
100
90
80
70
60
50
40
30
20
10
0
6/116
21/113
8/116
26/113
9/116
19/113
69/116
25/113
5/116
5/113
5/116
0/113
0/116
0/113
14/116
19/113
Much Improved
Moderately Improved
Minimally Improved
No Change
Minimally Worse
Moderately Worse
Much Worse
Not Evaluated
Placebo
Gabapentin

Study No. 5 - Dallochio 2000 – PDPN – GABAPENTIN VS. AMITRIPTYLINE OPEN LABEL TRIAL SUMMARY, ONLY FOR SAFETY OUTCOMES – FINAL – July 23, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane safety hierarchy only – open trial)	Comments/conclusions of Dr. Perry
Study No. 5 Dallochio C, Buffa C, et al. Gabapentin vs. Amitriptyline in Painful Diabetic Neuropathy: An Open-Label Pilot Study. J. Pain and Symptom Management. 2000; 20: 280-283. Support: Parke-Davis SpA, Milan, Italy is co-author. Dates: Trial performed in 1997 (p. 285).	Painful diabetic peripheral neuropathy (PDPN): Inclusion: • Painful DPN ≥ 6 months • Pain score ≥ 2 on a 4-point categorical scale (0= no pain to 3=severe pain) • *"each patient was asked to rate average pain during previous use of gabapentin or amitriptyline"* Exclusion (interpreted from apparent typographical error at p. 281): • Renal, hepatic, CV insufficiency • *"other adjuvant analgesics, such as TCA's, mexilitine, carbamazepine, or other anticonvulsants..."* for 1 month Overall group characteristics: Age range: 61-83	Study design: 12-week open, parallel-group single centre trial of gabapentin up to 2400 mg/d vs. amitriptyline up to 90 mg/d for a total of 12 weeks. Drugs were titrated over 4 weeks, starting from G=1200 mg/d and A-30 mg/d, then maintained at maximum tolerated dosage for 8 weeks. Patient flow: • Screened: not reported • Randomized: 25 (randomization procedure not described) • randomization: G=13; A=12 • All 25 patients "completed trial" NB: there is no flow diagram nor way to confirm that all 25 patients completed an 8-week, relatively high dose trial, which is not in keeping with other studies.	Because this is an open-label trial, this analysis will only look at safety outcomes – definitions at pp 31-32 of unpublished report appear to be compatible with other gabapentin studies.	Mean Achieved Doses: G (N=13): 1785 mg/d (351) A (N=12): 53 mg/d (16) Mortality: not reported Serious Adverse Events (number of patients or number of events): not reported Withdrawal Due to Adverse Events: not reported Total patients with AE's: G=4/13 P=11/12 (P=0.003, Fisher's exact test) Total AE's (patients may have > 1): Not reported Characteristic AE for combined groups: Not enumerated in detail	1. Low quality open study which may not have been randomized, is open-label, and has no placebo group. 2. Unusual to have no drop outs in older patients in an 8 week study at large doses. 3. Reporting of AE inadequate to meta-analyse. Inappropriate to meta-analyse total patients with AE's as we cannot be sure patients were randomized. 4. Unusual to ask patients about their response to gabapentin or amitriptyline prior to randomization – unclear why this was done or how it might have affected "randomization" or outcomes. 5. Outcomes are claimed to favour G over A, but are not comparable to other pain outcomes and not reliable.

Notes: This is an open-label trial which is not suitable for meta-analysis, even for safety outcomes.

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 6 Reckless, J Parke-Davis (Berlin, Germany) 945-224 UNPUBLISHED 7 week DBRCT May 29, 1998 – Sept. 7, 1999 Final Protocol: February 23, 1998 (p. 175/3214) Investigators meeting March 6-7, 1998 59 European, 2 South African sites Last statistical protocol specified October 15, 1999 Blind broken October 26, 1999	Painful diabetic peripheral neuropathy (PDPN): Inclusion/exclusion: • No prior treatment with gabapentin ("enrichment bias") • No chronic kidney disease (Cr clearance ≥ 60 mL/min predicted (violated for some patients) • Pain score (Likert) ≥4 on daily pain diary before randomization • Pain score (VAS) ≥ 4 at screening and	Placebo vs. gabapentin (3 x/day) titrated over 3 weeks to 600 mg/d, 1200 mg/d, or 2400 mg/d; then 4 weeks steady dose. Number screened = 432, randomized = 325. P = 77 randomized (77 reported for safety, 77 for efficacy; 65 completed 7weeks) G600 = 82 randomized (82 reported for safety, 82 for efficacy; 70 completed 7 weeks) G1200 = 82 randomized (82 reported for safety, 82 for efficacy; 76	Predefined outcomes: Primary: Pain (Likert 0-10 score) as group mean of individual means from patients' last 7 available scores while on study medication (up to end of Week 7) from daily diary records of previous 24 hours (LOCF for noncompleters, protocol specifies BOCF for any subject taking drug who had no post-baseline assessment – p. 14 of protocol). Change in pain was also assessed by comparison of group means of individual patient differences from baseline (screening) determined from last 7 available daily pain scores during screening and during double blind treatment (up to end of Week 7). NB: 1 patient in G2400 group was not evaluable due to missing screening data. Other patients with protocol violations, e.g. 14 patients with baseline score < 4, were evaluated (p. 44).	Mortality (p. 84): P = 0; Gabapentin groups = 0 Serious Adverse Events (p. 84): P = 4/77 G600 = 5/82 G1200: 2/82 G2400: 3/84 Withdrawal Due to Adverse Events (WDAE): P = 8/77 G600 = 8/82 G1200 = 3/82 G2400 = 11/84 ("Associated AE's" appear higher (8/84) in G2400 group) Total withdrawals: P=12/77 G600=12/82 G1200=6/82 G2400=19/84 Total patients with AE's P=36/77 G600=40/82 G1200=35/82	1. Despite "enrichment" by excluding patients who had previously used gabapentin, (partly during a period when the Backonja publication of Study 245-210 *"…gave rise to hish expectations concerning the analgesic effects of gabapentin"* (p. 136) this study shows no beneficial effect on primary or secondary outcomes of any dose of gabapentin from 600-2400 mg/day for painful DPN. Secondary outcomes which purport to be significant are results of multiple comparisons and are probably not statistically significant. 2. The study confirms other findings of dose dependent neurotoxicity, but did not find evidence for dose-dependent efficacy, despite finding nearly a nearly linear dose-concentration relationship for mean plasma

Final report February 7, 2000	randomization (SF-MPS) NB: A few patients sneaked through screening without meeting criteria Baseline characteristics: • Mean pain score (Likert NRS, 0-10): P (N=77/77): 6.18 (SD 1.68) Range: 1.0 - 10 G600 (N=82/82): 6.30 (SD 1.49) Range: 3.1 – 10 G1200 (N=82'82): 6.10 (SD 1.58) Range: 3.1 - 10 G2400 (N=83/84): 6.23 (SD 1.58) Range: 3.7-10– 1 had no baseline score • Groups appear generally similar. Some in each group had creatinine clearance <	completed 7 weeks) G2400 = 84 randomized (84 reported for safety, 83 for efficacy; 65 completed 7 weeks) This study appears to be true ITT-LOCF as all patients randomized except for 1 patient in G2400 group who lacked baseline pain score appear to have been reported for efficacy. It does not report on all patients at true endpoint, and could exaggerate apparent efficacy of higher dose gabapentin if efficacy determinations were made at times of early patient withdrawal due to adverse neurologic effects (p. 91)	Sample size estimation (p. 32) was calculated based upon results of Study 245-210 (final report December 30, 1998, p. 159) showing group mean difference at endpoint on NRS (Likert) score of 1.3 for target dose of 3600 mg/d vs. placebo. Designers of 245-224 must have been aware by early 1998 of results of 245-210. Analysis by ANCOVA with treatment and cluster (pooled centres) as fixed effects and baseline mean score as covariate – similar to 245-210. (p. 32) Analysis on ITT-LOCF population appears to be complete except for 1 patient (see above). *"…Both results of original data and transformed data were o be displayed and discussed. In case of failure of data transformation, a nonparametric ANCOVA given by Conover was to be applied…"* (p. 33) Secondary: NB: all secondary outcomes are <u>dependent,</u> not independent of primary outcome, as they all measure various aspects of the same thing (pain relief). There was no difference between placebo and gabapentin groups for any outcome, so this will not be discussed further	G2400=45/84 Total patients with AE did not differ between groups (p. 84), but "Associated AE's" affecting nervous system showed the usual pattern for gabapentin: P= 6/77 (8%) G600=10/82 (12%) G1200=10/82 (12%) G2400=19/84 (23%) No test of statistical significance reported. The authors comment (p. 90): *"…The highest incidence of withdrawals due to adverse events was found in the 2400 mg gabapentin group. In this group especially adverse events of the nervous system resulted in withdrawal of the patients. While 8 pagtients were withdrawn from the 2400 mg gabapentin group due to adverse events of the nervous system, only 1 patient discontinued the study due to adverse events of the nervous system in the 600 and 1200 mg gabapentin group, respectively. In the placebo group thre was no adverse event leading to withdrawal that was affecting the nervous system."* (p. 91 Table 39) Total AE: not reported Weight: (mean, or mean change, by group) Not reported in complete report (? Appendices) <u>Primary outcome (endpoint):</u> Group mean pain scores at "endpoint" = ITT-LOCF ("endpoint" = last observation carried forward as if all endpoints were at 7 weeks): P (N=77): 4.5 (SD 2.3) G600 (N=82): 4.9 (SD 2.3)	concentrations at steady state. 3. It appears to have assessed all but one patient (in 2400 mg/d group) for primary efficacy outpoints (true ITT-LOCF) and thus appears to be superior in quality to other trials. 4. Exploratory or pre-specified analyses of secondary outcomes found no benefit of gabapentin at 600-2400 mg/day for: • % responders • % "pain-free" or "virtually pain-free" • patient global impression of change • clinician global impression of change 5. During open-label extension, the authors noted that *"…The higher patients were titrated, the more paracetamol*they *took."* (Table 55, p. 117) THIS OBSERVATION, ALONG WITH THE PRIMARY OUTCOME DATA, CHALLENGES THE ASSUMPTION THAT THERE IS DOSE-DEPENDENT EFFICACY FOR GABAPENTIN, WHEREAS

	screening criterion.		here. Additional information from secondary outcomes and post-hoc comparisons apparently described (? Statistical protocol) prior to unblinding data (p. 36): • Dose of paracetamol (acetaminophen) by number of days taken and total dose ingested during 4-week fixed dose phase of trial, by group • Number and % of "responders", defined as patients in each group attaining ≥ 50% reduction in individual mean endpoint pain score vs. baseline mean , who did not withdraw for non-efficacy and did not take any forbidden medication during days used to calculate endpoint NRS (this definition could include people who withdraw due to adverse events!) – ITT – see p. 54/3214 of final study report In an additional analysis responders were evaluated. Responders were defined as patients with at least 50% reduction in pain score from baseline to Week 7/Termination, who did not withdraw from the study due to lack of efficacy and did not take any forbidden medication during the study days included in the endpoint calculation. Seven patients with at least 50% reduction in pain were defined as non-responders because they took forbidden medication during the days included in the calculation (placebo: pat. no. 8908; 600 mg gabapentin: 1513, 7209; 1200 mg gabapentin: 5701, 5804, 7905, 8102). Table 15 displays the responders in the treatment groups. TABLE 15. Responders/Non-responders (ITT Population) Treatment Group Placebo N = 77 / Gabapentin 600 mg N = 82 / Gabapentin 1200 mg N = 82 / Gabapentin 2400 mg N = 83 Responders, N (%) 19 (24.7) / 13 (15.9) / 33 (40.2) / 25 (30.1) Non-Responders, N (%) 58 (75.3) / 69 (84.1) / 49 (59.8) / 58 (69.9) Total, N (%) 77 (100.0) / 82 (100.0) / 82 (100.0) / 83 (100.0) • Number of "pain-free" (endpoint individual mean NRS score = 0) and "virtually pain-free" (endpoint individual mean NRS score	G1200 (N=82): 3.9 (SD 2.4) G2400 (N=83/84): 4.1 (SD 2.5) Change from baseline: P: -1.7 (SD 2.1) G600: -1.4 (SD 2.0) G1200: -2.2 (SD 2.2) G2400: -2.1 (SD 2.5) There was no difference between any gabapentin group vs. placebo, nor pooled 1200/2400 gabapentin groups vs. placebo. The report authors state: *"…This means that in this study efficacy of the chosen doses of gabapentin in controlling pain associated with diabetic neuropathy could not be proven."* Figure 3 p. 53) shows this visually. <u>Secondary outcomes:</u> Paracetamol (acetaminophen) consumption during 4-week fixed-dose period (not all patients used it): P (N=32): 16 days mean use; 26 g mean ingestion G600 (N=26): 18 days mean use; 38 g mean ingestion G1200 (N=28): 16 days mean use; 32 g mean ingestion G2400 (N=35): 20 days mean use; 43 g mean ingestion The authors note *"… The analysis of total intake revealed that the higherst amounts were taken in the 2400 mg gabapentin group and the lowest amounts in the placebo group…"* "Responder" analysis<u>≥</u>50% reduction in pain from baseline	DOSE-DEPENDENT TOXICITY IS A CONSISTENT FEATURE OF ALL STUDIES. THE AUTHORS CONCLUDE (p. 135 et seq): *"…In this study, none of the tested gabapentin doses was superior to placebo on the primary endpoint weekly mean pain score; …* *"… The failure to demonstrate efficacy on the primary outcome measure may be in part due to a high placebo effect in this study…* *"…Compared to study 945-210 the rate of all adverse events as well as of associated adverse events was much lower in study 945-224….Thus, the decreased effect with regard to efficacy parameters of lower doses of gabapentin is coupled with a decreased rate of adverse events…"* 6. Publication of this trial would have FUNDAMENTALLY ALTERED INTERPRETATION OF THE SMALLER BACKONJA TRIAL AND REFERENCES TO IT!

			between 0 and 1) for each group – ITT-LOCF	(note conditions: this definition could include people who withdraw due to adverse events!) – this is almost certainly not a pre-defined analysis in original protocol): TLP conclusion: this outcome cannot be used for meta-analysis as it is not pre-specified. P = 19/77 (25%) G600 = 13/82 (16%) G1200 = 33/82 (40%) G2400 = 25/84 (ITT: 30%) Statistical significance is claimed for G1200 vs. placebo but there is no correction for multiple comparisons – the authors note placebo was better than G600 and G1200 better than G2400! (p. 57) - Analysis of "virtually/totally pain-free" patients (post-hoc): P = 8 virtually, 0 totally pain-free G600 = 4 virtually, 1 totally pain-free G1200 = 6 virtually, 1 totally pain-free G2400 = 12 virtually, 4 totally pain-free NB: these could include patients who withdrew due to adverse events. The authors found no significant difference between gabapentin groups and placebo group. (p. 58) Sleep interference scores at endpoint: P (77/77): 3.87 (SE 0.24) G600 (82/82): 3.85 (SE 0.23) G1200 (82/82): 2.80 (SE 0.23) G2400 (82/84): 3.01 (SE 0.23) – not ITT (2 missing) Authors claim significant reduction in G1200 and G2400 groups (difference vs. placebo = 0.85-1.1, p = 0.001) but do not describe correction for multiple comparisons. Placebo also lowered sleep	

				interference. Patient Global Impression of Change at endpoint(PGIC): No significant difference was found between placebo vs. gabapentin groups. Many observations missing from 3 of 4 groups. Imputation of missing observations as "no change" or "worse" would reduce any apparent differences in graph at p. 73, Figure 9. TLP conclusion: Although many missing observations, this can be used for meta-analysis by using ITT denominators, i.e. PGIC: P = 26/77 (34%) G600 = 22/82 (27%) G1200 = 36/82 (44%) G2400 = 36/84 (ITT: 43%) TABLE 26. PGIC Score: Descriptive Statistics (ITT Population) Treatment Group Patient Status / Placebo N = 77 / Gabapentin 600 mg N = 82 / Gabapentin 1200 mg N = 82 / Gabapentin 2400 mg N = 83 **Patients assessed** 72 (100.0) 73 (100.0) 81 (100.0) 73 (100.0) Very Much Improved, N (%) 10 (13.9) 9 (12.3) 14 (17.3) 14 (19.2) Much Improved, N (%) 16 (22.2) 13 (17.8) 22 (27.2) 22 (30.1) Minimally Improved, N (%) 21 (29.2) 23 (31.5) 27 (33.3) 19 (26.0) No Change, N (%), 16 (22.2) 18 (24.7) 13 (16.0) 11 (15.1) Minimally Worse, N (%) 5 (6.9) 7 (9.6) 4 (4.9) 5 (6.8) Much Worse, N (%) 2 (2.8) 3 (4.1) 1 (1.2) 1 (1.4) Very Much Worse, N (%) 2 (2.8) 0 (0.0) 0 (0.0) 1 (1.4) **Overall Scores**[a] Mean (SD) 0.9 (1.4) 0.9 (1.3) 1.3 (1.2) 1.3 (1.3) Median 1.0 1.0 1.0 1.0 Range -3 - 3 -2 - 3 -2 - 3 -3 -3 PGIC = Patient global impression of change; SD = Standard deviation. [a] Based on: 3 = Very much improved; 2 = Much improved; 1 = Minimally improved; 0= No change; -1 = Minimally worse; -2 = Much worse; -3 = Very much worse.	

				Clinician's GIC (CGIC) at endpoint: Authors claim difference favouring G1200 group only vs. placebo (p. 75) but do not report correction for multiple comparisons. Many missing observations from other 3 groups. Gabapentin plasma concentrations (p. 82): P (N-65): 0 mg/L G600 (N=65): 2.27 mg/L G1200 (N=79): 3.71 mg/L G2400 (N=72): 7.01 mg/L These were measured at end of double-blind fixed dose phase and *"were within the expected range"*, demonstrating close to linear kinetics for group means.	

VAN DE VUSSE 2004 – GABAPENTIN FOR CRPS-1 – DBR CROSSOVER TRIAL (published) – FINAL **– SUMMARY – Study No. 7**

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 7 Van de Vusse, Stomp-van den Berg et al. Randomised controlled trial of gabapentin in Comples Regional Pain Syndrome type 1 [ISRCTN84121379]. BMC Neurology 2004, 4: 13 doi:10.1186/1471-2377-4-13. (9 pages) Support: Parke-Davis supplied gabapentin and matching placebo capsules and financial support for 2 authors to attend 1 congress. Dates: Patients enrolled and completed between November 1998 – December 1999 Trial design: Independent. DBR Crossover Trial, 8 weeks including 2 treatment periods of 3 weeks separated by 2 week washout, comparing gabapentin (G) with placebo to final dose of G=1800 mg/d	Chronic CRPS-1 (complex regional pain syndrome type 1, synonymous with "reflex sympathetic dystrophy") Inclusion: • 18-75 years • pain > 3 on a visual analog scale (VAS) of 0 (no pain) -100 (worst pain imaginable) • long-standing CRPS known to academic hospital pain service with functional impairment anatomically separate from initial trauma Exclusion: • *"known kidney and/or severe liver disease:* • diabetes	Study design: 8 week double blind crossover RCT comparing G with P as 2 arms: P/G x 3 weeks with 2 week washout between treatments vs. G/P with 2 week washout between treatments. Patient flow (Fig 1, p 4/9): • Screened (files): 188 • Screened (invited): 151 • Excluded: 93 (mostly non-consenting or different diagnosis) • Randomized: 58 as P/G=29, G/P=29 • Completed crossover: 46/58 (79%) as P/G=24/29 (83%), G/P=22/29 (76%)	Predefined outcomes: Primary: VAS (0-10 point) pain rating for last 24 hours at end of phase 1, end of washout, end of phase 2 Secondary: • "Global perceived effect (GPE) on pain" as 7 categories from "worst ever" to "best ever". • "Neuropathic pain scale." • Sensibility of skin • Mechanical allodynia test • Physical examination abnormalities	Mortality: Not reported Serious Adverse Events: Not reported Withdrawal Due to Adverse Events: interpreted for this table as total from each sequence (by treatment) over total exposed (completers + withdrawals for each drug): P=0/51; G=3/54 These appear suitable for meta-analysis Total withdrawals: P=6/56; G=4/53 Total patients with AE's: interpreted for this table as total from each sequence (by treatment) over total exposed per treatment from Table 5. NB: these totals differ slightly for P (N=56) and for G (N=53) from the interpolated number for patients exposed to each drug, but the denominators are so close that it is preferable to use the numbers from Table 5 for this analysis, as reported: P total = 21/51 (41%) G total = 36/54 (67%) These appear suitable for meta-analysis Most important AE's (Table 5): interpreted for this table as total from each sequence (by	1. This is an unusual study which is not directly comparable with any other study. Doctors were unblinded, and patients were unblinded after crossover. The authors conclude that *"Gabapentin had a mild effect on pain in patients with CRPS 1 …A subpopulation of CPRS patients may benefit from gabapentin, but then for each individual patient the benefit has to be weighed against the frequently occurring side effects."* 2. Outcomes other than safety are not suitable for meta-analysis. The number of patients shown as

Concealment: identical placebo capsules Randomization: *"assignment scheme was generated by our hospital pharmacy from a table of random numbers. The closed envelopes containing the assignments were prenumbered and kept at the pharmacy.."* (p. 2/9)	Allowable drugs: usual analgesics allowed Baseline characteristics: Mean age: 44 (range 24-75)	• Exposed to drug (completers + withdrawals for each drug): P=56, G=53) • Completed assigned treatments: P=50/56; G=49/53 • Withdrawn from treatments: P=6/56; G=4/53; washout=2/? Drug doses/titration (p. 2112): Titration from G=600 mg/d on day 1-2 to 1800 mg/d by day 5, then stable to end of week 3. Statistical Analysis: (p. 3/9) Unusually complicated description. See original report.	NB: none of these scores are comparable with any other commonly used scales. Test of blinding: Both investigators and subjects were unblinded (p. 3/9)	treatment) over total exposed per treatment from Table 5. NB: these totals differ slightly for P (N=56) and for G (N=53) from the interpolated number for patients exposed to each drug, but the denominators are so close that it is preferable to use the numbers from Table 5 for this analysis, as reported: Dizziness: P=2/51 (3.9%); G=20/54 (37%) Somnolence: P=3/51 (5.9%), G=15/54 (28%) Lethargy: P=1/51 (2.0%); G=11/54 (20%) "Drunken" or "disturbed gait" (ataxia): P=0/51 (0%); G=8/54 (15%) These appear suitable for meta-analysis, using total of "drunken or disturbed gait" as equivalent to "ataxia" reported in other studies. Total AE's (patients may have > 1 as total exceeds total patients with AE): Not reported Disability: not reported > 50% reduction in NRS pain score at endpoint vs. baseline: not reported (not an outcome) Primary outcome VAS pain score: Completer analysis only, not suitable for meta-analysis. Numbers also are only presented graphically. Secondary outcomes: See original report. None are comparable to other	exposed for safety outcomes are so close to the total randomized that they suffice as denominators, although it was not possible to confirm from the article whether the denominators are exactly as shown.

				studies, nor are clearly clinically meaningful. PGIC: not reported	

STUDY NO. 8 - STUDY DETAIL SUMMARY AND ANALYSIS: SIRKKU LARSSON
STUDY NUMBER 945-271 – POST-OPERATIVE AND POSTTRAUMATIC PAIN (POPP) STUDY

The information in the following tables was taken from:

- Gabapentin vs. Placebo in Patients with Neuropathic Pain. A Randomized, Double-Blind, Cross-Over, Multi-Center Study in the Nordic Area. Final Report of Study ISN 945-271. The POPP Study. 2003-03-07. Coordinating Investigator Assoc. Prof. Torsten Gordh. Authors Gunilla Borg, Ph.D., Sirkku Larson, M Sc. Pharm.
- Analysis Plan Protocol 945-271. Gabapentin vs. Patients with Neuropathic Pain. A Randomized, Double-Blind, Cross-Over, Multi-Center Study in the Nordic Area. Post-Operative and Posttraumatic Pain Study (POPP Study). 23.02.2001.

This trial may not have been published because the results show considerably less difference between gabapentin and placebo than were described in published trials for:

- "50% pain reduction" (as assessed - see details in table)
- Difference in group mean pain scores (VAS) at end of treatment (minimal, << 10/100, where a 11/100 difference was pre-defined as the minimal clinically significant difference; note that 10/100 VAS is presumably approximately "equivalent" to 1/10 NRS)
- PGIC, the only outcome where results can be used in our meta-analysis (because a standard 7-point rating scale was utilized and the correct ITT denominators can be used): P=8/111(7.2%); G=21/113 (18.6%)

According to P. 31 of the final report, the" ITT" population consisted of all randomized patients who completed both treatment periods (n = 98; Gabapentin-Placebo Arm = 48, Placebo-Gabapentin Arm = 50). This is not the correct definition of ITT, but rather a "completer" or "per protocol" analysis. To analyze on the basis of ITT, the outcomes of all patients are analysed with the group to which they were originally assigned, whether or not they completed the protocol.

There are several dependant comparisons made throughout this study, however no correction was employed to account for this (e.g. Bonferrroni's correction).

According to page 46 and Table 32, 21/107 (19.6%) of patients taking Gabapentin were treated with a dose of Gabapentin of less than 2400 mg (average does was 2243 mg, SD = 402). In comparison, 7/103 (6.8%) of patients on placebo were treated with less than 2400 mg (mean = 2363 mg, SD = 172). The final report calls this a difference that could be seen which one would assume to mean statistical significance in which would in turn indicate that people found it difficult to reach the maximum dose of Gabapentin for this study, 2400 mg, when in fact patients are often prescribed up to 3600 mg of Gabapentin.

No carry-over effects were observed which implies the washout period was adequate; therefore, the use of a crossover design was appropriate. Period effect were deemed significant, however, details are sparse. For both "ITT" (completer population) and PP (Per Protocol) analyses, those who took Gabapentin first saw almost no reduction in pain score when on placebo (reduction = 0.5 for "ITT" or completer population and 0.7 for PP) compared to greater reductions when on placebo seen when placebo taken first (6.9 for "ITT" or completer population, 7.1 for PP), this would seem to indicate unblinding due to an inactive placebo. Also, MPIS

shows no improvement over placebo in the “ITT” (completer population) and PP populations (P = 0.20, P = 0.16 respectively), the “ITT” (completer population) only included those who completed both trials, Therefore, the results are probably even less significant when one accounts for withdrawals.

This study precluded past Gabapentin use, this leads to enrichment bias.

With regard to Quality of life (“ITT” or completer population), it is stated that there were significant improvements in Vitality, Role Emotional, Mental Health, and a borderline improvement in bodily pain, as compared with placebo. Although a marker can be statistically significant is it clinically significant? For example, mental health supposedly improved by 3.95189 after treatment with Gabapentin but what does that mean? Is there actually a noticeable difference? Furthermore, the tables for the QoL markers (before and after Gabapentin or placebo) are listed in the back (Tables 38, 39, and 40, page 60, 61 of the March report) however the calculated value for change in Gabapentin – change in placebo are not consistent (Table 40 values are not consistent with values in table 39). The corrected version of the tables shows a larger improvement in Role Physical, Bodily Pain, and Social Functioning with placebo. There are similar problems with the QoL tables for the PP population.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Kelsey Innes
Study No. 8 Study Manager: Sirkku Larson. Coordinating Investigator: Torsten Gordh Randomized, double-blind, placebo-controlled, cross-over, multicentre study. Protocol Number: ISN 945-271 Clinical Study Protocol approved April 7, 1998 (1 amendment implemented before enrolment, 2 addenda during course of study, see. Pp.27-28 for details) Date First Patient Included: 12-November-1998	Neuropathic pain due to nerve injury. Inclusion Criteria: • Male or female, at least 18 years of age • Patients with a peripheral nerve injury who have experienced this form of pain for greater than 6 months • The diagnosis according to ICD-10 will include o Post-traumatic neuralgia o Postoperative neuralgia • Patients who is judged by the investigator to fulfill a pain score of greater than 30 on a VAS (0-100) at randomization • Randomization procedure explained on page 19 of the March report, state that the randomization list is in appendix 7 (we don't have appendices)	<u>Study Populations:</u> • According to P. 31 of the final report, the "ITT" population consisted of all randomized patients completed both treatment periods (n = 98) (Gabapentin-Placebo – 48, PI-G – 50). This is not the definition of ITT, but is in actuality the completer population see comments for details. • The safety analysis was based on all patients who took at least one dose of study medication. <u>Patient Flow:</u> Screened: 159 Randomized: 120 Gabapentin-Placebo Arm: 61	NB: The number of patients randomized was 120. The number of patients reported as "ITT" was 98, in reality this "ITT" population consisted only of those patients who completed both treatment periods. The Per Protocol (PP) population consisted of 85 patients, this was the number of patients with no major protocol deviations. • Before any statistical analyses were performed, decisions were made, see p. 28 for details. • P. 27 of March report: study was expected to have at least 80% power to detect a clinically significant difference between P and G (a diff of < 11 on a 100 mm VAS not considered clinically significant) o They say this but continuously point out VAS results less than 11 mm as if they are something significant (e.g. with mean sleep interference score on p.37, with ¶4 of discussion p. 49) • If no carry over effect then SE was to be reduced by 1.4 → 80% power to detect an 8-unit effect difference o Note that period effects but no carry-over effects were detected. <u>Primary Variable</u>	<u>1. Mortality:</u> P = 0/111, G = 0/113 <u>TLP: Mortality OK for meta-analysis</u> <u>2. Serious Adverse Events</u> • See definition on p. 24 of March report • See table 61 on page 72 for details. <u>TLP: Number of patients with SAE OK for meta-analysis</u> Number of patients with SAEs: P = 3 / 111 (2.7%) G = 2 / 113 (1.8%) <u>TLP: Total SAE OK for descriptive statistics</u> Total number of SAEs: P = 3 G = 4 (i.e. 2 patients experienced 4 SAEs	1. MPIS, MSIS, and each dimension of SF-36 were analyzed by means of standard normal-theory based methods, ANCOVA, adjusting for the baseline… (See p. 26 of March report for details). Treatment and period were used as explanatory variables; however, it does not seem as though treatment centre was used as a possible explanatory variable, it should have been. 2. According to P. 31 of the final report, the "ITT" population consisted of all randomized patients completed both treatment periods (n = 98) (Gabapentin-Placebo – 48, PI-G – 50). This is not the definition of ITT, rather, is the completer population. As far as I know, to analyze on the basis of ITT, the outcomes of all patients are analysed with the group to which they were originally assigned, whether or not they completed the protocol. 3. There are several dependant comparisons made throughout this study, however not correction was employed to account for this (e.g. Bonferrroni's correction). 4. According to page 46 and Table 32,

Date Last Patient Completed: 30-November-2001

Date of Report: 7-March-2003, note there is a second sub-study report dated 2003-09-18. The main report will be referred to throughout this document as the March report.
All page numbers and Table numbers refer to the March report.

Publication: Not Published

Unpublished Report: Gabapentin vs. Placebo in Patients with Neuropathic Pain. A Randomized, Double-Blind, Cross-Over, Multi-Center Study in the Nordic Area.

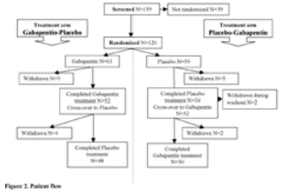
Randomization code was broken for one patient (pt. # 5158, due to the occurrence of an SAE), the code breaking was performed in accordance

- Must show presence of hyper- or hypo phenomena in sensibility tests within a neuro-anatomical distribution area
- Able to understand and cooperate with study procedures
- Capable of completing the study
- Written and informed consent given
- At randomization
  - An average of 14 measurements of pain score greater than 30 on a VAS (0-100) during the last week of screening

Exclusion Criteria

- Pregnant and lactating women, and fertile women not using appropriate contraception
- Previous treatment with Gabapentin
- Decreased renal function
- Serious hepatic, respiratory or hematologic illnesses, unstable cardiovascular disease or symptomatic peripheral vascular disease

Placebo-Gabapentin Arm: 59
Exposed to G: 113
Exposed to P: 111



- See Figure 2 p. 29 for diagram
- Time point for withdrawals given in Table 3, p. 30 of March report.
- Reasons for withdrawal in Table 4, p. 30

Study Procedure
Baseline: 2 weeks
Titration: 2 weeks
Treatment at Fixed Dose: 3 weeks
Washout: 3 weeks
Crossover
Total: 15 weeks
(see diagram on p. 10 of protocol, p. 16 of March report)

- Titration began at 300 mg daily increased to max of 2400 mg daily

Mean Pain Intensity Score (VAS) (P. 22 of March report)

- Was calculated based on last 14 pain assessments during run-in, T1, Washout, and T2, needed at least 10/14 (was changed to 9/14 before data analyses) . There is no LOCF analysis for those patients who withdrew early.
  - This is a "completer: analysis.
- No carry-over effect (i.e. drugs taken in treatment period 1 had no residual effect in treatment period 2, washout effective)
- Period effects were significant however, I would assume this might have something to do with unblinding because of use of inactive placebo (see comments)
- Figure 3 (P. 36 of the March report) shows MPIS by week, note relative ineffectiveness of Gabapentin in treatment phase II.

MPIS "ITT population" (Completer Population)
Treatment Period 1:

Gabapentin-Placebo
N: 48
Baseline: 52.2 (16.4)
Week Five: 45.2 (23.6)
Difference: 7.2 (17.8)

Placebo-Gabapentin
N: 50
Baseline: 54.1 (15.4)

while on Gabapentin, 3 patients experienced 3 SAEs while on Placebo)

3. Withdrawals Due to Adverse Events:

WDAE Total = 11
TLP: WDAE OK for meta-analysis

P = 4/111 (3.6%)
G = 7 / 113 (6.19%, not 5.8% as stated in passage, as N = 113, not 120, see reasoning below)

WDAE during phase 1:
P = 2/59 (3.39%)
G=6/61 (9.84%)

WDAE during washout:
P = 1 /59 (1.69%) (after taking placebo)
G = 0 / 61 (0.0%)

WDAE during phase 2:
P = 1/52 (1.92%)
G = 1/52 (1.92%)

- See Table 62, p. 72, Table 4 p. 30
- Table 3 lists the phases in which the withdrawals occurred but doesn't specify which withdrawal occurred where.

21/107 (19.6%) of patients taking Gabapentin were treated with a dose of Gabapentin of less than 2400 mg (average does was 2243 mg, SD = 402). In comparison, 7/103 (6.8%) of patients on placebo were treated with less than 2400 mg (mean = 2363 mg, SD = 172). The final report calls this a difference that could be seen which one would assume to mean statistical significance in which would in turn indicate that people found it difficult to reach the maximum dose of Gabapentin for this study, 2400 mg, when in fact patients are often prescribed up to 3600 mg of Gabapentin.

5. In total 22/120 (~18%) patients were non-compliant (P. 34 of March report) compliance so low? Was this accounted for?
6. No carry-over effects → adequate washout and therefore crossover appropriate. Period effect significant, details are sparse. However, for both "ITT" (completer population) and PP analyses, those who took Gabapentin first saw almost no reduction in pain score when on placebo (reduction = 0.5 for "ITT" or completer population and 0.7 for PP) compared to greater reductions when on placebo seen when placebo taken first (6.9 for "ITT" or the completer population, 7.1 for PP), this would seem to indicate unblinding due to an inactive

with the requirements (see p. 20 of the March report for requirements)	• Other pain that may confound assessment or self-evaluation of the neuropathic pain • History of chronic alcohol or drug abuse within previous 3 years • Patient not expected to complete the trial • Participation in other experimental and/or drug studies. Note: by not allowing prior treatment with Gabapentin, creating bias in favour of the drug as those who have used it and have not had it work will be excluded from study. Allowable Treatments: • Occasional use of NSAID for other type of pain will be allowed during the study • Use of benzodiazepines, zolpidem or zopiclon for insomnia will be allowed, if they are prescribed before inclusion Prohibited: • TENS • Regular use of weak	(see Table 2 of March report, p. 20, for recommendations). Titration schedule) • During 3-week treatment period the study medication dosage must be unaltered. (For recommended dosing schedule see P. 26 of protocol) <u>Compliance</u> • See table 11.3 (P. 34 of the March report)	Week Five: 47.1 (22.2) Difference 6.9 (15.5) Treatment Period 2: Gabapentin-Placebo N: 48 Baseline: 50.9 (21.6) Week Thirteen: 49.9 (24.3) Difference: 0.5 (9.7) Placebo-Gabapentin N: 50 Baseline: 52.6 (21.1) Week Five: 47.2 (25.1) Difference: 5.1 (11.6) ANCOVA shows no difference between the treatments (P = 0.20) <u>MPIS PP Population (Per Protocol)</u> NB: Total PP Population: N= 85 Gabapentin-Placebo for PP population: n = 43 Placebo-Gabapentin for PP population: n = 42 • For Gabapentin-Placebo arm reduction in mean pain score during Gabapentin treatment was 8.1 m, 0.7mm with placebo (n = 43) • For Placebo-Gabapentin arm reduction in pain score during Gabapentin treatment was 4.7, and 7.1 mm with placebo. (n = 42) ANCOVA shows no difference between the two treatments (p = 0.16)	• Additionally, 1 patient withdrew due to lack of efficacy while on Gabapentin (2 on placebo) <u>4. Total Withdrawals:</u> • A total of 22 patients withdrew from the study <u>TLP: Total patient withdrawals OK for meta-analysis</u> Placebo: 11/111 (9.91%) • Adverse Events: 4/111 (3.60%) • Non-Compliance:1/111 (0.9%) • Consent-Withdrawn: 3/111 (2.70%) • Other o Lack of efficacy: 2/111 (1.80%) o Use of Prohibited Drug: 1/111 (0.9%) Note that two patients withdrew during the washout period after having taken placebo in phase 1: 1 patient withdrew due to adverse effects and one patient withdrew consent. These patients were included in the placebo withdrawals. Gabapentin: 11/113 (9.73%) • Adverse Events: 7/113 (6.19%) • Non-Compliance:2/113 (1.77%) • Consent-Withdrawn: 1/113	placebo. 7. MPIS shows no improvement over placebo in the “ITT” (completer population) and PP populations (P = 0.20, P = 0.16 respectively), the “ITT” (completer population) population only included those who completed both trials, Therefore, the results are probably even less significant when one accounts for withdrawals. • Furthermore, given that this study precluded past Gabapentin use (a criteria for which no rationale is given), anyone who had used Gabapentin earlier only to have it not work was precluded from the study. 8. With regard to mean reduction in mean sleep interference score in the “ITT” population (completer population), the Gabapentin-Placebo arm saw a mean reduction of 10.2 mm when taking Gabapentin and 0.5 mm when taking placebo. The Placebo-Gabapentin arm saw a reduction of 3.8 when taking Gabapentin and 6.3 when taking placebo. With regard to the PP population the Gabapentin-Placebo arm saw a mean reduction of 11.0 mm when taking Gabapentin and 0.7 mm on placebo while the Placebo-Gabapentin arm saw a 3.5 mm reduction when taking Gabapentin and a 6.4 mm reduction when taking placebo. Supposedly these

	opioids and tramadol not allowed • No concomitant medication that might affect neuropathic pain include: o Antidepressive drugs o Skeletal muscle relaxants with centrally acting properties o Mexiletine o Antiepileptic drugs o Dextromethorphan o Narcotics o Capsaicin o Anxiolytics Escape Medication • Paracetamol with ± codeine, dextropropoxyphen as rescue medication was permitted (according to protocol this was an allowable medication) • In amendment 1, Escape Medication was more clearly defined as "any other medication taken for pain" Protocol deviations: (see P. 31), note also in p. 14		<u>Secondary Analysis</u> Median Pain Intensity • In the analysis plan, it is stated that a secondary analysis was going to be done on median pain intensity; however, the March report does not contain any results pertaining to this. <u>Secondary Variables:</u> Weekly mean sleep interference score (VAS) (P. 22, p. 37 of March report) "ITT" population (completer population): Treatment Period 1: Gabapentin-Placebo N: 48 Baseline: 37.9 (26.0) Week Five: 28.0 (26.1) Difference: 10.2 (15.6) Placebo-Gabapentin N: 50 Baseline: 37.4 (21.8) Week Five: 31.4 (20.9) Difference: 6.3 (12.5) Treatment Period 2: Gabapentin-Placebo N: 48 Baseline (week eight): 32.3 (25.5) Week Thirteen: 31.0 (26.5) Difference: 0.5 (10.5)	(0.88%) • Other: o Lack of efficacy: 1/113 (0.88%) o Use of Prohibited Drug: 0/113 (0%) <u>5. Total Adverse Events:</u> Denominators corrected to show patients who received at least one dose of Gabalentin or Placebo – True ITT. N = 113 for Gabapentin and 111 for placebo not 120 for both as reported, as only 113 patients were exposed to Gabapentin and 111 were exposed to placebo. <u>Adverse Events:</u> Percentages in brackets <u>TLP: Total patients with AE OK for meta-analysis</u> Total Patients with AEs: P = 72 / 111 (64.9%) G = 91/113 (80.5%)	results favour Gabapentin (p = 0.0016 for "ITT" or completer population, p = 0.0024 for PP). This makes no sense to me for a few reasons • In both "ITT" (completer population) and PP populations the Placebo-Gabapentin arm saw a greater decrease in sleep interference while taking placebo. This is clearly demonstrated by Figure 4 (p. 39 of March report) • The largest decrease seen in either arm in both "ITT" (completer population) and PP populations was 11.0 mm. The report clearly states on page 27 that a VAS score of less than 11.0 mm is not considered to be clinically significant. • None of the withdrawals were considered in this. Several patients withdrew due to adverse effects (7 on Gabapentin) and 3 due to unacceptable pain. I am still trying to figure out when those experiencing unacceptable pain left but I imagine those with AE and pain were not experiencing great improvements in mean sleep interference score. 9. With regard to Quality of life ("ITT" Population or the completer population). • It is stated that there were significant improvements in Vitality, Role

			Placebo-Gabapentin N: 50 Baseline (week eight): 32.9 (21.1) Week Thirteen: 28.6 (22.6) Difference: 3.8 (9.3) Using ANCOVA to adjust for baseline values, Gabapentin superior to placebo in reducing mean sleep interference score (p = 0.0016) PP Population: NB: Total PP Population: N= 85 Gabapentin-Placebo for PP population: n = 43 Placebo-Gabapentin for PP population: n = 42 Mean reduction in score for Gabapentin-Placebo arm was 11.0 mm when taking Gabapentin, and 0.7 mm for placebo. For the Placebo-Gabapentin arm, the mean reduction was 3.5 mm when taking Gabapentin and 6.4 mm when taking placebo. Supposedly these results favour Gabapentin (p = 0.0024) however I cannot understand how. (see comments column) Quality of Life (SF-36) "ITT" Population (completer population) (P. 22 of March report) NB:	TLP: Total number of AE OK for descriptive statistics Total Number of AEs: P = 168 G = 241 Most common AE's (N adjusted from 120 to 113 and 111 for G and P respectively) Dizziness and Vertigo P = 9 / 111 (8.1%) G = 39 / 113 (34.5%) Malaise and Tiredness P = 17 / 111 (15.3%) G = 31 / 113 (27.4%) Headache including migraine P = 20/111 (18.0%) G = 18/113 (18.9%) Nausea and Vomiting P = 10 / 111 (9.0%) G = 8/113 (7.1%) Infections P = 15 / 111 (13.5%) G = 10 / 113 (8.8%) Skin Disorders P = 5 / 111 (4.5%) G = 10/113 (8.8%) Confusion P = 2/111 (1.8%) G = 16 / 113 (14.2%) Mouth Dryness P = 3/111 (2.7%) G = 9/113 (8.0%)	Emotional, Mental Health, and a borderline improvement in bodily pain, as compared with placebo. Although a marker can be statistically significant is it clinically significant? For example, mental health improved by 3.95189 after treatment with Gabapentin but what does that mean? Is there actually a noticeable difference? • There was an effect of period, i.e. for these markers, people felt better after the first round of treatment (G or P) which is not surprising and should be considered given that people were most likely excited / hopefully to be on a new drug. • Finally, the tables for the QoL markers (before and after Gabapentin or placebo) are listed in the back (Tables 38, 39, and 40, page 60, 61 of the March report) however the calculated value for change in Gabapentin – change in placebo DO NOT MATCH i.e. Table 40 values are not consistent with values in table 39. • In the Predefined Outcomes / Issues in Statistical Analysis column 40 a corrected version of Table 40 has been included (Difference in the 8 dimensions of SF-36 after Gabapentin vs. after

<table>
<tr>
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<td>Total “ITT” or completer Population: N= 98
Gabapentin-Placebo for “ITT” or completer population: n = 48
Placebo-Gabapentin for “ITT” or completer population: n = 50

• According to P. 39 of the March report, Gabapentin was found to be statistically significantly superior to placebo in improving
o Vitality (p = 0.012)
o Role-Emotional (0.024)
o Mental Health (p = 0.0017)
o Bodily Pain, borderline (p = 0.056)
• Significant period effect for General Health, borderline significance (p < 0.1) for Role Physical, Bodily Pain, Role Emotional, and Mental Health.
o In all cases better improvement in QoL at end of first treatment period.
o HOWEVER, these looking at Table 40, Difference in the 8 dimensions of SF-36 after Gabapentin vs. after placebo, Treatment Arms Combined, “ITT” Population (completer population) the values do not match my findings which makes me think the p-values are off as well.
o Below is my version of table 40 (I have not calculated p-values as this would be extremely labour intensive, I will if needed though), note my values do not match those in table 40.
<table><tr><td>Dim.</td><td>ΔGaba</td><td>ΔPlacebo</td><td>ΔG- ΔP</td></tr></table></td>
<td>• Because of the above discrepancies, all the percentages listed are incorrect; above I have listed the correct percentages.
• Dizziness and vertigo were with two exceptions in the placebo group, always regarded as drug-related as well as confusion and mouth dryness. See comments.

<u>6. Validated measures of improvement in global function including return to work, study, activities of daily living</u>

• None reported for this study.

<u>7. > 50% reduction in pain score (NRS, VAS) from baseline to endpoint</u>

<u>Not suitable for meta-analysis</u> as this endpoint is not based on comparison of patient final VAS versus baseline VAS.

For the Pain/Relief Scale one of the questions asked is pain at least half gone during treatment, the proportion of yes’ was as follows:</td>
<td>placebo, Treatment Arms Combined, “ITT” Population or completer population); note my table values do not match the values in table 40.
• Note larger improvement in Role Physical with placebo
• Placebo also better with Bodily pain, and Social functioning
• Similar problems as above for the PP population and have also included my own table for the table analogous to table 40 but for the PP population in the Predefined Outcomes / Issues in Statistical Analysis column
10. The discussion says that “the improvement during the 5 weeks of Gabapentin treatment was statistically better than during the placebo treatment, but the absolute improvement was small. However, 5 weeks is a short period of time and a longer study might be necessary to confirm the beneficial effect of Gabapentin in that respect.” First off this may not even be true given that the calculations were completely inaccurate but also, is 5 weeks a short time, there seems to be nothing in this study to indicate that this period of time is too short to detect a benefit and no reasons are given as to why a longer study would detect such a change. One familiar</td>
</tr>
</table>

			<table><tr><td>PF</td><td>2.98151</td><td>1.27835</td><td>1.70316</td></tr><tr><td>RP</td><td>-0.2139</td><td>9.35374</td><td>-9.56764</td></tr><tr><td>BP</td><td>2.22449</td><td>2.69398</td><td>-0.46949</td></tr><tr><td>GH</td><td>0.66072</td><td>-0.88302</td><td>1.54374</td></tr><tr><td>VI</td><td>5</td><td>1.87075</td><td>3.12925</td></tr><tr><td>SF</td><td>-0.2551</td><td>3.35578</td><td>-3.61088</td></tr><tr><td>RE</td><td>3.95189</td><td>1.08418</td><td>2.86771</td></tr><tr><td>MH</td><td>3.43878</td><td>0.37755</td><td>3.06123</td></tr></table> • Note that according to my values placebo much better in Role Physical, and also slightly better in Bodily Pain and Social Function. PP population (p. 39) NB: Total PP Population: N= 85 Gabapentin-Placebo for PP population: n = 43 Placebo-Gabapentin for PP population: n = 42 • Says the results were generally similar to the “ITT” population (completer population) • However, I have the same problem with Table 43 (Difference in the eight dimensions of SF-36 after Gabapentin vs. after Placebo, Treatment arms Combined, PP population) as I did with its analog in the “ITT” population (completer population) (Table 40), see my table below. • Notice with y table, the effect for Role Physical from placebo was much much better than that for Gabapentin. Social functioning improved more with placebo as did bodily pain. <table><tr><td>Dim.</td><td>ΔGaba</td><td>ΔPlacebo</td><td>ΔG- ΔP</td></tr><tr><td>PF</td><td>3.13208</td><td>1.24549</td><td>1.88698</td></tr><tr><td>RP</td><td>-5.81186</td><td>8.72549</td><td>-14.53735</td></tr></table>	The paper reports: G = 22 / 98 P = 8 / 98 However, this is not true ITT, therefore: G = 22/113 (19.47%) P = 8/111 (7.21%) • According to the March report, statistically significantly more patients reported that the pain had subsided half during Gabapentin treatment (G = 22, P = 8, p = 0.012) however this p-value again was most calculated using N=98 which is not true ITT but is the completer population, therefore is not useful. If using the variable “Response to Treatment: The paper reported ≥ 50% Pain Reduction as G = 13 /98 P = 9 / 98 However, taking the true ITT population into account ≥ 50% Pain Reduction G = 13 /113 (11.50%) P = 9 / 111 (8.12%)	study (Gilron I, Bailey JM et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005; 352:1324 – 34) of patients suffering from neuropathic pain did see significant improvements in QoL for Morphine and Gabapentin-Morphine combo after 5 weeks total on the drug (3 of which were titration, 1 dose tapering, and only 1 of which was maximal dosage). The power of this study should have been enough to detect benefit. Furthermore, if a drug for pain takes longer than 5 weeks to improve quality of life, is it very good? 11. With regard to pain relief (“ITT” or completer population) and the question measuring the degree of pain relief on a 5 point rating scale (1 = complete pain relief…5 = no pain relief) • The numbers did not add up in the tables for the placebo group implying sloppy work. • Even though significantly more patients supposedly had better pain relief with Gabapentin than with placebo, 54/98 (55.1%) patients still had no pain relief with Gabapentin. If you include the 13 who only had some pain relief that means that 67 / 98 (68.4%) experienced none or some pain relief with Gabapentin i.e. less than moderate pain relief. 12. With regard to CGIC

				• P-value = 0.29 Note this p-value was probably used with N=98 therefore is most likely not useful. • Also note that here p-values are with regard to the significance of the number more of patients who responded to Gabapentin treatment than to placebo treatment 8. Mean between-group difference in change of pain score (NRS, VAS) from baseline to pre-defined endpoint by true intention to treat (ITT) –where this was the pre-defined primary endpoint in a trial This outcome is not meta-analyzable for two reasons. First of all because the mean between-group difference in change of VAS pain score from baseline to pre-defined endpoint was not the primary efficacy variable, mean pain intensity during the last week of each treatment period was. Furthermore, this data cannot be meta-analysed because the number of patients used in calculations did not reflect the true ITT population but instead, the completer population.	• The March report states that "*Statistically significantly more patients had, in the opinion of the clinician, improved more during Gabapentin treatment than during placebo treatment*" however, clinicians were not asked to compare the two treatments, they were asked at the end of each period how they felt their patient's pain had improved over the treatment period so the wording is misleading. • Significantly more people improved more on Gabapentin than on placebo, p = 0.037 but... • Only 29 / 98 patients (29.6%) improved much or moderately, whereas there was no change 38 / 98 (38.8%). If you include the 12 who became minimally or moderately worse, we get 50/98 (51.0%) of patients, according to their doctor, saw no improvement or worsened. 13. With regard to PGIC, the March report states that "*Statistically significantly more patients, had in their own opinion improved more during Gabapentin treatment than during placebo treatment*" (p = 0.023). However… • Patients were not asked to compare the two treatments, they were asked

BP	2.48235	2.94846	-0.4611
GH	0.23235	0.16988	0.06247
VI	4.82353	1.82353	3
SF	-1.17647	3.72374	-4.90021
RE	4.7619	1.30404	3.45786
MH	3.44706	-0.3647	3.81176

Consumption o f Escape Medication (P. 22 of March report)

- Not mentioned in protocol but is in analysis plan
- Only counted number of days escape medication needed, no attn. paid to amount of daily intake.
- "ITT" population (completer population)
  - 66.3% took no escape medication when on Gabapentin, 62.2% during placebo.
  - 3 had to take escape medication all days when on Gabapentin and 3 when on placebo.
  - 16 patients had fewest days on escape medication during Gabapentin treatment vs. 22 on placebo, not significant (p = 0.9, very large)

Pain / Relief Scale(P. 23,40 of March report)

For the question regarding pain relief with treatment with 5 responses, "ITT" POP (completer population) (Completed, marked, moderate, some, no)

			Note that for the following results the denominator is 98 which does not reflect the true ITT, rather the completer population Complete G = 0/98 P = 0/98 Marked G =18/98 P = 5/98 Moderate G = 13/98 P = 9/98 Some G = 13/98 P = 14/98 No Pain Relief G = 54/98 P = 70/98 • The numbers for placebo in table 14 and figure 7 do not add up to 98 for the placebo group o The "some" column for placebo adds up to 14, not 13 as written and demonstrated in figure 7 o The no pain relief column for placebo adds up to 70, not 59 as shown in figure 7 and table 14; however, the writing on page 41 says 70. o With the above changes, the placebo group adds up to 98 • The analysis plan stated that *"the two-alternative question and the 5-alternative one are analysed in the same way: for each*	Regardless, the results for VAS pain intensity are listed below. • Note was assessed on a 100 mm VAS scale (0 = no pain, 100 = worst possible pain) • Also note that the primary efficacy variable was not the change from baseline but was MPIS (mean pain intensity score) during last week of each treatment period (adjusted for baseline score) <u>MPIS "ITT" (completer population) population</u> Treatment Period 1: Gabapentin-Placebo N: 48 Baseline: 52.2 (16.4) Week Five: 45.2 (23.6) Difference: 7.2 (17.8) Placebo-Gabapentin N: 50 Baseline: 54.1 (15.4) Week Five: 47.1 (22.2) Difference 6.9 (15.5) Treatment Period 2: Gabapentin-Placebo N: 48 Baseline: 50.9 (21.6)	at the end of each treatment period how they felt their pain had improved over the treatment period so the wording is misleading. • 36/98 patients (36.7%) experienced no change on Gabapentin. When you include those patients who felt that their condition worsened you can see that 52/98 (53.1%) felt that they made no change or worsened. Again would you want to take this drug? • With regard to PGIC and CGIC nothing is stated as to whether or not the period was significant. This seems rather crucial and is left out. 14. With regard to adverse effects • Table 20 on page 47 of March report lists the adverse effects and corresponding percentages. The incorrect N was used for Gabapentin. The table says N = 120, however, 61 patients had Gabapentin treatment in Treatment 1 while only 52 of the initial 59 randomized to placebo first went on to take Gabapentin. Therefore N = 113 similarly the table states that N = 120 for placebo however, 59 had placebo during Treatment I and only 52 crossed over to placebo after, therefore N = 111 for placebo. N = 120 was used throughout the March

			patient we check which of the two treatments gave the best relief; and then a sign test is performed." However, the March report, states that pain relief was analysed after a transformation (detailed on p.27) and analysis was done with a Mainland-Gart test…different. • The Mainland-Gart test is also used on binary variables in order to determine which was better; it is usually used in crossover trials when asking patients which treatment period they preferred. This was not asked and instead a data transformation was made in order to change this variable to binary (when there were 5 responses) the transformation done is fairly unclear and I am not sure if this is valid. For the question with two responses to "pain at least half gone"... (Note that for the following results the denominator is 98 which does not reflect the true ITT, rather the completer population) Half Pain Gone During Treatment (Yes) G = 22 / 98 P = 8 / 98 Half Pain Gone During Treatment (No) G = 76 / 98 P = 90 / 98 • According to the March report, statistically significantly more patients reported that the pain had subsided half during Gabapentin treatment (G = 22, P = 8, p = 0.012)	Week Thirteen: 49.9 (24.3) Difference: 0.5 (9.7) Placebo-Gabapentin N: 50 Baseline: 52.6 (21.1) Week Five: 47.2 (25.1) Difference: 5.1 (11.6) ANCOVA shows no difference between the treatments (P = 0.20) 9. % of patients achieving "much improved" or "moderately improved" TLP: % of patients OK for meta-analysis • Note here that the denominators have been changed from 98 (as reported in the study) to 113 for the Gabapentin group, and 111 for the placebo group (true ITT populations) G = 21/113 (18.58%) P = 8/111 (7.21%) 10. Histogram presentation of all PGIC 7-point results • See end of document for histogram.	reports so all the percentages are inaccurate. • N = 39 in the Gabapentin group who experienced Dizziness and Vertigo which was considered as drug-related, n = 9 in placebo group who experienced this effect however 2 of these cases were not considered as drug-related. Therefore, 39/113 (34.5%) vs. 7/111 (6.3%) experienced this side effect which could have easily caused unblinding • Table 62, Listing of Adverse Events Leading to Withdrawal from Study lists, among other things, the 11 patient numbers of those patients who withdrew from the study and the period. They say in this table that the period is Gabapentin run-in which I think is meant to mean titration. A run-in is usually a period in which no drugs are taken. This would make sense as according to this table, 7 patients WDAE in a run-in period (G and P) where as the text says 7 patients WDAE during titration periods. • The adverse events for placebo do not add up. Table 55 on page 70 would imply that there were 145 adverse events on placebo while table 56 (and the rest of the study for that matter) states that there

			<u>Clinical Global Impression of Change</u>(P. 23 of March report) <u>"ITT" Population</u> (completer population) Note that for the following results the denominator is 98 which does not reflect the true ITT, rather the completer population Much Improved: G = 7/98 P = 2/98 Moderately Improved G = 22/98 P = 11/98 Minimally Improved G = 19/98 P = 14/98 No Change G = 38/98 P = 58/98 Minimally Worse G = 8/98 P = 12/98 Moderately Worse G = 4/98 P = 1/98 Much Worse G = 0/98 P = 0/98 • See table on p. 23 of March report • See table 16 and figure 8 on p. 42 of March report (numbers do add up this time)		were 168 adverse; events for placebo. Not a big deal overall, but again, is sloppy. • Furthermore, people on Gabapentin were more likely to experience more adverse events (see excel graph at end of document). Only 29/113 (25.7%) patients taking Gabapentin did not experience any adverse events 48/11 (43%) of those taking placebo experienced no adverse events. • The discussion states that adverse effects were 60/40 Gabapentin/Placebo; however, this is only one, and possibly the best way of looking at it. If you calculate the average number of AE's experienced by Gabapentin patients you get 241/113 = 2.13, and either 168/111 =1.51 or 145/111 = 1.31 (depending on which number is correct, the report implies both) for placebo. This implies up to 60% more AEs on Gabapentin than on placebo. The 60/40 is just a more convenient way to look at it. 15. With regard to "Response to Treatment" we do see a significant difference in Placebo and Gabapentin for most of the criteria, however, for all categories more patients seemed to not respond to treatment than did respond to treatment. 16. For PGIC and CGIC, patients and

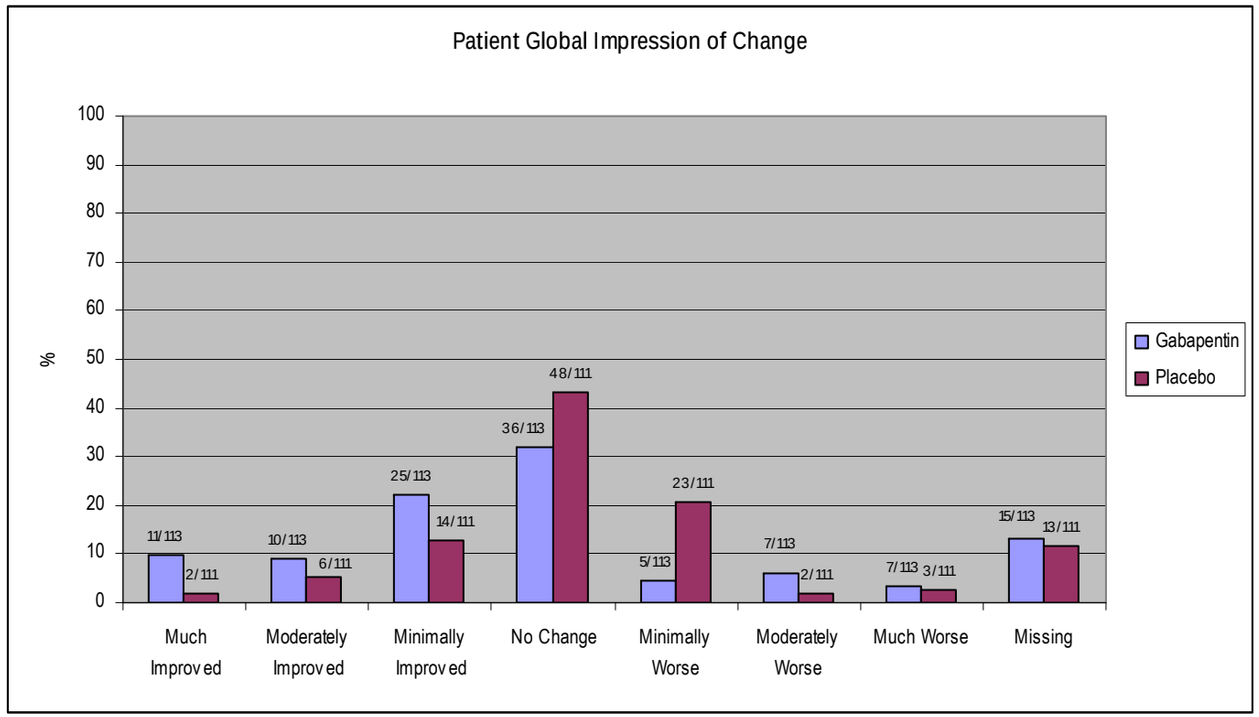
			• Statistically significantly more patients had, in the opinion of the clinician, improved more during Gabapentin treatment than during placebo treatment, but see comments. Patient Global Impression of Change ITT Population • Note here that the denominators have been changed from 98 (as reported in the study) to 113 for the Gabapentin group, and 111 for the placebo group to reflect the true ITT population sizes as this efficacy variable was suitable for meta-analysis. Much Improved: G = 11/113 (9.73%) P = 2/111 (1.80%) Moderately Improved G = 10/113 (8.85%) P = 6/111 (5.41%) Minimally Improved G = 25/113 (22.12%) P = 14/111 (12.61%) No Change G = 36/113 (31.86%) P = 48/111 (43.35%) Minimally Worse G = 5/113 (4.42%) P = 23/111 (20.72%) Moderately Worse G = 7/113 (6.19%) P = 2/111 (1.80%) Much Worse		clinicians compared the improvement at the end of each treatment period with the status prior to the study; however, patients/clinicians cannot have been expected to remember exactly how they felt given that at least 15 weeks had passed, further regression to the mean is not taken into account, and order effects are not addressed. It is preferable in a crossover design to compare baseline with end of treatment 1, and measurement after washout with end of treatment 2. This is addressed in the discussion (p. 49) however no mention of regression to the mean is made. 17. The discussion states that results may have been hampered due to study design. Crossover designs are more powerful than parallel designs if, as stated, the underlying condition does not change over time and if the washout is adequate (i.e. no carry over effects). • There are no qualms in this study about carry-over effects. As stated in the conclusion “statistical analysis could not reveal any carry-over effect”; in addition, the blood plasma levels of Gabapentin returned to 0. • Taking into account this issue of disease fluctuation, the passage points out that, for the primary efficacy variable, the scores after the washout period were lower than at baseline. However, for the

			G = 4/113 (3.54%) P = 3/111 (2.70%) Missing: G = 15/113 (13.27%) P = 13/111 (11.71%) • See table on p. 23 of March report • Statistically significantly many patients believed they improved more during Gabapentin treatment than during placebo treatment p = 0.023, but again assume p-value uses the non-ITT sample size of 98 for this calculation. <u>Response to Treatment</u>(p. 44) "ITT" Population (completer population) Note that for the following results the denominator is 98 which does not reflect the true ITT, rather the completer population Also note that here p-values are with regard to the significance of the number more of patients who responded to Gabapentin treatment than to placebo treatment and were also most likely calculated with N = 98, the value for the completer population not the true ITT population and are therefore less useful. <u>≥</u> 50% Pain Reduction G = 13/98 P = 9/98 P-value = 0.29 <u>≥</u> 30% Pain Reduction		Gabapentin-Placebo arm the score at baseline was 52.2 (SD =16.4) while the score at week 8 was 50.9 (21.6), a difference of 1.3 mm. For the Placebo-Gabapentin arm the baseline score was 54.1 (15.4) while at week at the scores were 52.6(21.1), a difference of 1.5 mm. These differences are so small, much lower than the MCID. • The discussion then goes on to note that the placebo effect was greater in the first treatment period (6.9 mm) than in the second (0.5 mm) where as the Gabapentin effects were of the same magnitude (7.20 mm during first period, 5.09 during the second period). This seems to be a sign of unblinding i.e. those who received Gabapentin in the first period, due to side effects such as vertigo etc., knew they were on placebo in the second treatment period. 18. The last statement in the discussion of the March report states that "this study indicates that Gabapentin may be of benefit for patients with neuropathic pain" however no evidence is given here. Furthermore, there was no improvement in the primary variable; and although the improvements in certain other variables were statistically significant compared with placebo, they study, in my opinion,

			G = 29/98 P = 19/98 P-Value = 0.04 At Least Marked Pain Relief G = 18/98 P = 5/98 P-value = 0.007 At Least Moderate Pain Relief G = 31/98 P = 14/98 P = 0.003 • This is called responders in analysis plan and the definition has changed slightly (in analysis plan the definition for one indicator is at least 25% pain relief, here it is 30). o With regard to marked and moderate pain relief, the analysis says that this was measured on a 5-alternative question; the report doesn't mention this…same 5-alternative question from Pain Relief Scale? o These changes are not mentioned in any amendments to the study. <u>Plasma sampling (concentration of Gabapentin)</u> • See p. 25, 46 of March report for details • Table 19 displays details but serum concentration of Gabapentin was slightly lower during the second treatment period (i.e. in patients in Placebo-Gabapentin arm) as compared with those who were treated with the active drug in the first treatment		failed to demonstrate that Gabapentin had any marked improvements. All the "significant" improvements were extremely small.

			period, a paired t test I did on my own showed that this difference was not significant. The serum concentrations (µmol/L) of Gabapentin by treatment period and Study population mean are listed below ("ITT" or completer population), standard deviations are in brackets. Gabapentin-Placebo Arm: Titration I: 40.3 (20.4) Treatment I:38.7 (23.7) Washout: 0 Titration II: 0 Treatment II: 0 Placebo-Gabapentin Arm: Titration I: 0 Treatment I: 0 Washout: 0 Titration II: 38.0 (20.77) Treatment II:34.3 (20.73) <u>General Physical Exam</u> • At visit 1 and 7 or termination visit • Weight, height, vital signs Brief Neurological Exams • At visit 1 and 7 or termination visit • Reflexes and gait • Sensibility in pain area also evaluated as compared to contralateral side at visit 1		

			<u>Additional Variables:</u> Pain during other parts of treatment period Analysis of carry-over effects and Analysis of period effects • It is stated in the analysis plan that an analysis of period effects and an analysis of carry-over effects would be performed however, I can find nothing in the March report that says anything about this analysis besides that there were not carry-over effects but there were period effects…what were they? <u>Subgroup analysis by duration of pain</u> • See p. 44 of March report • No difference in treatment effect could be seen when time since diagnosis was taken into consideration		


Patient Global Impression of Change
%
100
90
80
70
60
50
40
30
20
10
0
11/113
2/111
10/113
6/111
25/113
14/111
36/113
48/111
5/113
23/111
7/113
2/111
7/113
3/111
15/113
13/111
Much Improved
Moderately Improved
Minimally Improved
No Change
Minimally Worse
Moderately Worse
Much Worse
Missing
Gabapentin
Placebo

STUDY NO. 9 - STUDY DETAIL SUMMARY AND ANALYSIS: RICE STUDY NUMBER 945-295 – POST HERPETIC NEURALGIA – FINAL – JULY 27, 2008

Summary:

Information taken from:
a) Rice A.S.C., Maton S., Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomized, double-blind, placebo controlled study. Pain, 2001; 94: 215-224. Referred to as the Pain report
b) Parke-Davis research report number RR-430-00124 dated April 3rd, 2000, referred to as the unpublished report.

The exclusion criteria for this study lead to enrichment bias. See table for details.

The Pain report describes the primary outcome as the change in average daily pain score from the baseline week to the final study week. However, the study protocol (83 of 1357 of unpublished report) states that the primary outcome will be the mean weekly pain score. The Inferential Analysis Plan states (193 of 1357, unpublished report) that the primary objective is to compare the mean pain scores from the final week of the daily pain diary for each dose of Gabapentin compared with placebo. Furthermore, the "Main Model" section of the October 30th, 1998 final protocol (87 of 1357 of unpublished report) and the "Inferential Analysis Plan" (193 of 1357 of unpublished report) clearly show that the predefined outcome was not change from baseline and that the change from baseline was "not to be subjected to statistical analysis" (p. 193 of 1357).

According to page 17 (22 of 1357) of the unpublished report, "*The study was analysed on an intention to treat basis, therefore no patients were excluded from the analysis population. Other than diary assessments made after the cessation of study medication no individual visits or assessments were excluded."* In fact, an ITT-LOCF was used to analyse certain endpoints. ITT without excluding or dropping patients should show the same sample sizes for assessments of each treatment group (placebo, Gabapentin 1800 mg/day, and Gabapentin 2400 mg/day) as at randomiation:

- The number of patients randomized to placebo, Gabapentin 1800 mg/day, and Gabapentin 2400 mg/day) was 111, 115, and 108 respectively.
- For sleep interference score, page 17 (22 of 1357) states that *"One of these patients could not be included in the analysis of sleep diaries as there were no baseline sleep entries"* this patient I assume was in the placebo group as the baseline numbers (Table 9, p. 26, 31 of 1357) state that N = 110, not 111 for the placebo group. However, this table indicates that at the end of study, N = 111 for the placebo group. One wonders how this could have occurred.
- The number of patients analysed for the patient global impression of change (PGIC) efficacy variable were 105, 107, and 98 for the placebo, Gabapentin 1800 mg/day, and Gabapentin 2400 mg/day groups

This study involves a number of dependent comparisons but no correction is made. This is acknowledged in both the protocol and the statistical analysis plan. A correction should have been made if statistical significance is to be claimed..

The Pain report did state the mean duration of treatment for each treatment group of this study. From the unpublished report it is clear that patients assigned to gabapentin took the medication for less time. However standard deviations for these results cannot be located in the unpublished report making it hard to assess statistical significance. Reported duration of treatment:

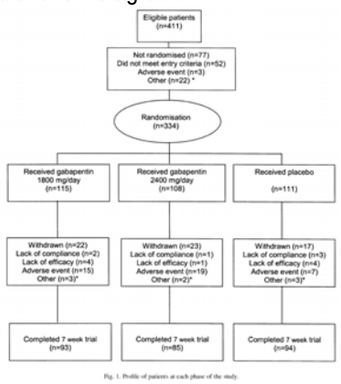
- 46.0 days for placebo
- 43.3 days for Gabapentin 1800 mg/day
- 43.7 days for Gabapentin 2400 mg/day

The Pain report and the unpublished report both seem to contain no information regarding the statistical significance for difference between placebo vs. gabapentin (1800 mg/d or 2400 mg/d) of adverse effects or withdrawals. As in other studies, adverse events and withdrawals appear much more common in the gabapentin treatment groups.

P. 222 of the Pain report states (in the discussion) that "*The study was not set up to show equivalence between the 2 doses and no statistical comparison was made between them. A visual inspection of the data suggests no difference between the 1800 and 2400 mg groups".* It is peculiar to design a trial using two dose groups and then not compare them. The raw data suggest that G2400 mg/d is not superior to G1800 mg/d, but may cause more AE. This adds to evidence from other studies that benefits from gabapentin are not dose-dependent, whereas harms are.

"Responder" analysis appears to include patients with ≥ 50% reduction in weekly pain score, even if they dropped out due to AE. In this sense, a "response" is not necessarily beneficial. This is common to other "responder" analyses in the similar P-D/Pfizer trials.

Examination of Figure 2 of the Pain report (Change from baseline in average daily pain scores, p. 219), suggests that for ITT-LOCF observations, a group mean difference from placebo is discernible within the first week, whereas both gabapentin group curves then follow placebo quite closely for the remainder of the trial. This observation is mirrored in the graph of mean daily sleep scores (see appendix C of unpublished report for details). Week 1 pain scores are the average of patient pain or sleep ratings during a week when the starting dose was lower than the final Day 7 dose, indicating that any effect discernible by patients from gabapentin may occur before the end of Week 1. This phenomenon was observed by Dr. Jewell, UC Berkely statistician, while analyzing the Backonja trial, and was also observed for the Gilron data. Patient unblinding due to obvious effects of gabapentin (at least in some patients) may cause this initial drop in the pain score. This experiment strengthens the evidence that gabapentin effects typically are discernible early, and at lower daily doses, both for benefits and harms.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Kelsey Innes/Dr. TL Perry
Study Number: 945-295 Study Design: Multicentre, double blind, randomized, placebo controlled study (UK and Ireland), consultant anaesthetists' outpatient pain clinics and "specialist research GP practices) (p. Study manager: ImroTramarko Ltd. For Parke-Davis UK, "study advisor" Dr. Andrew Rice Protocol finalized October 30, 1998 Investigators meeting February 27, 1999 Study Duration: 7 weeks Medication Dosage:	Postherpetic neuralgia Inclusion Criteria: • At least 18 years of age • Pain present for more than 3 months after the healing of the acute herpes zoster rash • Average pain scores of 4 or more based on an 11-point Likert scale on the week before commencing study medication. o Note that according to the unpublished report 13 patients were randomised to treatment despite having a mean baseline pain score less than 4 o 11of these cases the mean score was greater than 3.5. Exclusion Criteria	<u>Patient Flow:</u> • Number of patients screened: 411 • Number of patients randomized: 334 • Number of patients randomized to placebo: 111 • Number of patients randomized to Gabapentin 1800 mg/day: 115 • Number of patients randomized to Gabapentin 2400 mg/day: 108 • See figure 1 from page 218 of Pain report – patient flow diagram.  Fig. 1. Profile of patients at each phase of the study. <u>Study Design:</u> • 1 week baseline • After baseline patients randomized to either Gabapentin or placebo • Week 1: 4-day forced titration to 1200 mg/d then 3 days stable dose • Start of week 2: dose increment to 1500	<u>Predefined Outcomes:</u> Primary Efficacy Variable: average daily pain score from final study week (p. 193/1357 unpublished report). • Evaluated from daily pain diary for Week 7 or LOCF • 11-point Likert Scale with 0 as no pain and 10 as worst possible pain. • Baseline score consisted of the mean of the last seven pain diary entries preceding randomisation • The final weekly mean pain score was defined as the mean pain score from the last 7 days preceding the final visit or the last 7 days on the study medication for patients who did not complete the study (LOCF) • The author's performed a percent change transformation on the data however, the raw data is included in Table 8 (29 of 1357 of the unpublished report), and this table has been included at the end of this document. NB: Pain report (Rice 2001) reports the primary outcome as the CHANGE from baseline (comparison of means for each group); whereas both the "Main Model" in the final protocol of October 30, 1998 (at p. 87/1357) and the inferential analysis plan (part of experimental protocol) at p.	<u>1. Mortality (Table 3 on P. 221 of Pain Report):</u> Placebo: 0 / 111 Gabapentin 1800 mg/day: 0/115 Gabapentin 2400 mg/day: 1/108 • The patient in the Gabapentin 2400 mg/day group, who died, died outside the 1 month follow-up after study completion. Death was recoded as other causes and not related to the adverse events ongoing at the time. o See Table 15, p. 39/1357 of unpublished report at end of document • For details regarding this patient see end of document, although it is unlikely that Gabapentin treatment caused the death of this patient, few details surrounding his death are given in the unpublished and published reports. TLP recommendation: since we cannot interpret this and the authors report it as death in gabapentin group, we should record it in meta-analysis as shown	1. The exclusion criteria cause a marked "enrichment bias" This would artificially reduce the number of patients enrolled who are unlikely to respond to Gabapentin as well as the number of adverse events suffered during this trial. 2. In this study Intent-to-Treat is defined properly; however, ITT-LOCF is used, which does not account fully for all patients. The graphs from Pain report and unpublished report do not display the numbers reporting at each week. 3. This study involves a number of dependent comparisons, and multiple statistical comparisons but no correction is made. This is acknowledged in both the protocol and the statistical analysis plan. Specifically, the analysis plan states on page 195 of the unpublished report that "there are a large number of inferential analyses of various assessments of pain. As stated in the protocol no adjustment will be made for these. The nomination of a

1800 mg/day, 2400 mg/day

Patients Randomized: 334

Randomization Procedure: computer-generated randomization list in blocks of 6 (p. 216 of published report)

Number of Study Centers: 48 hospital outpatient clinics and three general practices.

Study Dates: April 1999 – December 1999

Study Approval: The South and West Multicentre Research Ethics Committee as well as each centre's Local Research Ethics Committees

PUBLISHED: Rice A.S.C., Maton S., Postherpetic Neuralgia Study Group. Gabapentin in

- Failure to respond to previous treatment with Gabapentin at ≥ 1200 mg/day
- Failure to respond to Gabapentin at any dose level due to side effects
- Contraindications to Gabapentin treatment

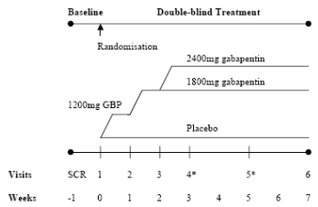
Concomitant Medications:

- The following medications were permissible at a stable dose prior to and during study (could not be initiated during study)
  - Antidepressants
  - Mild opiates (e.g. aspirin, codeine)
  - NSAIDS

mg/d x 1 day, then 1800 mg/d

- Start of week 3: increment to 2100 mg/d x 1 day for those patients randomized to the 2400 mg/day group
- then placebo, G 1800 mg/d or G 2400 mg/d stable x final 4 weeks
- For details see page 216-217
- See Figure 1 from page 4 (9 of 1357) of unpublished report.

Figure 1 – Study Design



Study Power

- Study was estimated to have a 90% power to detect a difference of 1.0 on the pain diary scale as statistically significant (P < 0.05, 2 sided)
- The observed power was 95% to detect the specified difference

Study Populations:

The intent-to-treat population was defined as patients who, once randomized, received at least one dose of study medication.

Statistical Analysis

- ANCOVA was employed to assess between group (P vs. G1800/d vs.

193/1357 clearly shows that the predefined outcome was NOT the change from baseline, and that change from baseline but was "not to be subjected to statistical analysis"! (p. 198/1357) The final protocol appears to distinguish weekly pain scores and change from baseline to endpoint in group mean scores as "supplemental analyses", but does not make clear how these were to be regulated, other than to state that no adjustments were to be made for multiple comparisons, but that some comparisons would appear significant by chance alone.

Secondary Efficacy Variables:

- Mean weekly pain and sleep interference score (11-point Likert scale)
- Short Form-McGill Pain Questionnaire (SF-MPQ)
- Clinician Global Impression of Change (CGIC) assessed on a 7-point scale at study endpoint (LOCF)
- Patient Global Impression of Change (PGIC) assessed on a 7-point scale at study endpoint (LOCF)
- Quality of Life (QoL) using the Short Form-36 (SF-36) Health Survey
- Percentage of patients achieving a 50% or greater reduction in pain
  - Note that this is not specified as a secondary efficacy variable in the protocol but rather as an additional analysis. P. 193 of the unpublished report (in the analysis plan) does specify this as a secondary objective.

by authors.

2. Serious Adverse Events (Table 3 on P. 221 of Pain Report):

- Placebo: 1/111 (0.90%)
  - Depression
- Gabapentin 1800 mg: 3/115 (2.61%)
  - Fever
  - Infection
  - Retinal vein thrombosis and haemoptysis
- Gabapentin 2400 mg: 1/108 (0.93%)
  - Congestive heart failure

3. Withdrawals Due to Adverse Events (Table 3 on P. 221 of Pain Report):

- Placebo: 7 /111 (6.31%)
- Gabapentin 1800 mg: 15/115 (13.04%)
- Gabapentin 2400 mg/day: 19/108 (17.59%)

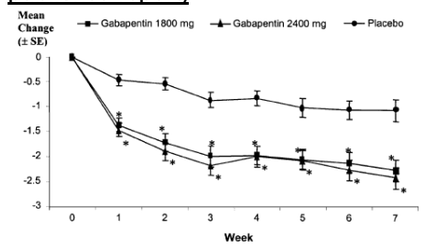
See Appendix B.2 (P. 167 of 1357) of unpublished report for narratives and details relating to withdrawals.

4. Total Withdrawals (p. 217 of Pain report,)
*Also see unpublished report, page 17 (22 of 1357)

Total of patients who withdrew: 62

primary efficacy parameter (mean pain scores from the final week of the daily pain diary) ensures the overall type I error rate for the whole study is controlled at 5%. However, due to the large number of secondary analyses being performed, some significant results are expected to occur by chance alone. Undue consideration will not be given to any particular significant difference: rather, interpretation of the results will be based on patterns of significant differences." A correction should have been made, and the pre-defined primary efficacy test is in fact NOT reported as the primary efficacy outcome.

4. A test called Dunnett's test to correct for the multiplicity of comparing two doses of Gabapentin with 1 dose of placebo was made. This was not stated in the protocol but was in the inferential analysis plan, specifically, the analysis plan states on page 196 that "Although not stated in the protocol adjustment will be made in the primary efficacy analysis for multiplicity involved in comparing 2 doses of Gabapentin with placebo. In order to control the overall probability of claiming a

postherpetic neuralgia: a randomized, double-blind, placebo controlled study. Pain, 2001; 94: 215-224. Final study report (unpublished): Parke-Davis research report number RR-430-00124 dated April 3rd, 2000. PD Authors include, Sarah-Jane Bibby, Steve Maton, & Dr Jan Paul Rosen		G2400/d) changes in pain and sleep scores. Group mean change from baseline to be tabulated, but not analysed statistically. (p. • CMH chi-square for 50% "responders", repeated comparison of G1800 mg/d vs. placebo, G2400 mg/d vs. placebo; patients withdrawing due to lack of efficacy to be regarded as non-responders, whereas WDAE may qualify as responders if NRS pain score declines sufficiently prior to withdrawal (see p. 197/1357) • PGIC/CGIC to be analysed by modified ridit transformation and CMH procedure • See pp. 193-200/1357 of unpublished report for details.	Average Daily Pain Score (p. 218-19 of published report)  Fig. 2. Change from baseline in average daily pain scores. *$P < 0.01$ vs. placebo (Mantel Haenszel). Above is Figure 2 from page 219 of the Pain report showing weekly average daily pain scores, below are the average daily pain scores for the week at baseline and week 7 along with Standard Deviations. Placebo: Baseline: 6.4 (SD = 1.6) Week Seven:5.3 (SD = 2.4) Week Seven-LOCF: 5.3 (SD = 2.3) Change in Average Daily Pain Score: -1.1 Percent Change: -15.7% Gabapentin 1800 mg/day: Baseline: 6.5 (SD = 1.7) Week Seven: 4.1 (SD = 2.5) Week Seven – LOCF :4.3 (SD = 2.5) Change in Average Daily Pain Score:-2.2 Percent Change: -34.5% Gabapentin 2400 mg/day Baseline: 6.5 (SD = 1.6) Week Seven:4.2 (SD = 2.0) Week Seven – LOCF: 4.2 (SD = 2.1) Change in Average Daily Pain Score:-2.3 Percent Change: -34.4%	Placebo: 17/111 (15.32%) Gabapentin 1800 mg: 22/115 (19.13%) Gabapentin 2400 mg/day: 23 /108 (21.30%) The reasons listed for withdrawal were: • Lack of Compliance: o Placebo: 3/111 (2.70%) o Gabapentin 1800 mg: 2/115 (1.74%) o Gabapentin 2400 mg: 1/108 (0.93%) • Lack of Efficacy o Placebo: 4/111 (3.60%) o Gabapentin 1800 mg: 2/115 (1.74%) o Gabapentin 2400 mg: 1/108 (0.93%) • Adverse Event o Placebo: 7/111 (6.31%) o Gabapentin 1800 mg: 15/115 (13.04%) o Gabapentin 2400 mg: 19/108 (17.59%) • Other o Placebo: 3/111(2.70%) o Gabapentin 1800 mg: 3/115 (2.61%) o Gabapentin 2400 mg: 2/108 (1.85%) 5. Total Adverse Events: Number of patients in each group	significant advantage of Gabapentin over placebo comparisons with placebo for the primary efficacy analyses will be made using Dunnett's procedure." It is not clear whether this is an appropriate post-hoc statistical approach. 5. An interesting observation, although not a predefined outcome, was the mean duration of treatment during the study. It was 46.0 days for placebo, 43.3 days for Gabapentin 1800 mg/day, and 43.7 days for Gabapentin 2400 mg/day. Clearly those on Gabapentin took the medication for less time - likely reflecting earlier dropouts. However; standard deviations for these results cannot be located in the Pain report nor in the unpublished report making it impossible to assess statistical significance. 6. According to page 18 of the unpublished report, "Four patients were entered into the study with less than 4 days sleep diary although all had sufficient pain diary data. One of these patients could not be included in the analysis of sleep diaries as there were no baseline sleep entries. All other patients have been included

			Difference between Gabapentin 1800 mg and placebo: 18.8%, P < 0.01 Difference between Gabapentin 2400 mg and placebo: 18.7%, P < 0.01 • I have highlighted the percent changes in red because they are not the values obtained when using the normal formula for percent change (i.e. (week 7 – baseline)/baseline) those values are then o Placebo: -17.2% o Gabapentin 1800 mg/day: -33.8% o Gabapentin 2400 mg/day: -35.4% • This discrepancy is because data were percent change transformed due to non-normality o Note that percent change from baseline was not a prespecified outcome. Mean Sleep Interference Score: • The author's report that for the last week the difference between placebo and Gabapentin 1800 mg was 0.9, P < 0.01. However, the LOCF changes from baseline for mean sleep interference score for placebo and Gabapentin 1800 mg/day were -0.9 and -1.7 respectively, an absolute difference of 0.8. • The authors report that the difference between placebo and Gabapentin 2400 mg was 1.1, P < 0.01. However, the LOCF changes from baseline for mean sleep interference score for placebo and	who experienced adverse events • Placebo: 55/111 (49.55%) • Gabapentin 1800 mg: 81/115 (70.43%) • Gabapentin 2400 mg/day: 81/108 (75%) Total adverse events were • Placebo: 112 o Mild:57 o Moderate:47 o Severe:8 • Gabapentin 1800 mg/d: 180 o Mild: 89 o Moderate: 67 o Severe: 24 • Gabapentin 2400 mg/d: 206 o Mild:96 o Moderate:80 o Severe: 30 Note that table 3 on page 221 of Pain report lists the Adverse Events Occurring in > 5% … • Dizziness o Placebo: 11/111 (9.91%) o Gabapentin 1800 mg: 36/115 (31.30%) o Gabapentin 2400 mg: 36/108 (33.33%) • Somnolence o Placebo: 7/111 (6.31%) o Gabapentin 1800 mg: 20/115 (17.39%) o Gabapentin 2400 mg: 22/108 (20.37%)	in the analysis… The initial SF-36 questionnaires in 5 patients at one centre were administered after the start of treatment. These patients have been excluded from the analysis of SF-36." – However, the sample sizes do not add up! They are all different for the efficacy analysis and baseline numbers for SF-36 = same as number randomized? 7. The Pain report states that "Three hundred and twenty-one patients completed the SF-36 questionnaire at baseline and 289 had evaluable SF-36 results from the treatment period." What does this mean? What is evaluable? 8. The Pain report and the unpublished report both seem to contain no test of statistical significance for adverse effects in each group. As in other studies adverse events are much more common in the Gabapentin groups. 9. P. 222 of the Pain report (discussion) states "*The study was not set up to show equivalence between the 2 doses and no statistical comparison was made between them. A visual inspection of the data suggests no difference between the 1800 and*

			Gabapentin 2400 mg/day were -0.9 and -2.1 respectively, an absolute difference of 1.2. Placebo: Baseline: 4.0 (SD = 2.6) Week Seven: 3.2 (SD = 2.6) Week Seven-LOCF: 3.1 (SD = 2.6) Change in Daily Sleep Interference Score: -0.9 Gabapentin 1800 mg/day: Baseline: 4.0 (SD = 2.8) Week Seven: 2.0 (SD = 2.5) Week Seven – LOCF : 2.3 (SD = 2.6) Change in Daily Sleep Interference Score: -1.7 Gabapentin 2400 mg/day Baseline: 4.4 (SD = 2.7) Week Seven: 2.1 (SD = 2.5) Week Seven – LOCF: 2.3 (SD = 2.6) Change in Daily Sleep Interference Score: -2.1 SF-MPQ (Page 219 of Pain Report) • The pain report states that *"The SF-MPQ showed improvements in all parameters during treatment with greater improvements in Gabapentin treated patients. The difference between Gabapentin and placebo was statistically significant (P < 0.05) for the sensory score (both doses); total score (both doses); and visual analogue scale of pain*	• Peripheral oedema o Placebo: 0/111 (0%) o Gabapentin 1800 mg: 6/115 (5.22%) o Gabapentin 2400 mg: 12/108 (11.11%) • Asthenia o Placebo: 4/111 (3.60%) o Gabapentin 1800 mg: 7/115 (6.09%) o Gabapentin 2400 mg: 6/108 (5.56%) • Dry Mouth o Placebo: 1/111 (0.90%) o Gabapentin 1800 mg: 7/115 (6.09%) o Gabapentin 2400 mg: 5/108 (4.63%) • Diarrhoea o Placebo: 1/111 (0.90%) o Gabapentin 1800 mg: 7/115 (6.09%) o Gabapentin 2400 mg: 5/108 (4.63%) NB: For all positive outcomes (e.g., Average Daily Pain Score, Mean Sleep Interference Score, etc.) significance testing has been performed and is reported. However, for adverse events, no statistical significance is reported; the raw data suggest that significantly more adverse events (serious, severe, moderate and mild) occurred in	*2400 mg groups" It* is odd to establish two dose groups without comparing them. The reasonable inference is that there is no efficacy advantage to the larger dose, as appears in the raw statistics. 10. This study suggests like other studies that separation of NRS score (LOCF) occurs at week 1 for Gabapentin vs. placebo, and then levels off. A longer time does not appear necessary to discern this effect. 11. Note patients who dropped out due to adverse effects could qualify as "responders" in 50% responder analysis. This means that even if pain response benefit occurred in a patient experiencing intolerable AE, the patient could count as a "responder", i.e. "response" is not necessarily desirable. 12. One of the inclusion criteria was that the average pain scores of 4 or more based on an 11-point Likert scale on the week before commencing study medication, yet according to page 18 (23 of 1357) of the unpublished report 13 patients were randomised to treatment despite having a mean baseline pain score less than 4

during the previous week (2400 mg only)."

Patient Global Impression of Change (P. 219 of Pain report)

- The Pain report only gives the data for much improved/very much improved
- Table 12 from the unpublished report (p. 35/1357) summarizes the data for PGIC and has been included at the end of this document
- The unpublished report and the Pain report state the sample sizes for this outcome as Placebo = 105, Gabapentin 1800 mg = 107, and Gabapentin 2400 mg = 98 this can bee seen from Table 12 of the unpublished report on page 35 of 1357.
- The table below uses for the denominators the actual number of patients randomized to each group i.e. Placebo = 111, Gabapentin 1800 mg = 115, and Gabapentin 2400 mg = 108 therefore the percentages are smaller than those indicated in either report.

	Placebo N=111	Gabapentin 1800 mg N=115	Gabapentin 2400 mg N=108
Very Much Improved	7/111 (6.31%)	18/115 (15.65%)	12/108 (11.11%)
Much Improved	17/111 (15.32%)	26/115 (22.61%)	30/108 (27.78%)
Minimally Improved	23/111 (20.72%)	22/115 (19.13%)	21/108 (19.44%)
No change	45/111 (40.54%)	34/115 (29.57%)	27/108 (25.00%)
Minimally	7/111	3/115	3/108

the Gabapentin groups as compared with placebo

6. Validated measures of improvement in global function including return to work, study, activities of daily living

- None reported in this study

7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint

Placebo: 16/111 (14%)
Gabapentin 1800 mg/day 37/115 (32%)
Gabapentin 2400 mg/day: 37/108 (34%)

- Proportion of patients showing a 50% or greater reduction in mean pain score between baseline and end of treatment was significantly higher in both the Gabapentin groups (P = 0.001)
- Note patients who dropped out due to adverse effects could qualify as "responders" in above analysis, i.e. "response" is not necessarily desirable.

8. Mean between-group

Worse	(6.31%)	(2.61%)	(2.78%)
Much Worse	3/111 (2.70%)	3/115 (2.61%)	5/108 (4.63%)
Very much worse	3/111 (2.70%)	1/115 (0.87%)	0/108 (0%)
Missing observation	6/111 (5.41%)	8/115 (6.96%)	10/108 (9.26%)
Mean (SD) Median	3.5 (1.3) no change	2.9 (1.3) minimally improved	2.9 (1.3) minimally improved

Clinical Global Impression of Change (P. 219-20 of Pain report)

- The Pain report only gives the data for much improved/very much improved
- Table 13 (36/1357) of the unpublished report summarizes the data for CGIC and has been included at the end of this document.
- The unpublished report and the pain report state the sample sizes for this outcome as Placebo = 107, Gabapentin 1800 mg = 108, and Gabapentin 2400 mg = 103, while the number of patients randomized to each group was Placebo = 111, Gabapentin 1800 mg = 115, and Gabapentin 2400 mg = 108
- The table below reflects the true ITT sample sizes and therefore the percentages listed are smaller than those in either of the reports.

	Placebo N =111	Gabapentin 1800 mg N = 115	Gabapentin 2400 mg N = 108
Very Much Improved	6/111 (5.41%)	14/115 (12.17%)	12/108 (11.11%)
Much Improved	14/111 (12.61%)	34/115 (29.57%)	33/108 (30.56%)
Minimally Improved	30/111 (27.03%)	16/115 (13.91%)	26/108 (24.07%)
No change	46/111 (41.44%)	37/115 (32.17%)	25/108 (23.15%)

difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF :

NB: the group differences from baseline were NOT the pre-defined primary endpoint (see column to left). The difference from baseline appears to be a post-hoc secondary analysis, although it is common to other studies. TLP concludes it is reasonable to meta-analyze the comparison of group mean changes from baseline to LOCF endpoint. as shown below:

Placebo (N=111):
Baseline: 6.4 (SD = 1.6)
Week 7: 5.3 (SD = 2.4)
Week 7-LOCF: 5.3 (SD = 2.3)
Change in Average Daily Pain Score (LOCF): -1.1

Gabapentin 1800 mg/day (N=115):
Baseline: 6.5 (SD = 1.7)
Week 7: 4.1 (SD = 2.5)
Week 7–LOCF :4.3 (SD = 2.5)
Change in Average Daily Pain Score: (LOCF) - 2.2

Gabapentin 2400 mg/day(N=108):
Baseline: 6.5 (SD = 1.6)
Week 7: 4.2 (SD = 2.0)
Week 7–LOCF: 4.2 (SD = 2.1)

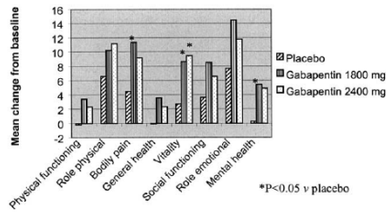
				Change in Average Daily Pain Score (LOCF): -2.3 • **Difference between Gabapentin 1800 mg and placebo:** show numerically P < 0.01 indicate statistical technique (? ANCOVA) • **Difference between Gabapentin 2400 mg and placebo:** show numerically P < 0.01 indicate statistical technique (? ANCOVA) <u>9. PGIC, % of patients achieving "much improved" or "moderately improved" (equivalent to PGIC in US studies, but expressed with similar but different words in UK/Ireland):</u> • Note that in this report, the scale used to assess PGIC was as follows: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse. o The scales employed in other studies have generally been as follows: 1 = much improved, 2 = moderately improved, 3 =	

Minimally Worse	8/111 (7.21%)	5/115 (4.35%)	4/108 (3.70%)
Much Worse	3/111 (2.70%)	1/115 (0.87%)	3/108 (2.78%)
Very Much Worse	0/111 (0%)	1/115 (0.87%)	0/108 (0%)
Missing	4/111 (3.60%)	7/115 (6.09%)	5/108 (4.63%)
Mean (SD) Median	3.4 (1.1) No Change	2.9 (1.3) Minimally Improved	2.9 (1.2) Minimally Improved

Quality of Life Questionnaire (p. 220 of Pain report):

- *The pain report states that "Three hundred and twenty-one patients completed the SF-36 questionnaire at baseline and 289 had evaluable SF-36 results from the treatment period."* What does this mean? What is evaluable?
- The Pain report states the number of patients to complete the questionnaire in each group as
  - Placebo: 106
  - Gabapentin 1800 mg/day: 105
  - Gabapentin 2400 mg/day: 95
- According to the Pain report…
  - Patients receiving either dose of Gabapentin experienced significantly greater improvements in mean score for the vitality scale (P < 0.05)
  - Patients receiving the 1800 mg dose of Gabapentin also showed significantly greater improvements in mean score for scales of bodily pain (P < 0.01) and mental health (P < 0.05) than those receiving placebo

Figure 3: Summary of changes in domains of the SF-36 (P. 220 of published report)

			 Proportion of Patients Achieving at Least 50% Pain Reduction Placebo: 16/111 (14%) Gabapentin 1800 mg/day 37/115 (32%) Gabapentin 2400 mg/day: 37/108 (34%) • Proportion of patients showing a 50% or greater reduction in mean pain score between baseline and end of treatment was significantly higher in both the Gabapentin groups (P = 0.001) • Note patients who dropped out due to adverse effects could qualify as "responders" in above analysis, i.e. "response" is not necessarily desirable. • See page 26 of 1357 of unpublished report and page 219 of Pain report. • It should also be noted that the achievement of 50% reduction in mean pain scores was not listed as a secondary outcome o It is listed on page 89 or 1357 of the unpublished report (Section 9.1.1.5 of the protocol) as a supplementary analysis o *"To compare the percentage of patients achieving a 50% reduction*	minimally improved, 4 = no change, 5 = minimally worse, 6 = moderately worse, 7 = much worse o The scales are clearly analogous and therefore, for this study we analysed the percentage of patients achieving "very much improved" or "much improved" According to page 219 of Pain report, the percentage of patients achieving "very much improved" or "much improved" were: • Placebo: 24/105 (23%) of patients • Gabapentin 1800 mg: 44/107 (41%) • Gabapentin 2400 mg: 42/98 (43%) These are more conservatively and appropriately shown as: Placebo: 24/111 (22%) Gabapentin 1800 mg/d: 44/115 (38%) Gabapentin 2400 mg/d: 42/108 (39%) TLP: we should consistently use the ITT denominator for all such % calculations.	

			in mean pain scores from the daily pain diaries for each dose of Gabapentin with that for placebo." Is also listed on page 193 of 1357 of the unpublished report (in the statistical analysis plan) as a secondary objective.	<u>10. Histogram presentation of all PGIC 7-point results</u> • See histograms at end of document. • Note that in the denominator I have used the total number of patients randomized to each group, NOT the numbers given as denominators in the Pain/unpublished reports. • Also notice that upon observation the groups do not look so significantly different.	

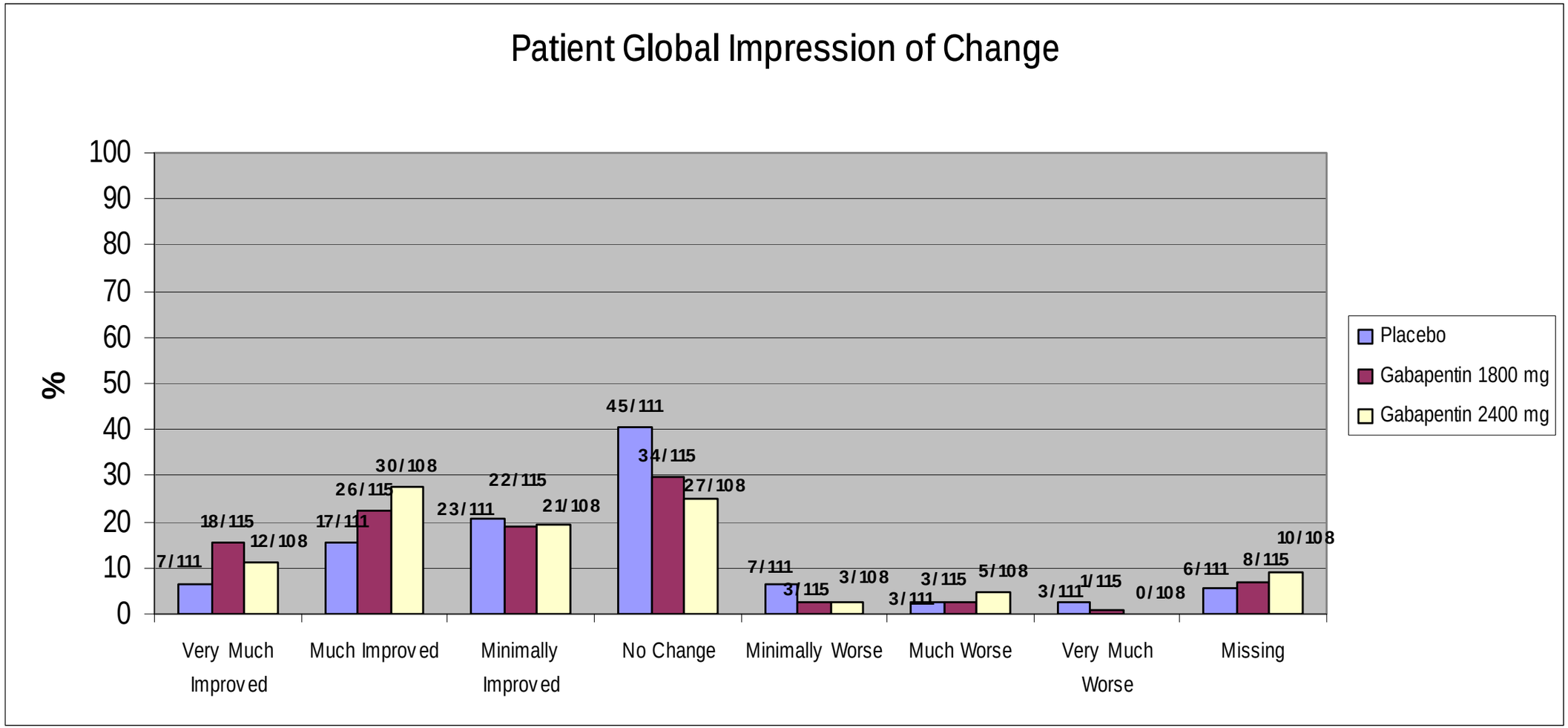

Patient Global Impression of Change
%
100
90
80
70
60
50
40
30
20
10
0
7/111
18/115
12/108
17/111
26/115
30/108
23/111
22/115
21/108
45/111
34/115
27/108
7/111
3/115
3/108
3/111
3/115
5/108
3/111
1/115
0/108
6/111
8/115
10/108
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Much Worse
Very Much Worse
Missing
Placebo
Gabapentin 1800 mg
Gabapentin 2400 mg

Table 8 – Daily Pain Diary (raw data)

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Baseline, N	111	115	108
Mean (SD)	6.4 (1.6)	6.5 (1.7)	6.5 (1.6)
P value vs. placebo [a]		Not sig.	Not sig.
Week 1, N	109	113	106
Mean (SD)	5.9 (2.0)	5.1 (2.2)	5.0 (1.8)
P value vs. placebo [a]		<0.01	<0.01
Week 2, N	107	103	98
Mean (SD)	5.8 (2.0)	4.7 (2.3)	4.7 (2.1)
P value vs. placebo [a]		<0.01	<0.01
Week 3, N	103	99	95
Mean (SD)	5.5 (2.2)	4.4 (2.4)	4.4 (2.1)
P value vs. placebo [a]		<0.01	<0.01
Week 4, N	99	95	92
Mean (SD)	5.6 (2.1)	4.4 (2.3)	4.5 (2.2)
P value vs. placebo [a]		<0.01	<0.01
Week 5, N	96	94	88
Mean (SD)	5.3 (2.3)	4.4 (2.4)	4.5 (2.0)
P value vs. placebo [a]		<0.01	<0.01
Week 6, N	95	94	88
Mean (SD)	5.3 (2.3)	4.3 (2.5)	4.3 (2.0)
P value vs. placebo [a]		<0.01	<0.01
Week 7, N	91	92	85
Mean (SD)	5.3 (2.4)	4.1 (2.5)	4.2 (2.0)
P value vs. placebo [a]		<0.01	<0.01
End of study (LOCF), N	111	115	108
Mean (SD)	5.3 (2.3)	4.3 (2.5)	4.2 (2.1)
P value vs. placebo [a]		<0.01	<0.01

[a] based on Dunnet's test

Table 8 from page 29 of 1357 of the unpublished report

Table 9 – Daily Sleep Interference Diary

	Placebo	Gabapentin 1800 mg	Gabapentin 2400 mg
Baseline, N	110	115	108
Mean (SD)	4.0 (2.6)	4.0 (2.8)	4.4 (2.7)
P value vs. placebo [a]		Not sig.	Not sig.
Week 1, N	109	113	106
Mean (SD)	3.6 (2.5)	2.8 (2.5)	2.9 (2.5)
P value vs. placebo [a]		P<0.01	P<0.05
Week 2, N	107	103	98
Mean (SD)	3.3 (2.6)	2.6 (2.5)	2.4 (2.4)
P value vs. placebo [a]		P<0.05	P<0.01
Week 3, N	103	99	95
Mean (SD)	3.1 (2.5)	2.4 (2.6)	2.1 (2.4)
P value vs. placebo [a]		P<0.05	P<0.01
Week 4, N	99	95	92
Mean (SD)	3.1 (2.5)	2.2 (2.4)	2.1 (2.5)
P value vs. placebo [a]		P<0.05	P<0.01
Week 5, N	96	94	88
Mean (SD)	3.1 (2.5)	2.2 (2.4)	2.2 (2.5)
P value vs. placebo [a]		P<0.05	P<0.01
Week 6, N	95	94	88
Mean (SD)	3.1 (2.5)	2.2 (2.5)	2.1 (2.4)
P value vs. placebo [a]		P<0.05	P<0.01
Week 7, N	91	92	85
Mean (SD)	3.2 (2.6)	2.0 (2.5)	2.1 (2.5)
P value vs. placebo [a]		P<0.01	P<0.01
End of study (LOCF), N	111	115	108
Mean (SD)	3.1 (2.6)	2.3 (2.6)	2.3 (2.6)
P value vs. placebo [a]		P<0.01	P<0.01

[a] based on Dunnet's test

Table 9 from page 31 of 1357 of the unpublished report

Table 12 Summary of Patient Global Impression of Change

[Number (%) of Patients]

	Placebo N=105	Gabapentin 1800 mg N=107	Gabapentin 2400 mg N=98
Very much improved	7 (7)	18 (17)	12 (12)
Much improved	17 (16)	26 (24)	30 (31)
Minimally improved	23 (22)	22 (21)	21 (21)
No Change	45 (43)	34 (32)	27 (28)
Minimally worse	7 (7)	3 (3)	3 (3)
Much worse	3 (3)	3 (3)	5 (5)
Very much worse	3 (3)	1 (1)	0 (0)
Mean (SD) *	3.5 (1.3)	2.9 (1.3)	2.9 (1.3)
Median	No change	Minimally improved	Minimally improved

* Based on 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Table 12: Summary of Patient Global Impression of Change, from page 35 of 1357 of unpublished report.

Table 13 Summary of Clinical Global Impression of Change

[Number (%) of Patients]

	Placebo N=107	Gabapentin 1800 mg N=108	Gabapentin 2400 mg N=103
Very much improved	6 (6)	14 (13)	12 (12)
Much improved	14 (13)	34 (31)	33 (32)
Minimally improved	30 (28)	16 (15)	26 (25)
No Change	46 (43)	37 (34)	25 (24)
Minimally worse	8 (7)	5 (5)	4 (4)
Much worse	3 (3)	1 (1)	3 (3)
Very much worse	0 (0)	1 (1)	0 (0)
Mean (SD) *	3.4 (1.1)	2.9 (1.3)	2.9 (1.2)
Median	No change	Minimally improved	Minimally improved

* Based on 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Table 13: Summary of Clinical Global Impression of Change, from page 36 of 1357 of unpublished report

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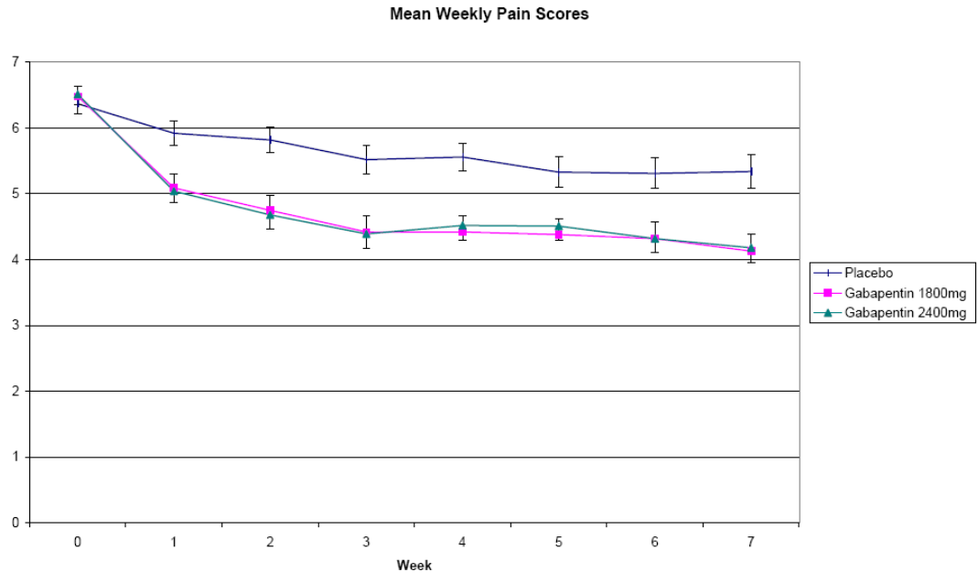
Table 15: Overview of Adverse Events (AEs)

[Number (%) of patients if not otherwise indicated]

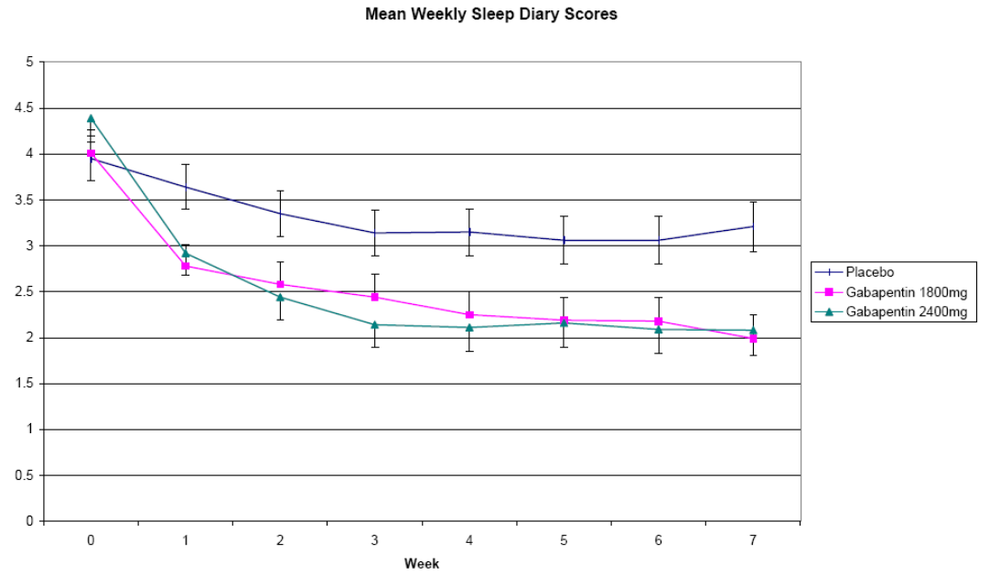
	Placebo N=111	Gabapentin 1800 mg N=115	Gabapentin 2400 mg N=108
Patients with AEs			
All AEs	55 (49.5)	81 (70.4)	81 (75.0)
Associated [a] AEs	31 (27.9)	65 (56.5)	65 (60.2)
Patients with AEs by Maximum Intensity			
All AEs	112	180	206
Mild	57	89	96
Moderate	47	67	80
Severe	8	24	30
Number of Deaths [b]	0	0	1 (0.9)
Patients with Serious Non-fatal AEs [c]	1 (0.9)	3 (2.6)	1 (0.9)
Patients Withdrawn due to AEs			
All AEs	7 (6.3)	15 (13.0)	19 (17.6)
Associated AEs	5 (4.5)	14 (12.2)	15 (13.9)

[a] Considered by the investigator to be possibly, probably or definitely related to study drug, or as insufficient information.
[b] All events were considered by the investigator as unrelated to study drug
[c] One patient died outside the one month follow-up after study completion. Death was recorded as 'other causes' and not related to the AEs ongoing at the time.

Table 15: Overview of Adverse Events, page 39 of 1357 of unpublished report.



Unpublished report, Appendix C.1a: Mean Weekly Pain Score, ITT-LOCF (181 of 1357)



Unpublished report, Appendix C.1b: Mean Weekly Sleep Diary Scores, ITT-LOCF (182 of 1357)

Changes from baseline in mean pain scores will be tabulated but will not be subjected to statistical analysis.

The above is taken from 198 of 1357 of the unpublished report (Inferential Analysis Plan).

9.1.1.3. Main Model

The primary analysis will compare the final weekly mean pain score between the treatment groups of the studied population using analysis of covariance (ANCOVA) with treatment (fixed effect) and cluster (fixed effect) in the model and the screening mean pain score as covariate[11].

The above is taken from 88 of 1357 of the unpublished report (The Protocol)

9.1.1.5. Supplemental Analyses

Supplemental analyses of weekly mean pain score will be:

- Analysis of mean pain score for each week separately.
- Change of weekly mean pain score from baseline at end point and at each week separately.

These supplemental analyses will include the same model as the main model.

In addition, age, duration of pain and use of tricyclic antidepressants will be investigated for their effect on the conclusions.

- The percentage of patients achieving a 50% reduction in mean pain scores will be analysed.

The above is taken from 89 of 1357 of the unpublished report (The Protocol)

Deceased Patient: Supplemental Information:

The patient who died was an 88-year-old male born December 22nd, 1910. His patient number was 46 (centre 17), initials BCW and was randomized to the Gabapentin 2400 mg/day treatment group (p. 485 of 1357). According to page 1135 of 1357 he was screened at centre 17 on April 22nd, 1999 and the date of his first visit, as well as the date that he started his dose was April 19th, 2999; his last dose was on June 16th, 1999. According to appendix E.13 he had no elective surgeries during the study. At study day -7, which one assumes is at the beginning of baseline or one-week prior to treatment, his vital signs were as follows (p. 523 of 1357):

- Weight: 58 (assume 58 kg, although units not specified)
- Sitting heart rate: 88
- Sitting Blood Pressure: 110/70
- Standing Heart Rate: 90
- Standing Blood Pressure: 106/68

At study day 50, which one can assume, is following 7 weeks of treatment, his vitals were as follows (p. 523 of 1357):

- Weight: 60 (assume 60 kg, although units not specified)
- Sitting heart rate: 84
- Sitting Blood Pressure: 136/80
- Standing Heart Rate: 86
- Standing Blood Pressure: 130/76

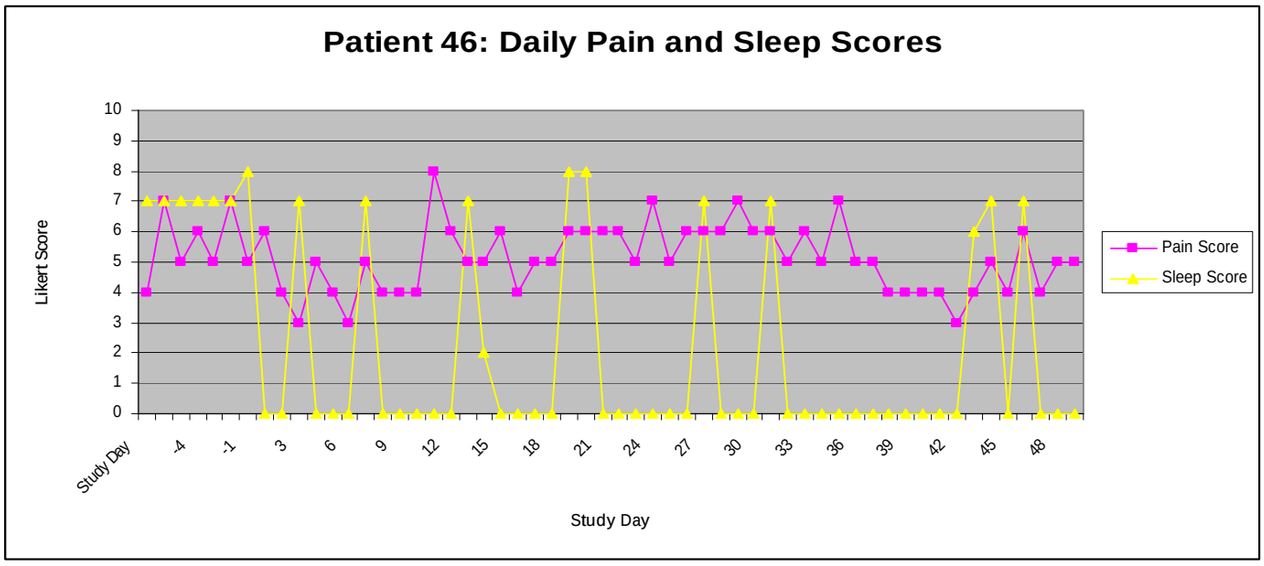
According to page 1153 of 1357 the medications he was taking concurrently were:

- Becotide
- Co-amilofruse (Frumil)
- Nifedipine
- Quinine
- Ventolin Salbutamol
- Salazopyrin

His Significant Medical/Surgical History / Concurrent Illnesses were as follows (p. 556-57 of 1357)

Condition	Start Date	End Date
Ulcerative Colitis	80	Continuing
Airflow Obstruction	91	Continuing
Cardiac Failure	91	Continuing
Iron Deficiency / Anemia	91	Continuing
Herpes Zoster	92	92
Intermittent Claudication: Leg Cramps at Night	94	Continuing
Prostatectomy	94	94
Hernia Repair	96	96
Vertigo	98	Continuing
Septal Perforation-Nasal	99	Continuing

From his pain score data (p. 731-32 of 1357) patient 46 submitted pain and sleep scores for the entirety of the study. Furthermore, according to p. 1095 of 1357 he was listed as compliant at all three visits; no capsules are listed as returned. He completed the study on day 49 and was seen on day 50 (p. 1118 of 1357). No data is listed for PGIC or CGIC for this patient (p. 1125 of 1357).



According to 1301-02 of 1357

- The patient suffered a single episode of peripheral oedema (ankle swelling) on day 43 for which the duration is listed as 50 (unknown whether or not this 50 is 50 day duration or the oedema resolved itself on day 50 of the study); the severity was deemed moderate and the investigator deemed this event unlikely related to the study drug.
- On day 19 he suffered a single episode of back pain, duration 75, severity moderate, deemed unlikely related to the study drug
- On day 2 he suffered dizziness (bouts of giddiness) and ataxia (off balance) both of continuous duration. Both were deemed mild and possibly related to the study drug.
- All the above adverse events were treatment emergent.

No comments for this patient are listed in appendix E.16. No narratives regarding his death are listed in appendix b. There is no information given pertaining to cause of death except for that the investigator deemed this death unrelated to the study drug.

Study No. 10 PARKE DAVIS/PFIZER 945-430-306 (MIXED NEUROPATHIC PAIN), Serpell et al 2002 – PUBLISHED (2002) AND UNPUBLISHED (2000) TRIAL SUMMARY - Thomas L. Perry, M.D. – FINAL – July 26, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 10 Published Serpell, MG, Neuropathic Pain Study Group. Gabapentin in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Pain 2002; 99: 557-66 Unpublished Parke-Davis (Eastleigh, UK) 945-430-306 Research Report No. RR 430-00135,	Mixed neuropathic pain (including complex regional pain syndrome, PHN, radiculoparhy, postlaminectomy, etc.): Inclusion: • Various characteristics of neuropathic pain • Pain score (Likert) ≥4 on daily pain diary before	(from final study report, p. 84/1358) Placebo vs. gabapentin (3 x/day) titrated over first 3 days to 900 mg/d, then held at 900 mg/d until end of week 2. At "visit 2" (end of week 2) increase to 1200 mg/d-1800 mg/d further titration, if target 50% NRS mean pain reduction not reached. At "visit	Predefined outcomes: Primary: ("Main model", from p. 74/1358, final study report): NRS pain score (Likert 0-10 scale) as group mean of individual means from patients' last 7 available scores while on study medication (up to end of Week 8) from daily diary records of previous 24 hours, compared with baseline. Endpoint for non-completers of 8 week trial is LOCF. Supplemental analysis is	Mortality: P = 2, G = 0 (final study report, p. 36/1358) P = 0; G = 0 (calculated by TLP)* * p. 36/1358 states "Two patients died within one month of receiving their last dose of placebo medication, one due to ischemic heart disease and one due to heart failure. Full narratives are provided in Appendix B.1." Appendix B.1. (148/1358) clarifies that it does not seem reasonable to attribute these deaths to placebo, and the published report makes no mention of them (p. 562). Serious Adverse Events (non-fatal) (pp. 35-36/1358): NB: TLP cannot tell how these numbers are derived in final report. They are not reported in the publication (Serpell, 2002). Appendix B.1. shows that for P=2, G=2 SAE, the event arose before, or well after the end of the trial and is not plausibly related … for patient 06-417, the event arose after open-label gabapentin was prescribed to a patient who had taken placebo as study drug. Patients experiencing SAE (non-fatal): P = 2/152 (final report); 2/152 (TLP calculation) G = 4/153 (final report); 2/153 (TLP calculation)	1. "Enrichment" by excluding patients who had failed to respond to gabapentin at ≥ 900 mg/d or had not tolerated it. Many potentially eligible patients may have been exposed prior to commencement of study in June 1999, due to publication of JAMA articles in December 1998 and promotion of gabapentin even earlier. Published report (2002) refers to N=351 "eligible patients" (i.e. not gabapentin "failures", whereas final study report (2000) refers to N=351 as screened. Neither reports N of patients rejected for prior gabapentin "failure".

May 5, 2000 8 week DBRCT June 17, 1999 – February 8, 2000 UK and Ireland Final Protocol: February 3, 1999, amended July 7, 1999 (p. 8/1358) Investigators meeting:May 7,1999 Investigators were UK and Irish consultant anesthetists who run outpatient chronic pain clinics. (p. 8/1358 of final study report). Dr. Michael Serpell (Glasgow, Scotland) was "study advisor". Randomization: Central randomization sequentially to assignment to G or P in block sizes of 4 Data analysis:	randomization Exclusion: • Failure to respond to gabapentin at ≥900 mg/day or failure to tolerate any dose of gabapentin ("enrichment bias") • nown chronic kidney disease or Cr clearance ≤ 60 mL/min Baseline characteristics: Mean pain score (Likert NRS, 0-10): P (152/152): 7.3 (SD 1.5) G (152/153): 7.1 (SD 1.6) Groups appear generally similar (Table 1,	3" (end of week 4), increase to 2100mg/d-2400 mg/d if target 50% NRS mean pain reduction not reached (or maintain at 900 mg/d or 1800 mg/d) for "responders" to end of study (end of week 8) or early drop out. Screened: 351 Randomized: 307 (ITT = 305 - 2 patients withdrew prior to receiving drug) P = 152 (152 reported for safety analysis,148 reported for responder analysis, varying numbers for LOCF for primary	weekly mean pain scores from baseline to week 8 or dropout (LOCF). ANCOVA for these analyses was problematic, so "a decision was made to perform a rank based analysis of the data …" (p. 19/1358 and elsewhere). "Responder" analysis: because a 50% reduction in mean pain score at end of week 2 (visit 2) and end of week 4 (visit 3) was a criterion for titration decisions, and this is specified in the experimental protocol, it is reasonable to accept this as a pre-specified outcome (unclear in other study reports). Percentage responders analysed by Manetel-Haenzel Chi-square test adjusting for cluster (groups of trial centres with few patients each). Patients withdrawing early due to lack of efficacy were classed as "non-responders". It appears that patients who "responded" (achieved mean NRS pain score ≤ 50% of baseline) but withdrew due to adverse events or other	Total SAE (non-fatal): NR Calculated from Appendix B.1. SAE narratives and patient assignments Appendix: P = 2 (TLP calculation) G = 2 (TLP calculation) TLP recommendation: I suggest we use for mortality P=0, G=0, and either NOT include these non-fatal SAE in Cochrane meta-analysis, or alternatively we use the recalculated total non-fatal SAE (2 in each group). Withdrawal Due to Adverse Events (WDAE, p. 30/1358): P = 25/152 G = 24/153 Total withdrawals: P=41/152 G=32/153 Total patients with Adverse Events (p. 30/1358): P = 103/152 G = 117/153 Total Adverse Events: P = 223 G = 336 Specific AE: Dizziness: P=12/152 (7.9%); G=37/153 (24.2%) Somnolence: P=8/152 (5.3%); G=22/153 (14.4%) Infection: P=19/152 (12.5%); G=14/153 (9.2%) Headache: P=21/152 (13.8%); G=14/153 (9.2%)	2. The primary outcome (difference from baseline in group mean NRS pain scores at study week 8 endpoint) was not significantly different: change for P = -1.3, for G = -1.6; difference = -0.3 points, p=0.31, nor for LOCF-endpoint: change for P = -1.0, for G = -1.5; difference = -0.5 points, p=0.046, or p=0.0.57, or p=0.06 (variously reported). If the LOCF difference were statistically significant, there is no meaningful clinical difference to a 0.5 point mean difference between treatment with P and G. The weekly (LOCF) plot of group mean change from baseline (Figure 3 in Serpell 2002, p. 171/1358 in final report) indicates that any separation of groups occurred DURING FIRST WEEK, at G = 900 mg/d, whereas separation of groups was no longer apparent at end of trial … THIS SUGGESTS THAT EFFICACY (IF ANY) IS NOT DOSE-DEPENDENT ABOVE 900 mg/d. 3. A pre-defined aspect of the

Parke Davis Biometrics Group, Eastleigh handled data entry and analysis (/ 4/1358, final report)	publication), but neither publication nor final report gives breakdown by type of pain condition, so one cannot tell if groups are balanced for type (e.g. CPRS) without manually calculating from appendices. Median age = 57	endpoint, 112 completed trial) G = 153(153 reported for safety analysis, 150 for responder analysis, varying numbers for LOCF for primary endpoint, 122 completed trial) This study appears NOT to be true ITT-LOCF as P=4, G=3 patients patients randomized appear NOT to have been reported for efficacy. It does not report on all patients at true endpoint.	reasons would be classified as "responders", even though this does not make clinical sense as a good outcome. Secondary: NB: all secondary outcomes are <u>dependent,</u> not independent of primary outcome, as they all measure various aspects of the same thing (pain relief). The study made no adjustments for multiple comparisons. • Individual pain symptoms • SF-MPQ • PGIC, CGIC • SF-36 QOL survey • Safety Since most of the dependent secondary outcomes are not part of systematic review, only PGIC and safety will be discussed further.	<u>Primary outcome, difference from baseline at endpoint:</u> Baseline N, final scores (SD) P (152/152): 7.3 (1.5) G (152/153): 7.1 (1.6) Week 8 N, final scores(SD), difference (SD): P (111/152): 6.0 (2.8), difference -1.3 G (120/153): 5.4 (2.6), difference -1.6; p=0.31 Endpoint (LOCF) N, final scores: (SD), difference (SD): P (148/152): 6.3 (2.6), difference -1.0 G (150/153): 5.6 (2.6), difference -1.5; p=0.048 (0.057) or p=0.06 (Appendix C.2, p. 176/1358 vs. p. 27/1358 in final study report; published report Serpell 2002 reports "p=o.048, rank-based ANCOVA") This difference does not appear to be significant according to the pre-specified protocol (presentation of statistics confusing). TLP suggests we use the LOCF endpoint N's for consistency in Cochrane meta-analysis, with understanding they are LOCF, not true ITT endpoints. Responder rate (≥50% reduction in NRS at LOCF endpoint – appears to include WDAE if they achieved >50% reduction): P = 22/152 (14%) G = 32/153 (21%); p=0.16 (p. 561 publication, p. 28/1358 final report; these are reported by both published and unpublished report to show P=22/148, G=32/150, whereas TLP has adjusted above	primary outcome, which was a determinant of titration strategy, the % of patients achieving > 50% reduction from baseline on weekly NRS pain scale is not significantly different: P = 22/152 (14%) G = 32/153 (21%); p=0.16 4. For PGIC, a secondary outcome, the claimed statistical significance of the apparent difference between "very much or much improved" categories, favouring gabapentin, is doubtful. The statistical analysis does not appear to specify this comparison, which is one of multiple comparisons not appropriately tested. (see detailed notes and references in adjacent column.) Accepting the numbers of patients achieving this outcome (LOCF) expressed with the ITT denominators, as in adjacent column, seems appropriate for Cochrane meta-analysis which

				to show true ITT denominators for each group. The rounded % are identical to those in the published and final study reports.) Patient Global Impression of Change at endpoint(PGIC): (p. 197/1358 statistical analysis plan suggests that "Objective G" (PGIC and CGIC) will be analysed by CMH ridit transformation, but does not-prespecify grouping by any categories – the following table from p. 31/1358) shows the original presentation of data. Grouping of categories 1 and 2 ("very much or much improved", similar to "much improved or moderately improved" in other PGIC scales) appears to be a post-hoc comparison.) As a conservative assumption, it may be more reasonable to report percentages as the number reporting the outcome divided by the ITT denominator: "Very much or much improved": P = 22/152 (14%) G = 48/153 (31%) (This does not appear to be statistically significant, as not a pre-defined outcome) NB: both the published report (Serpell 2002 and the final study report (p. 31/1358) state these data as: P = 22/138 (16%) G = 48/141 (34%) "p=0.03, Mantel-Haenszel" However, there is no correction for multiple tests of significance and this is of doubtful statistical significance, as the statistical analysis document (p. 193/1358 notes that given the number of secondary analyses, some apparently "significant" results will occur by chance alone, in the absence of correction.	also shows all other categories – i.e. achieving a pre-specified meta-analytic outcome for all trials where suitable pre-specified PGIC data are available. 5. The published report's conclusions are not justified by the data presented.

The summary statistics in the original table show that the mean change is similar between groups:
P (N=138/152): 3.6 (1.2)
G (N=141/153): 3.2 (1.4)
No claim is made for an overall difference between groups in the PGIC

Table 10 - Summary of Patient Global Impression of Change

[Number (%) of Patients]

	Placebo N=138	Gabapentin N=141
Very much improved	9 (7)	18 (13)
Much improved	13 (9)	30 (21)
Minimally improved	31 (22)	21 (15)
No Change	63 (46)	55 (39)
Minimally worse	13 (9)	8 (6)
Much worse	6 (4)	6 (4)
Very much worse	3 (2)	3 (2)
Mean (SD) *	3.6 (1.2)	3.2 (1.4)
Median	No change	Minimally improved

* Based on 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Study No. 11 - BONE 2002 – GABAPENTIN FOR POSTAMPUTATION PHANTOM LIMB PAIN – DBR CROSSOVER TRIAL (Published) - SUMMARY

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 11 Bone M, Critchley P, Buggy DJ. Gabapentin in Postamputation Phantom Limb Pain: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study. Reg Anesth Pain Med 2002; 27: 481-6 Support: Pfizer supplied study medication, Prof. David Rowbotham advised on statistical analysis. Trial design: independent DBRCT, 15weeks . After 1 week run-in, randomization to 6 weeks of placebo (P) or gabapentin (G) – to maximum tolerated dose of G, ceiling of 2400 mg/d; then 1-week washout, followed by crossover to the alternative arm for 6 weeks.	Post-amputation phantom limb pain Inclusion: • 18-75 years • Phantom limb > 6 months • "Pain score > 40 on a 100 mm VAS" at screening Exclusion: • Epilepsy • "significant hepatic or renal insufficiency", etc. Allowable drugs: TCA's could be continued, patients *"asked to discontinue muscle relaxants, other anticonvulsants, and topical analgesics".* Baseline characteristics:	Study design: 14 week double blind crossover trial RCT gabapentin (target dose 2400 mg/d) with placebo as 2 arms: P/G x 6 weeks, each with 1 week washout between treatments; vs G/P x 6 weeks, each with 1 week washout between treatments Patient flow (Fig 2, p 483): • Sceened: 33 • Excluded: 14 • Randomized: 19 as P/G=9, G/P=10 • Completed crossover: 14/19 as: P/G = 6/9 G/P = 8/10 • Withdrawn from treatments: NB: the patient flow figure and text do not allow ascertainment of the number of patients who dropped out of each treatment phase/group, nor the timing of drop outs.	Predefined outcomes: Primary ("endpoint vs. baseline"): VAS pain intensity difference from baseline to end of each treatment. "Categorical pain intensity of episodes of phantom pain", documented daily as a 4-point score where 0=none, 1=mild pain, 2-moderate pain, 3=severe pain. Secondary (all compared at "endpoint vs. baseline"): NB: all secondary outcomes are <u>dependent,</u> not independent of primary outcome, as they all measure various aspects of the same thing (pain relief). See report p. 482-3 for details.	TLP: for this trial, <u>no outcome</u> is suitable for meta-analysis. Mortality: Not reported Serious Adverse Events: Not reported Withdrawal Due to Adverse Events: Not reported Total withdrawals: not reported so that treatment group during which withdrawal occurred can be identified - not interpretable Total patients with AE's: not reported Total AE: not reported Most frequently reported AE's, reported as number of patients (Table 5): Somnolence: P=2, G=7 Dizziness: P=1, G=2 Headache: P=1, G=2	1. This is a very low quality study which claims a difference in mean change in VAS pain score at 6 weeks vs. baseline, favouring gabapentin. However, this is clearly unsupportable, as there is no ITT analysis, and even the completer numbers are not apparent. The authors conclusion that *"After 6 weeks, gabapentin monotherapy was better than placebo in relieving postamputation limb pain" is not supported by the experimental report. No other differences are claimed.* 2. The description of patient flow and presentation of statistics is inadequate, but suggests that the report concerns only completers, i.e. 14/19 patients. It is not clear how the crossover design is analysed in an unusual statistical analysis. 3. Presentation of safety data is inadequate and the methods section

Drugs described as "identical tablets" (p. 482) or described alternatively as "gabapentin and placebo capsules" supplied by Pfizer Pharmaceuticals (p. 485). Patients screened and enrolled between February 1999-March 2000 (p. 482). Randomization: *"The randomization technique was by computer-generated random numbers, which was organized by our hospital pharmacist."*	G/P arm: N=10/19 P/G arm: N=9/19 Mean age: 56 (17.5) Age range: 24-68 Pain characteristics: VAS weekly mean for screening week: These appear to be reported as mean VAS (SD) for the combined groups starting each treatment (e.g. for placebo, P1 and P2 groups) – the N's are not determinable: P: 6.7 (1.9) G: 6.1 (1.8)	crossover 6 weeks are Drug doses/titration (p. 484): Titration schedule not detailed. Median final dose of gabapentin was 2400 mg/d (range 1800-2400 mg/d). Statistical Analysis: (p. 483) Unusually complicated description. See original report. *"…All analyses were conducted using the intention-to-treat population, defined as all randomized patients who received at least 1 dose of study medication. Patients with no data recorded for a parameter were automatically excluded from the analysis of that parameter…"* This indicates that the analysis was at best "completer" analysis, and was NOT ITT, nor ITT-LOCF.	Barthel Index (see text) could be relevant to disability, but the authors claim no difference for gabapentin vs. placebo, and the lack of ITT analysis makes this unsuitable for meta-analysis – therefore not described in detail in this summary table.	Nausea: P=1, G=2 Primary outcome(s): NB: number of patients is << number randomized but not determinable for each treatment group – numbers are noted below but not reliable due to non-ITT and other issues (Table 2, p. 484). No explanation is provided for why average pain is reported for "week 6" whereas categorical pain is reported for "end of therapy": : <u>For average pain</u> (100 mm VAS): Placebo: Baseline: 6.7 (1.9) Week 6: 5.1 (2.2) Gabapentin: Baseline: 6.1 (1.8) Week 6: 2.9 (2.2) – "P=.025" for comparison with placebo at week 6, not further described, multiple comparisons – authors *claim "a significant difference was observed at week 6"* only. <u>For categorical pain</u> (4 point scale from 0-3):	does not discuss how safety was assessed. TLP: I don't think we can meta-analyse any of these results with any credibility. It is better to present this study on its own, as a negative study.

				Placebo: Baseline: 1.8 (0.9) End of therapy: 1.6 (1.2) Gabapentin: Baseline: 1.5 (0.9) End of therapy: 1.5 (1.0) No difference is claimed for groups. Secondary outcomes: Barthel index: See Table 4 (p. 484) for details. No difference is claimed between groups.	

Notes: This is a low quality study, which did not contribute any data to the 2005 Cochrane review, although the review cited it as showing "only a significant difference in pain intensity difference in week 6 of treatment". It is not suitable for meta-analysis.

Study No. 12 – CARACENI 2004 – NEUROPATHIC CANCER PAIN (Parke Davis **945-420-276** – GABAPENTIN VS. PLACEBO DBRCT - detailed study summary prepared by Dr. T. L. Perry - FINAL – July 26, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane safety hierarchy only – open trial)	Comments/conclusions of Dr. Perry
Study No. 12 Parke-Davis 945-420-276 Caraceni A, Zecca E, et al. Gabapentin for Neuropathic Cancer Pain: A Randomized Controlled Trial From the Gabapentin Cancer Pain Group. J. Clin Oncol 2004; 22: 2909-17 Support: funded by Pfizer Italy and Pfizer Spain.. Dates: August 1999-May 2002 Trial design: 11 (8 Italian, 3 Spanish) palliative care and oncology units during 10-day parallel DBRCT, Italy and Spain. Randomization: *"nonstratified block-of-3 randomization list"* to P or G in	Neuropathic cancer pain (infiltration or compression of nervous structures with "neuropathic" characteristics) Inclusion: • Age ≥ 18 • Pain score ≥ 5on an 11-point NRS pain scale • Regular opioid therapy without sufficient analgesia • Life expectancy ≥ 30 days and Karnofsky performance score ≥ 40 Exclusion: • Creatinine clearance ≤ 60 mL/min • Previous or current gabapentin use • Active chemotherapy or radiotherapy	Study design: 10-day, parallel-group multi-centre trial of gabapentin up to 1800 mg/d vs placebo. Drugs were titrated daily as needed for average 24-hour pain score ≥ 3, if tolerated. Patient flow (p. 691): • Screened: 691 • Randomized: 121 • randomization: P=41, G=79 • total withdrawals: P=10, G=21 • lost to follow-up before Day 4: P=2/41, G=3/79 • completed: P=31, G=58/79 Analysis: (p. 2911) Complex plan with multiple comparisons – see published report. Protocol and final study report not available for comparison. Achieved Doses of Gabapentin: 600 mg/d: 6/79 1200 mg/d: 18/79 1800 mg/d: 55/79	Primary outcome: Average response to treatment over the whole follow-up period as defined by the average daily pain score from diary. Secondary: Subcomponents, i.e. various subjective types of pain, and use of as needed analgesics, safety. Statistical analysis: This study attempted to establish "average" pain scores over time, with imputations for missing scores. This is not comparable to any other study, and not meta-analysable. No discussion is offered of	Mortality: P=0; G=1 NF Serious Adverse Events (number or patients): P=0, G=1 (see Table 4, p. 2916) NB: a patient died after 3 doses of gabapentin from sedation/coma on a background of liver failure. A second patient developed respiratory depression after taking 1200 mg gabapentin on the second day and required reversal of opioid analgesia. Withdrawal Due to Adverse Events: P=3/41; G=6/79 Total withdrawals: P=10/41 G=21/79 Total patients with AE's: (combines WDAE and other AE) P=10/41 G=35/79 Total AE's (patients may have > 1):	1. Unusual study in very sick patients with high morbidity and potentially high mortality. 2. Gabapentin associated with one early death and one near-death requiring opioid reversal. 3. Results cannot be meta-analysed. 4. The study does not provide real evidence in support of gabapentin for palliative care/cancer pain. 5. The authors' abstract conclusion that *"Gabapentin is effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids"* is not supported by the data, nor by the discussion, which suggests only that *"…Our conclusion is that the association of 300 mg*

a 1:*2 ratio; "all study participants were blinded to allocation sequence"* Concealment: identical capsules of 300 mg G or placebo *"allocated in random sequence by the pharmacy department"* Data analysis: power calculation of sample sizes, analysis of primary and secondary longitudinal efficacy measures by ANCOVA by *"intent to treat … imputing missing longitudinal data with the average of observed data …"* with "modified ITT" for remaining analyses and "sensitivity analysis using LOCF and worst value observed for missing data imputation" … (see report, p. 2911) … strange definitions e.g. "70%" pain response appears to be 23% pain response in conventional terms …	Allowed other analgesic drugs: Multiple Overall group characteristics: Age (mean): 59 Pain score (NRS) at baseline (mean): P: 7.7 (1.3) G: 7.0 (1.4) Morphine dose at baseline (mg/d, mean): P: 107 (87); N=41 G: 117 (118); N=80		multiple comparisons in the publication. An unpublished Pfizer report, if available, might have more discussion.	Not reported Specific AE: (combines WDAE and other AE) Somnolence/sedation: P=4/41 (9.7%); G=19/79 Dizziness: P=0/41; G=8/79 Functional improvement: NR ≥ 50% reduction in NRS pain at endpoint vs. baseline: NR Mean NRS pain score reduction from baseline to endpoint: NR PGIC: NR Outcomes reported: See report pp. 2911-5. These outcomes are totally different from any other study, and there does not appear to be any significant difference between groups, allowing for multiple comparisons and missing data, other than toxicity.	*gabapentin to the opioid drug regimen is usually safe, but in frail patients … a more cautious titration schedule is recommendable…"* 6. Both senior Italian authors and one other Italian author disclose having received more than $2,000 a year from Pfizer Italy for either of the last 2 years before submission in 2003 or publication in 2004.

Notes:

Study No. 13 - PFIZER 945-411 LADPN(2000-2001, FINAL REPORT 2002)–PAINFUL DIABETIC PERIPHERAL NEUROPATHY – SUMMARY – Final – July 26, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane safety hierarchy only – open trial)	Comments/conclusions of Dr. Perry
Study No. 13 Pfizer/Parke-Davis Protocol 945-411 "Phase 3" (unpublished report) vs. "Phase IV" (published report) A Randomized, Open Label Trial to Determine the Relative efficacy and Safety of a Fixed Dose of Gabapentin Versus Optional Titration to Effect for the Treatment of Painful Diabetic Peripheral Neuropathy UNPUBLISHED final report dated November 5, 2002; 492 pages total, TLP has a 74/492 page print version. Study dates: February 16, 2000 – December 4, 2001 Report date November 5, 2002 Pfizer_LKnapp_006623 (June 2, 2005 Clinical Study Synopsis is identical) Sponsor's reviewers/Department Approval: RadhiAbdulnabi Ph.D., Thomas J. Purcell, M.S., Lloyd	Painful diabetic peripheral neuropathy (PDPN): Inclusion: • Painful DPN • Creatinine clearance $\geq$ 60 mL/min Exclusion: • Previous treatment with gabapentin • Creatinine clearance < 60 mL/min Overall group characteristics: Mean age: 56	Study design: 7-week open, parallel-group, 33 "centre" trial of gabapentin 900 mg/day fixed dose vs. gabapentin titrated over up to 4 weeks to dose necessary to achieve 50% reduction on NRS (11-point Likert score) pain scale, or to a maximum of 3600 mg/day; then steady dose (except reduction for toxicity) for remainder of 7 weeks. Safety assessments at each of 5 visits, i.e. 3 post-randomization visits up to and including 7 weeks • Screened: 421 • Randomized: 339 (randomization procedure not described in unpublished main report nor published report) • randomization: G_{900}=170, $G_{titrated}$=169 ITT population for safety appears to be 339/339 patients enrolled (randomized). No further details presented in published report nor in pp. 1-74/492 page unpublished report.	Because this is an open-label trial, this analysis will only look at safety outcomes – definitions at pp 31-32 of unpublished report appear to be compatible with other gabapentin studies.	NB: analysis is based on pp. 16-17/492 of unpublished final report and published report (Gomez-Perez et al., 2004): Mean daily dose per group (published report, details from unpublished not available to TLP): G_{900}900 mg/day ;$G_{titrated}$ = 1,936 mg/day NB: the mean dose of 900 for G_{900} group appears unlikely, as it would require all 170 patients randomized to have taken exactly 900 mg/day for the full period. Mortality (p. 176 published): G_{900} = 0/170 (0%) ;$G_{titrated}$ = 0/169(0%) Serious Adverse Events – number of patients experiencing SAE (p. 176 published): G_{900} = 3/170 (1.8%) ;$G_{titrated}$ = 4/169(2.4%) Serious Adverse Events – total SAE: not reported Withdrawal Due to Adverse Events (pp. 176-7 published): G_{900} = 9/170 (5.3%) ;$G_{titrated}$ = 7/169(4.1%)	1. Probable enrichment bias by exclusion of patients previously treated with gabapentin may reduce chance of observing toxicity. 2. Toxicity (AE) findings are similar to other studies. Exclusion of patients with creatinine clearance < 60 mL/min and relatively low age biases study in favour of gabapentin, vs. more frequent AE expected in clinical practice. It is not possible to comment meaningfully about dose-dependent toxicity, but the absolute numbers and percentages of patients experiencing typical gabapentin-induced AE are slightly higher for titrated dose group than for fixed dose group. Appendices to this report not available.

Knapp, PharmD, K. Chartier, Ph.D., C. Hoseyni, Ph.D., MBA PUBLISHED report: Gomez-Perez, Perez-Monteverde, et al. Gabapentin for the treatment of painful diabetic neuropathy: dosing to achieve optimal clinical response. Br. J. Diabetes Vasc. Dis. 2004; 4: 173-8 NB: publication specifies (p. 177) that data analysis was conducted by Quasy, a contract research organization and data analysis was conducted by Quasy and Pfizer. (unpublished final report "Statistical Analysis and Safety Report" is submitted by Quasy, Mexico – see p. 18/492). Authors Mitisya EM and Parsons B of published report are from Pfizer, New York.				Total patients with AE's: G_{900} = 82/170 (48%) ;$G_{titrated}$ = 85/169(50%) Total AE's (patients may have > 1): Not reported Characteristic AE for combined groups (N=339) - (p. 17/492 of unpublished report), by number of patients (? Patients may have experienced > 1 AE; if similar to reporting of other studies, the following would be the dominant AE experienced by patient): For total group (N=339/339) Somnolence: 60/339 (18%) Dizziness: 51/339 (15%) For groups by dose: Somnolence: G_{900} = 26/170 (15%) ;$G_{titrated}$ = 34/169(20%) Dizziness: G_{900} = 23/170 (14%) ;$G_{titrated}$ = 17/169(50%)	

Study No. 14 – Levendoglu 2004 – GABAPENTIN FOR SPINAL CORD INJURY PAIN – DBR CROSSOVER TRIAL (published) – FINAL **– July 26, 2008**

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 14 Levendoglu F, Ogun CO., et al. Gabapentin Is A Firse Line Drug for the Treatment of Neuropathic Pain in Spinal Cord Injury. Spine 2004; 743-751. Support: *"No funds were received in supprt of this work. No benefits in any form have been or will be received from a commercial party related directrly or indirectly to the subject of this manuscript."*. Dates: not specified, presumably 2002 or earlier, MS submitted February 2003. Trial design: Independent. DBR Crossover Trial, 18 weeks including 2 treatment periods of 8 weeks separated by 2 week washout, comparing gabapentin (G) with placebo to final dose of	Spinal cord injury "neuropathic" pain Inclusion: • 20-65 years • complete traumatic SCI, hospitalized • "neuropathic" pain > 6 months • pain > 4 on 11-point (0-10) neuropathic pain score (NPS) at baseline Exclusion: • severe cognitive impairment • seizure disorder • use of anticonvulsants or antidepressants • major depression or score > 16 on Beck Depression Inventory at baseline • *"hypersensitivity"* to gabapentin:	Study design: 18 week double blind crossover RCT comparing G with P as 2 arms: P/G x 8 weeks with 2 week washout between treatments vs. G/P with 2 week washout between treatments. Titration during weeks 0-4, stable dose weeks 5-8. Patient flow (p. 744) - not described: • Sceened: not reported • Excluded: not reported Randomized: 20; allocation to sequences not described • Completed crossover: 20/20 • Withdrawn from treatments: P=6/56; G=4/53; washout=2/? Drug doses/titration (p. 2112): Titration from G=900 mg/d in first week, to 1800 mg/d in week 2, 2400 mg/d in week 3, and 3600 mg/d in week 4,	Predefined outcomes: Primary: This is not clearly explained. The order of presentation suggests that overall NPS pain may have been the primary outcome, at 4 and/or 8 weeks vs. baseline, but the baseline scores and the qualitative subcomponents are not described sufficiently well to understand what was the pre-specified outcome. Secondary: Also not described in detail, but appears to be VAS pain scale, and a "LQ" questionnaire (see text, p. 744).	Achieved doses: Mean dose G "without side effects": 2235 mg/d (501), range 900-2700 mg/d Mean maximum tolerated dose 2850 mg/d (751), range 1200-3600 mg/d Mortality: Not reported Serious Adverse Events: Not reported Withdrawal Due to Adverse Events: P=0/20; G=0/20 These appear suitable for meta-analysis Total withdrawals: P=0/20; G=0/20 Total patients with AE's: P = 5/20 (25%) G = 13/20 (65%) These appear suitable for meta-analysis Most important AE's (Table 5): Weakness ("asthenia"): P=2/20 (10%); G=5/20 (25%) Vertigo ("dizziness"): P=1/20 (5%); G=3/20 (25%) Sedation (somnolence): P=0/20 (0%), G=3/20 (15%) Edema: P=0/20 (0%); G=3/20 (15%)	1. This is an unusual study which is not directly comparable with any other study. Doctors were probably unblinded, and patients were also likely to have been unblinded. 2. It is not clear whether the patients had access to any other analgesics. 3. The results purported are surprising insofar as: a) no patients dropped out; b) the apparent effects shown graphically are much more dramatic than any other study; c) there is no purported separation from placebo at end of week 2 (1800 mg/d), in contrast

G=3600 mg/d Concealment: *"identically appearing capsules"* (p. 744) Randomization: not described (p. 744) Test of blinding: none mentioned; physicians who were "blinded" assessed patients for "side effects" and adjusted gabapentin dose accordingly. ? Blinded?	Allowable drugs: not described – no opioids ar mentioned Baseline characteristics: Mean age: 36 (range 22-62) Baseline VAS, NPS scores: Not presented for P/G or G/P groups	"regardless of any efficacy achieved at lower doses", decreased one dose step for "intolerable adverse reactions". Statistical Analysis: (p. 744) No primary outcome or secondary outcome hierarchy is described. Power calculation on basis of Tai study 2002. No description of correction for multiple comparisons.	NB: none of these scores are comparable, or presented so as to be comparable, with any other commonly used scales. Analysis: the description of statistical plan is inadequate to understand what was done, let alone multiple comparisons. Test of blinding: Not described. The description of adverse effects suggests that physician evaluators may not have remained blinded.	These appear suitable for meta-analysis, using "weakness". Total AE's (patients may have > 1 as total exceeds total patients with AE): P=6; G=17 Disability: not reported > 50% reduction in NRS pain score at endpoint vs. baseline: not reported (not an outcome) Primary outcome VAS pain score: Not comparable to any other study. Not meta-analysable. The purported changes (see graphs in original report) are much larger than any other study of gabapentin, whether crossover or parallel group. Secondary outcomes: See original report. None are comparable to other studies, nor are clearly clinically meaningful. PGIC: not reported	with virtually every other study of gabapentin; d) adverse effects are less than most studies 2. Outcomes other than safety are not suitable for meta-analysis.

STUDY NO. 15 - STUDY DETAIL SUMMARY AND ANALYSIS: GILRON, NEJM 2005

July 27, 2008 – FINAL VERSION

All information in the following document was taken from the article *Morphine, Gabapentin, or Their Combination for Neuropathic Pain,* published by Ian Gilron, M.D., et al in the March 31st, 2005 issue of the New England Journal of Medicine (Volume 352, issue 13). The PowerPoint slides contain no information which is not already included in the report.

To be included in the efficacy analysis in this study, a patient had to complete at least two rounds of treatment. Therefore, included in the efficacy analysis were 3 patients who withdrew sometime after completing two treatment periods.

This study did not report a number of important values.

- First of all, what constituted compliance for this particular study is not defined anywhere in this report and the degree of compliance or adherence to the study protocol has not been included. It is unclear whether or not compliance was even monitored.
- Mortality is not mentioned and neither are serious adverse events.
- The number of withdrawals due to adverse events is also unclear (see table for details)

Adverse events were only mentioned in this report if they were moderate to severe and had and incidence of greater than 5% for any treatment.

- No definition is given as to what would constitute a moderate to severe adverse event.
- Adverse events were compared only with active placebo (lorazepam) and with the Gabapentin-morphine combination treatment, and, the nature of the significance is unclear (see table for details).

This study employed an active placebo, lorazepam, which has been shown to induce sedation but not analgesia. This could potentially reduce the period effects seen in other Gabapentin/placebo studies, which were most likely caused by unblinding due to the sedative effects of Gabapentin. In fact, the statistical analysis in this study demonstrated no significant period effects. Furthermore, during each treatment period, a "blinding" questionnaire was completed by both patients and research nurses in order to gauge which treatments the patients and their research nurses thought they were receiving which is another interesting way to assess the degree of unblinding. However, although the results of the questionnaire are reported, the paper offers little interpretation.

This study has inappropriately used Standard Error. The preferred presentation of descriptive statistics in a clinical trial is mean $\pm$ SD; the preferred presentation of an estimate and its precision is mean and 95% confidence interval. Presenting the estimate and its precision as the mean $\pm$ standard error, as is done in this paper, is discouraged because it is commonly confused with the mean $\pm$ standard deviation but standard error is always smaller (usually substantially so) than the standard deviation and can therefore be misleading. Since this report is not very clear on the numbers of patients used for specific analyses, it is difficult, if not impossible, to determine the standard deviation from the standard error in this case and therefore difficult to make any comparisons independently.

Numerical values for the baseline pain intensity for each sequence group, or for new baselines at end of treatment phase washouts, are not reported. They are only represented visually in Figure 2A such that one can estimate them. This makes it impossible to assess precisely the change in pain intensity from original baseline or each new post-washout baseline for each treatment sequence group.

Related to the above paragraph, although Table 2 on page 1332 of this report reports the scores of the short-form McGill pain questionnaire (MPQ), the Brief Pain Inventory (BPI), Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36), and Beck Depression Inventory (BDI), the table only provides standard error, and not standard deviation or the number of patients in each assessment. The standard deviation of the differences between baseline and treatment for each patient is also not provided making it impossible to assess the change from baseline.

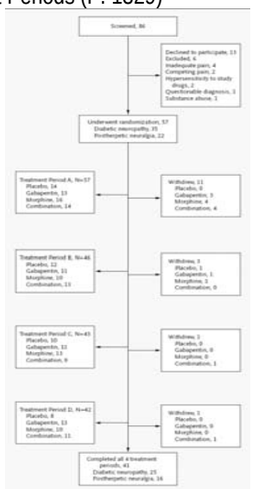
Extremely odd is the fact that the standard errors reported in Table 2 for MPQ, and BPI are identical for the baseline, active placebo (lorazepam), Gabapentin, morphine, and combination groups; furthermore, for the SF-36. In fact, the standard errors in each row of this table are identical or nearly identical for all treatment groups.

With regard to the titration schedule, for the first three weeks of each five-week treatment period, the dose was escalated towards a maximal tolerated dose or a target ceiling dose, whichever was reached first. The target ceiling dose for Gabapentin treatment alone was 3200 mg / day; however, the mean maximal tolerated dose was 2207 mg / day (SE = 89 mg) which appears to reinforce findings of other studies that Gabapentin is less tolerable at high does (has dose-dependent toxicity).

The dosing schedule may artificially discriminate against morphine (at least for efficacy) insofar as the relative reduction in target/ceiling dose is more for morphine than for Gabapentin in older patients (> half of those randomized) and during the combination (M + G) phases of crossover treatment. The reduced mean dose of morphine used in the (M + G) combination group may be at least partly an artefact of the trial design, which allowed 50% lower ceiling doses of morphine in this arm.

The report does not provide any information on the age of completers, so it is not possible to know whether older patients responded differently to any treatment than younger ones, or how doses compared in younger vs. older patients.

Careful inspection of the red or azure curves for week-by-week pain scores in Figure 2A suggests that at least in 2/4 sequence groups including 23/43 of the completing patients, gabapentin had no analgesic effect. A new figure created at the end of this document attempts to compare the treatment groups more directly by combining imputed pain score measurements (obtained by interpolation from Figure 2A) for all patients in the “completer” analysis who were exposed to each treatment. This provides an alternative way of looking at the data, which may clarify the relative effects on pain of active placebo (lorazepam), gabapentin, morphine, and (morphine + gabapentin) in this experiment.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Kelsey Innes/ TL Perry, M.D.
Published: Gilron I, Bailey JM et al. Morphine, Gabapentin, or their Combination for Neuropathic Pain. N Engl J Med 2005; 352:1324 – 34. Support: Independent, Canadian Institutes of Health Research. Pfizer supplied Gabapentin (Neurontin) but had no other input to study. Lead author and 1 other author report membership on Pfizer paid advisory board or research support from Pfizer. Study Design: Randomized, double-blind, active placebo-controlled, four-period crossover trial. Study Duration: 5 weeks. Patients received daily active placebo, lorazepam, (P),	PDPN and PHN Baseline Characteristics: • See page 1325 DPN: • Distal symmetric, sensory diabetic polyneuropathy as determined on the basis of their medical history and… • Either an unequivocal decrease in response to pinprick, temperature, or vibration or absent ankle jerk reflexes. PHN: • Had had an eruption of herpes zoster rash not more recently than six months before enrolment.	Patient Flow Figure 1: Enrolment, Randomization, Withdrawals, and Completion of the Four Treatment Periods (P. 1329)  • 86 were screened, 29 excluded, 57 randomized and 16 withdrew during treatment periods o 13 before completing second treatment period (B) o 3 due to AEs but after completing at least 2 treatment periods. o 41 completed the trial Design: • Balanced Latin-square design (see table below)	Analysis • 40 patients for 80% power to detect a 2-sided alpha of 0.05 a mean difference in pain intensity at week 4 among the treatments that was equivalent to 1 point on a scale from 0 – 10. • Was estimated that if 58 enrolled, 40 would complete all 4 treatment periods. • Had to complete at least two treatment periods to be included in efficacy analysis • Linear mixed model with drug regimen, sequence, treatment period, and first-order carryover effect were fitted with pain intensity data. Sensitivity analysis (by each treatment period): *"The level of change in the intensity of pain during each treatment period was calculated as the difference between the score for pain at baseline* (mean of last 3 days before period A or ? last 3 days of washout periods) *and the scores for pain during treatment* (mean of last 3 days at maximum tolerated dose)"…% change = change in pain score/baseline pain score x 100%. NB: The intent/purpose of this "sensitivity analysis" is not further described, but no difference was found between groups except for combination vs. active placebo (lorazepam) (see below and p. 1328, p. 1330 discussion).	1. Mortality: not reported 2. Serious Adverse Events: not reported 3. Withdrawals Due to Adverse Events: • 3 patients WDAE in total • 2 assigned to the sequence G, M, GM, P withdrew after completing two treatment periods so assume withdrew during combination treatment (in period C) • 1 assigned to the sequence M, P, G, GM withdrew after completing three periods, so again, assume withdrawal during combination treatment. • Most common adverse events included Constipation, Sedation and Dry Mouth. • Note that figure 1, p. 1329 suggests that there were 14 withdrawals before the end of Treatment Period B but states at p. 1328 text that 13 withdrew during the same period 4. Total Withdrawals (see pt. flow diagram, p. 1329) Total Withdrawals: 16 • Active placebo (lorazepam): 1 of 44 (2.27%) who started active placebo	1. Design of trial with disproportionally reduced target/ceiling dose of morphine vs. Gabapentin (50% less for M, 25% less for G) for older patients (> half of all patients – Table 1 median age, p. 1330) and disproportionately reduced target/ceiling morphine dose (50% less for M vs. 25% less for G) for combination therapy produced (not-unexpectedly) the lower mean doses of M and G used in combination group, and may have reduced the apparent efficacy of M (or MG combination) groups vs. active placebo (lorazepam). Clinical significance of AE from morphine-induced constipation hard to weight against other AE. Combining M with G (MG) appears to increase some AE vs. G or M alone. 2. Trial employed use of an active placebo, lorazepam. This was intended to reduce

sustained-release morphine (M), Gabapentin (G), or a combination of Gabapentin and Morphine (GM), not necessarily in that order, each given orally for 5 weeks.

Study Number: N/A (independent)

Protocol approved by an institutional ethics review board.

Patients recruited between February 2001 and November 2003.

Test of unblinding: YES

Inclusion Criteria

- Daily moderate pain for three months or more
- Age of 18-89 years
- Serum alanine aminotransferase or aspartate aminotransferase level less than 1.2 times the normal level
- Creatinine level less than 1.5 times the upper limit of the normal range
- Sufficient language skills to communicate with research staff

Exclusion Criteria

- Hypersensitivity to study medications
- Another painful condition as severe as the DPN/PHN
- Any recent myocardial infarction (doesn't specify how recent)
- Unstable angina or

M	P	G	GM
P	GM	M	G
G	M	GM	P
GM	G	P	M

- Notice that you have one of each of M, P, G and GM in each row and column
- Latin Square (LS) designs make it possible to assign the order of the treatments to subjects to avoid confounding treatment conditions with order
- LS designs also enable the independent assessment of condition and order.
- P. 1325-26 describes random allocation of patients to treatment order.

Treatment Regimen

- Medication placed in blue and grey capsules, blue capsules twice daily, grey capsules 3X daily. See table below and p. 1326.

T_x	Blue	Grey
M	30 mg, SR morphine	Lactose placebo
GM	15 mg SR morphine	300 mg Gabapentin
G	Lactose placebo	400 mg Gabapentin
P	0.2 mg lorazepam	0.1 mg lorazepam

- Target daily dose ceilings (see p. 1326

Primary Outcome Measure

Mean Daily Pain Intensity (PI) in Patients Receiving a Maximal Tolerated Dose:

- Figure 2A Mean Weekly Pain shows weekly mean scores for daily pain intensity throughout the trial for each of the four treatment sequences. It was too large for this column and is therefore found at the end of this document.
- Another figure was created using figure 2A which combines all of the treatment periods. (See appendix 1).
- Mean intensity of pain on a scale from 0 – 10.
  - 0 = no pain, 10 = worst pain ever
  - Ratings averaged over 7 days in which the patients were receiving the maximal tolerated dose of the study drug.
- P. 1333 in discussion notes surprise that Gabapentin did not produce significantly better results than active placebo (lorazepam) with regard to this primary outcome. (See new figure plotted by K. Innes summarizing effects for all patients by treatment, shown separately at end of this table after original Figure 2(A) from Gilron)
- Note: "mean pain intensity" is analogous to "NRS pain scale" in other studies

Active placebo (lorazepam)
Mean PI at Week 4: 5.72

(lorazepam) treatment.
  - During Treatment period B
- Gabapentin: 4 of 48 (8.33%) who began treatment with Gabapentin
  - 3 during treatment period A
  - 1 during Treatment period B
- Morphine: 5 of 49 (10.20%) of those who began treatment with morphine.
  - 4 in treatment period A
  - 1 in treatment period B
- Gabapentin-Morphine: 6 of 47 (12.77%) who began the combination treatment.
  - 4 in treatment period A
  - 1 in treatment period C
  - 1 in treatment period D

5. Total Adverse Events: not reported

- Table 3 on p. 1333 lists adverse events in percentages with no associated numbers for each group. Since it is not specified where during a given treatment period a specific patient dropped out, it is difficult to determine the numbers associated with each percentage

Gabapentin:

Dose Titration (Weeks 1-3)
The following adverse events occurred for those taking Gabapentin during titration and were significantly less compared to

the potential period effects which have occurred in other studies, by preventing unblinding. This drug also employed a blinding questionnaire to assess which treatments the patients and the research nurse thought the patients were receiving and was completed by both patients and the nurse when the patients were taking the maximal tolerated dose of the assigned study drug. It is less clear how to interpret the findings regarding blinding/unblinding.

3. This study inappropriately used Standard Error for presentation of descriptive statistics, except in Table 1 (baseline characteristics). The preferred presentation of the descriptive statistics is mean ± SD. The preferred presentation of an estimate and its precision is mean and 95% CI. The standard error is smaller than the SD always and is therefore misleading. Presenting an estimate and its precision as

congestive heart failure
- Any central neurologic disorder (including seizures)
- A serious mood disorder
- A history of serious drug or alcohol abuse
- Pregnancy
- Lactation
- Lack of a primary care physician.

<u>Excluded / Permitted Medication</u>
- Non-opioid drugs other than Gabapentin permitted at steady dose throughout trial
- Procedural pain therapies forbidden.
- Patients were given docusate sodium (100 – 300 mg per day) as prophylaxis against constipation.
- Sennosides were

or table below)
- Certain adjustments made for those over 60 and those weighing less than 60 kg (see p. 1326)

T_x	Target Daily Dose Ceiling
M	120 mg
GM	Morphine: 60 mg Gabapentin: 2400 mg
G	3200 mg
P	Lorazepam: 1.6 mg

- For mean tolerated doses and SEs see page 1328.
- NB: the design virtually guarantees that patients in combination phases will take a lower mean dose of M and G than during M and G phases – results at p. 1328 and Figure 2 (C) are pre-determined, not experimental outcomes. (TLP)<u>Titration / Treatment / Washout</u>
- For first three of five weeks dose escalated towards max. tolerated dose / target ceiling dose (whichever hit first)
  - See comments
  - For details on how max. tolerated dose was determined see p. 1326 / <u>1327</u>
- <u>4th week pt. received maximal</u> tolerated dose for particular treatment
- 5th week – 4-day dose tapering and three-day complete washout.

SE : 0.23

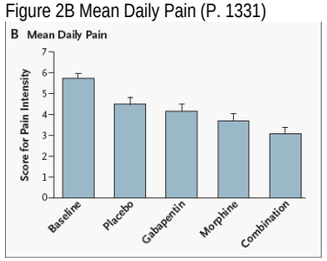
Gabapentin:
Mean PI at Week 4: 4.49
SE: 0.34

Morphine:
Mean PI at Week 4: 3.70
SE: 0.34

Gabapentin-Morphine:
Mean PI at Week 4: 3.06
SE: 0.33

- Pain treated with GM combination was lower than with morphine alone (P = 0.04)
- Pain treated with GM combination was lower than with Gabapentin alone (P < 0.001) or active placebo (lorazepam) (P < 0.001)
- No additional p-values are reported.

Figure 2B Mean Daily Pain (P. 1331)



- The above figure shows the mean (<u>+</u> SE) daily pain scores during week 4 at the maximal tolerated dose of each regimen.

the Gabapentin morphine combination treatment. (p < 0.05)
- Constipation 4.2% (20.9% for GM)
- Sedation 10.4%, (20.9% for GM)
- Dry Mouth 8.3% (20.9% for GM)

Significantly less compared to active placebo (lorazepam) (p < 0.05)
- Insomnia (4.2%), (25.6% for active placebo)
- Vomiting (0%) – note that this makes no sense since vomiting for placebo was also 0%

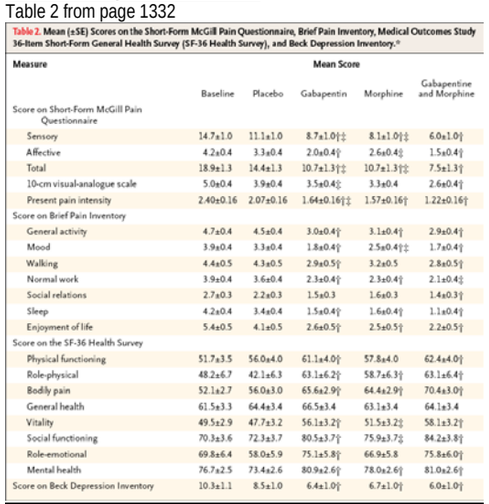
At Maximal Tolerated Dose, Week 4
The following adverse events occurred for those taking Gabapentin during week 4 at maximal tolerated dose and were significant compared to the Gabapentin morphine combination treatment.
- Constipation 2.1 % (20.9% for GM)
- Edema 0% (9.3 % for GM)

<u>Morphine:</u>
Dose Titration (Weeks 1-3)
The following adverse events occurred for those taking morphine during titration and were significantly less compared to active placebo (lorazepam) treatment. (p < 0.05)
- Constipation, 43.2% versus 4.7% for active placebo (lorazepam).

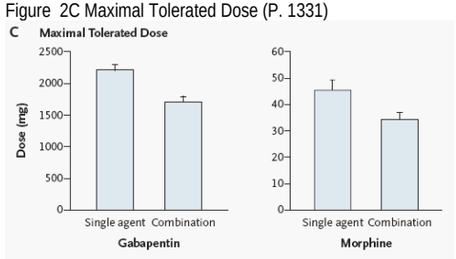
At Maximal Tolerated Dose, Week 4

the mean <u>+</u> SE, as is done in this paper, is usually discouraged because it is commonly confused with the mean <u>+</u> SD. Furthermore, mean <u>+</u> SE is not a 95% confidence interval as is almost inferred here.
- This is particularly frustrating in this paper as sample sizes for efficacy variables (e.g., MPQ, BPI, etc.) are not given and it cannot be assumed that all patients were assessed for each of these variables due to inconsistencies in the sample sizes in for other endpoints (e.g. blinding questionnaire, see below)

4. With regard to the titration, for the first 3 weeks of each 5-week period, the dose was escalated toward a maximal tolerated dose or the target ceiling dose, whichever was reached first. This would seemingly allow patients to maintain only a dose they were comfortable with,

	given (17 – 34 mg twice daily) to those who developed constipation.		<u>Secondary Outcomes:</u> Table 2 from page 1332  **Table 2. Mean (±SE) Scores on the Short-Form McGill Pain Questionnaire, Brief Pain Inventory, Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36 Health Survey), and Beck Depression Inventory.*** **Measure** / **Mean Score** Baseline / Placebo / Gabapentin / Morphine / Gabapentine and Morphine Score on Short-Form McGill Pain Questionnaire Sensory 14.7±1.0 / 11.1±1.0 / 8.7±1.0†‡ / 8.1±1.0†‡ / 6.0±1.0† Affective 4.2±0.4 / 3.3±0.4 / 2.0±0.4† / 2.6±0.4‡ / 1.5±0.4† Total 18.9±1.3 / 14.4±1.3 / 10.7±1.3†‡ / 10.7±1.3†‡ / 7.5±1.3† 10-cm visual-analogue scale 5.0±0.4 / 3.9±0.4 / 3.5±0.4‡ / 3.3±0.4 / 2.6±0.4† Present pain intensity 2.40±0.16 / 2.07±0.16 / 1.64±0.16†‡ / 1.57±0.16† / 1.22±0.16† Score on Brief Pain Inventory General activity 4.7±0.4 / 4.5±0.4 / 3.0±0.4† / 3.1±0.4† / 2.9±0.4† Mood 3.9±0.4 / 3.3±0.4 / 1.8±0.4† / 2.5±0.4†‡ / 1.7±0.4† Walking 4.4±0.5 / 4.3±0.5 / 2.9±0.5† / 3.2±0.5 / 2.8±0.5† Normal work 3.9±0.4 / 3.6±0.4 / 2.3±0.4† / 2.3±0.4† / 2.1±0.4‡ Social relations 2.7±0.3 / 2.2±0.3 / 1.5±0.3 / 1.6±0.3 / 1.4±0.3† Sleep 4.2±0.4 / 3.4±0.4 / 1.5±0.4† / 1.6±0.4† / 1.1±0.4† Enjoyment of life 5.4±0.5 / 4.1±0.5 / 2.6±0.5† / 2.5±0.5† / 2.2±0.5† Score on the SF-36 Health Survey Physical functioning 51.7±3.5 / 56.0±4.0 / 61.1±4.0† / 57.8±4.0 / 62.4±4.0† Role-physical 48.2±6.7 / 42.1±6.3 / 63.1±6.2† / 58.7±6.3† / 63.1±6.4† Bodily pain 52.1±2.7 / 56.0±3.0 / 65.6±2.9† / 64.4±2.9† / 70.4±3.0† General health 61.5±3.3 / 64.4±3.4 / 66.5±3.4 / 63.1±3.4 / 64.1±3.4 Vitality 49.5±2.9 / 47.7±3.2 / 56.1±3.2† / 51.5±3.2‡ / 58.1±3.2† Social functioning 70.3±3.6 / 72.3±3.7 / 80.5±3.7† / 75.9±3.7‡ / 84.2±3.8† Role-emotional 69.8±6.4 / 58.0±5.9 / 75.1±5.8† / 66.9±5.8 / 75.8±6.0† Mental health 76.7±2.5 / 73.4±2.6 / 80.9±2.6† / 78.0±2.6† / 81.0±2.6† Score on Beck Depression Inventory 10.3±1.1 / 8.5±1.0 / 6.4±1.0† / 6.7±1.0† / 6.0±1.0† <u>Pain (rated according to MPQ)</u> • Scale of 0 – 45 with higher numbers indicating more severe pain • Total scores for GM were lower than… o P (P < 0.05) o G (P < 0.05) o M (P < 0.05) <u>Adverse Effects</u> • GM had a higher frequency of constipation than Gabapentin (P = 0.006) but not morphine • GM higher incidence of dry mouth than morphine (p = 0.03) but not Gabapentin • See table 3 on page 1333 for more details	The following adverse events occurred for those taking morphine during week 4 at maximal tolerated dose and were significant compared to the Gabapentin morphine combination treatment. • Dry mouth 4.6% versus 20.9 % for GM Significant compared to active placebo (lorazepam) (P < 0.05) • Constipation 38.6% versus 4.7% for active placebo (lorazepam). <u>Gabapentin-Morphine:</u> Dose Titration (Weeks 1-3) The following adverse events occurred for those taking the Gabapentin-Morphine combination during titration and were significantly less compared to active placebo (lorazepam) treatment. (p < 0.05) • Constipation, 44.2% compared to 4.7% on active placebo (lorazepam). • Dry mouth, 32.6% versus 2.3 % on active placebo (lorazepam) • Insomnia 2.3% versus 25.6% on active placebo (lorazepam). At Maximal Tolerated Dose, Week 4 The following adverse events occurred for those taking the Gabapentin-morphine combination during week 4 at maximal tolerated dose and were significant compared to active placebo (lorazepam)	which would minimize adverse effects. This is closer to good clinical practice, as opposed to the forced titration used in most other studies. 5. The secondary outcome measure **Global Pain Relief**, which was assessed in response to questions from the research nurse on the following scale: pain worse, no relief, slight relief, moderate relief, a lot of relief, complete relief. This scale seems skewed towards relief and, it patients experienced worse pain, the degree of "worsening" would not be captured, in comparison with the conventional 7-point PGIC reported in most other studies. 6. Table 2 (p. 1332) reports, among other things, the scores on the SF-36 QoL questionnaire. They have only provided standard error, not standard deviation. It is also impossible to determine the number of patients on which

			○ It is difficult to see trends in table 3; therefore, I have made excel tables included at the end of this document to make it easier to understand. <u>Maximal Tolerated Dosages</u> • See page 1328 • Mean maximal tolerated dose (MTD) for each drug, including active placebo (lorazepam), listed below with Standard Error in brackets • See comments in column 2 of this table: maximum tolerated doses were obligatorily lower for G and M in GM combination group than in G or M groups, due to experimental design. Active placebo (lorazepam) MTD: 1.38 (0.05) mg Morphine MTD: 45.3 (3.9) mg Gabapentin MTD: 2207 (89) mg Gabapentin-Morphine MTD Morphine: 34.4 (2.6) mg MTD Gabapentin: 1705 (83) mg • P-value for morphine in combination less than vs. morphine alone was < 0.05 • P-value for Gabapentin alone vs.	(P < 0.05) • Constipation 20.9% vs. 4.7% on active placebo (lorazepam) • Dry mouth 20.9% versus 0% for active placebo (lorazepam) • <u>6. Validated measures of improvement in global function including return to work, study, activities of daily living:</u> • None reported for this study. <u>7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint:</u> • Not reported for this study. <u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial</u> • Change from baseline was not assessed in this study. • This is not true ITT, nor ITT-LOCF as only patients who completed two rounds of treatment were included in the efficacy analysis. • The primary outcome was mean daily pain intensity for those patients receiving the maximal tolerated dose.	the SE is based and therefore, no confidence interval can be created. The SD of the difference is also not provided making it impossible to double check the p-values. • Also not that in Table 2 the standard errors reported for MPQ, and BPI are identical for the baseline, placebo, Gabapentin, morphine, and combination groups; furthermore, for the SF-36, the standard errors for Gabapentin and Morphine are identical and nearly identical are the other groups. Lastly, all treatment groups have a standard error of 1.0 for BDI and baseline has a standard error of 1.1. 7. All patients did not complete the Blinding Questionnaire, P. 1327 states that *"A 'blinding' questionnaire to assess which treatments the patients and the research nurse thought the patients*

			Gabapentin in combination was < 0.05 Figure 2C Maximal Tolerated Dose (P. 1331)  • The above figure shows the mean (+ SE) maximal tolerated doses of Gabapentin and morphine administered as single agents as compared with them in combination. <u>Mood</u> • Assessed according to Beck Depression Inventory on a scale from 0 – 63 o Higher numbers indicating more severe depression • When receiving Gm lower than o P (P < 0.001) o M (P = 0.03) <u>Quality of Life / Health Status</u> • Assessed according to medical outcomes study, SF-36 • Higher numbers indicate better health-related QoL. • Results in Table 2 of page 1332. • GM higher scores for vitality and social functioning than active placebo (lorazepam) (P = 0.007 and p = 0.004	• Mean intensity of pain on a scale from 0 – 10. o 0 = no pain, 10 = worst pain ever Mean Pain Intensity at week 4 at the maximum tolerated dosage was as follows for each treatment group. Note that baseline pain intensity is included in Figure 2B as a comparison only and was not used in efficacy analysis. It is impossible to determine the precise values for baseline pain scores for each treatment group (sequence) from this paper (see figure 2A, p. 1331). The paper does state that the baseline pain intensity for patients with diabetic neuropathy was 5.8 (SE = 1.8) and 5.6 (SE = 1.6) for patients with post-herpetic neuralgia (Table 1, p. 1330). The mean PI for all patients at baseline is given below. Mean pain score (Pain Intensity), all subjects at baseline (randomization), N=57: Mean PI baseline: 5.72, SE : 0.23 (p. 1328) For PDPN: 5.8 (1.8); for PHN: 5.6 (1.6) (SD in parentheses) Mean pain score (Pain Intensity) At week 4 (completers, baseline mean pain scores for these patients are not reported and baseline for entire group	*were receiving was completed by both patients and the nurse when the patients were taking the maximal tolerated dose of the assigned study drug"* By counting patients who completed each drug in each period (not those who dropped out during a given treatment period) one should theoretically get the upper bound of the number of people who completed each blinding questionnaire. Therefore, referring to Table 1 (p. 1329) we see that 43 completed Active placebo (lorazepam) treatment, 44 completed Gabapentin treatment, 44 completed morphine treatment, and 41 completed the Gabapentin morphine combination treatment. Looking at one example, it states that 25 (66%) of those who completed active placebo (lorazepam) treatment guessed that they were on placebo. However, 25 / 43 is 58% meaning that the number used was smaller than 43 (most likely n used

			respectively) • GM higher scores than morphine for vitality and social functioning (P = 0.03, P = 0.04 respectively) <u>Pain related interference:</u> • Assessed according to Brief Pain Inventory o Scale from 0 – 10 o 0 = no interference, 10 = complete interference • See page 1328 for results as well as Table 2 on page 1332 • Gabapentin-morphine combination scores for pain interference with mood lower than active placebo (lorazepam) (P < 0.001) or morphine (P = 0.03) • Scores for pain-related interference with general activity, normal work, sleep, and enjoyment of life were significantly lower when patients were receiving any of the active treatments. <u>Mental Status:</u> • See page 1329 • Mini-mental state examination (scale from 0 – 30, lower numbers indicating impaired mental status) Active placebo (lorazepam) Score ± SE: 28.9 ± 0.3 Gabapentin Score ± SE: 28.8 ± 0.3 Morphine	was not used in efficacy analysis, therefore changes from baseline are not meaningful) – week 4 scores, (SE) from p. 1328: Active placebo (lorazepam) (N=?): 4.49 (0.34) Gabapentin: 4.15 (0.33) Morphine: 3.70 (0.34) Gabapentin-Morphine: 3.06 (0.33) • Pain score for GM combination < M alone (p= 0.04),Pain score for GM combination < G alone (p < 0.001) • Pain score for GM combination < active placebo (lorazepam) (p < 0.001) <u>9. % of patients achieving "much improved" or "moderately improved"</u> • The global pain relief scale employed in this study differs from the more commonly used PGIC 7-point scale and was a 6-point scale as follows: o Pain worse o No relief o Slight relief o Moderate Relief o A lot of relief o Complete relief The only data reported for this indicator	was 38. The other percentages for this variable similarly prove that not all possible patients completed this efficacy assessment and therefore it is likely that certain patients did not complete the other efficacy assessments (e.g. MPQ, BPI etc.) and actual number of assessments completed for each of these efficacy variables are not reported. 8. Compliance is not mentioned in this report making it impossible to determine the degree to which patients adhered to the protocol. 9. P. 1328, states that *"16 withdrew during the treatment periods —13 before completing the second treatment period (period B), and 3 because of adverse effects but after completing at least two treatment periods"* • It is assumed then that 3 patients WDAE • Reasons for the withdrawal of the other 13 are unclear. Fruthermore, the patient

			Score ± SE: 29.0 ± 0.2 Gabapentin-Morphine Score ± SE: 29.0 ± 0.3 <u>Global Pain Relief</u> • See page 1329 • Assessed by research nurse on following scale (see comments) o Pain Worse o No Relief o Slight relief o Moderate Relief o A lot of Relief o Complete Relief Active placebo (lorazepam) N of patients who reported at least moderate pain relief: 13/43 (31%) * note that a calculation for this number yields 30% not 31% as reported by the paper. P-value: < 0.05 for the comparison with all treatments. Gabapentin N of patients who reported at least moderate pain relief: 27/44 (61%) P-value: not reported Morphine: N of patients who reported at least moderate pain relief: 35/44 (80%)	was the number of patients who achieved at least moderate pain relief, the results as reported in the paper are as follows: Active placebo (lorazepam): 13/43 (30%) Gabapentin: 27/44 (61%) Morphine: 35/44 (80%) Gabapentin-Morphine: 32/41 (78%) However, these denominators only account for the number of patients who completed a given treatment. Using the number of patients who began a given treatment (ITT analysis for patients starting treatment with any of P, G, M, GM): Active placebo (lorazepam): 13/44 (29.55%) Gabapentin: 27/48 (56.25%) Morphine: 35/49 (71.43%) Gabapentin-Morphine: 32/47 (68.1%) • These results cannot be included in meta-analysis because the grouped category “at least moderate pain relief” may be equivalent (as it comprises the best 3 of 6 possible categorical scores) with a “much or moderately better” grouped category which includes only the best 2 of 7 categorical scores in the usual PGIC. <u>10. Histogram presentation of all PGIC</u>	flow diagram would imply 14, not 13 withdrew before the end of treatment period B. • In addition, adverse effects are only reported if they were “moderate to severe” and had and incidence of greater than 5% for any treatment. 10. No comparisons of the adverse events are reported except for the comparison with active placebo (lorazepam) and the comparison with the G-M combination. Furthermore, certain comparisons make no sense: during the titration, Gabapentin was listed as having P < 0.05 when compared with active placebo (lorazepam) in terms of vomiting, however, according to the chart 0% of Gabapentin patients and 0% of active placebo (lorazepam) patients experienced vomiting during titration.

			P-value: not reported Gabapentin-Morphine: N of patients who reported at least moderate pain relief: 32/41 (78%) P-value: not reported However, these denominators only account for the number of patients who completed a given treatment. When we include the number of patients who began a given treatment (Figure 1, p. 1329, patients starting Treatment Periods A-D), we see slightly different results: Active placebo (lorazepam): 13/44 (29.55%) Gabapentin: 27/48 (56.25%) Morphine: 35/49 (71.43%) Gabapentin-Morphine: 32/47 (68.1%) TLP comment: These figures corrected for true denominators appear to be closer to an ITT analysis and could be used if we were to attempt to use these figures in meta-analysis. <u>Blinding Questionnaire:</u> • Number of correct guesses of patients with respect to treatment assignment (p. 1329) Active placebo (lorazepam): 25 (66%) Gabapentin: 16 (42%) Morphine: 16 (44%) Gabapentin – Morphine: 8 (25%)	<u>7-point results</u> • It is impossible to create the specified histogram for this study as the number of patients in each category for PGIC is not reported.	

			• Number of correct guesses of **research nurses** with regard to a patients' treatment were (p. 1330) **Active placebo (lorazepam):** 29 (71%) **Gabapentin:** 18 (43%) **Morphine:** 14 (33%) **Gabapentin-Morphine:** 21 (53%)		

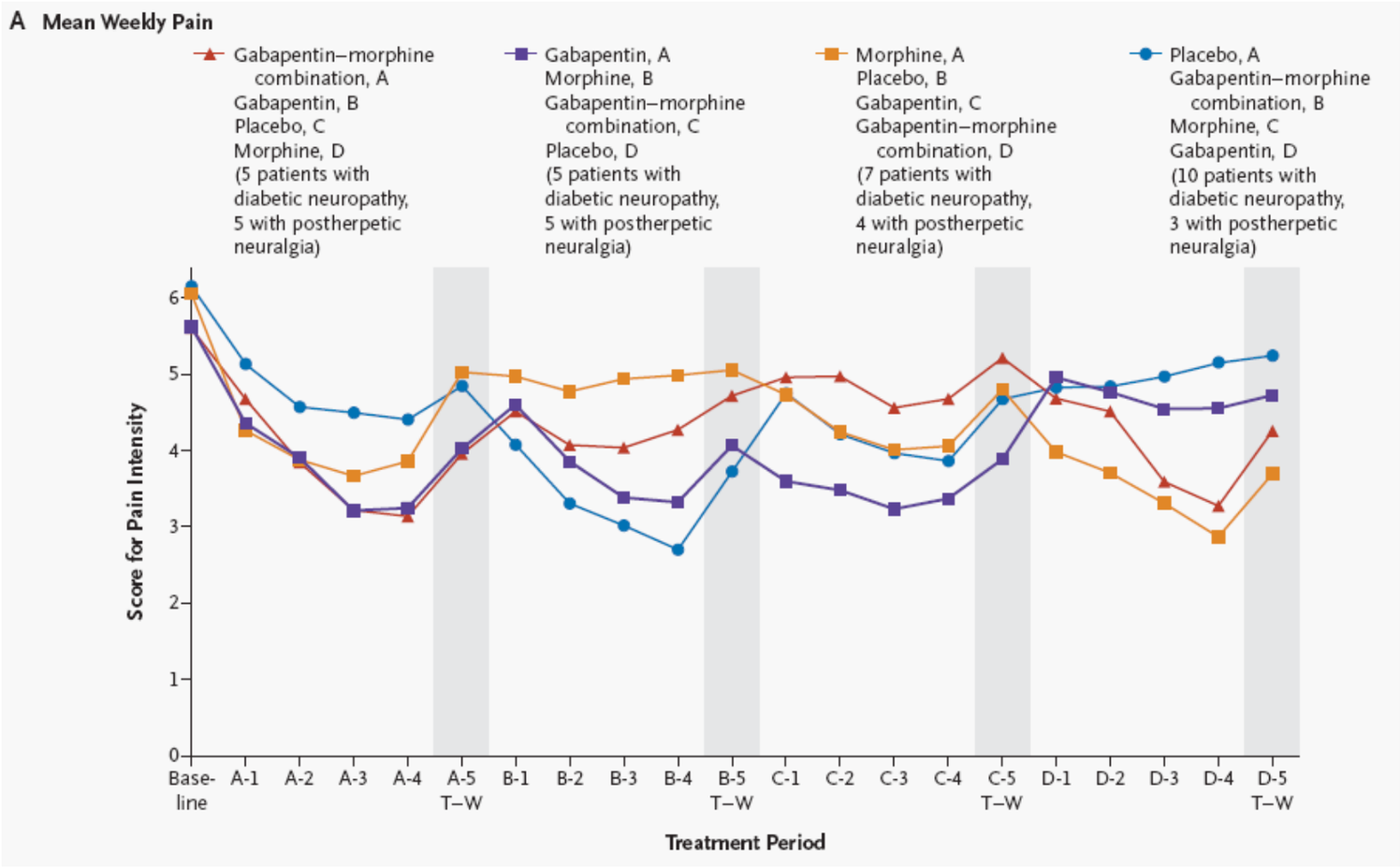
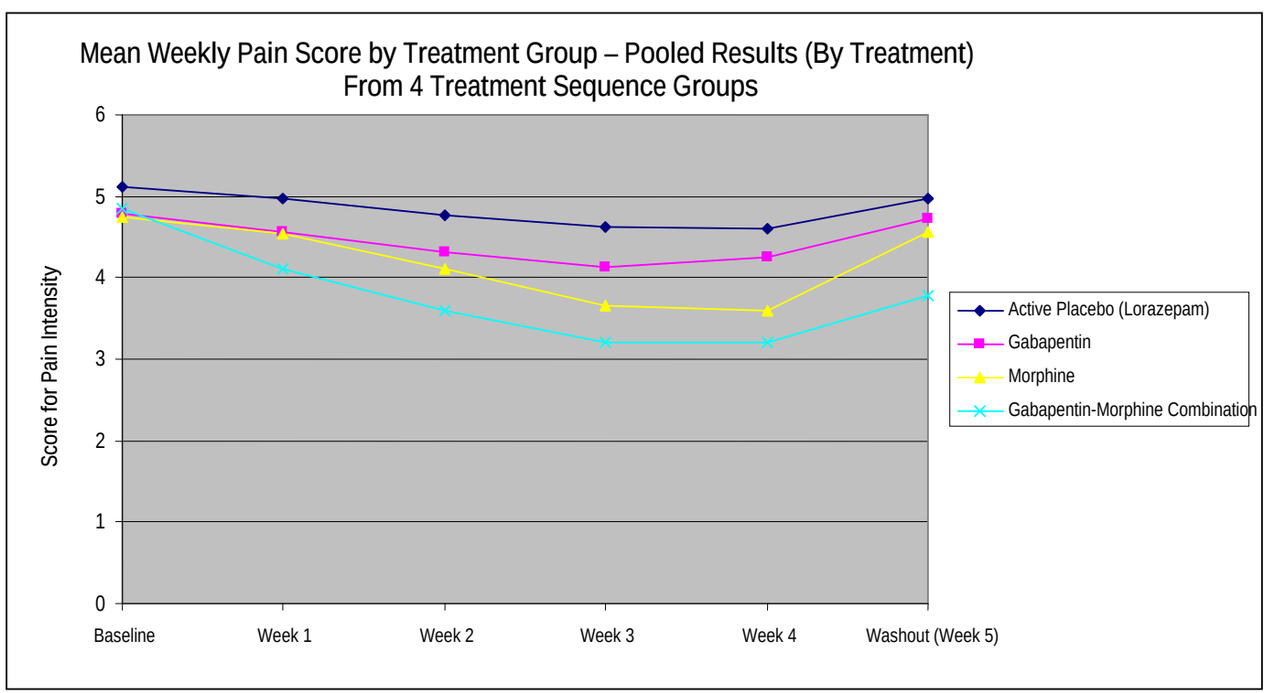


Figure 2A – Mean Weekly Pain (p. 1331)

APPENDIX 1: MEAN WEEKLY PAIN SCORE BY TREATMENT GROUP – POOLED RESULTS (BY TREATMENT) FROM TREATMENT SEQUENCE GROUPS

The figure below t was derived using Figure 2A. The justification for the creation of this figure is that no period or sequence effects were observed throughout this trial and therefore, it seemed reasonable to combine treatment periods by extracting periods on each drug (or combination) from each of the 4 sequence groups. Measurements for average pain score (at baseline, week 1, week 2, week 3, week 4, and week 5/washout) for each treatment group (Placebo, Gabapentin, Morphine, Gabapentin-Morphine Combination) during each treatment period (A, B, C, D) were extrapolated as precisely as possible by inspection of figure 2A. For each week (and baseline) of each treatment period, these averages for a given treatment were multiplied by the number of patients assigned to that treatment, for that treatment period. These products were then totalled for each of baseline, and weeks 1, 2, 3, 4, 5/washout For example, the Gabapentin total for week 1 was (mean score pain score for Gabapentin treatment week 1, period A)*(number of patients assigned to Gabapentin in treatment period A) + (mean score pain score for Gabapentin treatment week 1, period B)*(number of patients assigned to Gabapentin in treatment period B) + (mean score pain score for Gabapentin treatment week 1, period C)*(number of patients assigned to Gabapentin in treatment period C) + (mean score pain score for Gabapentin treatment week 1, period D)*(number of patients assigned to Gabapentin in treatment period D). The totals were then divided by the total number of patients who were, at some point in the study, assigned to the treatment in question in order to produce the graph below. Note that for subsequent treatments of a given sequence, the end of washout (week 5) value for mean pain score of the immediately preceding treatment period became the baseline mean pain score for the subsequent treatment period, except for the final washout.

Notice that the Gabapentin treatment group has a lower baseline compared with the active placebo (lorazepam) treatment group but parallels almost exactly the progress of the active placebo, indicating no major difference between the two groups. (The difference between these two groups remains the same throughout the course of 5 weeks). While Gilron et al report that the combination group (M + G) is significantly superior to other treatments, the azure curve (M + G) below diverges markedly from the yellow morphine treatment curve only in week 1 and then seems to parallel the morphine treatment group, until regressing to a lower new baseline at end of the final washout.



PFIZER 945-1008 - Study No. 16 - UNPUBLISHED TRIAL – SUMMARY – FINAL – July 15, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 16 Pfizer Protocol 945-1008 Phase IV A 15 week, multi-center DBRCT of gabapentin for efficacy and quality of life in patients with painful diabetic peripheral neuropathy UNPUBLISHED, 63 pages April 4, 2002 – November 11, 2003 Report date March 24, 2005 Pfizer_LKnapp_0062222 (June 2, 2005 Clinical Study Synopsis is identical) Sponsor's signatories: Bruce Parsons, M.D., Ph.D., Guy Cohen, Ph.D. NB: Original protocol of December 4, 2001 and amendments of May 2, 2002 and August 7, 2002 are not available but are referred to at pp 37-38 of report. Statistical analysis plan (SAP) original of	Painful diabetic peripheral neuropathy (PDPN): Inclusion: • Type 1 or 2 DM under stable Rx • Painful distal polyneuropathy due to DM for ≥ 3 months • No prior treatment with gabapentin ("enrichment bias") • No chronic kidney disease (Cr clearance ≥ 60 mL/min predicted (violated for some patients) • Pain score (Likert) ≥4 and pain score (VAS) ≥ 4 at baseline Exclusion:	Study design: 15 week randomized, double-blind, placebo-controlled, parallel-group, 43 "centre" trial of gabapentin • Screened: 724 • 1 week placebo lead-in prior to determination of eligibility at baseline, randomization • randomization: G=200, P=189 • 2 week forced titration phase: Day 1 G=300 mg/d; Day 2 600 mg/d; Day 3 900 mg/d; Day 7 1800 mg/d; end of week 2 3600 mg/d (appears to be step change on each day) • subjects who could not tolerate medication during titration could decrease to 1800 mg/d, but if still intolerant were withdrawn from study and were to have final "end of study" assessment done within 1 week	Predefined outcomes: Primary: Pain score (Likert 0-10 score) as group mean of individual means from patients' last 7 available scores while on study medication (up to end of Week 12) from daily diary records of previous 24 hours (LOCF for noncompleters). Analysis by ANCOVA with treatment and center as fixed effects and baseline mean score as covariate (p. 31) NB: Patients who took study drug for only 2-7 days (P=2; G=4) apparently were not evaluated at all for outcomes and are dropped from "ITT analysis". Patients who took study drug for 8-14 days (P=9, G=20) may have completed first post-treatment efficacy assessments at start of week 3 (visit 3) – not clearly	Mortality (p. 40): P = 1/189 (0.5%) ; G = 1/200(0.5%) Serious Adverse Events (p. 53): P = 15/189 7.9%); G = 15/200 (7.5%) Total Withdrawals (p. 40/63): P=54/189 (29%); G=64/200 (32%) Withdrawal Due to Adverse Events (p. 55): Permanent (true WDAE): P = 17/189 (9.0%); G = 25/200 (12.5%) Temporary/dose reduction: P = 9/189 (4.8%); G=28/200 (14%) Total Withdrawals: not reported in main report (apparently shown in Table 13.4.1, see p. 10/63 of paper version of study report (24 March 2005). Total patients with AE's: P = 126/189 (67%); G = 159/200 (80%) Total AE's (patients may have > 1): P=326; G=521	1. Enrichment bias by exclusion of patients who previously did not tolerate gabapentin or failed to benefit at high dose. 2. Toxicity (AE) findings are similar to other studies. Exclusion of patients with creatinine clearance < 60 mL/min biases study in favour of gabapentin, vs. more frequent AE expected in clinical practice. 3. Claimed significance for primary endpoint using very high dose gabapentin is based on non-ITT analysis which excludes early dropouts, and LOCF analysis of later dropouts. Sensitivity analysis using BOCF for the later dropouts (still missing Week 1 dropouts) renders primary outcome trivial and not significant.

June 10, 2003, updated March 16, 2004 also not available. This trial appears to be primarily a "marketing trial" insofar as it is labeled "Phase IV" and as the "centers" appear to be primary care physicians ("PCP's") and no institutional review boards nor ethics committees were involved (see page 14 of report).	• Intolerant to gabapentin or failed previously to achieve pain relief from gabapentin @ ≥1800 mg/d • Exposed to gabapentin within 30 days • Severe pain from other causes • Creatinine clearance < 60 mL/min • Plantar ulcers within 3 months NB: This creates "enrichment bias" Allowable drugs: ASA, aceteminophen, NSAID's including coxibs, SSRI's Excluded drugs: "mediations commonly used for neuropathic pain, hypnotics, analgesics, antiepileptics, certain antidepressants, antacids" Baseline characteristics: see next column. Details	• 12 weeks at steady dose of G or P • outcome evaluations at baseline, weeks 2, 6, 10, 14 Patient flow: (no flow diagram available) • Screened: 724 patients (43 centers) • Randomized: 389 • Gabapentin 200; completed 136 (68%); discontinued 64 (32%) • Placebo 189; completed 135(71%); discontinued 54 (29%) Analysis: (protocol not available, so analysis plan taken from final report, p. 30) • "ITT" population defined as subjects who took at least one dose of study medicine and had at least 1 post-treatment efficacy measurement – this excludes patients who could not tolerate titration phase and did not reach week 2 first assessment (not true ITT, nor ITT-LOCF) – see p. 30	stated in text as no numbers are shown in report for patient assessments at each week from Week 3 onwards. (p. 44) A "sensitivity analysis" is described (p 34) to impute BOCF for missing scores, but this may apply only to the Week 1 dropouts??? Secondary: NB: all secondary outcomes are dependent, not independent of primary outcome, as they all measure various aspects of the same thing (pain relief). • Weekly mean pain scores • "responders" analysis: compared by CMH test between treatment groups for proportion of patients with ≥ 50% or ≥ 30% reduction in individual pain score at "endpoint" vs baseline • weekly mean sleep-interference scores • CGIC and PGIC at final visit, compared by CMH test between treatment group for proportion "very much improved or much improved", etc.	NB: As for other studies, gabapentin caused more nervous system AE in particular. Patients experiencing > 1 AE per body system were counted as if they had 1 AE for that body system, i.e. "dizziness" and "somnolence" in the same person would count only as 1 event (p. 37). Excerpted results: • Nervous system (all): P = 19.6% ; G=39.5% (p. 55) • Nervous system (all) counted from table at p. 56: P=33/189 (17%); G=83/200 (43%) • Dizziness: P=15/189 (7.9%); G=38/200 (19%) • Somnolence: P=8/189 (4.2%); G=31/200 (16%) • Aesthenia: P=8/189 (4.2%); G=22/200 (11%) • Peripheral edema: P=7/189 (3.7%); G=33/200 (17%) "Treatment related AE" (p 57) showed a similar pattern: P=58/189 (31%); G=98/200 (49%). While the report does not cite statistical significance, the above figures are comparable to all other studies, i.e. NNH is about 4-5 for the most typical AE such as dizziness/somnolence/asthenia, etc. Weight: (mean, or mean change, by group)	4. Dichotomous outcome from responder analysis is consistent with some other studies which report this outcome, e.g. difference in 50% pain reduction is: P=45/189 (24%); G=75/200 (38%); Difference = 14%; p=0.002 NNT = 7 e.g. difference in PCIC for patients reporting "very much improved or much improved" is: P=50/189 (26%); G=85/200 (43%); Difference = 17% p=0.0003 NNT = 6 5. Details of analysis are not available as appendices to this report not available. 6. Publication of this trial with much larger numbers than Backonja trial would have reduced the estimate of apparent group difference

	of baseline outcome scores are not presented.	• "evaluable" population includes patients who could tolerate > 1800 mg/d G for > 4 weeks fixed dose – this eliminates patients who did not like gabapentin and will not be considered further here • safety population is all patients • "Sensitivity Analysis" (see p. 51) imputes BOCF (baseline observation carried forward) to P=52, G=60 patients who discontinued after Week 1, but not to the P=2, G=4 patients who discontinued during Week 1 Randomization: "subjects were assigned at the site, in the order in which they were enrolled into the study, to receive their allocated treatment sequence, in a 1:1 manner, according to a computer-generated randomization scheme prepared by Pfizer prior to the start of the study" (p. 24) Blinding: medications prepared as matching capsules by Pfizer; no	• SF-MPQ • Treatment Outcomes in Pain Survey (TOPS) • Hospital Anxiety and Depression Scale (HADS) Safety: all patients randomized who took 1 dose of study drug	Not reported in complete report (? Appendices) <u>Primary outcome:</u> Group mean pain scores at "endpoint"– not ITT and "endpoint" = last observation carried forward as if all endpoints were at 12 weeks (p. 45): N: P=186/189; G=195/200 Baseline: P=6.51 +/- 0.10 (SE); G=6.28 +/- 0.11 (SE) Endpoint: P=4.82 +/- 0.17 (SE); G = 3.94 +/- 0.17 (SE) LSM adjusted endpoint from ANCOVA: P=4.78 =/-0.18 (SE); G = 4.01 +/- 0.17 (SE) Difference = -0.765 (-1.21, -0.32); p = 0.0008 (favours G) <u>"Sensitivity analysis" renders group mean differences non-significant (pp 50-51):</u> NB: Week one dropouts are not accounted for (P=2, G=4). Sensitivity analysis using baseline observation carried forward (BOCF) values for the other early dropouts (P=52, G=60) but not including P=2, G=4 who dropped out during week 1, nor 1 other subject from each group reduces LSM adjusted differences from baseline:	between placebo and gabapentin, increased evidence that higher dose gabapentin is not more efficacious for pain, and reinforced evidence that toxicity generally outweighs benefit as NNH=4-5 for neurological adverse effects vs. NNT = 6-7 for patient's global impression of moderate or greater improvement in pain or ≥ 50% reduction in NRS pain score.

		test of blinding described; blind broken for one placebo-treated patient who had cardiac arrest.		$P_{baseline}$= 6.51 +/- 0.10 (SE) – (N=186/189) $P_{endpoint}$ = 5.07 +/- ? (SE) $P_{endpoint}$ = 5.11 +/- ? (SE) - LSM adjustment from ANCOVA: $G_{baseline}$= 6.28 +/- 0.11 (SE) – (N=195/200) $G_{endpoint}$ = 4.56 +/- ? (SE) $G_{endpoint}$= 4.54 +/- ? (SE) - LSM adjustment from ANCOVA: <u>Baseline vs LSM adjusted endpoint:</u> P=-1.40 +/- 0.17 (SE); G=-1.74 +/- 0.16 (SE) Difference = -0.34 (-0.77, 0.09); p=0.12 This more conservative analysis, which still omits P=3, G=5 patients, renders the difference on primary outcome of group mean pain score at endpoint both trivial and non-significant. Given the non-ITT analysis of subjects randomized who dropped out early, this “BOCF sensitivity analysis” is more suitable to use for Cochrane meta-analysis, since it is more conservative and likely to be closer to the results of a true ITT analysis.	

				Weekly mean pain scores are referred to (p. 45) but not shown in report. <u>Secondary outcomes:</u> "Responder" analysis(expressed here by Dr. T. L. Perry as closer to true ITT by using the "responder" numerators presented at p. 46 but correcting for complete ITT denominators; this is still "ITT-LOCF" rather than true ITT because "endpoint" for some patients is still at dropout prior to 12 weeks, including more early dropouts from G group than from P group.): <u>≥</u>50% reduction in pain score: P=45/189 (24%); G=75/200 (38%); p=0.002 <u>≥</u>30% reduction in pain score: P=76/189 (40%); G=110/200 (55%); p=0.002 PGIC "very much improved or much improved" (expressed here by Dr. T.L. Perry as closer to true ITT by using the numerators provided at p. 48 but correcting for complete ITT denominators; this is still "ITT-LOCF" rather than true ITT because "endpoint" for some patients is still at dropout prior to 12 weeks, including more early	

				dropouts from G group than from P group.): P=50/189 (26%); G=85/200 (43%); p=0.0003 Other secondary outcomes: No difference claimed for SF-MPQ, Treatment Outomes in Pain Survey (TOPS), Hospital Anxiety and Depression "Scale (HADS). Does a larger dose have a greater effect?: At p. 52 endpoint mean pain scores are presented "for subjects who titrated to a maximum dose of 3600 mg/d", referring to N=186 for P and N=169 for G, whereas a "Duration of Treatment" chart at p. 44 suggests N= 178 for P and N=176 patients for G continued beyond 2 weeks. (This may reflect titration to 3600 mg/day BEFORE 2 weeks, something not discernable without reference to experimental protocol.) Amongst patients titrated to 3600 mg/day, the putative LSM (ANCOVA) group mean difference was -0.957 ("p=0.001") favouringgabapentin. This is interpreted by the authors as a "slightly larger difference between the treatment groups" (i.e. vs. -0.765 in the non-ITT analysis of all patients). While this result is intrinsically uninterpretable,	

				like other data it is not consistent with a clinically useful dose-response effect insofar as even if true, the group mean effect would be less than the clinical threshold for utility.	
				NB: Report does not discuss correction of multiple statistical tests for multiple comparisons.	

Study No. 17 - CHANDRA 2006 – GABAPENTIN vs. NORTRIPTYLINE FOR PHN – DBRCT (Published) - SUMMARY

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 17 Chandra K, Shafiq N et al. Gabapentin versus Nortriptyline in post-herpetic neuralgia patients: a randomized, double-blind clinical trial – The GONIP trial. International Journal of Clinical Pharmacology & Therapeutics 2006; 44: 358-63 Support: Pfizer India Ltd. Trial design: *"The study was partly funded by Pfizer who had no role in protocol design, data analysis or manuscript preparation."* DBRCT, 9 weeks including 1 week run-in, comparing gabapentin (G) with nortriptyline (NT) – to final doses (depending on patient	Post-herpetic neuralgia (PHN) Inclusion: • ≥ 18 years old • PHN pain ≥ 8 weeks after healing of rash • Pain intensity > 4 (VAS) at screening and randomization • Mean pain score (Likert 0-10) ≥ 4 during baseline week • Muscle relaxants, anticonvulsants, topical analgesics, antivirals stopped ≥ 1 week before screening Exclusion: • Priortreatment with or hypersensitivity to NT, G	Study design: 9 week "double blind" (see comments re description of randomization), parallel group RCT comparing NT with G – without placebo control Patient flow (Fig 1, p 362): • Sceened: 110 • 1 week run-in period (not described further) • Excluded: 34 (22 due to low baseline pain scores) • Randomized: NT=38, G=38 • "ITT" (?ITT-LOCF – Fig 1 and text do not clarify whether patients completed or simply provided at least 1 post-baseline evaluation): NT=36, G=34 • "Lost to follow up": NT=2, G=3 TLP: we will consider this an ITT-LOCF analysis in absence of evidence that NT=36, G=34 completed 8 week treatment.	Predefined outcomes: Primary: Difference in mean Likert 11-point NRS pain score from baseline to end of study period. (TLP: we will assume LOCF for noncompleters as this is not discussed.). Secondary (all compared at endpoint vs. baseline): NB: all secondary outcomes are dependent, not independent of primary outcome, as they all measure various aspects of the same thing (pain relief). • SF-MPQ • 5-category pain score using words (e.g. "no pain" … "excruciating pain" • sleep (VAS) • disability rated categorically "no, mild, moderate, severe disability" where *"mild disability implied pain that*	Mortality:Not reported Serious Adverse Events (Not reported in standard fashion, but surmisable from text (p. 361): NT = 1/38 (severe urinary retention); G = not reported Withdrawal Due to Adverse Events: Not reported Total patients with AE's (p. 361 text, and p. 362, Table 3): NT=21/38 (55%, ITT); G= not reported Most important AE's (Table 3): Dry mouth: NT=18 patients; G=0 Postural hypotension: NT=12 patients; G=0 Constipation: NT=8; G=0 Sleepiness: NT=6; G=4 Total AE's (patients may have > 1 as total exceeds total patients	1. This study does not claim any difference in outcomes and has no placebo group. The NRS pain rating change attributed to both drugs is somewhat larger than what is claimed in most studies, and is LOCF with no indication of the number of patients contributing to the scores. Given the lack of a placebo group, and the lack of information on sample size (LOCF) the reported NRS pain score changes can not be pooled with other studies in a meta-analysis. 2. The determination of patients with AE and total AE is not described in sufficient detail to pool in meta-analysis. 3. The main lesson one can learn from this trial is that it is at least reasonable in principle to assess "disability"; however without a placebo group in a condition where most patients improve rapidly (especially at this mean

response) of: NT = 150 mg/d G= 2700 mg/d No placebo comparator arm. *"Drugs placed in identical capsules to achieve blinding."* (p. 359) Patients screened and enrolled between January 2002 – January 2005 (p. 360) Randomization: *"Consecutive eligible patients were randomized to either NT or G in a 1:1 computer-generated random number table. The randomization code was supplied in sealed envelopes which was opened by the investigator only at the time of enrolment…. The pharmacist, the person involved in randomization allocation, the investigator evaluating the outcome and the trial subject were blinded to the treatment."* (p. 359) –	• "Hepatic or renal insufficiency" NB: This creates "enrichment bias"favouring both NT and G Allowable drugs: non-opioid analgesics not further specified Baseline characteristics: Mean age: NT 52.5, G 55.6 Daily pain score (Likert): NT 5.8 (1.4), G 5.6 (1.1) No apparent differences from Table 1, p. 361.	Drug doses: • initial dose x 2 weeks, both in divided doses: NT=50 mg/d, G=900 mg/d • optionaltitration up if drug well tolerated at 2 weeks: NT=75 mg/d, G=1800 mg/d; • titration up if drug well tolerated at 4 weeks: NT=150 mg/d, G=2700 mg/d Analysis: (p. 360) *"Assuming a SD of 1.5 and normally distributed responses … sample size of 25 pts/group was calculated to provide 90% poerwo detect a difference of 1.25 in primary endpoint (a change in the pain intensity score on 11-point scale from baseline to …week 8 … Each treatment arm was assessed by comparing the week 8 results to the baseline results using repeated measures ANOVA. Between-groups comparison was done by using ANCOVA. Global impression of therapy was analysed using Chi-square test.."*	*interfered only with some activities such as exercise, moderate disability implied pain significantly interfered with or prefented ADL such as dressing, wearing clothes, eating, cleaning or shopping, severe disability implied patient was in bed with pain for part or all of the day."* (p. 360) • "Clinical effectiveness" rated categorically as "excellent, good, improved but unsatisfactory or unchanged." (see p. 360) • self reported adverse effects and adverse effects ("side effects", not = adverse events) from checklist	with AE): NT=47; G=9 Primary outcome: Change from baseline to endpoint (presumably LOCF), NRS pain scale: NT = 2.18 (1.9); G = 1.97 (1.68); p=0.62 The number of patients assessed, and the timing of assessments, is not reported (LOCF rather than 8 week f/u probable, but not stated) NB: from Table 2, p. 361 – and text it is impossible to tell how many patients contributed to outcome assessment for each group, except that it is < the number randomized for each group – subsequent discussion concerning secondary outcomes suggests that at least for categorical "clinical effectiveness" rating, NT=4/36=11.1% and G=4/34=11.7% patients had no data available such that the total numerators for many observations were always < or << the number of patients randomized.)	age, the figures are meaningless . 4. An interesting observation is that at least 21/38 patients randomized to nortriptyline experienced dry mouth, confirming that this drug has potent anticholinergic effects. (Some experiments comparing NT with amitriptyline have claimed less frequent anticholinergic effects.)

Comment: were the investigators blind?				Disability rating (NB numbers of patients rated is not reported: "improved": NT 42%; G 40% "same": NT 50%; G 52% "worsened": NT 9%; G 8% (numbers rounded to nearest integer) > 50% reduction in NRS pain score at endpoint vs. baseline (NOT a pre-specified outcome, expressed here as patients reported as achieving endpoint over number randomized/group): NT: 9/38 (24%); G: 7/38 (18%) "Clinical Effectiveness" rating" (corrected to show numbers derivable from percentages at p. 361 divided by original randomized denominators, assuming dropouts and patients for which "no data were available" should be classified as unchanged): Unchanged: NT=12 G=14 Improved but not satisfactory: NT=10; G=8 Good: NT=12; G=8 Excellent: NT=4; G=8 NB: Report does not discuss	

				correction of multiple statistical tests for multiple comparisons, but claims no statistical significance for any comparison.	

RAO 2007 – Study No. 18 - GABAPENTIN FOR CANCER CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY – DBR CROSSOVER TRIAL (Published) - SUMMARY

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 18 Rao RD, Michalak JC. Efficacy of Gabapentin in the Management of Chemotherapy-induced Peripheral Neuropathy: A Phase 3 Randomized, Double-Blind, Placebo-controlled, Crossover Trial (N00C3). Cancer 2007; 110: 2110-8 Support: U.S. Public Health Service, North Central Cancer Treatment Group (IRB approval) and Mayo Clinic. Trial design: independent DBRCT, 14weeks . After randomization (no run-in), 6 weeks comparing gabapentin (G) with	Cancer chemotherapy-induced (painful) peripheral neuropathy (CIPN) Inclusion: • Adults with symptomatic (painful) CIPN > 1 month due to neurotoxic chemotherapy • "Average pain at baseline: ≥4 on 11-point numerical rating scale (NRS), OR score ≥1 on Eastern Cooperative Oncology Group 4-point neuropathy scale at screening and randomization • Creatinine (serum) ≤ 1.5 x ULN • Life expectancy estimated ≥ 6 months • Muscle relaxants, anticonvulsants, topical analgesics, antivirals stopped ≥	Study design: 14 week double blind crossover trial RCT gabapentin (target dose 2700 mg/d) with placebo as 2 arms: G/P x 6 weeks each with 2 week washout between treatments vs P/G x 6 weeks, each with 2 week washout between treatments. Patient flow (Fig 2, p 2113): • Sceened: 115 • Excluded: 0 • Randomized: 115 as G/P=57, P/G=58 • Completed crossover: 68/115 as: G/P = 32/57 (56%) P/G = 36/58 (62%) • Withdrawn from treatments: G = 21/100 exposed to G P = 22/99 exposed to P (derived from Figure 2, p. 2113) TLP: Results presented in	Predefined outcomes: Primary: Average pain assessed by 10-point NRS and 4-point ENS over 1 "particular" day, assessed weekly, compared at 6 weeks (end of first phase) and at 14 weeks (end of second phase) – NB: analysis appears to be of completers only, not ITT-LOCF and not ITT. Secondary (all compared at both 6 weeks and 14 weeks for completers vs. baseline): NB: all secondary outcomes are dependent, not independent of primary outcome, as they all measure various aspects of the same thing (pain relief).	TLP: I don't think we can meta-analyse any of these results with any credibility. It is better to present this study on its own, as a negative study. Mortality: Not reported Serious Adverse Events:Not reported Withdrawal Due to Adverse Events: Not reported Total patients with AE's: not reported Total AE: reported for completers only (Table 3, p. 2116 reports only AE "attributed to therapy", whereas Table 2, p. 2114 reports AE, grade > 2 (not further defined) for completers. By adding those from the relevant phases of G/P and P/G groups and dividing by the number completing in each group, one can	1. This study does not claim any difference in outcomes and concludes that*"this trial failed to demonstrate any benefit to using gabapentin to treat symptoms caused by CIPN". (p. 2110, abstract)* 2. The description of patient flow and presentation of statistics is inadequate, but suggests that the report concerns only completers, i.e. 78/115 patients at 6 week parallel comparison (phase 1 prior to crossover) and 68/115 patients at end of second 6 week parallel comparison. It is not clear how the crossover design is analysed in a complex and mysterious statistical analysis. 3. Presentation of safety data is inadequate and the methods section does not discuss how

placebo (P)– totarget dose of G=2700 mg/d regardless of efficacy at lower doses; then 2-week washout, followed by crossover to the alternative arm for 6 weeks. Drugs in identical capsules (p. 2112). Patients screened and enrolled between March 2002 2002 – December 2003 (p. 2113) Randomization: *"Randomization was performed by using a dynamic allocation procedure that balanced marginal distirbutions of stratification factors between treatment groups."* (p. 2112) Dose selection based on Backonja trial (JAMA 1998) and Gilron trial (NEJM 2005) - see p. 2112 – the latter reference may	Exclusion: • Other causes of symptomatic neuropathy • Patients using antidepressants, opioids, anticonvulsants, clonazepam, mexiltine, topical analgesics, etc. Allowable drugs: above drugs could be started during experiment, along with NSAIDs. Baseline characteristics: G/P arm: N=57 P/G arm: N=58 Mean age: 59 Age range: 25-84 Pain characteristics: NB: No SD are reported for any numerical values (Table 2, p. 2114) NRS 'average pain", ENS rating: G/P arm: NRS=4.3; ENS=1.9 P/G arm: NRS=3.6; ENS=2.0	Table 2, p. 2114 appear to be a "completers-6 week and completers-14 week" analysis, judging by the N's at the top row of Table 2, i.e. patients who completed first 6 weeks of G or P are compared at 6 weeks, and patients who completed first 6 weeks AND completed crossover 6 weeks are compared at 14 weeks. See "statistical analysis" below. Drug doses/titration (p. 2112): Titration schedule not detailed. *"Gabapentin incrementally escalated over 3 weeks to targer dose of 2700 mg/d … If toxic events occurred, the dose was reduced to apreviously well-tolerated dose level. After treatment with the maximal dose for 3 weeks, patients were weaned from the drug …"* (? Washout period) … Placebo was handled in a "similar manner" Statistical Analysis: (p. 2112-13) Unusually complicated	See report p. 2112 for details. Only outcomes relevant to Cochrane meta-analysis (TLP et al) are described below: (Disability outcome) WHO classification scale for neuropathy-related symptoms, 5-point categorical scale where: 0=none 1=paresthesias and/or decreased tendon reflexes 2=severe paresthesias and/or mild weakness 3=intolerable paresthesias and/or marked motor loss 4=paralysis Subject global impression of change: 7-point categorical scale which appears identical to PGIC used in other studies. However, these are reported only as mean outcomes (mean of ordinal scale values).	derive these results, which apply to completers and only for AE, "> grade 2": G = 75 AE 74 patients P = 79 AE in 71 patients NB: These are not ITT, nor ITT-LOCF and CANNOT be used in meta-analysis for safety outcomes (theywould almost certainly underestimate AE) – note this is a sick population compared with other studies, and many AE are likely to be unrelated to G, P. Most important AE's (Table 3): Not reported except for "AE attributed to therapy", therefore not shown here Primary outcome: NRS, ENS pain scores at 6 weeks, 14 weeks (for completers only) compared with baseline: For average pain NRS: G/P group: baseline = 4.3 (no SD); 6 weeks (treatment with G) = 3.3, 14 weeks (treatment with P) = 3.1 P/G group:	safety was assessed. 4. The report claims to have found that gabapentin was *"remarkably well tolerated"* (p. 2116) and suggests that the median maximum dose of gabapentin achieved was 2700 mg/d, which seems implausible given the results of other studies in less sick patients. TLP: I don't think we can meta-analyse any of these results with any credibility. It is better to present this study on its own, as a negative study.

refer to Gilron's protocol, since Gilron was in progress as of February 2001.	NB: NRS "average pain" at baseline could be < 4 for group (or individuals) because some patients could enter trial on basis of Eastern Cooperative Oncology Group ENS scale criterion. Groups appear balanced given likely substantial SD's and p=0.06 at baseline for NRS average pain, p=0.7 for ENS average pain WHO neuropathy scale (see column 4, this table): G/P = 1.5 P/G = 1.5 No apparent differences from Table 1, p. 2113	description. Power calculation toprovide 80% power to detect differences in average pain scores of 0.63 SD via Student t test with 2.5% Type 1 error rate with Bonferroni correction for 2 primary endpoints. *"Missing data were handled in a number of ways to assess the robustness or results obtained, relative to missing data… Results that used all available data without imputation are presented here.* Otherwise see original report.		Baseline – 3.6 (no SD); 6 weeks (treatment with P) = 3.0; 14 weeks (treatment with G) = 2.5 Comparisons from statistical model: G/P vs. P/G NRS at baseline: p=0.06 G/P vs P/G NRS at 6 weeks: p=0.8 G/P vs. P/G NRS at 14 weeks: p=0.2 No difference is claimed. Graphs of time course of pain in completers are shown after end of this table. "Disability"(WHO neuropathy score): No difference is claimed (see Table 2, p. 2114) SGIC (PGIC equivalent): Reported only as means in Table 2, p. 2114 (+ change = improvement) G/P at 6 weeks: +0.3 (no SD) G/P at 14 weeks: +0.5; P/G at 6 weeks: +0.2 P/G at 14 weeks: +0.1 For G/P vs P/G at 6 weeks, p=0.7 For G/P vs. P/G at 14 weeks, p=0.3 NO DIFFERENCE IS CLAIMED	

Notes: This is a negative trial which found no benefit from gabapentin for CIPN. However, the methodology and loss of patients make it impossible to include the results in a meta-analysis of outcomes

	Study No. 19 RINTALA ET AL, 2007 – PUBLISHED TRIAL SUMMARY				
Study/ Design/dates	**Inclusion criteria/baseline characteristics**	**Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study**	**Predefined outcomes/issues in statistical analysis**	**Outcomes hierarchy (Cochrane, investigators: primary/secondary)**	**Comments/conclusions of Dr. Perry**
Study No. 19 Publication: Rintala DH, Holmes SA et al. Comparison of the Effectiveness of Amitriptyline and Gabapentin on Chronic Neuropathic Pain in Persons with Spinal Cord Injury. Arch Phys Med Rehabil 2007; 88: 1547-60	Pain from spinal cord (SCI) at any level ("neuropathic pain" associated with or below spinal level) Inclusion: • Patients age 18-70 with SCI ≥ 12 months prior • Pain score (Likert) ≥5 when first recruited Exclusion: • Safety issues (e.g. cardiac) • "renal insufficiency" (not defined) No enrichment bias Allowable drugs: no analgesics except oxycodone 5 mg/acetaminophen 325 mg supplied up to 8 tablets/day for breakthrough pain	**Study design:** 31 week study with 1 week baseline run-in (no study drug) followed by 3 10-week periods during which patients started with diphenhydramine (D, active placebo), amitriptyline (A), or gabapentin (G)and crossed over to the other 2 drugs in 6 different permutations. Drug was titrated towards target dose during first 4 weeks, then maintained (or reduced, if not tolerated) for 4 weeks, then tapered during Week 9, then stopped for washout during Week 10. • Screened: 50 • Randomized: 38 patients were randomized in sets of 6 consecutive patients to 6 sequences (e.g. GAD, GDA, AGD, ADG, DGA,	Predefined outcomes: **Primary:** Pain score (Likert 0-10 score) as group mean of individual means from patients' last 7 available scores while on study medication (up to end of Week 12) from daily diary records of previous 24 hours (LOCF for noncompleters). Analysis by ANCOVA with treatment and center as fixed effects and baseline mean score as covariate (p. 31) **NB: Patients who took study drug for only 2-7**	**Mortality:** not reported **SAE:** not reported **WDAE (shown as WDAE divided by number of patients who started each treatment, i.e. WDAE over number who received drug and were therefore eligible to withdraw, ITT for each drug):** **Diphenhydramine: 2/31 Amitriptyline: 4/34 Gabapentin: 5/32** **This can be used for meta-analysis of WDAE for amitriptyline vs. gabapentin, but not for placebo, since diphenhydramine is active placebo with its own AE. Withdrawals (total -shown**	**1. Small study which is hard to interpret. 2. Adverse events cannot be compared with other studies. 3. Gabapentin <u>not</u> more effective than diphenhydramine. Amitriptyline may be effective also as antidepressant, according to author's sub-analyses by "depressive" status of patients. 4. Authors' literature review notes survey studies**

Independent study sponsored by US Veterans Affairs (VHARHDS grant) November 2001 – April 2004	**Baseline characteristics**:supplied for study completers (all 3 periods) vs non-completers (< 3 periods) Completers (N=22): mean pain intensity 5.6 +/- 2.2(VAS 10 pt scale); median 6, range 0.4-9.6; breakthrough tablets during baseline week = 16.9 =/- 17 Non-completers (N=16): mean pain intensity 6.6 +/- 2.3; median 6, range 3-10; breakthrough tablets during baseline week = 22.3 +/- 17.2	DAG) using a table of random numbers for each set, varied from set to set • Patients starting with D=13, A=12, G=13 • Gradual titration over 4 weeks toD=75 mg/day, A=150 mg/day, G=3600 mg/day, all in 3 divided doses • Subjects could take lower doses if experiencing "unacceptable side effects" or if pain relief achieved • Subjects could cross over early to next scheduled group after 1 week washout, if they could not tolerate AE • 4 weeks at steady dose if achieved/tolerated • outcome evaluations at clinic or home at baseline, weeks 2, 4 6 (for some participants), 8, 10 during each phase plus telephone contact 1-2 times/week throughout each 10 week phase	**days (P=2; G=4) apparently were not evaluated at all for outcomes and are dropped from "ITT analysis". Patients who took study drug for 8-14 days (P=9, G=20) may have completed first post-treatment efficacy assessments at start of week 3 (visit 3) – not clearly stated in text as no numbers are shown in report for patient assessments at each week from Week 3 onwards. (p. 44) A "sensitivity analysis" is described (p 34) to impute BOCF for missing scores, but this may apply only to the Week 1 dropouts???** **Secondary:** **NB: all secondary outcomes are <u>dependent,</u> not independent of primary**	**as withdrawals divided by number of patients who started each treatment, i.e. withdrawals over number who received drug and were therefore eligible to withdraw, [not including 1 w/d from A who "withdrew from study after completing all of this arm due to moving out of state" – not attributable to any group] - ITT for each drug)):** **Diphenhydramine: 3/31** **Amitriptyline: 6/34** **Gabapentin: 6/32** **Adverse Events:** **Patients with AE:** not reported **Total AE:** not reported in a manner which is interpretable **<u>Validated measures of improvement in global</u>**	**of patients with pain from spinal cord injury suggesting that neither amitriptyline nor gabapentin are very effective.**

		Patient flow: (complex – see diagram p. 1551) • Randomized: 38 • Completed all 3 crossover groups: 22/38 • Did not complete all 3 groups: 16/38 • Started D: 31/38 • Started A: 34/38 • Started G: 32/38 • Completed D: 25/31 • Completed A: 28/34 • Completed G: 26/32 **Analysis:** complex – see publication for details. Patients were analysed as a group, by completers vs. non-completers, by "depressive symptomatology group" at baseline (more depressed vs. less depressed patients by a depression score), etc. **Randomization:**see above and p. 1548 **Blinding:** medications prepared as matching capsules by	**outcome, as they all measure various aspects of the same thing (pain relief).** • Weekly mean pain scores • "responders" analysis: compared by CMH test between treatment groups for proportion of patients with ≥ 50% or ≥ 30% reduction in individual pain score at "endpoint" vs baseline • weekly mean sleep-interference scores • CGIC and PGIC at final visit, compared by CMH test between treatment group for proportion "very much improved or much improved", etc.	**function including return to work, study, activities of daily living** Not reported. **"Responder" analysis ≥ 50% reduction in pain from baseline:** Not reported **Primary outcome (endpoint):** **Not meta-analysable.** **The study reports on average week 8 final pain ratings for completers only, with no ITT nor ITT-LOCF analysis for non-completers – the outcome is not comparable to other studies.** The authors report mean VAS ratings for pain during week 8 for 22 completers (of 38 patients randomized) as:	

		commercial compounding pharmacy; no test of blinding described	• SF-MPQ • Treatment Outcomes in Pain Survey (TOPS) • Hospital Anxiety and Depression Scale (HADS) **Safety:** all patients randomized who took 1 dose of study drug	D: 5.11 (2.54) A: 3.46 (2.09) G: 4.85 (2.86) *"Repeated measures ANOVA indicated a main effect of medication (F=4.61, P=.016) … Follow-up paired t tests with Bonferroni adjustment … indicated that average pain intensity in week 8 with amitriptyline therapy was significantly lower than with gabapentin therapy (t=2.32, P=.03; effect size, Cohen d=.55) , or with diphenhydramine therapy (t=2.76, P=.012; Cohen d=.71)."* **Patient Global Impression of Change at endpoint(PGIC):** Not reported.	

Notes: This is a negative study which concluded: "… Gabapentin was no more effective than diphenhydramine (p=0.97)"….Amitriptyline is more efficacious in relieving neuropathic pain than diphenhydramine at or below the level of spinal cord injury in people who have considerable depressive symptomatology." The reporting is by completers and by groups depression scoreBecause of the large number of withdrawals and the analysis by completers rather than ITT or even ITT-LOCF, the analysis cannot be compared in meta-analysis with other trials.

Study No. 20 - Pfizer 0945-00S-P02 – GABAPENTIN FOR HIV-ASSOCIATED PAINFUL NEUROPATHY (PUBLISHED VERSION ONLY) – SUMMARY prepared by Dr. TL Perry – FINAL – July 27, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 20 Pfizer, apparently Protocol 0945-00S-P02 Hahn K, Arendt G, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. J. Neurol 2004; 251 : 1260-6 Support: Pfizer grant, apparently protocol. Dates: not identified, apparently prior to MS submission of August 14, 2003 Design: 5 week multicentre German outpatient DBRCT parallel group study of gabapentin vs. placebo. 1 week screening phase, 4 weeks double blind therapy, then 2 weeks open. (not summarized	HIV-associated sensory neuropathy (HIV-SN) (HIV-associated distal-symmetric polyneuropathy) Inclusion: • ≥ age 18 • painful HIV -SN • completion of baseline pain diary for 1 week • no apparent minimum pain score (range of medians: 1.5/10 - 9.3/10, see below! Exclusion: • taking tricyclic/tetracyclic antidepressant or other anticonvulsant, central analgesics (opioids), etc. • other causes of painful neuropathy	Study design: 5 week multicentre outpatient DBRCT parallel group study of gabapentin vs. placebo. 1 week screening phase, 4 weeks double blind therapy, then 2 weeks open. Gabapentin titrated from baseline as 400 mg/d (3 divided doses), then increased as tolerated every 4 days to 1200 mg/d by end of week 2, then increased for pain to masimum of 2400 mg/d. Patient flow: • Screened: not reported • Randomized: 26; P=11; G=15 • Withdrawals: P=1, G=1 • Dose attained: G1200 mg/d 4, G2400 mg/d 10 • Completed: P=10, G=14 Analysis: (p. 1262) Primary efficacy parameter – change in median pain score from baseline to 4th treatment week, evaluated by daily pain diaries. Score determined by calculating median pain score for baseline and week 4. Sleep interference calculated in same	Predefined outcomes: NB: Although this appears to be a Pfizer protocol (0945-00S-P02) the protocol and pre-defined outcomes and statistical analysis plan is not available. No other Pfizer protocol proposed analysis of median pain scores instead of mean pain scores – this may be a post-hoc analysis different from the original planned analysis. Primary: Pain score (VAS 100 mm scale) from SF-MPZ recorded in a diary by patients twice daily.	Doses attained: G400 mg/d: 1/15 (WDAE); G1200 mg/d: 4/15; G2400 mg/d: 10/15 Mortality: not reported Serious Adverse Events: not formally reported (1 patient discontinued G for "severe dizziness and somnolence" 2 days after treatment with 400 mg/day is shown below as SAE) P = 0/11 (0%) G = 1/15 (7%) Withdrawal Due to Adverse Events: P=0/11; G=1/15 Total Withdrawals: P=1/11; G=1/15 Total patients with AE's: Not reported Total AE's (patients may have > 1): Not reported Specific AE: Somnolence: P=2/11; G=12/15 Dizziness: P=5/11; G=9/15 Ataxia: P=3/11; G=7/15	1. Unusual trial insofar as it reports a very unusual analysis of "median" pain scores and enrolled patients of whom some had very low pain scores at baseline. 2. Toxicity (AE) findings are similar to other studies. 3. Claimed significance for primary endpoint is very doubtful, and it is impossible to tell whether the analysis was pre-planned or post-hoc. 4. Authors' claim that "gabapentin was more effective in reducing the pain and the sleep interference score … than placebo" is not

in this table) Randomization: not described in detail Concealment: identically appearing capsules Test of blinding: not reported	• "chronic renal insufficiency" Allowable drugs: NSAIDs – opioids not allowed Baseline characteristics Age as median (range): P: 44 (35-61) G: 46 (27-59) Duration of painful neuropathy as median (range): P: 28 weeks (4-240) G: 48 weeks (2-384) Pain score at baseline as median (range): P: 4.7 (1.5-9.3) G: 5.1 (1.7-8.7)	manner. Difference in change from baseline to endpoint analysed by Wilcoxon test. See text for other analyses. TLP cannot tell whether the summary statistics presented are: a) the group mean for P or G of weekly median pain scores for patients in those groups; b) the group median for P or G of weekly median pain scores for patients in those groups Randomization: *"… by producing a randomization schedule that assigned each patient to G or a matching placebo … Patients were sequentially assigned to a patient number"* (p. 1262) Concealment: *"identically appearing capsules"* Blinding: not tested	Primary outcome is reported in publication as the difference between weekly median pain score at week 4 endpoint, vs. baseline week. ITT or ITT-LOCF not specified, but only 1 dropout from each group. Secondary: Median weekly mean sleep-interference scores	Functional improvement: not reported ≥50% reduction in pain score: not reported Primary outcome: There is no indication whether analysis is ITT-LOCF reported as apparent ITT with all patients reported. As reported in publication (p. 1263), median pain score reduction from baseline to week 4: P (N=11) change of medians: 4.7-3.3 = 1.4 (p=0.646 for comparison of endpoint with baseline) G (N=15) change of medians: 5.1-2.85 = 2.25 (p<0.05 for comparison of endpoint with baseline) NB: the P, G group "median" pain scores are almost identical at endpoint (P=3.3/10; G=2.85/10) and TLP cannot tell whether these are the group means or group medians of individual patient median weekly pain scores. The authors report the differences from baseline to endpoint as "% reduction in pain". These results are not suitable for meta-analysis. Secondary outcomes: As above, but for sleep interference, a non-independent outcome. PGIC: not reported	really supported by the data. 5. Details of analysis are not available as unpublished Pfizer report not available.

Study No. 21- Arnold 2007 – GABAPENTIN FOR FIBROMYALGIA (PUBLISHED) – SUMMARY prepared by Dr. TL Perry – FINAL – July 27, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 21 Arnold LM, Goldengerg DL et al. Gabapentin in the Treatment of Fibromyalgia : A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial. Arthritis & Rheumatism. 2007 ; 56 : 1336-44 Support:: U.S. National Institute of Arthritis and Musculoskeletal and Skin Diseases grant N01-AR-1-2264. Lead author and one other author consult for Pfizer. Dates: September 2003 - January 2006 Design: 12 week 3-center U.S. outpatient DBRCT parallel group study of gabapentin vs. placebo. 7-60 day screening phase, then 12 weeks double blind therapy, then 1 week dose tapering phase.	Fibromyalgia Inclusion: • age 18 • ACR criteria for fibromyalgia • Average Brief Pain Inventory (BPI) score ≥ 4 (11 point scale 0-10) at screening and randomization (baseline) Exclusion: • Pain from other arthritic causes, etc. (opioids), • Unstable medical or psychiatric illness, or history of psychosis, mania, risk of suicide, etc. • Recent substance	Study design: 12 week 3-center U.S. outpatient DBRCT parallel group study of gabapentin vs. placebo. 7-60 day screening phase, then 12 weeks double blind therapy, then 1 week dose tapering phase. Dose titration: Gabapentin titrated from baseline as 300 mg/d (bedtime dose) for week 1, then 300 mg b.i.d. and 600 mg h.s. (1200 mg/d) for weeks 2-3, then divided doses as 1800 mg/d for weeks 4-5, then 2400 mg/d (divided doses, 1200 mg at bedtime) for remainder of study from week 6 on. If not tolerated, dose reduced to 1200 mg/d as divided doses. Doses stable for last 4 weeks of therapy, then tapered by 300 mg/d until discontinuation. Patient flow: (Figure 1, p. 1338) • Screened: 252 • Excluded: 102 • Randomized: 150; P=75; G=75 • Withdrawals: P=13/75, G=18/75 • Completed: P=62/75, G=57/75 • Total of 1077/1200 possible	Predefined outcomes: Primary (BPI, 11—point pain scale from 0-10): Primary analysis of BPI which measures pain severity during the past 24 hours was recorded at baseline (week 0) and weeks 1, 2, 4, 6, 8,10, 12; *"Longitudinal analysis of rate of change of BPI pain score during treatment between groups."* Secondary analysis *"changes from baseline to endpoint (ITT-LOCF)"* Response to treatment: defined as ≥ 30% reduction	Doses attained: median dose of G=1800 mg/d (interquartile range 1200-2400 mg/d) Mortality: not reported Serious Adverse Events: not reported Withdrawal Due to Adverse Events: P=7/75 (9%); G=12/75 (16%) Total Withdrawals: P=13/75; G=18/75 Total patients with AE's: Not reported Total AE's (patients may have > 1): Not reported Specific AE: Somnolence: P=6/75 (8%); G=14/75 (19%) Sedation: P=3/75 (4%); G=18/75 (24%) TLP: we will conservatively use "sedation" for meta-analysis, since we cannot combine the 2 categories, which probably overlap. Dizziness: P=7/75 (9%); G=19/75 (25%) Lightheadedness: P=1/75 (1%); G=11/75 (15%)	1. Trial reporting is hard to understand in terms of the statistical analysis. 2. Toxicity (AE) findings are similar to other studies. 3. Claimed significance for primary endpoint is uncertain, as multiple analyses were applied and Figure 2 does not show tests of significance at any point. 4. A secondary analysis (see original report at p. 1341 and 1342) assessing only adherent patients showed a slightly lower effect of

Randomization: not described in detail Concealment: "matching" Test of blinding: not reported	abuse • "treatment refractory" in opinion of investigator • prior treatment with gabapentin or pregabalin • drugs with CNS effects except for occasional use of sedating antihistamines • analgesics other than OTC Allowable drugs: acetaminophen or OTC NSAIDs Baseline characteristics Age (mean): P: 47 G: 49 BPI pain score at baseline as mean (SD): P: 6.0 (1.5) G: 5.7 (1.4)	study visits of which P=541/600; G=533/600 (from Figure 2), 989 visits while on study medication (numbers for P, G not reported and not calculable from Figure 2 for each experimental group as timing of dropouts from therapy is not shown) • Numbers persisting are generally similar over 12 weeks from Figure 2 (p. 1340) although gabapentin patients drop out more near end of experiment) Analysis: (p. 1338 et seq) Power calculation for 90% power to detect 0.60 effect size difference for gabapentin. BPI average pain severity score chosen a priori as primary outcome measure. Type 1 error of p=0.05 set. Secondary measures "intended to confirm the findings of the primary measure"; no adjustment for multiple comparisons performed. For continuous variables (primary outcome = BPI) longitudinal analysis of rate of change of outcome between groups, estimated by "random regression models as described elsewhere" … using all observations from all time points …(see text, p. 1339) As a secondary analysis, changes from baseline to end point (ITT-LOCF) were analysed using an ANOVA	in pain severity by BPI from baseline to endpoint Secondary: • Overall impact of fibromyalgia FIQ scale (0-80) • Tender point assessment by "dolorimeter" • Clinical Global Impression of Severity (CGIS; 7-point scale) • Patient Global Impression of Improvement (PGII, equivalent to PGIC; 7 point scale where 1=very much better …	TLP: we will use "sedation" for meta-analysis, since we cannot combine the 2 categories, which probably overlap. "Dizziness" is the more common term in other studies, and the ARI is similar for both. Edema: P=6/75 (8%); G=12/75 (16%) Aesthenia: P=5/75 (7%); G=6/75 (8%) Weight gain: P=0/75 (0%); G=6/75 (8%) Functional improvement: not reported ≥50% reduction in pain score: not reported (authors report ≥ 30% reduction in BPI at endpoint vs. baseline as: P=23/75 (31%); G=38/75 (51%); p=0.014 Primary outcome (BPI 11-point pain scale, over time): Primary analysis: Table 2 reports "Observed values and model-based estimates", not ITT or ITT-LOCF for the time course. Figure 2 reports what appears to be ITT-LOCF, which is not shown as significantly different at any time point, although number of patients assessed for G, P, is shown. Secondary analysis: from text (p. 1340): N for each group is not specified for ITT-LOCF although P=62/75, G=57/75 completed. Numerical values for each group shown in text at p. 1340 are different from numerical values for completers shown in Table 2 (table text does not clarify this). Baseline BPI: P=6.0 (1.5); G=5.7 (1.4)	gabapentin in this model, which does not make pharmacologic sense. 5. The reporting of "responder" analysis and PGIC is not compatible with other studies and therefore cannot be meta-analysed. 6. Although the authors claim improvement on functional scales such as an 8.4 point difference favouring G over P on an 80—point "Fibromyalgia Impact Questionnaire", they do not adduce evidence of substantive functional improvement.

		model. Primary analysis for response to treatment and participant ratings of global improvement was CMH test for end point values, using LOCF of all subjects who had at least one post-baseline assessment. Randomization: *"… randomly assigned to 1 of 2 treatment groups … in a 1:1 ratio"* (p. 1337) Concealment: *"Gabapentin or matching placebo"* Blinding: not tested	7=very much worse) • Medical Outcomes Study sleep measure • Montgomery Asberg Depression Rating Scale • MOS Short Form 36 (SF-36) NB: authors note they did not apply correction for multiple tests of statistical significance.	Endpoint BPI (LOCF): P=5.0 (2.6); G=3.8 (2.2) Difference (baseline – endpoint): P=1.0 (? SD); G=1.9 (? SD) "Estimated difference between groups": -0.95 (95% CI: -1.68, -0.23); p=0.010 TLP: It is not clear how to use these "secondary analysis" results for meta-analysis. Since they appear to be ITT-LOCF similar to other studies, it may be reasonable to include them. The multiple tests of statistical significance are problematic but this would give an optimistic estimate of the overall pain effect of gabapentin which is at least comparable in time to other studies. Secondary outcomes: See original report for secondary outcomes other than PGIC (pp. 1340-1). The "Medical Outcomes Study Sleep Problems Index Score" showed a relatively larger change favouring G over P, compared with the pain score, which authors interpret as evidence that gabapentin improved sleep, etc. PGIC: not reported by individual categories of 7-point scale, nor by best 2 categories. Figure 3 shows only bar graphs for "worse", "no change", or "better"; the "better" category comprises 3 categories and is not comparable to 2-category groupings used in other studies. No histogram can be generated.	

Study No. 22- Kimos 2007 – GABAPENTIN FOR CHRONIC MASTICATORY MUSCLE PAIN (PUBLISHED) – SUMMARY prepared by Dr. TL Perry – FINAL – July 27, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 22 Kimos P, Biggs C et al. Analgesic action of gabapentin on chronic pain in the masticatory muscles : A randomized controlled trial. Pain 2007; 107: 151-60 Support:: University of Alberta Fund for Dentistry (Grant No. 2003-01), Pharmascience (donated gabapentin and placebo) Dates: ? 2003 grant, recruitment over 10 months, completed before September 2005 (submission of MS) Design: Independent. 12 week 1-center Canadian outpatient DBRCT parallel group study of gabapentin vs. placebo. Screening not described, variable washout based on half-life of prior drugs, as needed. 12 weeks double blind therapy.	Chronic Masticatory Muscle pain (CMM) Inclusion: • Masticatory muscle pain ≥ 6 months • No traumatic, infectious, inflammatory cause • Baseline pain score ≥ 50 mm on 100 mm VAS scale • Pain on palpation in ≥ 3 of 6 possible points in temporalis or masseter muscles Exclusion: • Inflammatory TMD • Epilepsy, cardiac, renal,	Study design: 12 week 1-center Canadian outpatient DBRCT parallel group study of gabapentin vs. placebo. Screening not described. 12 weeks double blind therapy. Assessments by one investigator at baseline, week 4, week 8, and week 12. Dose titration: Gabapentin titrated from baseline as 300 mg/d, increased every 3 days until pain control with no adverse effects to a maximum of 4200 mg/d. Titration by telephone call from pharmacy research assistant (? Unblended – see p. 152 and 154) Patient flow: (Figure 1, p. 155) • Screened: 79 • Excluded: 29 • Randomized: 50; P=25; G=25 • Withdrawals: P=8/25, G=6/25 • Completed: P=17/25, G=19/25 • Assessed despite dropout at endpoint (ITT): P=20/25, G=24/25 • Early withdrawals with no follow-	Predefined outcomes: Primary (VAS 10 cm pain scale): Reported at baseline and each of 3 post-baseline visits for the previous week (no mention of pain score diaries). *"A pain reduction of 30% would be considered clinically significant."* Secondary: "Palpation index" (see text, p. 153) VAS-function *("patients were trained to understand that one end of the scale*	Doses attained: not reported, although some subjects in G group reached 4200 mg/d, *achieving "partial pain control or no pain control at all".* Mortality: not reported Serious Adverse Events: not reported Withdrawal Due to Adverse Events: Not reported Total Withdrawals: P=8/25; G=6/25 Total patients with AE's: Not reported Total AE's (patients may have > 1): Not reported Specific AE: Drowsiness (somnolence): P=5/25 (20%); G=7/25 (28%) Dizziness: P=2/25 (8%); G=7/25 (28%) Memory & cognitive impairment: P=1/25 (4%); G=4/25 (16%) Ataxia: P=0/25 (0%); G=1/25 (4%) Weight gain: P=0/25 (0%); G=1/25 (4%) TLP: these outcomes are meta-analysable.	1. Trial reporting is hard to understand in terms of the statistical analysis. 2. Claimed significance for primary and secondary endpoints is not reasonable, as multiple tests were performed. The graphical presentation does not allow comparison of the original numerical data. 3. Although the study makes a good effort to present patient flow, it's claim that it performs true ITT analysis

Randomization/Concealment: *"a computer-generated randomization code list was utilized to randomly allocate patients in two study groups. For double-blinding purposes, concealed randomization and the according allocation were implemented by a research assistant. Neither the patients nor the main investigator was aware of the random group allocation."* (p. 152) Concealment: "identical looking capsules" (p. 152) Test of blinding: not reported; *"subjects in this study received a weekly follow-up phone call by a pharmacy research assistant in order to help them reach their minimum effective dose and monitor for possible side effects. Follow-up phone calls were directed to both study groups … in order to keep patient's blinding uncompromised."* (TLP: suggests blinding may have been compromised by phone calls)	hepatic disorders • Dental/periodontal disease, neuropathic facial pain, etc. • Recent split users • Users of opioids, acetaminophen /opioid combinations, muscle relaxants Allowable drugs: TCA's, SSRI's, benzodiazepines if previously udsed regularly Baseline characteristics Not described in conventional style or adequately.	up observation: P=5/25; G=1/25 • Analysis: (p. 154) See original article. No power calculation. Randomization: *"a computer-generated randomization code list was utilized to randomly allocate patients in two study groups..".* (p. 152) Concealment: *"identical looking capsules"* Blinding: not tested; doubtful (from description of pharmacist contacts with patients)	*represented no impact at all and the other end was representative of extreme or severe impact, reflecting disability."*) NB: no discussion of correction for multiple tests	Functional improvement: not reported (not an outcome) ≥50% reduction in pain score: not reported (not an outcome) Primary outcome (VAS 10 cm pain scale, baseline vs. 4, 8, 12 weeks): Reported as significant at 12 weeks (NOT ITT-LOCF, appears to be observed cases at 12 weeks) Report is only as Figure 2 (p. 156) which does ot provide baseline nor week 4, 8, 12 scores, only SD's (scores are shown graphically). As repeated tests of statistical significance are performed and SD's at week 12 (P: 2.67; G: 2.37) appear to overlap more than the separation of graphed VAS pain scores, the difference does not appear to be statistically significant as claimed *("week 12, P=0.026"*) This VAS pain score outcome is not suitable for meta-analysis. Secondary outcomes: See original article. Not interpretable and not comparable to other studies. PGIC: not reported (not an outcome)	is incorrect, as only 44/50 patients are accounted for at the end of study. 4. Blinding almost certainly broken for gabapentin patients. 5. Overall, this study is uninterpretable and not suitable for meta-analysis except for safety outcomes.

Study No. 23 – McCleane 2001 – GABAPENTIN FOR LOW BACK PAIN (PUBLISHED) – SUMMARY prepared by Dr. TL Perry – FINAL – August 6, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 23 McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain ? A randomized, double-blind, placebo controlled study. The Pain Clinic 2001; 13: 103-07. **Support:** Not reported. Appears to be independent, approved by Regional Research Ethical Committee and U.K. Medicines Control Committee (non-approved use of gabapentin). **Dates:** ? 2000 or earlier (reported 2001) **Design**: 8 week single centre Northern Ireland outpatient DBRCT parallel group study of gabapentin vs. placebo. 2 week run-in, then 3 weeks dose escalation, then 3 weeks stable dose.	**Low back pain (lumbar and associated leg pain)** Inclusion: • Adults attending a hospital-based pain clinic • Paravertebral lumbar tenderness at 1 vertebral level and pain worse on extension of back Exclusion: • "Features of neuropathic pain" (shooting pain, paresthesia, numbness, allodynia) • adequate pain control from NSAIDs or codeine-based analgesics • previously treated with gabapentin or "known to be sensitive to it" • expected to change medication during study period or unable to complete forms	**Study design:** 8 week single centre Northern Ireland outpatient DBRCT parallel group study of gabapentin vs. placebo. 2 week run-in, then 3 weeks dose escalation, then 3 weeks stable dose. **Dose titration:** Gabapentin titrated from baseline as 300 mg/d for week 1; then 300 mg b.i.d. for week 2; then 300 mg t.i.d. for week 3; then 300 mg q.i.d. (1200 mg/day) during weeks 4-6. **Patient flow:** not described clearly nor shown as figure; deduced from text. • Screened: not reported • Excluded: not reported • Randomized: 80; P=40; G=40 • Withdrawals: not reported • Completed: P=34/40, G=31/40 **Analysis:** (p. 104) No discussion of pre-specified statistical approach. "Average pain scores were calculated and differences between study groups compared using Student's t-test.	**Predefined outcomes:** **Primary (NRS, 11—point pain scale from 0-10):** Not discussed conventionally in Method section. From text and Table II (p. 104, 105) the primary outcome appears to be the difference between mean NRS pain score for each patient for daily observations made during week 8 (final week of treatment) vs. mean NRS pain score for 2-week baseline period – for back pain at rest, back pain on movement, and leg pain. **Secondary:** Not discussed conventionally in Method section. From text (p. 104, 105) the secondary outcomes appear to be:	**Doses attained:** not reported; apparently 1200 mg/d for gabapentin completers (P=34/40, G=31/40) **Mortality:** not reported **Serious Adverse Events:** not reported **Withdrawal Due to Adverse Events:** not reported **Total Withdrawals:** not reported (8 patients "failed to attend for end of study review" but they are not reported by treatment group) **Total patients with AE's**: Not reported **Total AE's (patients may have > 1):** P=13; G=19 **Specific AE**: Reporting is different from other studies and does not clarify whether the numbers cited in Table III (p. 106) refer to the number of patients or the number of events. See original paper for details. **TLP: The above are not adequately reported and therefore not suitable for meta-analysis**	**1. Reporting of methodology and statistical analysis is relatively incomplete.** **2. Potential "enrichment" bias by exclusion of patients who had been treated previously with gabapentin or were "known to be sensitive to it".** **3. Back pain at rest appears to be the outcome most comparable to overall NRS pain score used in other studies, but recording may have been at different times of day (intended to be consistent for each patient) – most**

Randomization: not described in detail **Concealment:** "identical appearance" (capsules) **Test of blinding:** not reported	**Allowable drugs**: usual medications; no changes **Baseline characteristics** **Age (mean):** P: 47.8 (11.7) G: 41.3 (13.1) **Duration of pain (months):** P: 74.5 (82) G: 63.1 (45.3) **11-point NRS pain score (back pain at rest) at baseline as mean (SD):** P: 6.51 (1.90) G: 6.82 (2.08)	Regression analysis was used to assess relationships between duration of pain, age, sex and changes in pain scores. P values < 0.05 were considered statistically significant." No correction for multiple tests. **Randomization:** *"… randomly assigned in equal numbers to two groups, A and B using a computer generated random number list." (p. 104)* **Concealment:** *"Both study drugs were of identical appearance, and neither investigator nor study subject were aware of the identify of the study capsule." (p. 104)* **Blinding:** Not tested. "… the blinding codes were broken at the end of the study period …" (p. 105)	a) the difference between mean 11-point NRS back mobility score for each patient for daily observations made during week 8 (final week of treatment) vs. mean NRS pain score for 2-week baseline period, where a larger number reflected better mobility; b) daily consumption of concomitant analgesic as number of tablets taken per day. Note: While the discussion is inadequate compared with many other studies, the method using daily NRS scale "at the same time of day" for pain assessment for the previous 24 hours is similar to most studies, except that the time of day may not be on first morning arising, which is used in most other studies.	**Functional improvement:** not reported **≥50% reduction in pain score:** not reported (not an outcome) **Primary outcome (NRS 11-point pain scale, endpoint vs. baseline):** from Table II and text, p. 105 a) Back pain at rest, mean (SD): Baseline mean: P=6.51 (1.90); G=6.82 (2.08) Endpoint: P=6.52 (2.06); G=6.31 (2.07) Difference: P=+0.01 (1.98); G=-0.51 (2.07); "not significant"* (SD for differences calculated as mean of SDbaseline + SDendpoint) b) Back pain with movement, mean (SD): Baseline mean: P=7.33 (1.64); G=7.48 (1.60) Endpoint: P=7.34 (1.52); G=7.01 (1.82) Difference: P=+0.01 (1.58); G=-0.47 (1.71); "p<0.05"* (SD for differences calculated as mean of SDbaseline + SDendpoint) a) Leg pain, mean (SD): Baseline mean: P=6.57 (2.32); G=6.37 (2.27) Endpoint: P=6.33 (2.39); G=5.92 (2.61) Difference: P=-0.24 (2.35); G=-0.45 (2.44); "p<0.05"* (SD for differences calculated as mean of SDbaseline + SDendpoint) *It is unclear due to imprecision in method section what comparisons the p-values apply to. **TLP: For meta-analysis of NRS pain scores we have used for back pain at rest (closest to overall NRS pain score reported in other studies) the raw numbers and SDs for the within group (placebo, gabapentin) differences from**	**other studies asked for recording of pain scores upon morning awakening from sleep. If pain scores were recorded at other times, any soporific effect of gabapentin may be less obvious.** **4. Claimed statistical significance favouring gabapentin for outcomes of back pain with movement or leg pain (? Difference from baseline for gabapentin groups) is impossible to assess without more detail of statistical method, and there is no correction for multiple comparisons.** **5. Reduction of**

				baseline to endpoint. This does not require us to interpret the statistical analysis further. **<u>Secondary outcomes:</u>** a) Average mobility scores (11-point NRS): *"there was no significant change in average mobility scores in either group during the treatment period" (*p. 105; not reported further) b) Consumption of concomitant analgesics: P: not reported (*"There was a small but statistically insignificant increase in analgesic consumption in the placebo group."* G: Baseline=4.72 (2.83) doses/day; Endpoint=4.27 (3.15) doses/day; difference=0.45 doses/day (2.89); "p=0.05" **PGIC:** not reported (not an outcome) **Additional outcome reported:** At end of study unblinding, patients were offered the chance to continue their study medication. Of 40 patients initially randomized to gabapentin, 13/40 chose to continue open label gabapentin, self-titrated to ≤ 3600 mg/day. After a further 2 months, 5/13 (5/40 initially randomized to gabapentin) wished to continue gabapentin. The report does not state whether any patients randomized to placebo later took gabapentin.	**analgesic consumption in gabapentin group, although claimed to be "statistically significant" is not considered clinically significant by author. (p. 106)** **6. Author questions overall clinical benefit of gabapentin.**

Study No. 24 – SMITH 2005 – GABAPENTIN FOR CHRONIC PHANTOM LIMB & RESIDUAL LIMB PAIN – DBR CROSSOVER TRIAL (published) – FINAL

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 24 **Smith DG, Ehde DM et al. Efficacy of gabapentin in treating chronic phantom limb and residual limb pain. J Rehab Research & Development 2005; 42: 645-654** **Support**: private donor support to Harborview Medical Center for Limb Loss Research and National Institute of Child Health and Human Development and National Institute of Neurological Disorders and Stroke grant PO1 HD/NS33988 **Dates**: 1999-2003 (p. 653) **Trial design:** Independent. DBR Crossover Trial, 18 weeks including 2 treatment periods of 6 weeks (plus week 7 dose-tapering after first phase) separated by 5 week washout, comparing gabapentin (G) with placebo to final	**Chronic post-amputation phantom limb pain (PLP) or residual limb pain (RLP)** Inclusion: • ≥ 18 years • ≥ 6 months post-amputation (lower or upper limb) • average pain rating ≥ 3 on 11-point NRS scale during last month Exclusion: • anticonvulsant medication • > 2 alcoholic drinks/day • history of kidney disease or *"low estimated creatinine clearance"* (cutoff not specified) **Allowable drugs:** not	**Study design:** DBR Crossover Trial, 18 weeks including 2 treatment periods of 6 weeks (plus week 7 dose tapering after first phase) separated by 5 week washout, comparing gabapentin (G) with placebo to final dose of G≤3600 mg/d. **Patient flow (p. 646-7):** • Wide recruitment (p. 646) • Screened: 78 • Ineligible (insufficient pain, abnormal kidney function): 25 • Declined to participate (most common reasons - prior negative experience with gabapentin or not wanting to take it): 29 • Total exclusions: 54 • Randomized: 24 P/G=13 G/P=11 • Completed crossover: 24/24 (interpreted from text, p. 648, *"All participants received 6 weeks of therapy with gabapentin and 6 weeks of*	**Predefined outcomes:** **Primary:** NRS (0-10 point) pain rating for last 24 hours for PLP and RLP. This was assessed 3 times for average pain and worst pain during prior 24 hours during week prior to Phase I, week 6 of Phase 1, week 5 of washout prior to Phase 2, and week 6 of Phase 2 by telephone interview conducted by research study nurse. Mean of 3 pain ratings (average, worst) for PLP, RLP were used as weekly pain scores for baseline/endpoing in each phase. (p. 647-9)	**Dose achieved:** not reported **Mortality:** Not reported **Serious Adverse Events:** Not reported **Withdrawal Due to Adverse Events:** Interpreted from text at p. 656-7 (see patient flow) P=0/24; G=0/24 **Total withdrawals:** P=0/24; G=0/24 Interpreted from text at p. 656-7 (see patient flow) **These appear suitable for meta-analysis** **Total patients with AE's:** Not reported **Most important AE's:** Not reported **Total AE's (patients may have > 1 as total exceeds total patients with AE):** Not reported **Disability:** Not reported (data on "Functional Independence Measure" and Craig Handicap Assessment and Reporting Technique" appear to have been collected at pre-treatment baselines and at week 6 for each phase (p. 648) but are not reported in this publication.	**1. The reporting of this study is somewhat unusual and it is not clear why subtracting the mean endpoint scores from mean baseline scores produces a different result than the "Pre-Post" differences shown in Table 3, p. 651.** **2. This study found a numerically small but statistically non-significant larger effect of gabapentin than placebo on phantom limb and residual limb mean pain score difference from baseline to endpoint.** **The mean PLP pain score difference appears to be the most suitable value for meta-**

dose of G≤3600 mg/d **Concealment:** identical placebo capsules **Randomization:** *"the study pharmacist conducted the randomization technique using computer-generated random numbers."* (p. 648) **Test of blinding:** patients asked to guess therapy at end of each treatment phase	specified **Baseline characteristics**: • Mean age: 52.1 (range 25-76) • Mostly transfemoral, transtibial (3/24 patients upper limb) • Mostly injury/infection related amputations • 21/24 patients had phantom limb pain; mean rating (SD) = 4.38 (2.57) • 20/24 patients had residual limb pain; mean rating (SD) = 3.96 (2.73)	*therapy with placebo (lactose) in random order"* and from percentage calculations of unblinding at p. 649) • Exposed to drug: P=24, G=24 • Completed assigned treatments: apparently P=24/24, G=24/24 • Withdrawn from treatments: apparently P=0/24; G=0/24; not adequately reported **Drug doses/titration** (p. 648): Titration from G=300 mg/d increased as tolerated or to achievement of pain intensity rating =0 by 300 mg/d every 2-3 days to maximum of 3600 mg/d, with matching approach for placebo capsules. **Statistical Analysis:** (p. 649) Unusually complicated description with multiple paired samples t-tests. See original report.	**Secondary (p. 647-8):** • "Meaningfulness of change in pain" on a 5-point scale from 1="pain decreased to a meaningful extent" … 3= "no change in pain" … 5="pain increased to a meaningful extent" • "Overall benefit" on a 6-point scale from 1="benefits far outweighed negative side effects" …4="although both benefits and side effects, they were about equal"… 6="negative side effects far outweighed benefits"… **(This is analogous to, but not comparable to PGIC used in other**	**> 50% reduction in NRS pain score at endpoint vs. baseline:** not reported (not an outcome) **Primary outcome NRS pain score:** NS = not statistically significant **a) Average phantom limb pain, mean (SD):** Baseline: P=4.09 (2.44); G=4.38 (2.57) Endpoint: P=3.60 (2.67); G=3.43 (2.45) Difference: P=-0.49 (2.20); G=-0.94 (1.98), NS (Authors state "effect size" of 0.31 without explaining further how this is calculated. Difference G-P appears to = -0.45 but is not significant.) **b) Average residual limb pain, mean (SD):** Baseline: P=3.21 (2.43); G=3.63 (2.75) Endpoint: P=2.79 (2.28); G=2.26 (1.94) Difference: P=-0.74 (1.94); G=-1.22 (2.56), NS (Authors stated "effect size" of 0.36 without explaining further how this is calculated. Difference cited in Table 3, p. 651 differs numerically from the simple difference of the Baseline-Endpoint for both placebo and gabapentin, but this is not explained in text.) **For meta-analysis of mean pain score difference from baseline, we considered using the differences cited above for mean PLP and mean RLP. We chose mean PLP as the most comparable outcome for meta-analysis with NRS pain scores from other studies because it represents a mean pain score during 1 week at baseline and endpoint and because baseline NRS PLP scores were > 4 for both placebo and gabapentin phases,**	**analysis with other NRS pain score differences. The numerical difference for G-P is almost identical to that for RLP, so the choice is immaterial to the results of meta-analysis.** **3. The larger percentage of patients reporting the secondary outcome, "my pain decreased to a meaningful extent" favoured gabapentin at P<0.05 but there is no adjustment for multiple comparisons. Along with numerical excess of side effect complaint in gabapentin group, this may be analogous to PGIC reports from other studies, but is not suitable for meta-analysis.** **4. The authors conclude that "The findings suggest that, on average, gabapentin**

			studies.) • "Pain interference" with 7 daily acgtivities • SF-MPQ • Depressive symptoms on "CES-D" 20-item scale • "Functional Independence Measure" 18-item measure of disability • "Satisfaction with Life Scale" • "Craig Handicap Assessment and Reporting Technique", 27-item measure of disability • Temporal pattern of PLP (constant, variable intensity, some pain-free periods)	**making this the closest comparator to other studies which require NRS mean pain ≥ 4 at baseline.** **c) Worst phantom limb pain, mean (SD):** Baseline: P=5.59 (2.98); G=5.91 (3.15) Endpoint: P=4.82 (3.22); G=4.65 (3.05) Difference: P=-0.58 (2.86); G=-1.15 (2.41), NS (Authors stated "effect size" of 0.35 without explaining further how this is calculated. Difference cited in Table 3, p. 651 differs numerically from the simple difference of the Baseline-Endpoint for both placebo and gabapentin, but this is not explained in text.) **d) Worst residual limb pain, mean (SD):** Baseline: P=4.71 (3.00); G=4.71 (3.26) Endpoint: P=4.21 (3.23); G=3.35 (2.93) Difference: P=-0.65 (3.05); G=-1.22 (3.32) (Authors stated "effect size" of 0.32 without explaining further how this is calculated. Difference cited in Table 3, p. 651 differs numerically from the simple difference of the Baseline-Endpoint for both placebo and gabapentin, but this is not explained in text.) **Secondary outcomes**: No significant differences were found for secondary endpoints except for the "meaningfulness of change in pain": P=5/24 (20.8%) vs. G=13/24 (54.2%) reported at end of treatment phase that "my pain decreased to a meaningful extent"; p<0.05 by chi-square but no correction for multiple comparisons. The analogous statement "Treatment benefits outweighed side effects" is a composite of 2/6 possible answers and difference favouring gabapentin is non	**does not provide strong pain relief for these chronic pain conditions."**

			NB: none of these scores except for SF-MPQ are comparable with commonly used scales from other gabapentin DBRCT. **Test of blinding:** 15/21 patients who answered question guessed gabapentin after gabapentin phase;. 12/20 patients who answered question after placebo phase guessed placebo. (p=0.44) Authors consider patients were not unblended.	significant. A similar 2/6 statements composite "Treatment side effects outweighed benefits" favoured placebo but was non-significant. See original report pp. 649-52. **PGIC:** not reported	

Study No. 25 – Nikolajsen 2006 – GABAPENTIN FOR POST-AMPUTATION PAIN (PUBLISHED) – SUMMARY prepared by Dr. TL Perry – FINAL August 6, 2008

Study/ Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Study No. 24 **Nikolajsen L, Finnerup NB et al. A Randomized Study of the Effects of Gabapentin on Postamputation Pain. Anesthesiology 2006 ; 105 : 1008-15.** **Support:** Pfizer-Pharmacia, Denmark; gabapentin plus salary for research nurse. Apparently independent design; protocol approved by Regional Ethics Committee, Danish National Board of Health, Danish Data Protection Agency, and monitored by Unit of Good Clinical Practice, University of Aarhus. **Dates:** enrolment period May 13, 2002 – May 24, 2005 **Design**: 30 day single hospital Danish	**Post-amputation pain after lower limb amputation for peripheral vascular disease** Inclusion: • > 18 undergoing amputation for PVD Exclusion: • ipsilateral re-amputation or foot/toes only • dementia, psychiatric disease, inability to answer detailed pain questionnaire • severe cardiac, pulmonary, or liver disease • creatinine clearance ≤ 30 mL/min • alcohol or drug abuse • known allergy to gabapentin • treatment with anticonvulsant or TCA **Allowable drugs**: initial epidural analgesia, oral	**Study design:** 30 day single hospital Danish inpatient/outpatient DBRCT parallel group study of gabapentin vs. placebo. Randomization after amputation. Titration as tolerated from 300 mg/d on first post-operative day to 1200 or 2400 mg/d depending on kidney function; treatment to day 30. **Dose titration:** Titration as tolerated from 300 mg on day 1; 900 mg/d on days 2-4; 1200 mg/d on days 5-6; 1500 mg/d on days 7-8; 1800 mg/d on days 9-10; 2100 mg/d on days 11-12; 2400 mg/d on days 13-30. Patients with creatinine clearance ≥ 30 mL/min but ≤ 60 mL/min received maximum 1200 mg/d. Patients who could not tolerate 1200/2400 mg/d could stay on lower tolerated dose, but patients who did not tolerate at least 900 mg/d were withdrawn from study. **Patient flow:** (p. 1011) • Screened: 55 • Excluded: 9 did not consent • Randomized: 46; P=23/46; G=23/46	**Predefined outcomes:** **NB:** Not ITT; partial ITT-LOCF but only for 41/46 patients who completed 1 week of treatment and tolerated ≥ 900 mg gabapentin were included in data analysis – however no patients withdrawn due dose constraint (p. 1010-11). P=3/23 and G=2/23 patients are excluded from ITT-LOCF analysis due to week 1 drop out. **Primary (NRS, 11—point pain scale from 0-10):** a) Incidence (rates) of phantom pain at end of 30 day treatment period (calculated as a mean of	**Doses attained:** median dose of placebo = 8 capsules (N=20), median dose of gabapentin = 7 capsules/2100 mg/d, range 900-2400 mg/d (N=21) **Mortality:** not reported **Serious Adverse Events:** not reported **Withdrawal Due to Adverse Events:** P=2/23, G=2/23 **Total Withdrawals:** P=5/23; G=7/23 **Total patients with AE's**: P=8/23; G=9/23 **Total AE's (patients may have > 1):** Not reported **Specific AE**: Reporting is different from other studies. See original paper for details. **TLP: WDAE, total withdrawals, and patients experiencing AE are suitable for meta-analysis.** **Functional improvement:** not reported	**1. This is an entirely negative study.** **2. Reporting of median pain scores does not allow meta-analysis with mean pain scores reported by most studies.** **3. Adverse events reporting is not compatible with meta-analysis.** **4. Follow-up assessment of patients is hard to follow, as N's vary for different assessments and times.** **5. Gabapentin not only had no demonstrable analgesic effect, but also did not prevent phantom or stump pain in this DBRCT.**

inpatient/outpatient DBRCT parallel group study of gabapentin vs. placebo. Randomization after amputation. Titration as tolerated from 300 mg/d to 2400 mg/d. **Randomization:** computer-generated randomization list in block sizes of 8 and 10 **Concealment:** identical-appearing capsules prepared by the hospital pharmacy in identical containers marked with consecutive patient numbers **Test of blinding:** not reported	opioids, acetaminophen (paracetamol) – NSAIDs not used routinely **Baseline characteristics** **Age - mean (SD):** P: 69.8 (8.5) G: 70.8 (11.9) **Preoperative pain intensity on 11-point NRS score – median (range):** P: 8 (1-10) G: 8 (2-10) **Daily preoperative opioid consumption as mg/d of "morphine equivalents" – median (range):** P: 50 mg/d (0-270) G: 55 mg/d (0-280) **Patients with diabetes:** P=7/20 G=2/21; (P=0.07)	• Withdrawals: P=5/23; G=7/23 • Completed: P=18/23; G=16/23 **Analysis:** (p. 1010) Pre-specified goal to reduce incidence (risk) of post-amputation phantom pain from expected 70% to 30% (40% absolute risk reduction) and to reduce intensity of stump and phantom pain by 2 points on 11-point NRS scale. Phantom pain considered present if > 0 on NRS scale. Power calculation estimated sample sizes of 18 patients/group to detect at beta=0.2, alpha = 0.05. **Randomization:** *computer-generated randomization list in block sizes of 8 and 10" (p. 1009)* **Concealment:** *"identical-appearing capsules … in identical containers marked with the name of the project and consecutive patient numbers." (p. 1009)* **Blinding:** Patient and examiner asked whether patient was taking placebo or gabapentin at 30 days (last day on drug).	the last 7 daily pain scores) and at 6 months (prevention); b) Intensity of stump and phantom pain, recorded every evening and summarized as the mean for previous 7 days at 7, 14, 21, and 30 days post-amputation. 5 major post-operative interviews performed at 7, 14, 30 days (treatment phase) and 3 and 6 months (follow-up phase relevant to prevention of pain) **Secondary:** • Frequency, duration and intensity of phantom pain attacks • Descriptions of pain • Consumption of opioids at day 30 and at 6 months	**≥50% reduction in pain score:** not reported (not an outcome) **Primary outcome (NRS 11-point pain scale, endpoint vs. baseline):** not reported as group means as in similar studies, **therefore not suitable for meta-analysis.** Pre-specified primary outcomes for this study: a) incidence of phantom pain (by group) among 41 completers: P=52.6%; G=55.0% at 30 days; p=0.88 (total N=39) P=50.0%; G=58.8% at 6 months; p=0.59 (total N=37) b) intensity of phantom and stump pain (by group median) among 41 completers at 30 days: Phantom pain: P=1.2 (range 0-6.6); G=1.5 (range 0-9.0); p=0.60 (total N=33) Stump pain: P=1.0 (range 0-5.4); G=0.85 (range 0-8.2); p=0.68 (total N=33) The authors note no difference between gabapentin and placebo. **Secondary outcomes:** See publication for details. The authors note no difference between gabapentin and placebo for any secondary pain outcome, nor for post-operative opioid consumption. G: Baseline=4.72 (2.83) doses/day; Endpoint=4.27 (3.15)	

				doses/day; difference=0.45 doses/day (2.89); "p=0.05" **PGIC:** not reported (not an outcome) **Test of blinding:** After 30 days of treatment, 10/39 patients correctly identified treatment. **TLP: because pain scores are reported as medians only, they are not suitable for meta-analysis.**	

UNPUBLISHED

STUDY DETAIL SUMMARY AND ANALYSIS: DESJARDINS
PROTOCOL NUMBER 1032-001, RESEARCH REPORT 720-04378
POST-OPERATIVE DENTAL PAIN

Summary of Dr. T. L. Perry:

Study conducted from 05/14/99 – 08/02/99; report dated 02/17/00

The study authors state that "Better analgesia was demonstrated for 2 of the GBP/NPN combinations, GBP250/NPN250 and GBP125/NPN250, compared with their NPN component, GBP250, and with placebo." However, in terms of the primary pain efficacy variable, SPID6, these combination treatments were only slightly numerically superior, not statistically significant. For example, the p-value for the comparison of GBP250/NPN250 with NPN 250 was 0.0946 and the p-value for the comparison between GBP125/NPN250 and NPN250 was 0.0646, neither significant (let alone amongst multiple dependant comparisons). Furthermore, they are clinically meaningless as NPN550 produced a better SPID6 score. This does not, as the authors would have it, suggest the ability of Gabapentin to potentiate the analgesic effect of Naproxen.

Conclusion:

Single-dose Gabapentin does not add to the analgesic efficacy of Naproxen for post-operative dental pain.

NB: GBP = Gabapentin, NPN = Naproxen.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Authors (see Discussion / Conclusion, pp. 58-59 of 437) NB: Recorded for interest only and are not necessarily the opinion of Dr. T.L. Perry
Protocol Number: 1032-001 Protocol Date: March 30th, 1999 (report dated February 17th, 2000). Research Report No: RR720-04378 Study Design: Single dose, double-blind, placebo-controlled, comparative efficacy study of Gabapentin in Combination with Naproxen Sodium in patients with post-operative dental pain. Study Duration: single dose. Investigator: Daniels S, Desjardins P Medication Dosage (dependant): 1. Placebo	Postoperative Dental Pain Inclusion Criteria: • If female, negative pregnancy test (at Screening and, if different, predose on Study Day 1) and use of a reliable form of contraception; • Age between 18 and 65 years (inclusive); • Negative alcohol breath test on day of surgery prior to surgery; • Understanding the nature of the study; • Written informed consent; • Reliable, cooperative, and in the opinion of the investigator, able to understand the	<u>Patient Flow:</u> Number of Patients Screened: 563 Number of Patients Randomized: 483 Number randomized to each treatment group: 1. Placebo: n=52 2. Gabapentin 250 mg: n = 50 3. Gabapentin 125 mg and Naproxen Sodium 125 mg: n = 50 4. Gabapentin 250 mg and Naproxen Sodium 125 mg: n = 52 5. Gabapentin 125 mg and Naproxen Sodium 250 mg: n=50 6. Gabapentin 250 mg and Naproxen Sodium 250 mg: n = 50 7. Naproxen Sodium 125 mg: n=50 8. Naproxen Sodium 250 mg: n=50 9. Naproxen Sodium 550 mg: n=79	<u>Predefined Outcomes:</u> Primary Efficacy Variable (more than 1): According to the protocol (p.68 of 437) the primary efficacy variables are as follows: • Time to onset of analgesia • Duration of analgesia • Pain Intensity Difference (PID) o PI measured on 4-point scale (0=none, 1 = mild, 2= moderate, 3 = severe) o At baseline only, PI measured on a 10 cm VAS o PID = difference between baseline pain intensity and the pain intensity at some other time point (negative indicates that PI higher at time point than at baseline) • Pain Relief (PR) o 5-point categorical scale: None = 0, a little = 1, moderate = 2, a lot = 3, complete = 4 • Pain Relief Intensity Difference (PRID) time-effect curves. o PRID = PID + PR at a given time point.	<u>1. Mortality</u> • No patient deaths occurred during this study (p. 56 of 437) <u>2. Serious Adverse Events</u> • No serious adverse events were reported during this study (p.57 of 437) <u>3. Withdrawals Due to Adverse Events</u> • No patients withdrew from this study due to an adverse event (p. 57 of 437) <u>4. Total Withdrawals (p. 217 of Pain report,)</u> • 2 patients did not complete this study because they left prior to the end of the 12-hour evaluation period. • 1 of these patients was in the Gabapentin 250mg group, the other was in the Naproxen Sodium 125 mg group. <u>5. Total Adverse Events:</u> Placebo: 23/52 (44.2%) GBP250: 25/50 (50.0%) GBP125/NPN125: 24/50 (48%) GBP250/NPN125: 23/52 (44%) GBP125/NPN250: 24/50 (48%) GBP250/NPN250: 17/50 (34%)	1. In the current study, better analgesia was demonstrated for 2 of the GBP/NPN combinations, GBP250/NPN250 and GBP125/NPN250, compared with their NPN component, GBP250, and with placebo. 2. The active comparator, NPN550, provided significantly better pain relief compared with placebo on the summed pain intensity difference over 6 hours (SPID6, p <0.001) and on the individual PI and PR evaluations at all time points (p <0.001). 3. The distribution of mean SPID6 scores across the 9 treatment arms appears to be consistent with and within the random variability inherent in the model. In addition, a dose response was demonstrated between

2. Gabapentin 250 mg (GBP250)
3. Gabapentin 125 mg and Naproxen Sodium 125 mg (GBP125/NPN125)
4. Gabapentin 250 mg and Naproxen Sodium 125 mg (GBP250/NPN125)
5. Gabapentin 125 mg and Naproxen Sodium 250 mg (GBP125/NPN250)
6. Gabapentin 250 mg and Naproxen Sodium 250 mg (GBP250/NPN250)
7. Naproxen Sodium 125 mg (NPN125)
8. Naproxen Sodium 250 mg (NPN250)
9. Naproxen Sodium 550 mg (NPN550)

Patients Randomized: 483

Study Center(s): Clinical Research Center of Scirex Corporation, Austin Texas.

Study Dates: 05/14/99 – 08/02/99

Study Approval: The

pain information required;
- Self-rated postoperative pain intensity on a 4-point categorical scale of moderate ors evere; and
- Self-rated postoperative pain intensity on a 100-mm VAS of ³45 mm.

Exclusion Criteria
- History or clinical evidence of renal disease;
- Surgery complication;
- Patient was a woman who was breastfeeding;
- History of serious adverse reaction to any analgesic agent or any medication to be used in the operative procedure or postoperative period;
- History of any bleeding disorder;
- Patient gabapentin

Study Design:

Gabapentin

Naproxen Sodium	0	125	250
0	X		X
125	X	X	X
250	X	X	X
550	X		

Figure 1: Gabapentin and Naproxen Sodium Dose combinations used in study (p. 15 of 437).

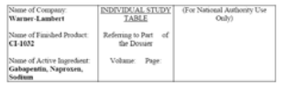

Name of Company: Warner-Lambert
Name of Finished Product: CI-1032
Name of Active Ingredient: Gabapentin, Naproxen, Sodium
INDIVIDUAL STUDY TABLE
Referring to Part of the Dossier
Volume: Page:
(For National Authority Use Only)

Table on pp. 6-11 of 437 of unpublished report.

Secondary Efficacy Variables (according to protocol):
- Patient global impression of the medication
  - 1=poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent

According to the report (p. 7 of 437,p. 20 of 437) as well as the analysis plan, p.333 of 437 (no date on analysis plan)

The primary efficacy measure was the summed pain-intensity difference over the first 6 hours post dose (SPID6).

Secondary measures
- Pain intensity difference (PID) from baseline
- Pain relief (PR),
- Summed pain relief and pain-intensity difference (PRID)
- Time-to-analgesia by 2 stopwatch procedure (T_ANALG),
- Time-to rescue medication (T_REMED), and
- Overall assessment of study medication (responder analysis).

NPN125: 20/50 (40%)
NPN250: 20/50 (40%)
NPN550: 30/79 (38%)

Note that not all of these values were reported and had to be inferred from Figure 12 (p. 51 of 437) and Table 17 (p.52 of 437). The report specifies total AE's in the groups placebo, GBP 250, all GBP/NPN combinations, NPN components, NPN 550.

6. Validated measures of improvement in global function including return to work, study, activities of daily living

- None reported in this study

7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint

- Not a predefined endpoint for this study.

8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial
- VAS/NRS NOT defined as primary outcome,
- Primary efficacy variable was SPID6

SPID-6 Results (appendix C.08, pp.208-211 of 437)

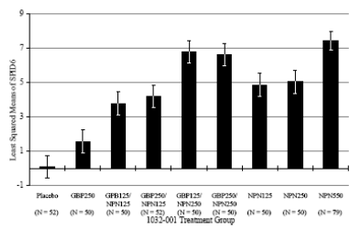
Placebo: n=52
Mean: 0.04
SD: 4.52
Gabapentin 250 mg: n = 50
Mean: 1.63
SD:6.05

250 and 550 mg NPN.

4. Of the baseline factors used to test the generalizability of the ANCOVA model, those that significantly influenced the SPID6 outcome were baseline pain intensity, race, age, and gender.

5. Results of this initial study strongly suggest that gabapentin may potentiate the analgesic efficacy of naproxen sodium. This potentiation is most apparent from 2 hours after dosing and persists through the 12-hour evaluation period. A BID dosing regime seems feasible in view of the persistence of the effect.

6. The results of this study also indicate that the interaction between gabapentin and nonsteroidal anti-inflammatory agents warrants further investigation. Potentiation was indicated at both the 125 and 250 mg doses of GBP, but no dose response was demonstrated. However, the use of NPN doses lower than 250 mg (ie, 125 mg) is not supported

duly constituted institutional review board of the Clinical Research Center. PUBLISHED: N/a Final study report (unpublished): Parke-Davis Research Report Number RR 720-04378 dated February 17th, 2000. Authors include Giordani AB, Buroker Kilgore M, Mundel T, Yan C.	use within the past 6 months; • Patient participated in Study 1032-001 earlier; or • Patient was taking or took an investigational agent or participated in another research • protocol within the previous 60 days (amended from 120 to 60 days). This is protocol Number 1032-001, why would a patient be excluded if they had participated in this study?			Gabapentin 125 mg and Naproxen Sodium 125 mg: n = 50 Mean: 3.76 SD: 5.27 Gabapentin 250 mg and Naproxen Sodium 125 mg: n = 52 Mean: 4.25 SD: 5.19 Gabapentin 125 mg and Naproxen Sodium 250 mg: n=50 Mean: 6.85 SD: 4.65 Gabapentin 250 mg and Naproxen Sodium 250 mg: n = 50 Mean: 6.60 SD: 5.25 Naproxen Sodium 125 mg: n=50 Mean: 4.82 SD: 4.88 Naproxen Sodium 250 mg: n=50 Mean: 5.10 SD: 4.76 Naproxen Sodium 550 mg: n=79 Mean: 7.42 SD: 5.48 *Note that the above means differ slightly from the least squares means found by ANCOVA which are reported in Appendix D.2 and figure 4.  Figure 4. SPID6 Results by Treatment Group (Least Squares Means) Figure 4 – p. 37 of 437	by this data. 7. In general, the single doses of study medications were well-tolerated. 8. Overall, CNS and digestive system adverse events were not statistically different from the placebo group for any treatment group. The absolute rates observed were also numerically no worse in the combination groups compared with the component groups in the combination. 9. In patients with pain resulting from dental surgery, this study demonstrated statistically significantly better analgesic effects (SPID6) of the GBP250/NPN250 and GBP125/NPN250 combinations compared with placebo and GBP250, and numerically superior effects compared with NPN250. In addition, efficacy was detected on PI, PIR, and PRID scales at times ranging between 3 and 6 hours postdose. The orally administered, single-dose combination therapy was

				SPID6 least squares means and pairwise comparisons for the treatment groups can be found in Appendix D.2 (pp.338-339 of 437). Note that in the Tables below (pulled from Appendix D.2) A = Naproxen 125 mg, B = Gabapentin 125 mg, and C = Naproxen 550 mg. Lsmeans of SPID6 Treatment Group / Lsmean / 95% CI Lower / 95% CI Upper Placebo 0.07438585 -1.2129 1.3617 2B 1.58035556 0.2676 2.8931 A+B 3.79275510 2.4800 5.1055 2A+B 6.80045457 5.4877 8.1132 A+2B 4.20669398 2.9194 5.4940 2A+2B 6.63275510 5.3200 7.9455 A 4.85275510 3.5400 6.1655 2A 5.05035556 3.7376 6.3631 C 7.46097786 6.4166 8.5054 *Note that the LS means listed below have been rounded to 4 decimal places. Placebo: LSMean: 0.0744 95% CI: (-1.2129, 1.3617) GBP250: LSMean: 1.5804 95% CI: (0.2676, 2.8931) GBP125/NPN125: LSMean: 3.7928 95% CI: (2.4800, 5.1055) GBP125/NPN250: LSMean: 6.8005 95% CI: (5.4877, 8.1132) GBP250/NPN125: LSMean: 4.2067 95%CI: (2.9194, 5.4940) GBP250/NPN250: LSMean: 6.6328 95% CI: (5.3200, 7.9455) NPN125: LSMean: 4.8528 95% CI: (3.5400, 6.1655)	well-tolerated with no remarkable adverse effects.

NPN250:
LSMean: 5.0504
95% CI: (3.7376, 6.3631)
NPN550:
LSMean: 7.4610
95% CI: (6.4166, 8.5054)

Analysis of SPID6

Source/Comparison	Estimate	Pvalue	95% CI Lower	95% CI Upper
2A - Placebo	4.97536971	0.0001	3.1373	6.8146
2A+2B - 2A	1.58239954	0.0946	-0.2742	3.4390
2A+2B - 2B	5.05239954	0.0001	3.1958	6.9090
2A+2B - C	-0.82822276	0.3325	-2.5057	0.8493
2A+2B - Placebo	6.55836925	0.0001	4.7198	8.3969
2A+B - 2A	1.75009901	0.0646	-0.1064	3.6066
2A+B - 2B	5.22009901	0.0001	3.3636	7.0766
2A+B - C	-0.66052329	0.4395	-2.3381	1.0171
2A+B - Placebo	6.72606872	0.0001	4.8874	8.5647
A+2B - 2B	2.62633843	0.0052	0.7878	4.4649
A+2B - A	-0.64606111	0.4902	-2.4847	1.1926
A+2B - C	-3.25428388	0.0001	-4.9120	-1.5966
A+2B - Placebo	4.13230813	0.0001	2.3118	5.9528
A+B - 2B	2.21239954	0.0196	0.3558	4.0690
A+B - A	-1.06000000	0.2625	-2.9165	0.7965
A+B - C	-2.66822276	0.0001	-5.3457	-1.9907
A+B - Placebo	2.71836925	0.0001	1.8798	5.5569
C - Placebo	7.38659201	0.0001	5.7230	9.0442
NPN125-NPN550	-2.60822276	0.0024	-4.2857	-0.9307
NPN125-Plac	4.77836925	0.0001	2.9398	6.6169
NPN250-NPN550	-2.41062230	0.0049	-4.0692	-0.7520
Root MSE	4.72394622	.	.	.
Treatment Main Effect	.	0.0001	.	.
Treatment*Baseline	.	0.3741	.	.

Tables 11 and 12 from the report also contain certain pairwise comparisons.

Table 11. P-Values and Min-Test[a] Results for SPID6 Endpoints: All GBP/NPN Combinations

	Combinations			
Comparators	GBP125/ NPN125	GBP250/ NPN125	GBP125/ NPN250	GBP250/ NPN250
PBO	0.0001[b]	0.0001[b]	0.0001[b]	0.0001[b]
GBP250	0.0196[b]	0.0052[b]	0.0001[b]	0.0001[b]
NPN125	0.2625	0.4902		
NPN250			0.0646	0.0946
Min-Test Result	negative	negative	negative	negative

[a] The min-test procedure indicates a statistically significant difference if the p-values of *all 3* simple comparisons are <0.05.
[b] Statistically significant difference

Table 11 (pp. 38 of 437)

Table 12. SPID6 Endpoints: P-Values for Simple Comparisons

	Combinations						
Comparators	GBP125/ NPN125	GBP250/ NPN125	GBP125/ NPN250	GBP250/ NPN250	Placebo	NPN125	NPN250
NPN125					0.0001[a,b]		
NPN250					0.0001[a,b]		
NPN550	0.0001[a]	0.0001[a]	0.4395	0.3325	0.0001[a]	0.0024[a,b]	0.0049[a,b]

[a]Statistically significant difference
[b]Ad hoc analysis

Table 12 – p.39 of 437

				• All 3 NPN treatment groups were significantly different from placebo
				  o (p = 0.0001 for all 3 NPN groups compared to placebo)
				• dose response was demonstrated for NPN:
				  o NPN125 and NPN250 were both significantly different from NPN550
				  o NPN125 to NPN550 p = 0.0024
				  o NPN250 to NPN550 p = 0.0049)
				
				GBP250/NPN250:
				• Significantly different from placebo (p = 0.0001)
				• Significantly different from GBP250 (p = 0.0001)
				• Not significantly different from NPN250 (p = 0.0946) but numerically superior
				
				GBP125/NPN250:
				• Significantly different from placebo (p = 0.0001)
				• Significantly different from GBP250 (p = 0.0001)
				• Not significantly different from NPN250 (p = 0.0646) but numerically superior
				
				GBP125/NPN125:
				• Significantly different from placebo (p = 0.0001)
				• Significantly different from GBP250 (p = 0.0196)
				
				GBP250/NPN125:
				• Significantly different from placebo (p = 0.0001)
				• Significantly different from GBP250 (p = 0.0052)
				• See Figure 4 (p.37 of 437), Table 11 (p.38 of 437) and Table 12 (p.39 of 437), for details)
				
				<u>9. % of patients achieving “much improved” or “moderately improved”</u>
				
				• Was not an outcome, global impression of change was assessed on a scale in which patients rated their medication	

				from 1=poor to 5 = excellent • Not a predefined outcome of this study how we have defined it but there was a responder analysis • Responders were defined as patients who, at 12 hours postdose or at the time of rescue medication, evaluated their study medication as “good,” “very good,” or “excellent” overall. The analysis used all available data for the ITT population. • The proportion of responders (patients who rated their study medication overall as “good,” “very good,” or “excellent”) in all 4 combination treatment groups was statistically significantly different from that of placebo and GBP250. • The proportion of responders in the GBP125/NPN250 and GBP250/NPN250 groups was not significantly different from that of NPN250 or NPN550. • No min-test comparisons of the responder analyses were significant for any GBP/NPN combination. Table16. P-Values for the CMH Analysis of Responders Combinations Comparators: GBP125/NPN125 | GBP250/NPN125 | GBP125/NPN250 | GBP250/NPN250 PBO: 0.002* | 0.001* | 0.001* | 0.001* GBP250: 0.022* | 0.007* | 0.001* | 0.001* NPN125: 0.550 | 0.841 | | NPN250: | | 0.401 | 0.401 NPN550: 0.001* | 0.001* | 0.362 | 0.362 * Statistically significant difference Table 16 – p-values for responder analysis (p. 49 of 437) <u>10. Histogram presentation of all PGIC 7-point results</u> • N/A	

UNPUBLISHED

STUDY DETAIL SUMMARY AND ANALYSIS: SUNSHINE & KATZ
PROTOCOL NUMBER 1032-002, RESEARCH REPORT 720-04479
ACUTE OSTEOARTHRITIS PAIN OF THE KNEE

Summary of Dr. T. L. Perry:

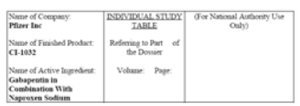
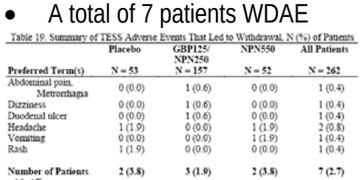
Study conducted from 12/20/99 – 6/19/00; unpublished report dated 10/31/00.

The authors state that "No conclusions regarding the performance of GBP125/NPN250 as an acute analgesic were possible due to the failure, in this multicenter implementation, of the OA flare pain model to separate active treatments from placebo." This can be seen by examining the 95% confidence intervals for the least squares means of the treatment groups for the primary efficacy variable, SPDI6, and noticing that they all overlap with the 95% confidence interval for placebo. There are also no significant p-values in the 2-way comparisons for the SPID6 least squares means. The authors assert that for patients with osteoarthritis of the knee, GBP125/NPN250 provided pain relief and performed on other outcome measures significantly better than placebo. However, GBP125/NPN250 was not statistically different from NPN550 on most Study Phase 2 measures.

Conclusion:

Single-dose Gabapentin at 125 mg was not efficacious for 6-hour acute pain relief in osteoarthritis. Twice daily Gabapentin at 250 mg/d was not efficacious for relief of osteoarthritis pain over 27 days, but numerically increased adverse events (37% of gabapentin patients vs. 25% for placebo and 29% for naproxen) and was associated with numerically increased incidence of edema, dizziness, somnolence, and asthenia (the typical adverse events known to be caused by gabapentin). This suggests that even low-dose Gabapentin causes neurological adverse events and edema.

NB: GBP = Gabapentin, NPN = Naproxen.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Authors (See Discussion and Conclusion pp. 69-70 of 580) NB: Recorded for interest only and are not necessarily the opinion of Dr. T.L. Perry
Protocol Number: 1032-002 Protocol Date: August 5th, 1999 (Research Report dated October 31st, 2000) Research Report No: RR720-04479 Sub-Studies: • Protocol 1032-003 (RR720-30044) o A long-term, open-label, multicenter, safety study of Gabapentin in Combination with Naproxen Sodium (CI-1032) in Patients with osteoarthritis of the knee. • Protocol 1032-004	Acute Osteoarthritis (OA) of the knee Inclusion Criteria: • OA of the knee, specifically: o Knee pain rated on a 5-point categorical scale as mild, moderate, or severe in intensity when walking on a flat surface. (Patients who rated their pain as extreme or none were excluded.); o Knee pain present for at least 15 of the preceding 30 days; o Grade 2, 3, or 4 OA by x-ray criteria as defined by the Kellgren and Lawrence Grading System of OA, 9	<u>Patient Flow:</u> Number of Patients Screened: 441 Number of Patients Randomized: 262 Number randomized to each treatment group: Placebo: n = 53 GBP125/NPN250 for entire study: n = 52 GBP 125 for dose 1, GBP125/NPN250 for phase 2: n = 51 NPN250 for dose 1 and GBP125/NPN250 for phase 2: n = 54 NPN550 for entire study: n = 52  Name of Company: Pfizer Inc INDIVIDUAL STUDY TABLE (For National Authority Use Only) Name of Finished Product: CI-1032 Referring to Part of the Dossier Name of Active Ingredient: Gabapentin in Combination With Naproxen Sodium Volume: Page: Table occurring on pp.7-13 of Research Report. <u>Study Populations/ Statistical Analysis</u>	<u>Predefined Outcomes:</u> According to the initial study protocol, dated August 5th, 1999 (p.82 of 580): The primary efficacy variable: • Summed pain intensity difference over the 6 hours of clinic evaluation on Day 1 (SPID-6) post dose. Secondary Efficacy Variables for Stage I (Day 1): • Pain intensity (PI) • Pain intensity difference (PID) • Pain relief (PR) time-effect curves over 6 hours • Total Pain Relief over the 6 hours of clinic evaluation (TOTPAR6) • PID and PR at 12 hours post dose • Percent of patients rescuing with acetaminophen • Time to Rescue	<u>1. Mortality</u> • No patients died during this study <u>2. Serious Adverse Events</u> • Two male patients in the GBP125/NPN250 group, aged 74 and 73 years, experienced serious adverse events during the study (Table 18, p.67 of 580). o Patient 007003 was hospitalized and found to have a duodenal ulcer with gastric erosion (duodenal ulcer) considered associated with treatment. o Patient 008009 was diagnosed with a stenosis of the carotid artery (peripheral vascular disorder) considered unrelated to treatment and underwent a carotid endarterectomy during the study. <u>3. Withdrawals Due to Adverse Events</u> • A total of 7 patients WDAE  Table 19. Summary of TESS Adverse Events That Led to Withdrawal, N (%) of Patients Preferred Term(s) / Placebo N = 53 / GBP125/NPN250 N = 157 / NPN550 N = 52 / All Patients N = 262 Abdominal pain, Metrorrhagia: 0 (0.0) / 1 (0.6) / 0 (0.0) / 1 (0.4) Dizziness: 0 (0.0) / 1 (0.6) / 0 (0.0) / 1 (0.4) Duodenal ulcer: 0 (0.0) / 1 (0.6) / 0 (0.0) / 1 (0.4) Headache: 1 (1.9) / 0 (0.0) / 1 (1.9) / 2 (0.8) Vomiting: 0 (0.0) / 0 (0.0) / 1 (1.9) / 1 (0.4) Rash: 1 (1.9) / 0 (0.0) / 0 (0.0) / 1 (0.4) Number of Patients with AEs: 2 (3.8) / 3 (1.9) / 2 (3.8) / 7 (2.7) TESS = Treatment emergent signs and symptoms. Table 19 (p. 68 of 580) a summary of treatment emergent adverse	1. The data from the second (4 week) phase of this study demonstrate that gabapentin in combination with naproxen sodium has potential for subacute or chronic treatment of OA. 2. The active comparator, NPN550, was reliably separated from placebo across most Study Phase 2 endpoints. 3. Statistical separation of GBP125/NPN250 from placebo was also observed during most of Study Phase 2, however significance levels in comparisons with placebo were generally higher for NPN550 than for GBP125/NPN250. 4. GBP125/NPN250 was not statistically different from NPN550 on most Study Phase 2 measures. 5. No separation of active treatments from placebo was demonstrated during

(RR720-04481)
- A 1-week, randomized, double-blind, Placebo- and Positive-controlled, parallel-group study of the protective effects of Gabapentin on Naproxen Sodium-induced upper gastrointestinal mucosal injury in volunteers.

Study Design: Randomized, Double-Blind, Placebo- and Positive- Controlled, Parallel-Group, Multicentre Study

Study Country: US

Study Duration: 4 weeks.

Investigators: Moskowitz R, Sunshine A, Schnitzer T, et al.

Medication Dosage (dependant):

documented with a report from an x-ray of the study joint taken either at Screening or within 1 year prior to Screening.
- Men or women of any race or ethnic group (women had to be postmenopausal, surgically sterilized, or using a method of contraception acceptable to the investigator);
- At least 45 years of age;
- Able (sufficient visual and auditory acuity with glasses or hearing aid) to complete the required assessment questionnaires, tests, and evaluations;
- In good health (other than the signs and symptoms associated with diagnosed OA) and capable of ambulating continuously without assistance (a cane was the only allowable ambulation aid) for at least 5 minutes;
- Concurrent diseases

- The analysis set was the intent-to-treat (ITT) population, defined as all patients randomized to treatment who received at least one dose of study medication.
- All Study Phase 2 efficacy analyses and comparisons included only the patients who were originally randomized to GBP125/NPN250, placebo, or NPN550.
- Only safety data were used for these patients for Study Phase 2.
- Study Phase 2 data imputation used the last observation carried forward method for missing efficacy data.

<u>List of Investigators:</u>

Table 1. List of Investigators

Center 1032-002	Investigator	Institution/City/State	Number of Persons Entered Study	Number of Persons Completed Study
-001	Roland Moskowitz, MD	University of Cleveland Cleveland, OH	14	14
-002	Abraham Sunshine, MD	Analgesic Development, Ltd New York, NY	14	14
-003	Thomas Schnitzer, MD, PhD	Northwestern University Chicago, IL	36	34
-004	James Tobom, MD	Midwest Arthritis Center Kalamazoo, MI	9	8
-005	Alan Kivitz, MD	Altoona Center for Clinical Research Duncansville, PA	52	47
-007	David Coval, MD and Bobon Benagmo, MD	NTouch Research Corporation Decatur, GA	8	5
-008	Maria Gerencroldt, MD	Advances in Medicine Rancho Mirage, CA	14	10
-009	Jacques Caldwell, MD	Halifax Clinical Research Institute Daytona Beach, FL	20	19
-010	Stanely Cohen, MD and Roy Fleischmann, MD	Metroplex Clinical Research Center Dallas, TX	28	24
-011	John Erves, MD	Center for Pharmaceutical Research Kansas City, MO	11	10
-012	Robert Levin, MD	Tampa Bay Medical Research Inc Clearwater, FL	16	16
-013	Walter Chase, MD, PA	Private Practice Austin, TX	19	17
-014	Charles Barbara, MD	Clinical Pharmacology Study Group Worcester, MA	21	16

Table 1: p.17 of 580.

Secondary Efficacy Variables for Stage 2 (Days 2-7):
- Average acetaminophen usage
- The change scores from baseline in the average daily pain scores and quality of sleep scores
- The change scores from baseline at day 7 in the Patient and Clinical Global Assessments of OA (osteoarthritis)
- Subscores on Western Ontario and McMaster University (WOMAC) subscales

Secondary Efficacy Variables for Stage 3 (Days 2-28):
- Same endpoints as in Stage 2
- SF-36

The analysis plan is dated December 22, 1999 and contains some amendments made at the investigator's meeting (see pp.175-208 of 580)

The primary efficacy variable (according to analysis plan):
- Summed pain intensity difference over the first 6 hours (SPID6)

events that led to withdrawal.

Placebo: 2/53 patients (3.8%)
- Headache
- Rash

GBP125/NPN250: 3/157 (1.9%)
- Abdominal Pain, Metroorrhagia
- Dizziness
- Duodenal Ulcer

NPN550: 2/52 (3.8%)
- Headache
- Vomiting

<u>4. Total Withdrawals:</u>

Study Phase I (Day 1):
GBP125/NPN250: 1/52 (1.9%)
- Adverse event

NPN250: 1/54 (1.9%)
- Adverse event

NPN550: 1/52 (1.9%)
- other

(3 total withdrawals in phase I)

Study Phase II (Days 2 – 28)

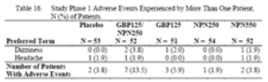
Placebo: 11 / 53 (20.75%)
- Lack of efficacy: 6/53 (11.3%)
- Adverse Event: 2/53 (3.8%)
- Other: 3/53 (5.7%)

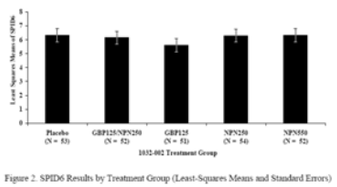
GBP125/NPN250: 13/157 (8.3%) (or 13 of the 155 who entered phase II, unsure which denominators to use, paper has used 157)
- Lack of efficacy: 5/157 (3.2%)

the single-dose evaluation, Study Phase 1. Thus the question of whether there is a therapeutic interaction between GBP and NPN that might permit the use of GBP125/NPN250 in the more acute flare setting was not answered.

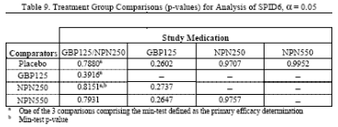
6. The generalizability analysis showed a strong treatment by center interaction. An examination of the characteristics of the centers that demonstrated assay sensitivity indicated that they had prior experience in acute analgesic trial methodology, enrolled large numbers of patients, or participated in a methodology training program.
7. For patients with OA of the knee, GBP125/NPN250 provided pain relief and performed on other outcome measures significantly better than placebo and not substantially differently from NPN550 during the 4-week portion of this study.
8. No conclusions regarding the performance of GBP125/NPN250 as an acute analgesic were possible due to the failure, in

In phase 1 (day 1), patients were randomized to receive a single dose of one of the following 1. Placebo 2. Gabapentin 125 mg and Naproxen Sodium 250 mg (GBP125/NPN250) 3. Gabapentin 125mg (GBP125) 4. Naproxen Sodium 250 mg (NPN250) 5. Naproxen Sodium 550 mg (NPN550) For the study phase (II) (days 2 – 28) patients were treated BID with study medication. Patients who received GBP125 or NPN250 in phase I were treated with GBP125/NPN250 in phase II. Number of Study Centers: 13 centers in the US Investigator's Meeting: October 29th, 30th, 1999 Study Dates: First patient randomized on	(e.g., coronary artery disease, diabetes, hypertension) under good control as determined by the investigator; • OA symptoms clearly less severe in joints other than the knee joint of interest; Exclusion Criteria: • Women who were pregnant or lactating; • Evidence of a clinically significant or unstable comorbid condition in addition to OA; • Anticipated need for surgery during the washout or double-blind treatment phase; • Current evidence, or history within 6 months prior to Screening, of myocardial infarction (MI), angioplasty, or coronary bypass; • Blood pressure >180 mm Hg systolic or >100 mm Hg diastolic, upon 3 repeated measures; • Clinically significant abnormal ECG (in the opinion of the investigator);		The secondary efficacy variables (according to the analysis plan) • PID at 0.5, 1,2,3,4,5,6,9 and 12 hrs o for scale see p.26 of 580 • PR at 0.5, 1,2,3,4,5,6,9 and 12 hrs o See p.27 of 580 for scale. • PRID at 0.5, 1,2,3,4,5,6,9 and 12 hrs • SPID6 and SPID12 • TOTPAR6 and TOTPAR12 • SPRID6 and SPRID12 • Time to rescue medication • Daily Quality Sleep score • Daily pain scores o P. 28 of 580 • Patient and Clinician Global Assessment of Osteoarthritis at baseline, Week 1 and Week 4 o P.28 of 580 (patient) o P.30 of 580 (clinical) • Patient Global Assessment of Study Medication at Week1, Week 2 and Week 4 o P. 28 of 580 • WOMAC Osteoarthritis index at Baseline, Week 1 and Week 4 o P. 29 of 580 • SF 36 Quality of Life at	• Adverse Event: 3/157 (1.9%) • Other: 5/157 (3.2%) NPN550: 5/52 (9.6%)(same problem with denominators since 51 entered phase 2 in this group) • Lack of efficacy: 2/52 (3.8%) • Adverse Event: 2/52 (3.8%) • Other: 1/52 (1.9%) For more details, see Table 8, p. 45 of 580 <u>5. Total Adverse Events:</u> Placebo: 14/53 (26.4%) • Mild: 8/53 (15.1%) • Moderate: 5/53 (9.4%) • Severe: 1/53 (1.9%) GBP125/NPN250: 65/157 (41.4%) • Mild: 29/157 (18.5%) • Moderate: 30/157 (19.1%) • Severe: 6/157 (3.8%) NPN550: 16/52 (30.8%) • Mild: 9/52 (17.3%) • Moderate: 7/52 (13.5%) • Severe: 0/52 (0.0%) Total During Study Phase I 15 patients experienced adverse events in phase 1, headache and dizziness were the only adverse events reported by more than 1 patient. Placebo: 2/53 (3.8%) GBP125/NPN250: 7/52 (13.5%) GBP125: 3/51 (5.9%) NPN250: 1/54 (1.9%) NPN550: 2/52 (3.8%)	this multicenter implementation, of the OA flare pain model to separate active treatments from placebo. 9. GBP125/NPN250 was well-tolerated over a 4-week course of treatment.

December 20th, 1999 last patient ended double-bind treatment on June 19th, 2000. The randomization code was broken on June 19th, 2000. Study Approval: PUBLISHED: N/a Final study report (unpublished): Parke-Davis Research Report Number RR 720-04479 dated October 31st, 2000. Authors include Buroker Kilgore M, Diaz F, Giordani AB, Mundel T, Sesti AM, Ventura AY	• Serum creatinine greater than 1.5 times the upper limit of normal (ULN); • Liver function tests greater than 2 times the ULN; or • Any laboratory value outside normal limits and considered clinically significant by the investigator.		Baseline and Week 4 o P. 30 of 580 The research report makes no reference to stages, only Phase 1 (Day 1) and Phase 2 (Days 2-28). I cannot find anything in the amendments that reconciles this. According to the research report: The primary efficacy variable (according to research report): • The summed pain intensity difference over the first 6 hours (SPID6) postdose Secondary Study Phase 1 measures of Efficacy (according to research report): • Included pain intensity difference (PID); • pain relief (PR); • pain relief intensity difference (PRID); • summed pain intensity difference over 12 hours (SPID12); • total pain relief over the first 6 and 12 hours (TOTPAR6 and TOTPAR12); • summed pain relief intensity difference over first 6 and 12 hours (SPRID6 and SPRID12); • percentage of patients	See table 16 on p. 65 of 580 for details.  Table 16. Study Phase 1 Adverse Events Experienced by More Than One Patient. N (%) of Patients Placebo / GBP125/NPN250 / GBP125 / NPN250 / NPN550 Preferred Term: N = 55 / N = 52 / N = 51 / N = 54 / N = 52 Dizziness: 0 (0.0) / 2 (3.8) / 1 (2.0) / 0 (0.0) / 1 (1.9) Headache: 1 (1.9) / 1 (1.9) / 0 (0.0) / 0 (0.0) / 1 (1.9) Number of Patients With Adverse Events: 2 (3.8) / 7 (13.5) / 3 (5.9) / 1 (1.9) / 2 (3.8) Total During Study Phase II: Placebo: 13/53 (24.5%) GBP125/NPN250: 58/157 (36.9%) NPN550: 15/52 (28.8%) See table 17 on p. 66 of 580 for details including most common side effects in phase 2. Table 17. Summary of Study Phase 2 Adverse Events Experienced by at Least 3% of Patients in Any Treatment Group, by Decreasing Frequency, N (%) of Patients Preferred Term / Placebo N=53 / GBP125/NPN250 N=157 / NPN550 N=52 Peripheral edema: 1 (1.9) / 9 (5.7) / 1 (1.9) Diarrhea: 1 (1.9) / 7 (4.5) / 2 (3.8) Infection: 1 (1.9) / 6 (3.8) / 1 (1.9) Constipation: 0 (0.0) / 5 (3.2) / 2 (3.8) Dizziness: 0 (0.0) / 5 (3.2) / 1 (1.9) Dyspepsia: 0 (0.0) / 5 (3.2) / 3 (5.8) Headache: 1 (1.9) / 5 (3.2) / 1 (1.9) Somnolence: 0 (0.0) / 5 (3.2) / 1 (1.9) Asthenia: 0 (0.0) / 4 (2.5) / 0 (0.0) Nausea: 0 (0.0) / 4 (2.5) / 1 (1.9) Pain: 0 (0.0) / 4 (2.5) / 0 (0.0) Accidental injury: 2 (3.8) / 3 (1.9) / 1 (1.9) Rash: 2 (3.8) / 0 (0.0) / 0 (0.0) Number of Patients With Adverse Events: 13 (24.5) / 58 (36.9) / 15 (28.8) <u>6. Validated measures of improvement in global function including return to work, study, activities of daily living</u> • None reported in this study. <u>7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint</u> • Not a predefined outcome.	

			rescuing; • time-to-rescue; • Proportion of responders from Patient Global • Assessment of Study Medication at Hour 12. Study Phase 2 efficacy measures included (according to research report): • Weekly average acetaminophen use; • Change from Baseline (Day 1) in mean (averaged by week) pain scores and quality sleep scores; • Change from Baseline (Day 1) in the Patient • and Clinician Global Assessments of OA at Days 7 and 28; • change from Baseline (Day 1) in Western Ontario and McMaster Universities Likert Version 3.1 (WOMACLK3.1) Osteoarthritis Index subscale scores at Days 7 and 28; • Change from Baseline (Day 1) in SF-36 Health Survey subscale scores at Day 28; • Proportion of responders from Patient Global Assessment of Study Medication at Days 7, 14, and 28.	<u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial</u> • SPID6 was the predefined primary efficacy variable SPID-6 Results (Appendix C.2.04, p.291 of 580) Placebo: n = 53 Mean: 6.37 SD: 4.26 GBP125/NPN250: n = 52 Mean: 6.06 SD: 3.98 GBP 125: n = 51 Mean: 5.58 SD: 4.44 NPN250:n = 54 Mean: 6.28 SD: 3.32 NPN550 for entire study: n = 52 Mean: 6.09 SD: 3.58 *Note that the means reported above differ slightly from the least squares means reported in Appendix D.2 (p. 450 of 580) and in Figure 2 (below)  Figure 2. SPID6 Results by Treatment Group (Least-Squares Means and Standard Errors) Figure 2 – p.47 of 580 Least Squares Means (Appendix D.2, p.450 of 580):	

				*Note that here, lsmeans have been rounded to 4 decimal places Placebo: n = 53 LSMean: 6.3101 95% CI: (5.3899, 7.2304) GBP125/NPN250: n = 52 LSMean: 6.1376 95% CI: (5.2208, 7.0543) GBP 125: n = 51 LSMean: 5.5830 95% CI: (4.6476, 6.5184) NPN250:n = 54 LSMean: 6.2868 95% CI: (5.3821, 7.1915) NPN550 for entire study: n = 52 LSMean: 6.3063 95% CI: (5.3896, 7.2229) P-Values and Effect Sizes (Appendix D.2, p.451 of 580) *Note that both the effect sizes and the p-values have been rounded to 2 decimal places. GBP125 – NPN250: Estimate: -0.70 P-Value: 0.27 GBP 125 – NPN550: Estimate: -0.72 P-Value: 0.26 GBP 125 – Placebo: Estimate: -0.73 P-Value: 0.26 GBP 125/NPN250 - GBP125: Estimate: 0.55 P-Value: 0.39 GBP 125/NPN250 – NPN250: Estimate: -0.15 P-Value: 0.82 GBP 125/NPN250 – NPN550:	

				Estimate: -0.17 P-Value: 0.79 GBP 125/NPN250 – Placebo: Estimate: -0.17 P-Value: 0.78 NPN250 – NPN550: Estimate: -0.02 P-Value: 0.98 NPN250 – Placebo: Estimate: -0.02 P-Value: 0.97 NPN550 – Placebo: Estimate: -0.00 P-Value: 0.9952 • No significant difference between GBP125/NPN250 and placebo, GBP125, or NPN250 was observed on the SPID-6 See table 9 (p.48 of 580) for details: Table 9. Treatment Group Comparisons (p-values) for Analysis of SPID6, $\alpha = 0.05$  [a] One of the 3 comparisons comprising the min-test defined in the primary efficacy determination [b] Min-test p-value • Was a significant centre effect on SPID <u>9. % of patients achieving "much improved" or "moderately improved"</u> • The study admits that the Likert scales were often mislabelled (see sections 4.5.1.5 and 4.5.1.8) o At Screening, Days 1, 7, and 28, or at time of Early Termination, patients were asked: "Considering all the ways your arthritis affects you, how has your arthritis been during the past 24 hours?" o The patient's response on a numeric Likert scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, or 4 =	

	Study Medication			
Comparator:	GBP125/NPN250	GBP125	NPN250	NPN550
Placebo	0.7880[a]	0.2602	0.9707	0.9952
GBP125	0.3916[a]	--	--	--
NPN250	0.8151[a,b]	0.2737	--	--
NPN550	0.7931	0.2647	0.9757	--

				Extremely Severe) was recorded o For most patients at some visits the Likert scale was mislabelled (0 = Very Good, 1 = Good, 2 = Fair, 3 = Poor, or 4 = Very Poor). o The descriptors had the same inherent order on both versions of the scale; however, no attempt was made to test whether both sets of descriptors elicited the same numerical responses from patients. • Due to frequently mislabelled liker scales the validity of these assessment data is uncertain • Again the PGIC were significantly different for GBP125/NPN250 and NPN550 compared with placebo by week 1 and differences continued to week 4, o no difference between GBP125/NPN250 and NPN550 • See appendix C.2.10 for details. See table 13 (60/58) for details, however, suggest not using data due to aforementioned problems. Table 13. Change in Patient and Clinician Global Assessment of OA[a]: Treatment Group Differences[b] and 95% Confidence Intervals GBP125/NPN250 vs Placebo; NPN550 vs Placebo; GBP125/NPN250 vs NPN550 Week 1 Patient 0.47 (0.11 to 0.83)* 0.43 (0.07 to 0.79)* 0.04 (-0.32 to 0.40) Clinician 0.33 (0.01 to 0.64)* 0.42 (0.10 to 0.73)** -0.09 (-0.41 to 0.22) Week 4 Patient 0.46 (0.08 to 0.85)* 0.64 (0.26 to 1.03)** -0.18 (-0.57 to 0.21) Clinician 0.50 (0.15 to 0.85)** 0.63 (0.28 to 0.98)*** -0.12 (-0.48 to 0.23) Positive change indicates improvement a For most patients at some visits, the numeric Likert scale descriptors were mislabeled. Because statistical analyses of these data only considered numerical responses, the validity is uncertain. b Lsmeans * p <0.05 ** p <0.01 *** p ≤0.001 • Responder analysis was patient global assessment of study medication o Responders were those who rated their medication as good, very good, or excellent o According to p.51 of 580, no difference in the proportion of responders among treatment groups were observed. o See appendix C.2.12, and C.2.13 for details. <u>10. Histogram presentation of all PGIC 7-point results</u> • N/a • Data not on 7-point scale and also not usable due to mislabelled scales, see above for details.	

UNPUBLISHED

STUDY DETAIL SUMMARY AND ANALYSIS: DESJARDINS
PROTOCOL NUMBER 1035-001, RESEARCH REPORT 720-04455
POST-OPERATIVE DENTAL PAIN

Summary of Dr. T. L. Perry:

Study conducted from 12/28/99 – 02/23/000; report dated 06/28/00

According to the authors, the GPB250/HC10 group provided significantly better pain relief than the placebo and GPB250 groups on most efficacy measures. This is not surprising since the effect is due to opioid analgesia.

The authors also point out that GBP250/HC10 combination provided analgesic relief more quickly than either of its components, however, the median time-to-analgesia of the GBP250/HC10 group (82 minutes) was statistically significantly longer than the APAP1000/HC10 group (32 minutes).

However, for the primary pain efficacy variable, SPID6, the GPB250/HC10 treatment was not significantly better than HC10 (p-value = 0.0771) and was significantly worse than the APAP1000/HC10 combination treatment (p-value = 0.0016). The estimated difference between GBP250/HC10 and APAP1000/HC10 was 2.8 (rounded), favouring APAP1000/HC10, much larger than the numerical difference of 0.6 between GBP250 and placebo (favours Gabapentin, P = 0.49).

Conclusion:

Single-dose Gabapentin did not add to the analgesic efficacy of hydrocodone in post-operative dental pain, and was inferior to acetaminophen.

NB: GBP = Gabapentin, HC = Hydrocodone.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Study Authors (see Discussion and Conclusion on pp. 48-50 of 371) NB: Recorded for interest only and are not necessarily the opinion of Dr. T. L. Perry
Protocol Number: 1035-001 Original Protocol Date: November 15th, 1999 Research Report No: RR720-04455 Date of RR720-04455: June 28th, 2000 Study Design: A single-dose, double-blind, placebo-controlled, comparative efficacy study. Study Country: US Study Duration: Single Dose	Postoperative Dental Pain <u>RR720-04455</u> Note that the inclusion / exclusion criteria for RR720-04483 were the same. Inclusion Criteria: • Age between 18 and 40 years (inclusive); • Scheduled for an outpatient oral surgical procedure to remove 1 to 2 ipsilateral third molars, at least 1 of which was mandibular and fully or partially impacted in bone; • Good health as determined by medical history and physical examination; • Negative alcohol breath test on day of surgery prior to surgery; • Written informed consent;	Table 6: p.32 of 371  <u>Patient Flow:</u> Number of Patients Screened: 375 Number of Patients Randomized: 325 Number randomized to each treatment group: Placebo: n=51 GBP250/HC10: n=75 GBP250: n=77 HC10: n=76 APAP1000/HC10: n= 46	According to the protocol (p.58 of 371), the outcomes were as follows: <u>Predefined Primary Outcome:</u> • The Summed Pain Intensity Difference over the first 6 hours. <u>Secondary Outcomes</u> • SPID 8 • Totpar 6, Totpar 8 (total pain relief at 6 and 8 hours) • SPRID 6, SPRID 8 (Sum of pain relief intensity difference over the first 6 and 8 hours) • PID (Pain intensity difference at 20, 40, and 60 minutes and every hour up to eight hours) • PR (Pain relief at 20, 40, and 60 minutes and every hour up to eight hours) • PRID (Pain relief intensity difference) at 20, 40, and 60 minutes and every hour up to eight hours) • Time to onset	<u>1. Mortality</u> • No patients died during this study (p.48 of 371) <u>2. Serious Adverse Events</u> • No patients experienced serious adverse events during this study (p.48 of 371). <u>3. Withdrawals Due to Adverse Events</u> • No patients withdrew due to an adverse event during this study (p.48 of 371). <u>4. Total Withdrawals:</u> • All patients completed this study (p.8 of 371). <u>5. Total Adverse Events:</u> • A total of 104 / 325 (32%) patients experienced an adverse event during this study • See table 15 on page 45 of 371 for details.	1. The GPB250/HC10 group provided significantly better pain relief than the placebo and GPB250 groups on most efficacy measures. 2. The GBP250/HC10 significantly outperformed the HC10 group the 3- and 4-hour PID and 4-hour PRID, giving positive min-test results for the combination at these time points. 3. The PR, PID, and PRID curves suggest that gabapentin potentiates the analgesic effects of HC10. • The GBP250/HC10 and HC10 curves are comparable for the first 2 hours. • After this time, HC10

Investigators: Desjardins P Medication Dosage (dependant): In phase 1 (day 1), patients were randomized to receive a single dose of one of the following 1. Placebo 2. Gabapentin 250 mg, hydrocodone 10 mg (GBP250/HC10) 3. Gabapentin 250 mg 4. Hydrocodone 10 mg (HC10) 5. Acetaminophen 1000 mg, hydrocodone 10 mg (APAP1000/HC10) Patients Randomized: Randomization Procedure: Number of Study Study Dates:	• Reliable, cooperative, and able to understand the information required in the pain questionnaire; • Self-rated postoperative pain intensity on a 4-point categorical scale as moderate or severe; and • Self-rated postoperative pain intensity on a 100 mm VAS of ≥ 45 mm. Exclusion Criteria: • History or clinical evidence of renal disease; • Occurrence of oral surgery complication; • History of serious adverse reaction to any analgesic agent or any medication to be used in the operative procedure or postoperative period; • History of any bleeding disorder; • Patient gabapentin use within the past 6 months; • Patient use of any analgesic, centrally acting, or anti-inflammatory medication within 24 hours of surgery; • Prior participation in		• Time to rescue medication • Patient global assessment of study medication was also a secondary efficacy parameter. This is mirrored by the research report (p. 7 of 371) Name of Company: Warner-Lambert | INDIVIDUAL STUDY TABLE | (For National Authority Use Only) Name of Finished Product: CI-1035 | Referring to Part of the Dossier Name of Active Ingredient: Gabapentin, Hydrocodone | Volume: Page: Table included on pages 6-9 of 371 of RR720-04455	Placebo: 13/51 (25.5%) • Mild: 1/51 (2.0%) • Moderate: 8/51 (15.7%) • Severe: 4/51 (8%) GBP250/HC10: 33/75 (44.0%) • Mild: 7/75 (9.3%) • Moderate: 14/75 (18.7%) • Severe: 12/75 (16.0%) GBP250: 14/77 (18.2%) • Mild: 6/77 (7.8%) • Moderate: 5/77 (6.5%) • Severe: 3/77 (3.9%) HC10: 30/76 (39.5%) • Mild: 10/76 (13.2%) • Moderate: 10/76 (13.2%) • Severe: 10/76 (13.2%) APAP1000/HC10: 14/46 (30.4%) • Mild: 5/46 (10.9%) • Moderate: 4/46 (8.7%) • Severe: 5/46 (10.9%) The most common side effects included: • Dizziness • Headache • Nausea • Vomiting • Somnolence See Table 16 on page 46 of 371 for all adverse events reported by >4% of patients in any treatment group.	begins losing potency, but GBP250/HC10 retains its potency through 8 hours. In this regard, the pain relief provided by GBP250/HC10 seems to mirror HC10 during the early time course and then GBP250 at later time points, providing more comprehensive pain relief than either component alone. 4. The GBP250/HC10 combination provided analgesic relief more quickly than either of its components. Although the median time-to-analgesia of the GBP250/HC10 group (82 minutes) was statistically significantly longer than the APAP1000/HC10 group (32 minutes), the median time-to-remedication was not significantly different between the groups. The latter finding suggests that a TID dosing schedule may be appropriate for

According to RR720-04455 • 12/28/99 – 02/23/000 • Note that RR720-04483 took place between 02/25/00 and 03/15/00 Study Approval: PUBLISHED: N/a Final study report (unpublished): RR720-04455 Parke-Davis Pharmaceutical Research, Divisions of Warner-Lambert Company, Ann Arbor Michigan. Number RR720-04455. Dated June 28th, 2000. PD Authors include Diaz F, Dougherty KM, Henry GC, Mundel T. Investigator listed as Desjardins P.	Study 1035-001; • Patient was taking or took an investigational agent or participated in another research protocol within the past 60 days.			Table 16. All Adverse Events Reported by >4% of Patients in Any Treatment Group [Number (%) of Patients] Adverse Event/ Preferred Term: Placebo N = 51; GBP250/HC10 N = 75; GBP250 N = 77; HC10 N = 76; APAP1000/HC10 N = 46 Dizziness 4 (7.8) 21 (28.0) 7 (9.1) 13 (17.1) 6 (13.0) Headache 8 (15.7) 9 (12.0) 4 (5.2) 5 (6.6) 1 (2.2) Nausea 5 (9.8) 7 (9.3) 3 (3.9) 13 (17.1) 6 (13.0) Vomiting 1 (2.0) 6 (8.0) 1 (1.3) 5 (6.6) 3 (6.5) Somnolence 0 (0.0) 5 (6.7) 1 (1.3) 4 (5.3) 2 (4.3) <u>6. Validated measures of improvement in global function including return to work, study, activities of daily living</u> • None reported in this study. <u>7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint</u> • Not a predefined primary endpoint of this study. <u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial</u> • Not a predefined outcome of this study • The primary endpoint here was SDID 6. Summary of SPID6 (Appendix C.2.01, p.211 of 371) Placebo: n:51 Mean: 1.30 SD: 4.49 GBP250/HC10: n=75	GBP250/HC10. 5. The results of this study suggest that while GBP250/HC10 is effective in relieving pain, it is not a Vicodin analog. The SPID6 results and the onset of action profile for the GBP250/HC10 treatment group are reminiscent of the results seen with Tramadol 100 mg in a dental pain model. Thus, the combination may prove to be more analogous to Tramadol 100 mg. 6. Single-dose treatment with GBP250/HC10 was generally well-tolerated. There were no withdrawals due to adverse events or serious adverse events. 7. The most frequent adverse events associated with GBP250/HC10 treatment were dizziness, headache, nausea, vomiting, and somnolence. • The incidence of dizziness in this

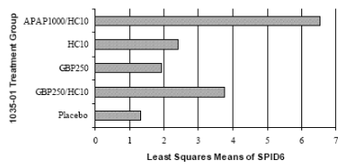
				Mean: 3.76 SD: 5.07 GBP250: n=77 Mean: 1.92 SD: 5.05 HC10: n=76 Mean: 2.44 SD: 5.00 APAP1000/HC10: n= 46 Mean: 6.57 SD: 4.93 See Figure 4, (p.33 of 371) for least squares means of SPID 6 for each treatment group.  Figure 4. SPID6 Results by Treatment Group (Least Squares Means) Table 7. p-values and Min-Test[a] Results for SPID6 Endpoints: GBP250/HC10 Combination **Combination** **Comparators** GBP250/HC10 Placebo 0.0044* GBP250 0.0155* HC10 0.0771 **Min-Test Result** Negative * Statistically significant difference, p <0.05. [a] The min-test procedure indicates a statistically significant difference if the p-values of *all 3* simple comparisons are <0.05.	group was additive of that seen in the GBP250 and HC10 groups. • Dizziness was the only adverse event seen at a significantly higher rate in the GBP250/HC10 group versus the placebo group. 8. In patients with pain resulting from dental surgery, this study demonstrated statistically significantly better analgesic effects (SPID6) of the GBP250/HC10 group compared with the placebo and GBP250 groups, and numerically better than the HC10 group. • In addition, efficacy was detected by positive min-test results on the PID at 3 and 4 hours postdose and PRID 4 hours postdose. • The GBP250/HC10 combination was well-tolerated with no

				Table 7: p-values and Min-Test results for SPID-6 Endpoints: GBP250/HC10 Combination (p.34 of 371) Table 8. p-values for Planned SPID6 Comparisons Treatment Comparisons — p-values APAP1000/HC10 vs GBP250/HC10 — 0.0016* APAP1000/HC10 vs GBP250 — 0.0001* APAP1000/HC10 vs HC10 — 0.0001* GBP250 vs Placebo — 0.4876 HC10 vs Placebo — 0.2014 * Statistically significant difference, p <0.05. Table 8: P-values for planned SPID 6 Comparisons (p.34 of 371). Appendix D.2 (see pages 297, 298 of 371) contains the lsmeans, and 95% CI's for SPID6 as well as the effect sizes, p-values and 95% confidence intervals for all the SPID6 comparisons.(note that estimates and the LS means have been rounded here to 4 decimal places) Treatment Group — Lsmean — 95% CI Lower — 95% CI Upper Placebo — 1.33622132 — 0.0508 — 2.6216 GBP250/HC10 — 3.76413333 — 2.7042 — 4.8240 GBP250 — 1.92165293 — 0.8756 — 2.9677 HC10 — 2.41736827 — 1.3644 — 3.4703 APAP1000/HC10 — 6.55316192 — 5.1998 — 7.9066 From page 297 of Appendix D.2 Placebo: LSMean: 1.3362 95% CI: (0.0508, 2.6216) GBP250/HC10: LSMean: 3.7641 95% CI: (2.7042, 4.8240) GBP250:	remarkable side effects.

				LSMean: 1.9217 95% CI: (0.8756, 2.9677) HC10: LSMean: 2.4174 95% CI: (1.3644, 3.4703) APAP1000/HC10: LSMean: 6.5532 95% CI: (5.1998, 7.9066) Analysis of SPID6 Source/Comparison | Estimate | Pvalue | 95% CI Lower | 95% CI Upper APAP1000/HC10-Placeb | 5.21694060 | 0.0001 | 3.3504 | 7.0835 GBP250-APAP1000/HC10 | -4.63150899 | 0.0001 | -6.3420 | -2.9210 GBP250-HC10 | -0.49571534 | 0.5116 | -1.9799 | 0.9885 GBP250-Placebo | 0.59543161 | 0.4876 | -1.0718 | 2.2427 GBP250/HC10-APAP/HC1 | -2.78902859 | 0.0016 | -4.5081 | -1.0700 GBP250/HC10-GBP250 | 1.94249040 | 0.0155 | 0.3533 | 3.3317 GBP250/HC10-HC10 | 1.34676506 | 0.0771 | -0.1472 | 2.8409 GBP250/HC10-Placebo | 2.42791201 | 0.0044 | 0.7619 | 4.0939 HC10-APAP1000/HC10 | -4.13579365 | 0.0001 | -5.8505 | -2.4211 HC10-Placebo | 1.08114695 | 0.2014 | -0.5805 | 2.7428 Root MSE | 4.66552832 | . | . | . Treatment Main Effect | . | 0.0001 | . | . Treatment*Baseline | . | 0.9984 | . | . P. 298 of Appendix D.2 APAP1000/HC10 – Placebo: Estimate: 5.2169 P-Value: 0.0001 GBP250 – APAP1000/HC10: Estimate: -4.6315 P-Value: 0.0001 GBP250 – HC10: Estimate: -0.4957 P-Value: 0.5116 GBP250 – Placebo: Estimate: 0.5854 P-Value: 0.4876 GBP250/HC10 – APAP1000/HC10: Estimate: -2.7890 P-Value: 0.0016 GBP250/HC10 – GBP250: Estimate: 1.8425	

				P-Value: 0.0155 GBP250/HC10 – HC10: Estimate: 1.3468 P-Value: 0.0771 GBP250/HC10 – Placebo: Estimate: 2.4279 P-Value: 0.0044 HC10 - APAP1000/HC10: Estimate: -4.1358 P-Value: 0.0001 HC10 – Placebo: Estimate: 1.0811 P-Value: 0.2014 <u>9. % of patients achieving "much improved" or "moderately improved"</u> • Not a predefined outcome. • Pain relief (PR) was assessed at time 0, at 20 and 40 minutes, and at hours 1 – 8 on a 5-point categorical scale: o 0 = None o 1 = A little o 2 = Moderate o 3 = A lot o 4 = Complete • The GBP250/HC10 curve was significantly better than the placebo group for hours 1-6 and better than the GBP250 group for hours 0.66 (40 minutes) through 3. • The GBP250/HC10 group was not significantly better than HC10 at any point. • At the 5- through 8- hour time points, PR scores	

				for the GBP250/HC10 and APAP1000/HC10 groups showed little or no separation from each other. • Mean PR scores over time can be seen in figure 7, p.39 of 371. • See appendix C.2.07, p.217 of 371 for PR measurements • See appendix D.5 (p.310 of 371) for PR comparisons at each time point. • Patients also performed an overall assessment of study medication • Patients also performed an overall assessment of study medication at the end of the 8-hour-in-clinic assessment period: o 1 = poor o 2 = fair o 3 = good o 4 = very good o 5 = excellent • Responders were defined as those patients who evaluated their study medication as “excellent,” “very good,” or “good” on the Patient Global Assessment of Study Medication at 8 hours postdose, or at time of rescue medication. • Significant differences in responder rates were detected among treatment groups. • The GBP250/HC10 group: o Had a significantly better responder rate (45.3%) than the placebo group (25.5%) (p = 0.026) o Was numerically better than the GBP250 group (31.2%) (p = 0.095),	

				○ Was no different than the HC10 group (36.8%) (p = 0.323). • APAP1000/HC10 group had the highest responder rate (76.1%) and was statistically significantly better than all other treatment groups. • See appendix C.2.04 for a complete summary of the Global Assessment of Study Medication (p.214 of 371) • See appendix D.14 (p.369 of 371) for analysis. <u>10. Histogram presentation of all PGIC 7-point results</u> • N/A – not a predefined outcome.	

UNPUBLISHED

STUDY DETAIL SUMMARY AND ANALYSIS: DESJARDINS
PROTOCOL NUMBER 1035-001, ADDENDUM B, RESEARCH REPORT 720-04483
POST-OPERATIVE DENTAL PAIN

Summary of Dr. T.L. Perry:

Initial study conducted from 12/28/99 – 02/23/000; Addendum B conducted from 02/25/2000 – 3/15/2000; report dated 10/31/00

This "Addendum B" study appears to have been an attempt to salvage statistical significance by adding more subjects, or by increasing the dose of Gabapentin. The results are unchanged.

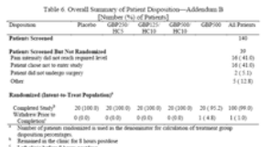
According to the authors, the GBP/HC combination groups tended to have greater pain relief than placebo! (hydrocodone effect)

No apparent analgesic benefit was obtained by increasing GBP to 500 mg in the combination, and the frequency of adverse effects increased with higher doses of Gabapentin (GBP500 43% vs. placebo 10%, p not given).

Conclusion:

Single-dose Gabapentin is not efficacious for post-operative dental pain, but increases adverse events.

NB: GBP = Gabapentin, HC = Hydrocodone.

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Study Authors (see Discussion and Conclusion on pp 34-36 of 245) NB: Recorded for interest only and are not necessarily the opinion of Dr. T. L. Perry
Protocol Number: 1035-001, Addendum B Original Protocol Date: November 15th, 1999 Note that addendum B of the protocol (p.127 of 245) explains the extension of the study with 100 more patients. The rationale is given. Addendum B has been copied into this document at the end of the table. This study, Addendum B of Protocol 1035-001, was conducted to collect data for pharmacokinetic / pharmacodynamic	Postoperative Dental Pain <u>RR720-04483</u> Note that the inclusion / exclusion criteria for RR720-04455 were the same. Inclusion Criteria: • Age between 18 and 40 years (inclusive); • Scheduled for an outpatient oral surgical procedure to remove 1 to 2 ipsilateral third molars, at least 1 of which was mandibular and fully or partially impacted in bone; • Good health as determined by medical history and physical examination; • Negative alcohol breath test on day of surgery prior to surgery;	<u>Patient Flow:</u> Number of Patients Screened: 140 Number of Patients Randomized: 101 Number randomized to each treatment group: Placebo: n=20 GBP250/HC5: n=20 GBP125/HC10: n=20 GBP500/HC10: n=20 GBP500: n=21  Table 6. Overall Summary of Patient Disposition—Addendum B (Number [%] of Patients) Disposition — Placebo — GBP250/HC5 — GBP125/HC10 — GBP500/HC10 — GBP500 — All Persons Patients Screened — — — — — — 140 Patients Screened But Not Randomized — — — — — — 39 Pain intensity did not reach required level — — — — — — 16 (41.0) Patient chose not to enter study — — — — — — 16 (41.0) Patient did not undergo surgery — — — — — — 2 (5.1) Other — — — — — — 5 (12.8) Randomized (Intent-to-Treat Population)[a] — — — — — — — Completed Study[b] — 20 (100.0) — 20 (100.0) — 20 (100.0) — 20 (100.0) — 20 (95.2) — 100 (99.0) Withdrew Prior to Completion[c] — 0 (0.0) — 0 (0.0) — 0 (0.0) — 0 (0.0) — 1 (4.8) — 1 (1.0) [a] Number of patients randomized is used as the denominator for calculation of treatment group disposition percentages. [b] Remained in the clinic for 8 hours postdose [c] Left clinic before 8 hours postdose Table 6, p.27 of 245	According to the Protocol (p.43 of 245) <u>Predefined Primary Outcome:</u> • The Summed Pain Intensity Difference over the first 6 hours. <u>Secondary Outcomes</u> • SPID 8 • Totpar 6, Totpar 8 (total pain relief at 6 and 8 hours) • SPRID 6, SPRID 8 (Sum of pain relief intensity difference over the first 6 and 8 hours) • PID (Pain intensity difference at 20, 40, and 60 minutes and every hour up to eight hours) • PR (Pain relief at 20, 40, and 60 minutes and every hour up to eight hours) • PRID (Pain relief intensity difference) at 20, 40, and 60 minutes and every hour up to eight hours) • Time to onset • Time to rescue medication	<u>1. Mortality</u> • No patients died during this study (p.33 of 245) <u>2. Serious Adverse Events</u> • No patients experienced serious adverse events during this study (p.33 of 245) <u>3. Withdrawals Due to Adverse Events</u> • No patients withdrew due to an adverse event during this study (p.33 of 245). <u>4. Total Withdrawals:</u> • 1/21 patient in the GBP 500 group did not complete the study • See table 6, p. 27 of 245 for details (also included in Interventions column. <u>5. Total Adverse Events:</u> • A total of 31 patients (31%) in this study	1. The GBP125/HC10 combination performed numerically better than the GBP250/HC5 and GBP500/HC10 combinations on all efficacy measures, and the GBP500/HC10 combination performed numerically better than the GBP250/HC5 combination. 2. The 1035-01 Main Protocol/Addendum A and Addendum B were conducted at the same center by the same personnel, with Addendum B commencing within 48 hours of the completion of the Main Protocol/Addendum A. 3. The different parts of the study had different

modeling of the gabapentin and hydrocodone combination. These data will be used to help determine the optimal doses of gabapentin and hydrocodone for use in future clinical studies. The pharmacokinetic results are summarized in a separate report. The same efficacy data were collected for Addendum B patients as for patients in the 1035-01 Main Protocol/Addendum A. The small number of patients in each treatment group precluded inferential analyses of these data. Research Report No: RR720-04483 (Protocol 1035-001, Addendum B). Date of RR720-04483: October 31st, 2000	• Written informed consent; • Reliable, cooperative, and able to understand the information required in the pain questionnaire; • Self-rated postoperative pain intensity on a 4-point categorical scale as moderate or severe; and • Self-rated postoperative pain intensity on a 100 mm VAS of ≥ 45 mm. Exclusion Criteria: • History or clinical evidence of renal disease; • Occurrence of oral surgery complication; • History of serious adverse reaction to any analgesic agent or any medication to be used in the operative procedure or postoperative period; • History of any bleeding disorder; • Patient gabapentin use within the past 6 months; • Patient use of any analgesic, centrally acting, or anti-inflammatory medication within 24 hours of surgery;		• Patient global assessment of study medication was also a secondary efficacy parameter. This is mirrored by the research report (p. 7 of 245) Name of Company: Warner-Lambert | INDIVIDUAL STUDY TABLE | (For National Authority Use Only) Name of Finished Product: CI-1035 | Referring to Part of the Dossier Name of Active Ingredient: Gabapentin, Hydrocodone | Volume: Page: Table included on each pages 6-8 of 245 of the Research Report.	experienced at least 1 adverse event • The percentage of patients who experienced adverse events ranged from 10% of the placebo and GBP250/HC5 groups to 55% of the GBP500/HC10 group. • Most patients (77%) experienced adverse events that were mild to moderate in intensity. Placebo: 2/20 (10.0%) • Mild: 0/20 (0%) • Moderate: 0/20 (0%) • Severe: 2/20 (10.0%) GBP125/HC10: 2/20 (10.0%) • Mild: 1/20 (5.0%) • Moderate: 0/20 (0%) • Severe: 1/20 (5.0%) GBP250/HC5: 7/20 (35%) • Mild: 2/20 (10.0%) • Moderate: 3/20 (15.0%) • Severe: 2/20 (10.0%) GBP500/HC10: 11/20 (55.0%) • Mild: 2/20 (10.0%) • Moderate: 7/20 (35%) • Severe: 2/20 (10.0%) GBP500: 9/21 (42.9%) • Mild: 3/21 (14.3%) • Moderate: 6/21 (28.6%) • Severe: 0/21 (0.0%) See Table 8 on p. 31 of 245 for more details. The most common side effects included: • Dizziness	treatment groups and sample sizes. Within these constraints, the results of 1035-01 Main Protocol/Addendum A and Addendum B were compared. 4. The SPID6 results obtained with GBP125/HC10 treatment appear consistent with those obtained with GBP250/HC10 treatment, 10 suggesting that GBP doses of 125 or 250 mg in combination with HC10 provide comparable pain relief (Table 9, p.35 of 245). • The pain relief provided by these combinations seems similar over time, as evidenced from plotting the mean PRID scores (Figure 4, p.35 of 245). • Also, no apparent analgesic benefit was obtained by increasing GBP to 500 mg in the combination (Figure

Study Design: A single-dose, double-blind, placebo-controlled, comparative efficacy study. Study Country: US Study Duration: Single Dose Investigators: Desjardins P Medication Dosage (dependant): Patients were randomized to receive one of the following: 1. Placebo 2. Gabapentin 250 mg/Hydrocodone 5 mg (GBP250/HC5) 3. Gabapentin 125 mg, Hydrocodone 10 mg (GBP125/HC10) 4. Gabapentin 500 mg, Hydrocodone 10 mg (GBP500/HC10) 5. Gabapentin 500 mg (GBP 500)	• Prior participation in Study 1035-001; • Patient was taking or took an investigational agent or participated in another research protocol within the past 60 days.			• Headache • Nausea • The adverse events reported by 2 or more patients per treatment group included dizziness, nausea, and headache. • Dizziness was the most frequent adverse event experienced by patients receiving the GBP/HC combinations. o For the combination treatment groups containing HC10, the incidence of dizziness increased with the amount of GBP in the combination. o The frequency of dizziness was 30% for the GBP125/HC10 group compared with 45% for the GBP500/HC10 group. o The frequency of dizziness for patients treated with GBP125/HC10 was similar to that of patients treated with GBP250/HC10 (28%). • For a detailed overview of adverse events, see Appendix C.3 (p.209 of 245) <u>6. Validated measures of improvement in global function including return to work, study, activities of daily living</u> • None reported in this study. <u>7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint</u> • Not a predefined primary endpoint of this study.	4, p.35 of 245), and increased side effects occurred with the GBP500/HC10 combination. 5. The SPID6 results suggest that the HC5 dose in combination with GBP250 is not as effective as the HC10 dose in the combination (Table 9, p.35 of 245). This trend is also observed with the mean PRID scores (Figure 5, p.36 of 245). 6. Single-dose treatment with the GBP/HC combinations was generally well-tolerated. • The frequency of dizziness increased with increasing doses of GBP and HC. 7. Based on summary statistics, GBP/HC combination groups tended to have greater pain relief than placebo. The greatest relief was seen in the GBP125/HC10 treatment group.

Patients Randomized: Randomization Procedure: Number of Study Study Dates: According to RR720-04483 • 02/25/2000 – 3/15/2000 • Note that RR720-04455 took place over 12/28/99 – 02/23/000 Study Approval: PUBLISHED: N/a Final study report (unpublished): RR720-04483 Pfizer Global Research & Development Ann Arbor Laboratories, Ann Arbor Michigan. Report Number RR 720-04483 dated October 31st, 2000. Authors include Authors include Diaz F,				<u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial</u> • Not a predefined outcome of this study • The primary endpoint here was SPID 6. Summary of SPID6 (p.28 or 245) Placebo: n:20 Mean: 0.78 SD: 2.99 GBP250/HC5: n=20 Mean: 2.08 SD: 4.51 GBP125/HC10: n=20 Mean: 3.45 SD: 4.94 GBP500/HC10: n=20 Mean: 2.30 SD: 6.47 GBP500: n=21 Mean: 0.46	

<table>
<tr>
<td>Dougherty KM, Henry GC, Mundel T. Investigator listed as Desjardins P.</td>
<td></td>
<td></td>
<td></td>
<td>SD: 4.68
See table 7 (p.28 of 245)

Table 7. AUC Efficacy Measures, By Treatment Group (Mean ± SD)
<table>
<tr><th>Efficacy Measure</th><th>Placebo
N = 20</th><th>GBP250/HC5
N = 20</th><th>GBP125/HC10
N = 20</th><th>GBP500/HC10
N = 20</th><th>GBP500
N = 21</th></tr>
<tr><td>SPID6</td><td>0.78 (2.99)</td><td>2.08 (4.51)</td><td>3.45 (4.94)</td><td>2.30 (6.47)</td><td>0.46 (4.68)</td></tr>
<tr><td>SPID8</td><td>0.93 (4.16)</td><td>2.64 (6.05)</td><td>4.65 (6.85)</td><td>3.35 (9.02)</td><td>0.70 (6.68)</td></tr>
<tr><td>SPRID6</td><td>3.31 (6.74)</td><td>7.89 (11.10)</td><td>10.52 (12.53)</td><td>8.70 (13.84)</td><td>3.71 (9.99)</td></tr>
<tr><td>SPRID8</td><td>4.16 (9.35)</td><td>10.34 (15.29)</td><td>14.27 (17.51)</td><td>12.35 (19.57)</td><td>5.34 (14.60)</td></tr>
<tr><td>TOTPAR6</td><td>2.53 (4.05)</td><td>5.80 (6.95)</td><td>7.07 (7.79)</td><td>6.39 (7.67)</td><td>3.25 (5.76)</td></tr>
<tr><td>TOTPAR8</td><td>3.23 (5.59)</td><td>7.71 (9.71)</td><td>9.62 (10.96)</td><td>8.99 (10.95)</td><td>4.63 (8.50)</td></tr>
</table>
SD = Standard deviation.

Table 9. Comparison of SPID6 Results for all 1035-01 Treatment Groups
<table>
<tr><th></th><th colspan="4">Gabapentin (mg)</th></tr>
<tr><th>Hydrocodone (mg)</th><th>0</th><th>125</th><th>250</th><th>500</th></tr>
<tr><td>0</td><td>1.30[a]/0.78[b]</td><td>NA</td><td>1.92[a]</td><td>0.46[b]</td></tr>
<tr><td>5</td><td>NA</td><td>NA</td><td>2.08[b]</td><td>NA</td></tr>
<tr><td>10</td><td>2.44[a]</td><td>3.45[b]</td><td>3.76[a]</td><td>2.30[b]</td></tr>
</table>
NA = Not applicable.
[a] Results from 1035-01 Main Protocol/Addendum A
[b] Results from 1035-01 Addendum B

Table 9 (p.35 of 245) contains a comparison of SPID 6 for the first part of the protocol

It would seem that RR720-04483 contains no table analogous to Appendix D.2 on page 298 of 371 of RR720-04455 in which the p-values for all the treatment comparisons for SPID 6 are given.

<u>9. % of patients achieving “much improved” or “moderately improved”</u>

• Not a predefined outcome.
• Pain relief (PR) was assessed at time 0, at 20 and 40 minutes, and at hours 1 – 8 on a 5-point categorical scale:
o 0 = None
o 1 = A little
o 2 = Moderate</td>
<td></td>
</tr>
</table>

				○ 3 = A lot ○ 4 = Complete • The GBP125/HC10 treatment group showed a maximal effect on the PR at 2 hours postdose. The GBP125/HC10 treatment group means at this time point were numerically better than those achieved by any other treatment group at any time point throughout the 8-hour time course. The effects seen for the GBP500/HC10 group were better overall than for the GBP250/HC5 group. The placebo and GBP500 groups had the smallest effect. • For a full summary of pain relief measurements see Appendix C.2.07 (p.205 of 245) • The report does not seem to contain information regarding the p-values of PR comparisons. • Patients also performed an overall assessment of study medication at the end of the 8-hour-in-clinic assessment period: ○ 1 = poor ○ 2 = fair ○ 3 = good ○ 4 = very good ○ 5 = excellent • Responders were defined as those patients who evaluated their study medication as “excellent,” “very good,” or “good” on the Patient Global Assessment of Study Medication at 8 hours postdose, or at the time of rescue medication. • The percentage of responders was highest for the GBP125/HC10 group (40%), followed by the GBP250/HC5 and GBP500/HC10 groups (35%	

				each). The GBP500 and placebo treatment groups had responder rates of 24% and 10%, respectively. • See appendix C.2.04 (p.202 of 245) for all details regarding responder analysis. <u>10. Histogram presentation of all PGIC 7-point results</u> • N/A – not a predefined outcome.	

Addendum B of Protocol 1035-001 (RR720-04483)

Protocol 1035-001
Addendum Issue Date: February 4, 2000

ADDENDUM B

A Single-Dose, Double-Blind, Placebo-Controlled, Comparative Efficacy Study of Gabapentin and Hydrocodone, Alone or in Combination, in Patients With Postoperative Dental Pain (Protocol 1035-001)

RE: Pharmacokinetic Sampling

The following section of this protocol have been addended:

9.4 Pharmacokinetic/Pharmacodynamic Analysis

ADDITION: Page 18, new subsection reads,

"9.4.1 Pharmacokinetic/Pharmacodynamic Analysis Extension

This extension will be conducted in 100 new patients who will be added to the main study population. These patients will sign a separate revised informed consent that explains the additional procedures, risks, and benefits of the serial PK sampling. Each of these patients will be randomized to 1 of 5 treatment groups, (placebo, gabapentin 250 mg/hydrocodone 5 mg, gabapentin 125 mg/hydrocodone 10 mg, gabapentin 500 mg/hydrocodone 10 mg, or gabapentin 500 mg), using the identical (moderate or severe pain) stratification criteria used for the main study patients. Twenty patients will be randomized to each treatment arm. Once randomized, these patients will follow the identical main study procedures and have 9 PK sample collections at the following time points: immediately prior to dosing, at 20 minutes, at 40 minutes, and at 1, 2, 3, 4, 6, and 8 hours postdose. Patients participating in Addendum B who require rescue medication will continue to have PK samples drawn according to the fixed schedule."

SAFETY: Patients participating in this extension will not be exposed to any additional procedural risks than those participating in the initial phase of the study. Extension patients will undergo the removal of 1 to 2 molars, receive the identical local anesthetics, a single dose of study medication, and have the identical 9 PK samples drawn over an identical 8-hour, follow-up period.

Gabapentin is approved as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. This approval was based on data from 3 multicenter placebo-controlled, double-blind clinical trials that utilized doses ranging from 600 mg/day once a day up to 1200 mg/day 3 times a day. The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic drugs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Protocol 1035-001
Addendum Issue Date: February 4, 2000

Approximately 7% of the 2074 individuals who received gabapentin in premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence (1.2%), ataxia (0.8%), fatigue (0.6%), nausea and/or vomiting (0.6%), and dizziness (0.6%).

The single doses of gabapentin to be used in this extension are within the ranges studied cited in the labeling. In addition, gabapentin 600 mg has also been reported to significantly increase pain threshold and tolerance in the cold-pressor test when administered 2 hours after receiving 60 mg of controlled-release oral morphine in healthy normal volunteers.[11] In this randomized, double-blind, placebo-controlled trial, the observed adverse events reported showed no significant difference between gabapentin and placebo compared to placebo alone. Those volunteers receiving morphine and placebo exhibited the expected opioid mediated side effects compared to those receiving placebo alone. There was no significant difference reported between those receiving morphine and placebo compared to those receiving morphine and gabapentin. The most frequently observed side effects were sedation, dizziness and nausea.

REFERNCE:

[11] Eckhardt K, Ammon S, Hofmann U, Riebe A, et al. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. Unpublished data.

RATIONALE: (SCIENTIFIC) The PK/PD modeling described in the following paragraphs is anticipated to serve at least 3 purposes: (1) confirm the accuracy of the modeling performed for the doses utilized in the initial phase of the trial, (2) predict the dose with the greatest analgesic effect for future clinical trials thereby reducing the number of patients potentially exposed to the combination during the development process, and (3) prospectively identify the pain relief associated with new combinations of gabapentin and hydrocodone. The type of data (ie, pain relief scores) collected in the present trial has been successfully modeled using a proportional odds model.[1,2] A similar model will be developed to describe the data, and simulation can then be used to predict the effects of both studied and unstudied combinations of gabapentin and hydrocodone. Data from the additional patients recruited under this extension will be used to assess the predictive performance of the model. This approach of utilizing PK data and sophisticated algorithms in the process of dose selection in clinical development programs has been explicitly endorsed by the ICH dose-response review committee.[3] In their published guidelines they state "agencies should also be open to the use of various statistical and pharmacometric techniques such as Baysisan and population methods, modeling, and pharmacokinetic-pharmacodynamic approaches." Parke-Davis, in collaboration with Pharsight Corporation, plans to utilize modeling and simulation to explore PK-PD relationships in the 1035-001 data in order to determine an optimal ratio and dose of gabapentin and hydrocodone to carry forward in future clinical trials.

A particularly powerful approach to biological modeling is to develop a model based on an initial set of data and then validate the model by predicting results for an additional set of data not including the initial set. In this manner, an initial model can be iteratively refined. Such an approach can be performed internally on the 1035-001 data set by splitting the data into a model generation subset and a validation subset. The main protocol population and the Addendum A patients have been designated the model generation subset. The data derived from this extension using a small subset of the data derived from these previously unexplored doses would provide an excellent validation set for the model and greatly increase confidence in the model predictions. In order for this additional data to be useful it should be collected under the same conditions as the main body of data. These conditions include the identical study personnel, clinical setting, and temporal collection of data. In a carefully conducted study, as few as 20 patients at each selected dose combination can provide valuable information regarding the effectiveness of an acute analgesic. The following selections (placebo, gabapentin 250 mg/hydrocodone 5 mg, gabapentin 125 mg/hydrocodone 10 mg, gabapentin 500 mg/hydrocodone 10 mg, or gabapentin 500 mg), were made in order to have a complete characterization of the effect of gabapentin administered with hydrocodone 10 mg. The single low-dose combination (hydrocodone 5 mg with gabapentin 250 mg) is included in the event that the interaction between gabapentin and hydrocodone is even larger than anticipated and the use of lower doses of hydrocodone appear feasible.

REFERENCES

1 Sheiner LB. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. Clin Pharmacol Ther 1994;56:3098-322.

2 Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. Clin Pharmacol Ther 1996;60:619-35.

3 ICH Guidline for Industry: Dose-response information to support drug registration. 59 FR 55972 Nov 9, 1994

Appendix C Detailed Study Safety Procedures

ADDITION: Page C-5 new Number 12 reads,

"12. STUDY MEDICATION DOSING RECORD/PLASMA GABAPENTIN AND HYDROCODONE CONCENTRATION DETERMINATIONS

Procedure for Blood Collection in Serial Sampling Group

Patients who have consented to serial PK sampling will be randomized by their pain status. For all patients in both strata, a blood sample will be drawn at 0 (immediately

prior to study medication administration), at 20 minutes, at 40 minutes, and at 1, 2, 3, 4, 6, and 8 hours postdose for multiple PK sampling. The samples will be drawn immediately following completion of the pain assessments at these time periods. PK sampling should be continued according to the fixed schedule for patients who withdraw from the study before the 8-hour evaluation period.

If blood cannot be withdrawn at the sampling time, the heparin lock line should be reflushed and the catheter moved slightly. The time of sample collection is to be recorded. No serial samples are to be collected by venipuncture as this may interfere with the assessment of pain relief. Exceptions will be allowed for the 8-hour collection point, which may be performed from a single venipuncture. Catheters should only be removed after the final sample collection or if they are irritating to the patient. Blood sampling should be attempted at all time periods even if previous samples are missed due to heparin lock line dysfunction.

At the time of sample collection 2 mL of venous blood should be withdrawn and discarded. Following this, 5 mL of venous blood should be withdrawn and placed in vacuum blood collection tubes containing 72 USP units of sodium heparin. After each blood withdrawal, the heparin lock line should be flushed initially with 5 mL saline and then 1 mL of heparin. Immediately (within 30 minutes) after the draw, blood samples will be centrifuged for 15 minutes at 3000 rpm, and the resulting plasma divided into 2 sample tubes and stored frozen at -20°C until analyzed for drug concentration. Protocol number, site number, patient number, date, and times of sample withdrawal documenting actual time of draw must be clearly and accurately indicated on tube labels and the appropriate CRF. Quintile Laboratories will provide supplies for the PK blood samples and frozen plasma samples will be shipped on dry ice to Quintiles Laboratories. Gabapentin and hydrocodone plasma concentrations will not be available to the Investigator until completion of the study. EACH sample tube must be labeled with the following information: protocol number, site number, patient number, date, and time sample was collected."

RATIONALE: Instructions for collection, handling, and shipping instructions for serial PK sampling

Protocol 1035-001
Addendum Issue Date: February 4, 2000

ADDENDUM B

A Single-Dose, Double-Blind, Placebo-Controlled, Comparative Efficacy Study of Gabapentin and Hydrocodone, Alone or in Combination, in Patients With Postoperative Dental Pain (Protocol 1035-001)

This addendum only affects the following sites: 1035-001-001 and becomes effective the date of IRB approval. Written IRB approval of this addendum must be obtained and forwarded to Parke-Davis.

Study Site Approval Signature(s)

_____ _____
Paul J. Desjardins, DMD, PhD Date
Investigator

Protocol 1035-001
Addendum Issue Date: February 4, 2000

ADDENDUM B

A Single-Dose, Double-Blind, Placebo-Controlled, Comparative Efficacy Study of Gabapentin and Hydrocodone, Alone or in Combination, in Patients With Postoperative Dental Pain (Protocol 1035-001)

Parke-Davis Approval Signatures

Study Manager: Greg Henry, MS, Clinical Scientist, CNS/Analgesia — 4 FEB 2000 (Date)

Drug Manager: Trevor Mundel, MD, PhD, Director, CNS/Analgesia — 2/4/00 (Date)

Statistician: Chongqing Yan, PhD, Statistical Project Manager — 2/4/2000 (Date)

Therapeutic Head: Michael Poole, MD, Senior Director, CNS/Analgesia — 2/4/2000 (Date)

UNPUBLISHED

STUDY DETAIL SUMMARY AND ANALYSIS: SUNSHINE A, KATZ JA
PROTOCOL NUMBER 1035-002, RESEARCH REPORT 720-04471
POST-OPERATIVE PAIN FOLLOWING MAJOR ORTHOPAEDIC SURGERY

Summary of Dr. T.L. Perry

Study conducted from 12/03/1999 – 08/25/2000; report dated 12/20/2000

The authors conclude "250 mg of gabapentin does not appear to substantially potentiate the analgesic efficacy of 10 mg of hydrocodone in this model."

For SPID6, Gabapentin was not superior to placebo. The GBP250/HC10 group did not significantly outperform the HC10 group on any of the efficacy measures examined.

Conclusions:

Single-dose Gabapentin 250 mg was not efficacious for treatment of post-operative pain following major orthopaedic surgery.

NB: GBP = Gabapentin, HC = Hydrocodone

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions of Authors (see Discussion and Conclusion, pp. 51-52 of 380) NB: Recorded for interest only and are not necessarily the opinion of Dr. T. L. Perry
Protocol Number: 1035-002. Original Protocol Date: October 5th, 1999 Research Report No: RR720-04471 Date of Research Report: December 20th, 2000 Study Design: A single-dose, double-blind, placebo-controlled, comparative efficacy study. Study Country: US Study Duration: Single Dose Investigators: Sunshine A, Katz JA Investigator's	Post-Operative Pain Following Major Orthopaedic Surgery. Inclusion Criteria: • Eighteen years of age or older; • Have undergone one of the following major inpatient orthopaedic surgical procedures: o Total knee replacement; o Total hip replacement; o Hip hemiarthroplasty (replacement of femoral head); o Total shoulder replacement; o Major rotator cuff tear repair (acute complete tears); o Osteotomy (major lower extremities only; Amendment 2 added upper extremities); o Open reduction internal fixation (isolated lower extremities without other o coexisting major trauma;	<u>Patient Flow:</u> Number of Patients Screened: 238 Number of Patients Randomized: 200 Number randomized to each treatment group: • Placebo: n = 49 • GBP250/HC10: 51 • GBP250: 50 • HC10: 50 Table 7. Overall Summary of Patient Disposition [Number (%) of Patients] Disposition — Placebo — GBP250/HC10 — GBP250 — HC10 — All Patients Patients Screened — 238 Patients Screened But Not Randomized — 38 Pain intensity did not reach required level — 13 (34.2) Patient chose not to enter study — 15 (39.5) Other — 10 (26.3) Randomized (Intent-to-Treat Population)[a] — 49 — 51 — 50 — 50 — 200 Completed Study[b] — 49 (100.0) — 50 (98.0) — 47 (94.0) — 43 (86.0) — 189 (94.5) Withdrew prior to completion — 0 (0) — 1 (2.0) — 3 (6.0) — 7 (14.0) — 11 (5.5) Adverse Event — 0 (0) — 1 (2.0) — 3 (6.0) — 6 (12.0) — 10 (5.0) Other — 0 (0) — 0 (0) — 0 (0) — 1 (2.0) — 1 (0.5) a. Number of Patients Randomized is used to the denominator for calculation of treatment group disposition percentages. b. Remained in the clinic for 8 hours postdose See table 7 (p. 33 of 380) for more details. Name of Company: Pfizer Inc — INDIVIDUAL STUDY TABLE — (For National Authority Use Only) Name of Finished Product: CI-1035 — Referring to Part of the Dossier Name of Active Ingredient: Gabapentin, Hydrocodone — Volume: Page: This table is contained on pages 6-9 of 380 of the Research Report.	<u>Predefined Outcomes:</u> According to the Study Protocol (p.62 of 380): Primary Efficacy Parameter: • SPID6, the sum of pain intensity difference over the first 6 hours. Secondary Efficacy Parameters: • SPID4 and SPID8 (sum of pain intensity difference over the first 4 and 8 hours) • TOTPAR4, TOTPAR6, and TOPAR8 (total pain relief over the first 4, 6, and 8 hours) • SPRID4, SPRID6, and SPRID8 (sum of pain relief intensity difference over the first 4, 6, and 8 hours) • PID (pain intensity difference at 20, 40, and 60 minutes and 2, 3, 4, 5, 6, 7, and 8 hours) • PR (pain relief at 20, 40, and 60 minutes and 2, 3, 4, 5, 6, 7, and 8 hours) • PRID (pain relief intensity difference at 20, 40, and 60	<u>1. Mortality</u> P = 1/49 (2.0%), no other deaths. • One patient died in this study due to cardiac arrest, the patient was in the placebo treatment group. • Patient 002131, Study 1035-002-002, a 73-year-old white male in a CI-1035 study for the treatment of pain due to total knee arthroplasty had a cardiac arrest and died on Study Day 2 (1 day post treatment) o History includes hypertension and irregular heartbeat and shortness of breath. o Concomitant medication consisted of digoxin, lisinopril and propafenone hydrochloride. o One day prior to the study, the patient had the total knee arthroplasty. • On Study Day 1, he was treated with a single dose of the study medication. o Following the study period, the patient began treatment with oxycodone hydrochloride for pain. o He developed confusion and had the cardiac arrest the following day, Study Day 2.	1. This study compared the pain relief provided by GBP250/HC10 after orthopedic surgery with that of the active comparator and component of the combination, HC10; the other component of the combination, GBP250; and placebo. 2. The HC10 group consistently outperformed the placebo group on all efficacy measures, demonstrating the validity of the trial. 3. The GBP250/HC10 group provided significantly better pain relief than the placebo and GBP250 groups on the majority of efficacy measures. 4. The GBP250/HC10 group did not significantly outperform the HC10 group on any of the efficacy measures examined.

Meetings:
November 18th, 1999
January 21st, 2000
*note that second meeting occurred after study began.

Medication Dosage (dependant):
Patients were randomly assigned to
1. Placebo
2. Gabapentin 250 mg, hydrocodone 10 mg (GBP250/HC10)
3. Gabapentin 250 mg
4. Hydrocodone 10 mg

Patients Randomized: 200

Randomization Procedure:

Number of Study Centres: 2 centers recruited patients in the United States.

Study Dates: 12/03/1999 – 08/25/2000

Study Approval:

Amendment 2 added upper extremities);
- Spinal fusions; or
- Amendment 2 added Triple arthrodesis.

- Have no clinically significant illness which would contraindicate the patient's participation in the trial as determined by medical history, physical examination, or laboratory findings as recorded in their hospital chart;
- Reliable, cooperative, and able to understand the information required in the pain questionnaire / analgesia diary;
- Experiencing self-rated postoperative pain on a 4-point categorical scale as moderate (2 points) or severe (3 points);
- Able to take oral medication.

Exclusion Criteria:
- Clinical evidence of renal disease with a serum creatinine level >2.0 mg/dL;
- Orthopedic surgery complication, that, in the opinion of the investigator, precluded the patient's participation in the study;
- History of serious adverse reaction to, or known allergy to hydrocodone, opioids, or Gabapentin;

Table 1. List of Investigators (Protocol 1035-002)

Center	Investigator	Investigator Address	Entered Study[a]	Completed Study[b]
001	Abraham Sunshine, MD	New York, NY	86	75
002	Jay A. Katz, MD	Tucson, AZ	114	114
Total			200	189

[a] Number of patients randomized
[b] Number of patients who remained in the clinic for 8 hours postdose

Table 1 (p.11 of 380) contains a list of investigators.

minutes and 2, 3, 4, 5, 6, 7, and 8 hours)
- Time-to-Onset (using 1-stopwatch method),
- Time-to-Rescue
- Patient Global Assessment

According to the final research report (pp.17,18 of 380) the primary and secondary efficacy outcomes are the same as defined in the original protocol.

- The investigator considered the fatal event unlikely related to the study medication.
  - The PGRD medical reviewer considered the labelled event unlikely related to the study medication.
- See page 50 of 380 for details.

2. Serious Adverse Events

P = 2/49 (4.1%)

- Two patients experienced a serious adverse event during this study (Table 20, p.51 of 380).
- Both patients were in the placebo group. Patient 002131 died due to heart arrest
  - The heart arrest occurred 1 day after study completion.
  - Patient 002108 had an accidental injury (fractured femur) during physical therapy. The accident, which occurred 1 day after study completion, resulted in surgery and the patient recovered.

Table 20. Patients With Serious Adverse Events

Treatment Group	Pt ID	Term: Preferred INVESTIGATOR	Study Day AE Began	Study Day AE Ended	Intensity	Relation to Study Med	Clinical Outcome
Placebo	002108	Accidental injury FRACTURED FEMUR	2	3	Severe	Definitely not	Recovered
Placebo	002131	Heart arrest CARDIAC ARREST	2	2	Severe	Unlikely	Died due to this AE

Table 20, p.51 of 380.

3. Withdrawals Due to Adverse Events

HC10: 6/50 (12.0%)
GBP250: 3/50 (6.0%)
GBP250/HC10: 1/51 (2.0%)

- The PR, PID, and PRID curves for the GBP250/HC10 group were very similar to the curves for HC10 group.
- Pain relieving effects of the active treatments (GBP250/HC10 and HC10) were seen as early as 40 minutes postdose.
- These data suggest that 250 mg of gabapentin does not potentiate the effects of 10 mg of hydrocodone in this model.
- This is in contrast to the apparent potentiation effects of gabapentin with hydrocodone in a dental pain model, Protocol 1035-001.

5. The study also examined the affect of baseline opiate concentrations and the ability to metabolize hydrocodone on the primary efficacy measure, SPID6.
   - No significant alteration in SPID6 results was seen when either of these factors was incorporated in the primary ANCOVA model.

PUBLISHED: N/a Final study report (unpublished): Pfizer Global Research & Development. Ann Arbor Laboratories, Ann Arbor Michigan. Report Number RR 720-04471 dated December 20th, 2000. Authors include Dougherty KM, Henry GC, Mundel T, Yan C.	• History of chronic opioid use or opioid abuse within 6 months prior to study entry; • History of any bleeding disorder; • Prior use of Gabapentin within the past 6 months; • Prior participation in Study 1035-001; and • Patient was taking or took an investigational agent or participated in another research protocol within the past 30 days.			• All 10 withdrawals were due to fever. • None of the cases of fever were considered associated with treatment. • See Appendix B.3 for details (p.191 of 380) 4. Total Withdrawals: Total Withdrawals: 11/200 (5.5%) Placebo: 0/49 (0.0%) GBP250/HC10: 1/51 (2.0%) • WDAE – 1/51 (2.0%) GBP250: 3/50 (6.0%) • WDAE 3/50 (6.0%) HC10: 7/50 • WDAE: 6/50 (12.0%) • Other: 1/50 (2.0%) Table 7. Overall Summary of Patient Disposition [Number (%) of Patients] Disposition / Placebo / GBP250/HC10 / GBP250 / HC10 / All Patients Patients Screened: 238 Patients Screened But Not Randomized: 38 Pain intensity did not reach required level: 13 (34.2) Patient chose not to enter study: 15 (39.5) Other: 10 (26.3) Randomized (Intent-to-Treat Population)[a]: 49 / 51 / 50 / 50 / 200 Completed Study[b]: 49 (100.0) / 50 (98.0) / 47 (94.0) / 43 (86.0) / 189 (94.5) Withdrew prior to completion: 0 (0) / 1 (2.0) / 3 (6.0) / 7 (14.0) / 11 (5.5) Adverse Event: 0 (0) / 1 (2.0) / 3 (6.0) / 6 (12.0) / 10 (5.0) Other: 0 (0) / 0 (0) / 0 (0) / 1 (2.0) / 1 (0.5) [a] Number of Patients Randomized is used as the denominator for calculation of treatment group disposition percentages. [b] Remained in the clinic for 8 hours postdose Table 7 – 33/80. 5. Total Adverse Events: Placebo: 13/49 (26.5%) • Mild: 7/49 (14.3%)	• The percentage of poor metabolizers of hydrocodone in this study was 8%. This is in close agreement with the 7% estimate of poor metabolizers among Caucasians. 6. Single-dose treatment with GBP250/HC10 was generally well-tolerated. 7. The most frequent adverse events associated with GBP250/HC10 treatment were somnolence and dizziness. No adverse events were experienced at a significantly higher frequency in the GPB250/HC10 group compared with the placebo group. 8. The combination of GBP250/HC10 was significantly better than placebo in relieving postsurgical pain; however, 250 mg of gabapentin does not appear to substantially potentiate the analgesic efficacy of 10 mg of hydrocodone in this model. A single oral dose of GBP250/HC10 was well-tolerated with no remarkable side effects.

				• Moderate: 4/49 (8.2%) • Severe: 2/49 (4.1%) GBP250/HC10: 9/51 (17.6%) • Mild: 5/51 (9.8%) • Moderate: 4/51 (7.8%) • Severe: 0/51 (0.0%) GBP250: 10/50 (20.0 • Mild: 3/50 (6.0%) • Moderate: 7/50 (14.0 • Severe: 0/50 (0.0%) HC10: 15/50 (30%) • Mild: 7/50 (14.0 • Moderate:8/50 (16.0 • Severe: 0/50 (0.0%) See table 18 (pp.47, 48 of 380) for more details. <u>6. Validated measures of improvement in global function including return to work, study, activities of daily living</u> • None listed in this study <u>7. > 50% reduction in pain score (NRS, VRS) from baseline to endpoint</u> • Not a predefined efficacy parameter. <u>8. Mean between-group difference in change of pain score (NRS, VRS) from baseline to pre-defined endpoint by ITT-LOCF –where this was the pre-defined primary endpoint in trial</u> • The primary efficacy parameter in this study was SPID6, the sum of pain intensity	

				difference over the first 6 hours. SPID 6 Results by Treatment Group (See Appendix C.2.01, p.212 of 380) Placebo: n = 49 Mean: -0.16 SD: 3.09 GBP250/HC10: n=51 Mean: 2.65 SD: 4.08 GBP250:n=50 Mean: 1.03 SD: 3.89 HC10: n=50 Mean: 2.53 SD: 3.92 The following are the p-values for the 2-way comparison of each treatment group with regard to SPID6 (see appendix D.2.1, p.276 of 380). Note that below, estimates have been rounded to 4 decimal places. GBP250 - HC10: Estimate: -1.5888 p-value = 0.0198 GBP250 - Placebo: Estimate: 1.1965 p-value =0.0799 GBP250/HC10 - GBP250: Estimate: 1.6576 p-value = 0.0146 GBP250/HC10- HC10: Estimate: 0.0688 p-value = 0.9187 GBP250/HC10 - Placebo:	

				Estimate: 2.8540 p-value = 0.0001 HC10 - Placebo: Estimate: 2.7853 p-value = 0.0001 • The GBP250/HC10 group was statistically significantly better than the placebo (p = 0.0001) and GBP250 groups (p = 0.0146) on the SPID6 primary efficacy measure (Table 8, p.35 of 380). o The GBP250/HC10 group did not separate from the HC10 group (p = 0.9187) o Min-test result was therefore negative. o In other planned comparisons, the HC10 group was significantly better than all other treatment groups except GBP250/HC10 (Table 9, p.35 of 380). • The SPID6 efficacy measure for the GBP250 group was not statistically significantly better than that of the placebo group. Table 8. p-Values and Min-Test[a] Results for SPID6 Endpoints:GBP250/HC10 Combination Comparators vs GBP250/HC10 Placebo 0.0001* GBP250 0.0146* HC10 0.9187 Min-Test Result Negative [a] The min-test procedure indicates a statistically significant difference if the p-values of *all 3* simple comparisons are <0.05. * Statistically significant difference, p<0.05 Table 8: p.35 of 380	

				Table 9. p-values for Planned SPID6 Comparisons Treatment Comparisons / p-values HC10 vs Placebo: 0.0001* HC10 vs GBP250: 0.0198* GBP250 vs Placebo: 0.0799 * Statistically significant difference, p <0.05 Table 9 – p.35 of 380. <u>9. % of patients achieving "much improved" or "moderately improved"</u> • Not a predefined efficacy outcome • A nurse observer queried patients regarding pain relief at the following target time points: 0.33 (20 minutes), 0.66 (40 minutes), 1, 2, 3, 4, 5, 6, 7, and 8 hours postdose. If rescue medication was administered, final assessment was made immediately before the dose was taken. • Pain relief was recorded using a 5-point categorical scale: o 0 = none o 1 = A little o 2 = Moderate o 3 = A Lot o 4 = Complete • The time effect curve for the GBP250/HC10 group was very similar to that of the HC10 group. • Separation between the placebo and GBP250/HC10 groups and the placebo and HC10 groups was observed as early as 40 minutes after administration of study medication. • The PR time effect curve for the GBP250/HC10 group was statistically significantly better than the placebo group for Hours 0.66 (40 minutes) through 5 and	

				the GBP250 group for Hours 0.66 (40 minutes) through 4 (Figure 6, p.41 of 380). • The PR time effect curve for the GBP250/HC10 group was not statistically significantly better than the HC10 group at any time point. • See Figure 6 (p.41 of 380) for more details • See Appendix C.2.07 for Summary of Pain Relief (p.218 of 380) • See appendix D.5 for analysis of Pain Relief (p.292 of 380) • Patients also completed a Global Impression of Study Medication • Only patient global impression was global impression of study medication on a 5-point scale, tested at end of 8-hours in clinic o 1=Poor o 2=Fair o 3=Good o 4=Very Good o 5=Excellent • Responders were defined as those patients who evaluated their study medication as "excellent," "very good," or "good" on the Patient Global Assessment of Study Medication at 8 hours postdose, or at the time of rescue medication. • See Appendix C.2.04 (215/280) and tables 16, 17 (p.45 of 380) for details. Responder rates were as follows: Placebo: 9/49 (18.4%) GBP250/HC10: 33/51 (64.7%) GBP250: 18/50 (36%) HC10: 30/50 (60%)	

				<u>10. Histogram presentation of all PGIC 7-point results</u> • N/A, no 7-point PGIC like in other trials.	

Acute Study No. 6 – Berry 2005 – Acute herpes zoster pain - DBR CROSSOVER TRIAL (published) – FINAL **– Dr. TL Perry, July 27, 2008**

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Acute Study No. 6 (Berry 2005) Berry JD, Peterson KL. A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. Neurology 2005; 65: 444-447 Support: Pfizer (investigator-initiated grant) Dates: November 2002 – December 2003 Trial design: Independent. DBR Crossover Trial comparing fixed dose gabapentin 900 mg (G) with placebo (P) for 6 hours, before or after a minimum 24 hour washout. Concealment: identical	Acute herpes zoster ("shingles") Inclusion: • Herpes zoster rash onset ≤ 45 days of enrolment • Average daily pain ≥ 40 mm on a 100-mm visual analog scale (VAS) Exclusion: • Current use of gabapentin • Other untreated pain as severe as HZ pain • Orthostasis • Renal insufficiency (not defined) Allowable drugs: stable topical analgesics, oral NSAIDs,	Study design: 6 hour double blind crossover RCT comparing G with P as 2 arms (P/G or G/P), with ≥ 24 hours washout between crossovers (medians: 2 days for each sequence; range: 1-6 days between crossovers). Patient flow (Table 1, text): • Screened: not reported • Excluded: not reported • Randomized: 26 as P/G=13 G/P=13 • Completed crossover: 26 • Exposed/completed drug: P=26, G=26 • Withdrawn from treatments: P=0/13; G=0/13 Drug doses:	Predefined outcomes: Primary: Pain severity (VAS;100 mm scale) at intervals during 6 hours after dose. Secondary: • Allodynia area • Allodynia severity • SF-MPQ • Category of pain relief • AE Test of blinding: not described	Safety outcomes: None of the following is suitable for meta-analysis because of short duration and single dose. Mortality: Not reported Serious Adverse Events: Not reported Withdrawal Due to Adverse Events: P=0/26; G=0/26 Total withdrawals: P=0/26; G=0/26 Total patients with AE's: not reported comparably to other studies Most important AE's (Table 5): not reported comparably to other studies NB: Authors note that *"sleepiness, lightheadedness, and unsteady gait were greater after gabapentin, but wer not correlated with reduction in pain severity …"* (insignificant and trivial square of correlation coefficient). However, they appear to have summed AE for which gabapentin at this dose in similar subjects did not cause any AE, with those AE for which it did (dilution of effect would negate any real correlation of sedation or dizziness with benefit)	1. This is an interesting study which is not directly comparable with any other study. Because it reports median pain scores, where most other studies report means, interpretation is more difficult. Presentation of both means and medians, and/or presentation of individual curves from patients during phase 1 and phase 2 would have been interesting. No data are presented on patients' overall preference for P or G phase, which would have been easy to ascertain and report. 2. No outcomes are suitable for meta-analysis. 3. The most interesting feature of this study is the suggestion that it

placebo Randomization: *"computer-generated, blocked, stratified on age (≥ 50 or < 50) and time since rash onset (> 14 or ≤ 14 days) was administered by a study pharmacist not otherwise involved in the study."* (p. 444)	acetaminophen, opioids, antidepressants, taken up to 2 hours before experimental medication Baseline characteristics: Mean age: 58 (range 21-80) Pain scores for P/G group, G/P group reported as medians (not means) See Table 1, p. 445	Single dose of 900 mg given at baseline (time 0) Statistical Analysis: (p. 444) Power calculation for sample size based on effect size of 30%, SD: 40%, 2-tailed alpha 0.05, beta 0.2. Test for carry-over planned. See original report.		Total AE's (patients may have > 1 as total exceeds total patients with AE): Not reported None of the above is suitable for meta-analysis because of short duration and single dose Disability: not reported > 50% reduction in NRS pain score at endpoint vs. baseline: not reported (not an outcome) Primary outcome VAS pain score: Scores are reported as medians at various time points and are not comparable with other studies, e.g. Gilron 2005. Figure (unnumbered) on p. 446 describing % reduction from baseline suggests curves separate after 1.5 hours and were waning by 6 hours, but reports medians, not means. (No comparable curve for sedation or dizziness is provided.) The reporting of outcomes is virtually impossible to understand, although the graph looks intriguing in suggesting that if gabapentin has an effect on patients, it is virtually immediate in this model (probably for AE as well as pain reduction). Secondary outcomes: See original report. None are comparable to other studies, nor are clearly clinically meaningful. PGIC: not reported	might be possible to tell after the first dose of gabapentin whether a patient's pain will improve, which is pharmacologically logical and similar to most oral or parenteral analgesics (e.g. acetaminophen, NSAID, opioid) and a notion very familiar to patients seeking symptomatic relief. 4. The argument that analgesia was not correlated with sedation or dizziness is undermined by the apparent inclusion of AE not associated with gabapentin in the correlation calculation (dilution effect). 5. Uncertain effect of exclusion of patients currently taking gabapentin.

TAI 2002 – Excluded Study No. 1 - GABAPENTIN vs. PLACEBO FOR NEUROPATHIC PAIN AFTER SPINAL CORD INJURY – DBR CROSSOVER TRIAL (Published) - SUMMARY

Study/Design/dates	Inclusion criteria/baseline characteristics	Intervention(s), experimental design, N of subjects randomized (ITT)/ N who completed study	Predefined outcomes/issues in statistical analysis	Outcomes hierarchy (Cochrane, investigators: primary/secondary)	Comments/conclusions of Dr. Perry
Excluded Study No. 1 Tai, Q, Kirshblum S, et al. Gabapentin in the Treatment of Neuropathic Pain After Spinal Cord Injury: A prospective, randomized, double-blind, crossover trial. J. Spinal Cord Medicine 2002; 25: 100-105. Support: American Academy of Physical Medicine and Rehabilitation, Eastern Paralyzed Veterans Association. Trial design: apparently spontaneous by investigators. Small study of 7 ionpatients and outpatients of the UMDNJ-New Jersey Medical School, New Jersey, USA. DBR placebo-controlled	Post spinal cord injury Inclusion: • 18-85 years old • "neuropathic pain confirmed by a spinal cord injury physician" • traumatic injury > 30 days old • 11-point "Neuropathic Pain Scale" score > 4 "representing moderate to severe pain" Exclusion: • severe cognitive impairment • major depression or score > 16 on Beck Depression Inventory • creatinine clearance < 60 mL/min Allowable drugs: concurrent medications already in use, including anticonvulsant, antidepressant, other analgesics, also new p.r.n. analgesics allowed NB: 3/7 subjects completing trial took continuous release oxycodone, ibuprofen, and	Study design: 10 week double blind crossover RCT comparing G with placebo, with 2 week washout on placebo before crossover. Patient flow(p. 101): • Sceened: not reported • 3 dayrun-in period (not described further) • Excluded: not reported • Randomized: 14 • Withdrew: 7 (1 WDAE, 6 other reaons) • Completed: 7 Drug doses: • Starting dose G=300 mg/d x 2 days • Then 600 mg/d x 5 days • Then 900 mg/d x 1 week • Then 1200 mg/d x 1 week • Then 1800 mg/d x 1 week (or equivalent placebo capsules, all in t.i.d. divided	Predefined outcomes: Primary: Not clearly specified in methods section. As interpreted from "Results" section, primary outcomes appears to be a difference at p < .05 for any of 10 possible sub-scores of "Neuropathic Pain Index". No indication is given of consideration for multiple comparisons.	Mortality:Not reported Serious Adverse EventsNot reported; (total of 2 or 3 SAE, from text, but not differentiable by group) Withdrawal Due to Adverse Events:3/14 (group not identified) Total patients with AE's: not reported (at least 3, group not identified) Most important AE's: not reported Primary Outcome Pain scores: not interpretable, claim of statistically significant difference in "unpleasant feeling" as 1/10 subscores of Neuropathic Pain Scale at p=0.028 by Wilcoxon signed rank test ignores multiple	1. This study makes no overall claim for efficacy of gabapentin., and the claim of 1 "significantly different" pain score out of 10 possible subscores is not valid statistically because of the tiny study size and multiple comparisons. Only 7/14 patients enrolled completed the study and the dropouts are not accounted for adequately. The outcome described is very different from other studies, and not suitable for meta-analysis. The safety data are deficient and not suitable for meta-analysis. 3/7 patients were taking chronic oxycodone, ibuprofen, and amitriptyline simultaneously, and others took oxycodone as needed, but the amounts are not reported. 2. We should exclude this study from further analysis because it is too seriously flawed to draw any reasonable conclusions.

crossover trial, totalling10 weeks, plus 3 day initial run-in. Patients randomized to placebo (initial group B) or gabapentin (initial group A) for 4 weeks at initial dose of G=300 mg/d (or placebo), titrated to 1800 mg/d by Day 22, then stable dose until Day 28; then washout x 2 weeks on placebo (? single blind), then treatment with alternative arm, also for 4 weeks. *"Drugs placed in identical capsules to achieve blinding."* (p. 359) Patients screened and enrolled before January 2002 (dates not indicated, publication submitted January 16, 2002 – p. 100) Randomization: *"Pharmacist used a random distribution table for assignment" to Group A* (initial treatment with G) or Group B (initial placebo control*)* (p. 101) Concealment:	amitriptyline during the trial and an unknown number took oxycodone/acetaminophen (pp. 102, 103, 104) Baseline characteristics: Age (range): 27-48 Mostly cervical cord injuries	doses) Analysis: Comparison of 11 point NRS scores for 10 different "neuropathic pain descriptors" at baseline, end of week 4 for each phase (P, G) – differences between gabapentin-treated vs. placebo-treated groups in either group (A or B) tested by Wilcoxon signed rank test, with significance set at $p < 0.05$. No adjustment for multiple comparisons specified in methods section. (p. 102)		comparisons.	

Both drugs in gelatin-coated capsule form with “identical shape and colour”					

Study / Design / Dates	Inclusion Criteria / Baseline Characteristics	Intervention(s), Experimental Design, N of Subjects Randomized (ITT) / N Who Completed Study	Predefined Outcomes / Issues in Statistical Analysis	Outcomes Hierarchy (Cochrane, investigators: primary / secondary)	Comments / Conclusions
Excluded study 2 Perez HE, Sanchez GF (Department of Medicine, Division of Endocrinology, Instituto Mexicano del Seguro Social, Monterrey, Mexico Date of Study: ? – given editing times, substantially prior to June 1, 2000 – NB: the Pfizer/Parke-Davis-sponsored LADPN open-label study was run from February 16 to 4 December 2001; LADPN published report does not indicate Perez HE or Sanchez GF as investigators for LADPN. 1 page letter published in American J. Medicine, June 2000: Perez HE, Sanchez GF. Gabapentin Therapy for Diabetic Neuropathic	Painful diabetic neuropathy. <u>Inclusion Criteria:</u> • Diabetic patients referred for management of neuropathic pain "after conventional treatment failed" • Diagnosis by clinical examination and electrophysiologic study (no details) • Pain score > 60 on 100-point VAS <u>Exclusion Criteria:</u> • None reported <u>Baseline Characteristics:</u> Mean age 54, duration of diabetes 14 years, HbA1c 9.1%	<u>Study Design:</u> Parallel group study described as "double-blind, controlled trial", but no details are provided. <u>Flow of Participants:</u> Letter does not state that patients were randomized, although Cochrane review suggests they were, based on unpublished subsequent correspondence with authors. No information is provided about technique of double-blind, concealment, randomization. Two groups are shown in a table: P = 15 G = 17 Total = 32 patients Gabapentin patients were started on 300 mg twice/day and titrated to maximum of 1200 mg/day in successive office visits, based on clinical	<u>Predefined Outcomes:</u> Appears to be a reduction of at least 50% in VAS pain score (vs. baseline) at each visit. ("Our goal was to decrease the self-reported pain score during all examinations by more than half.") NO STATISTICAL ANALYSIS PLAN IS DESCRIBED, AND NO METHODS WHATSOEVER ARE REPORTED.	<u>Mortality</u> Not reported <u>Serious Adverse Events</u> Not reported <u>Withdrawals Due to Adverse Events:</u> Not reported <u>Adverse Events:</u> Not reported <u>Total Patients with Adverse Events:</u> Not reported <u>Primary outcome</u> (<u>></u> 50% reduction in VAS pain score, from baseline, at <u>all visits</u>): Not reported	1. This report is so incomplete that it is impossible to determine whether it describes a real experiment or not. There is no description of methods sufficient to determine whether patients were randomized, whether patients or investigators were blinded, whether patients experienced any of the expected adverse effects, or whether observations of patients' self-reported pain score were recorded "during all examinations" as the authors indicate would have been the primary outcome. One cannot reasonably include this report in any meta-analysis, nor consider it valid for any purpose. It does not make sense for the Cochrane systematic review (2005) to have included these data, which relate to a "greater than 50% reduction of VAS pain score", not to a "Patient Global Impression of Change/PGIC", and which are also completely disparate from all similar data (Figure 1, p. 16 of Wiffen PJ et al. Cochrane systematic review 2005), yet are included also in Figure 5 of the same review.

Pain (letter) American J. Medicine 2000; 108: 689 Purportedly a DBRCT but no details provided in report; Cochrane review 2005 (Wiffen PJ et al) states that correspondence with authors clarified randomization, but gives no details.		symptoms. Patients were observed for 3 months with multiple office visits (number and timing not reported). Authors state that patients were observed for 3 months but present data only for "pain relief at 1 month" defined as "at least 50% reduction in pain score".		The authors report only number and % of patients achieving this endpoint at 1 month, although they state that patients were observed for 3 months: P = 2/15 (13%) G = 14/17 (82%) p reported as 0.00012 ("Fisher's exact test or Student's t test") THIS IS NOT A RELIABLE STATISTICAL TEST AS THE OUTCOME REPORTED APPEARS TO BE A POST-HOC ANALYSIS OF A SINGLE TIME POINT, RATHER THAN THE APPARENT PRE-DEFINED PRIMARY ENDPOINT (assessment of pain at multiple visits)	

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT – Forrest plots for gabapentin vs. placebo
Dr. Thomas L. Perry, July 30, 2008

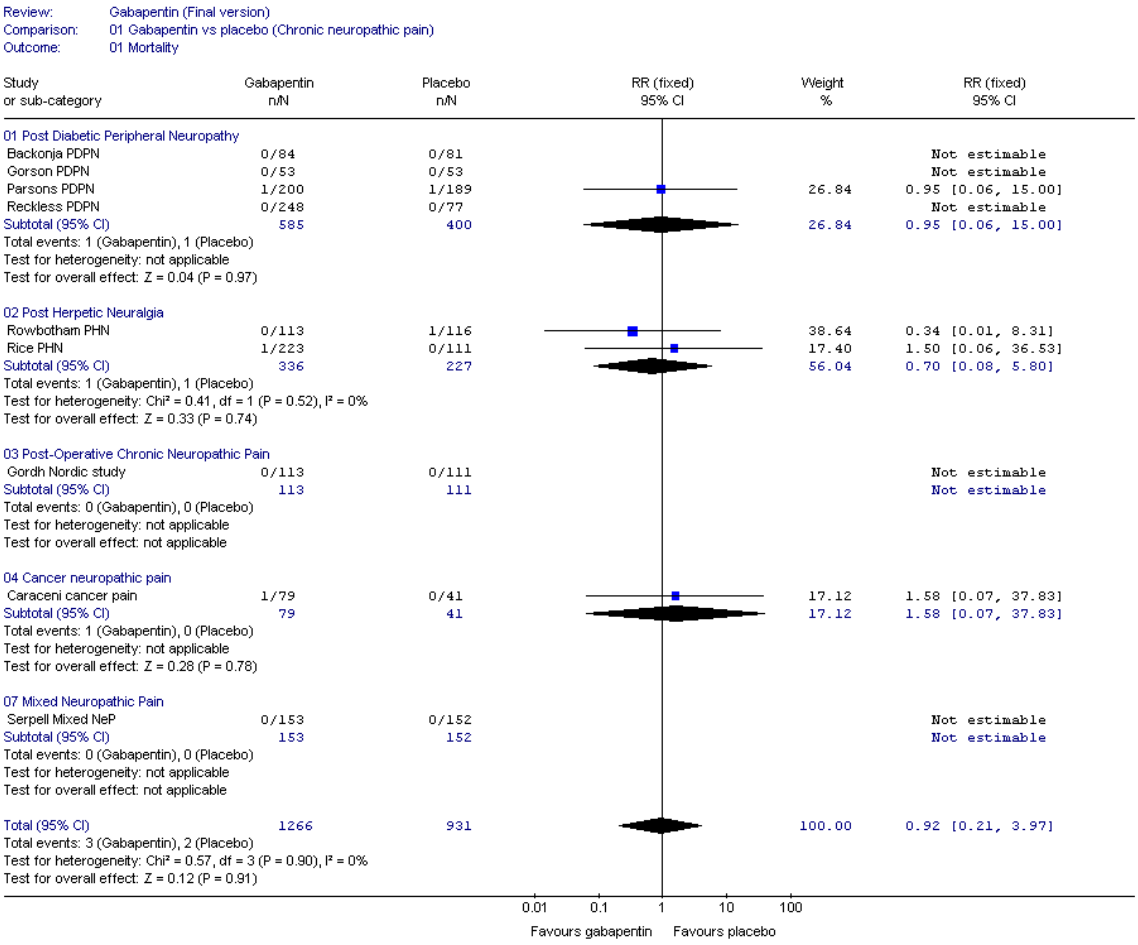
Thomas L. Perry MD.

Thomas L. Perry, M.D., FRCPC

Gabapentin project – Forrest plots for gabapentin vs. placebo

Dr. Thomas L. Perry, July 30, 2008

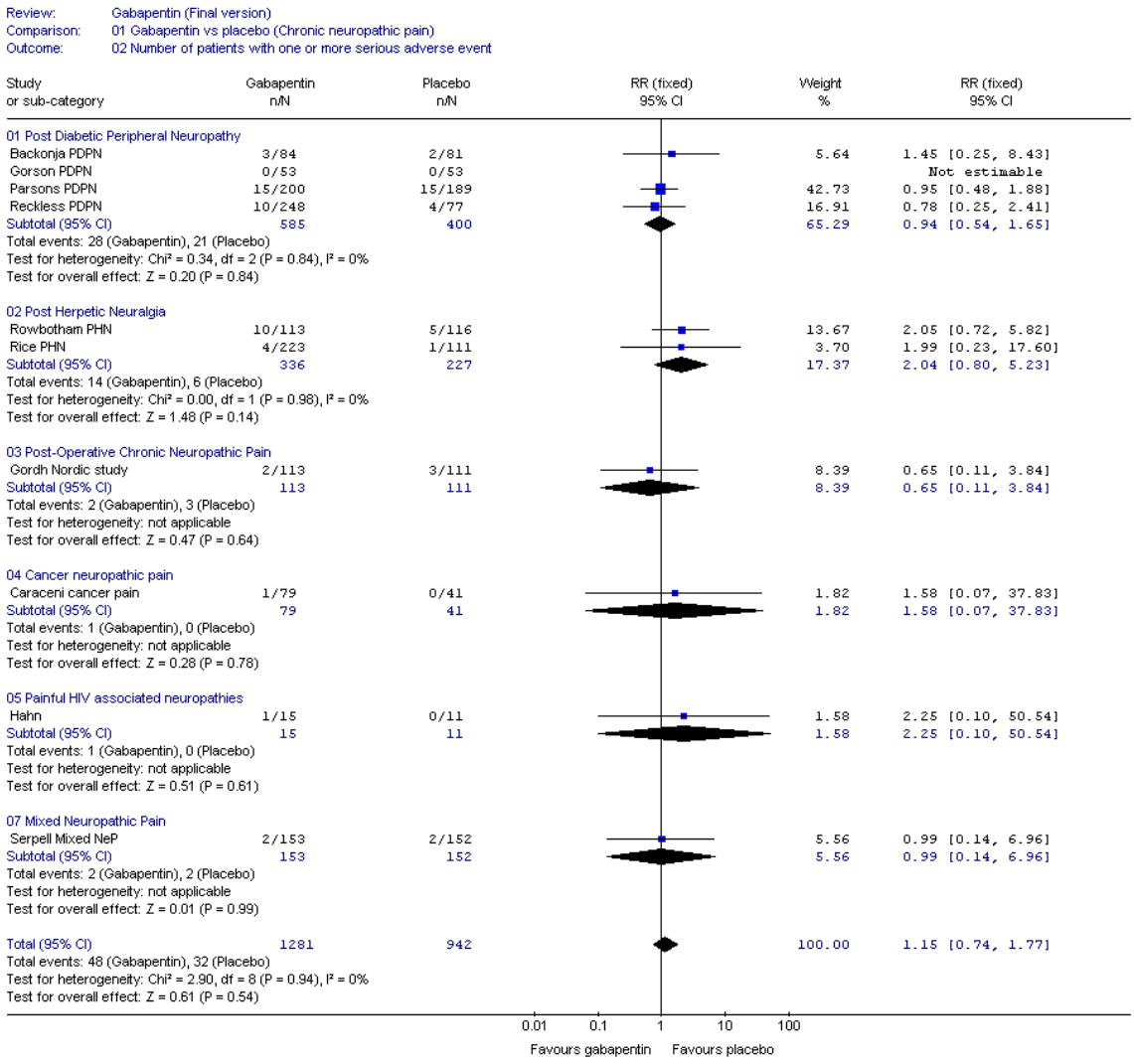
Mortality (Outcome 01)



Summary

Number of trials = 9; G =3/1266 (0.24%) and P = 2/931(0.21%)
RR with 95% CI = 0.92(0.21, 3.97)
No significant difference between gabapentin vs. placebo groups

Number of patients with 1 or more serious adverse event/SAE (Outcome 02)



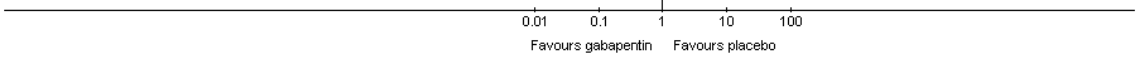
Summary

Number of trials = 10; G =48/1281 (3.7%) and P = 32/942(3.4%)
RR with 95% CI = 1.15(0.74, 1.77)
No significant difference between gabapentin vs. placebo groups.

Total withdrawals (Outcome 03)

Review: Gabapentin (Final version)
Comparison: 01 Gabapentin vs placebo (Chronic neuropathic pain)
Outcome: 03 Total withdrawals

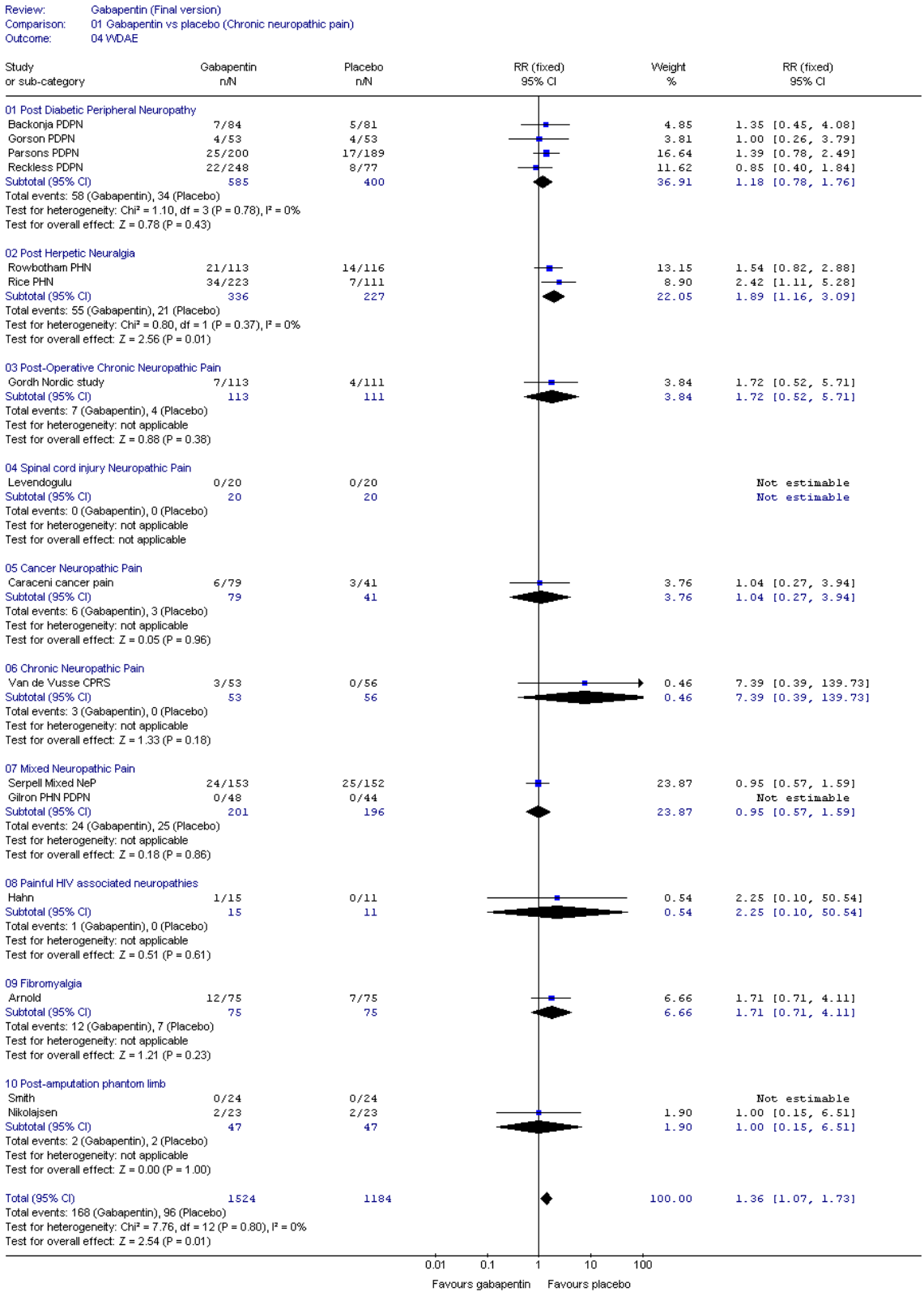
Study or sub-category	Gabapentin n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Post Diabetic Peripheral Neuropathy					
Backonja PDPN	14/84	16/81		7.05	0.84 [0.44, 1.61]
Parsons PDPN	64/200	54/189		24.04	1.12 [0.83, 1.52]
Reckless PDPN	37/248	12/77		7.93	0.96 [0.53, 1.74]
Subtotal (95% CI)	532	347		39.02	1.04 [0.81, 1.33]
Total events: 115 (Gabapentin), 82 (Placebo)					
Test for heterogeneity: Chi² = 0.70, df = 2 (P = 0.70), I² = 0%					
Test for overall effect: Z = 0.29 (P = 0.78)					
02 Post Herpetic Neuralgia					
Rowbotham PHN	24/113	21/116		8.97	1.17 [0.69, 1.98]
Rice PHN	45/223	17/111		9.83	1.32 [0.79, 2.19]
Subtotal (95% CI)	336	227		18.80	1.25 [0.87, 1.80]
Total events: 69 (Gabapentin), 38 (Placebo)					
Test for heterogeneity: Chi² = 0.10, df = 1 (P = 0.76), I² = 0%					
Test for overall effect: Z = 1.19 (P = 0.23)					
03 Post-Operative Chronic Neuropathic Pain					
Gordh Nordic study	11/113	9/111		3.93	1.20 [0.52, 2.78]
Subtotal (95% CI)	113	111		3.93	1.20 [0.52, 2.78]
Total events: 11 (Gabapentin), 9 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
04 Spinal cord injury Neuropathic Pain					
Levendogulu	0/20	0/20			Not estimable
Subtotal (95% CI)	20	20			Not estimable
Total events: 0 (Gabapentin), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
05 Cancer Neuropathic Pain					
Caraceni cancer pain	21/79	10/41		5.70	1.09 [0.57, 2.09]
Subtotal (95% CI)	79	41		5.70	1.09 [0.57, 2.09]
Total events: 21 (Gabapentin), 10 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
06 Chronic Neuropathic Pain					
Van de Vusse CPRS	4/53	6/56		2.53	0.70 [0.21, 2.36]
Subtotal (95% CI)	53	56		2.53	0.70 [0.21, 2.36]
Total events: 4 (Gabapentin), 6 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
07 Mixed Neuropathic Pain					
Serpell Mixed NeP	32/153	41/152		17.81	0.78 [0.52, 1.16]
Gilron PHN PDPN	4/48	1/44		0.45	3.67 [0.43, 31.57]
Subtotal (95% CI)	201	196		18.26	0.85 [0.57, 1.25]
Total events: 36 (Gabapentin), 42 (Placebo)					
Test for heterogeneity: Chi² = 1.96, df = 1 (P = 0.16), I² = 49.1%					
Test for overall effect: Z = 0.83 (P = 0.41)					
08 Painful HIV associated neuropathies					
Hahn	1/15	1/11		0.50	0.73 [0.05, 10.49]
Subtotal (95% CI)	15	11		0.50	0.73 [0.05, 10.49]
Total events: 1 (Gabapentin), 1 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
09 Chronic pain of masticatory muscle					
Kimos	6/25	8/25		3.46	0.75 [0.30, 1.85]
Subtotal (95% CI)	25	25		3.46	0.75 [0.30, 1.85]
Total events: 6 (Gabapentin), 8 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
10 Fibromyalgia					
Arnold	18/75	13/75		5.63	1.38 [0.73, 2.62]
Subtotal (95% CI)	75	75		5.63	1.38 [0.73, 2.62]
Total events: 18 (Gabapentin), 13 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
11 Post-amputation phantom limb					
Smith	0/24	0/24			Not estimable
Nikolajsen	7/23	5/23		2.16	1.40 [0.52, 3.77]
Subtotal (95% CI)	47	47		2.16	1.40 [0.52, 3.77]
Total events: 7 (Gabapentin), 5 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.51)					
Total (95% CI)	1496	1156		100.00	1.06 [0.90, 1.24]
Total events: 288 (Gabapentin), 214 (Placebo)					
Test for heterogeneity: Chi² = 7.28, df = 13 (P = 0.89), I² = 0%					
Test for overall effect: Z = 0.71 (P = 0.48)					



Total withdrawals (continued)

Summary
Number of trials = 15; G =288/1496 (19.3%) and P = 214/1156 (18.5%)
RR with 95% CI = 1.06(0.90, 1.24)
No significant difference between gabapentin vs. placebo groups

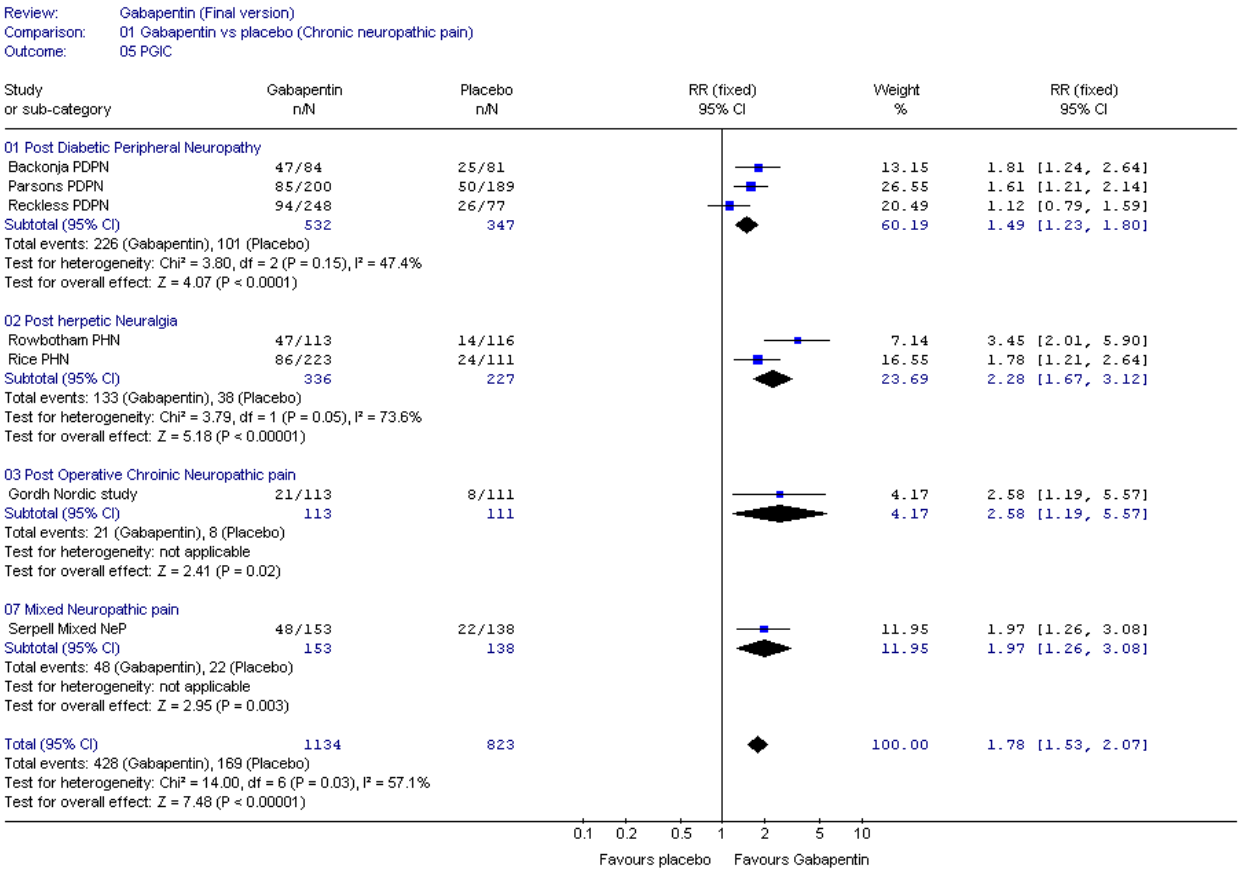
Withdrawal due to adverse events (Outcome 04)



Summary

Number of trials = 16; G =168/1524 (11.0%) and P = 96/1184 (8.1%)
RR with 95% CI = 1.36(1.07, 1.73)
ARI (absolute risk increase) = 2.9%, NNH = 35; favours placebo

PGIC (7 point scale) “moderately or much improved” as a pre-defined outcome (Outcome 05)

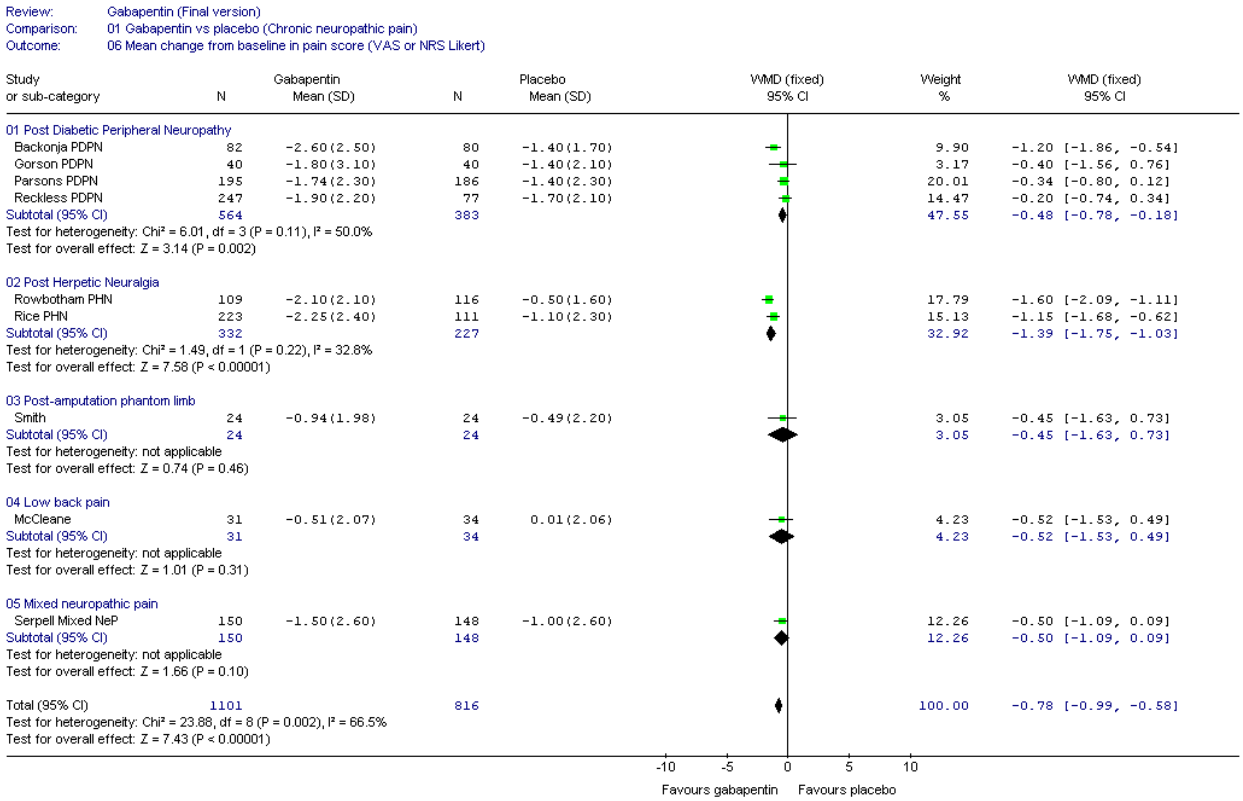


Summary

Number of trials = 7; G =428/1134 (37.7%) and P = 169/823 (20.5%)
RR with 95% CI = 1.78(1.53, 2.07)
ARR (absolute difference) = 17.2%, NNT = 6; favours gabapentin

Overall results heterogeneity is significant and may be due to the lower effect size of PDPN trials than the effect size for trials for other pain conditions.

Mean change from baseline in NRS/Likert or VAS pain score (Outcome 06)



Summary

Number of trials = 9; G =1101 and P = 816

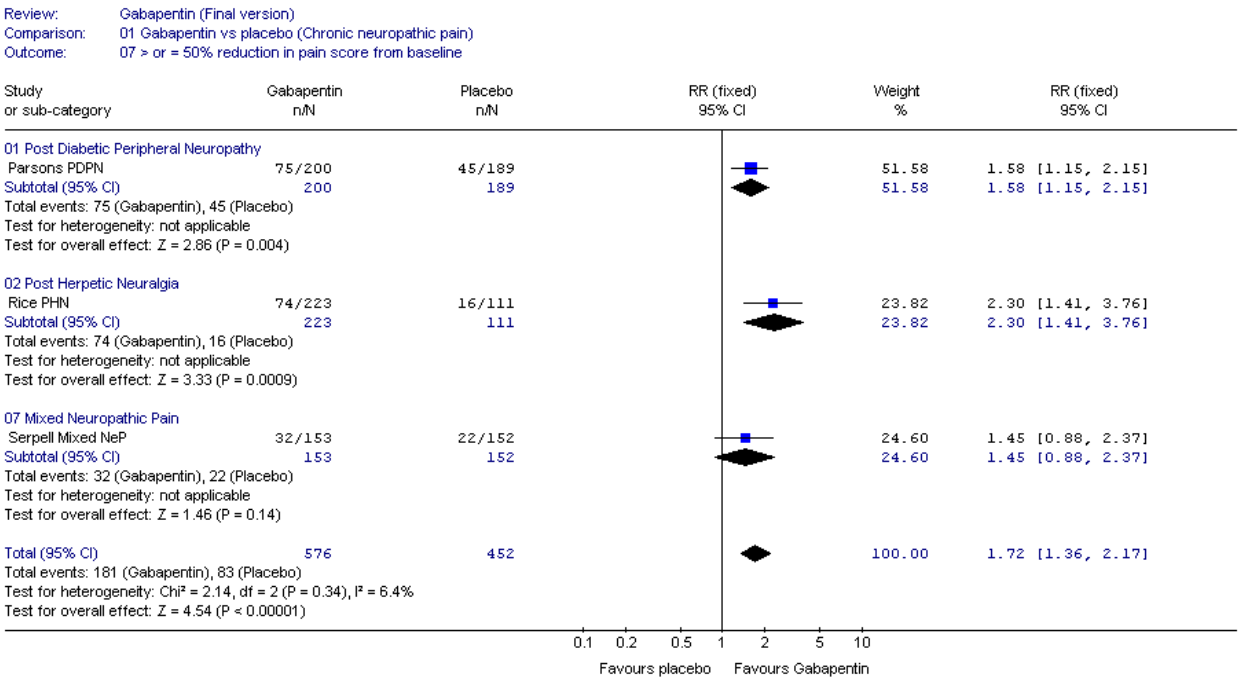
WMD with 95% CI = -0.78(-0.99, -0.58); favours gabapentin

There is significant heterogeneity present when PDPN trials and PHN trials are combined.

Notes:

1. There is no statistically significant heterogeneity (p =0.22) for PDPN trials. G =564 and P = 383
   For PDPN, WMD with 95% CI = -0.48(-0.78, -0.18) in the analysis shown above
2. The 95% CI of the WMD for PDPN and PHN trials are significantly different and do not overlap.

≥ 50% reduction in NRS/VAS pain score from baseline (Outcome 07)



Summary

Number of trials = 3; G =181/576 (31.4%) and P = 83/452(18.4%)
RR with 95% CI = 1.72(1.36, 2.17)
ARR (absolute difference) = 13%, NNT = 8; favours gabapentin

Specific adverse events (Outcome 08)
(Forrest plot on next page since it does not fit on one page)

ARI: absolute risk increase

Dizziness
# of trials = 13; G =300/1194 (25.1%) and P = 75/1023 (7.3%)
RR with 95% CI = 3.35(2.64, 4.24); ARI = 17.8%, NNH = 6

Somnolence
# of trials = 11; G =220/1061 (20.7%) and P = 48/892 (5.4%)
RR with 95% CI = 3.74(2.78, 5.02); ARI = 15.3%, NNH = 7

Confusion
# of trials = 2; G =23/197 (11.7%) and P = 3/192 (1.6%)
RR with 95% CI = 7.49(2.29, 24.5); ARI = 10.1%, NNH = 10

Ataxia
# of trials = 4; G =24/207 (11.6%) and P = 3/203 (1.5%)
RR with 95% CI = 4.89(1.96, 12.19); ARI = 10.1%, NNH = 10

Light headedness
# of trials = 1; G =11/75 (14.7%) and P = 1/75 (1.3%)
RR with 95% CI = 11.0(1.46, 83.08); ARI = 13.4%, NNH = 7.5

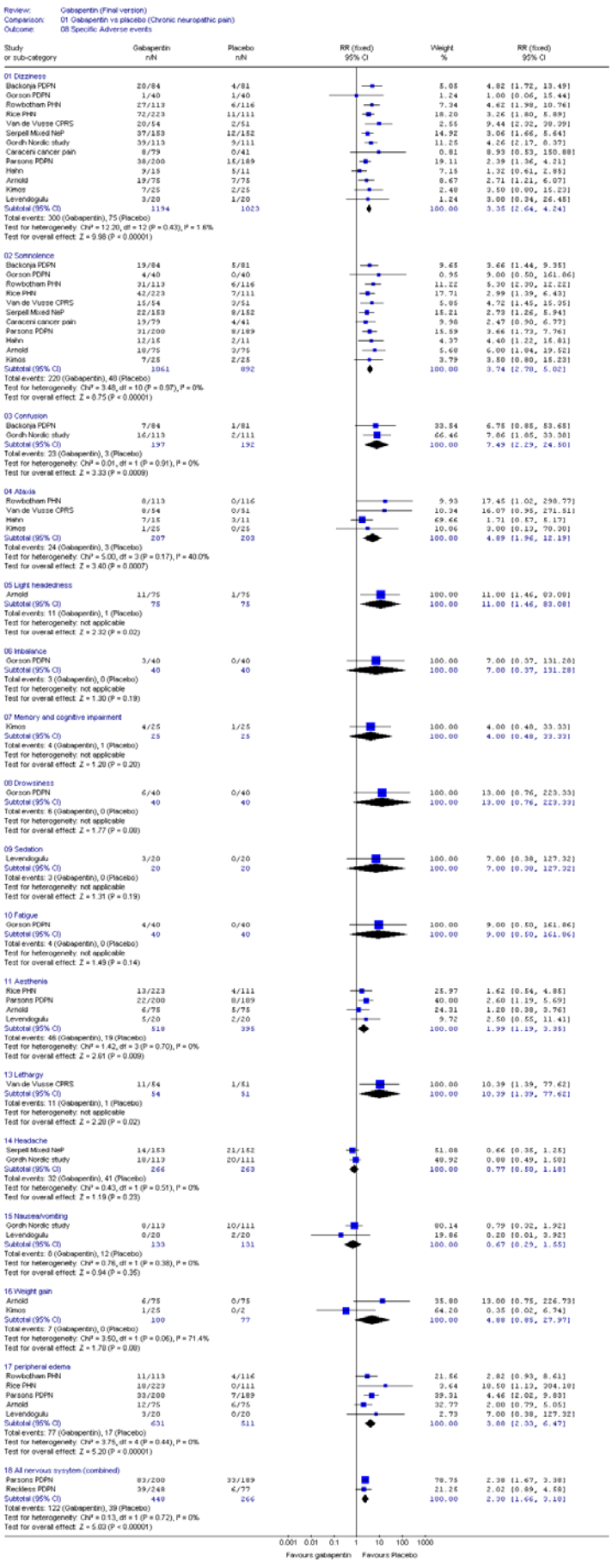
Aesthenia
# of trials = 4; G =46/518 (8.8%) and P = 19/395 (4.8%)
RR with 95% CI = 1.99(1.19, 3.35); ARI = 4.0%, NNH = 25

Lethargy
# of trials = 1; G =24/207 (11.6%) and P = 3/203 (1.5%)
RR with 95% CI = 4.89(1.96, 12.19); ARI =10.1 %, NNH = 10

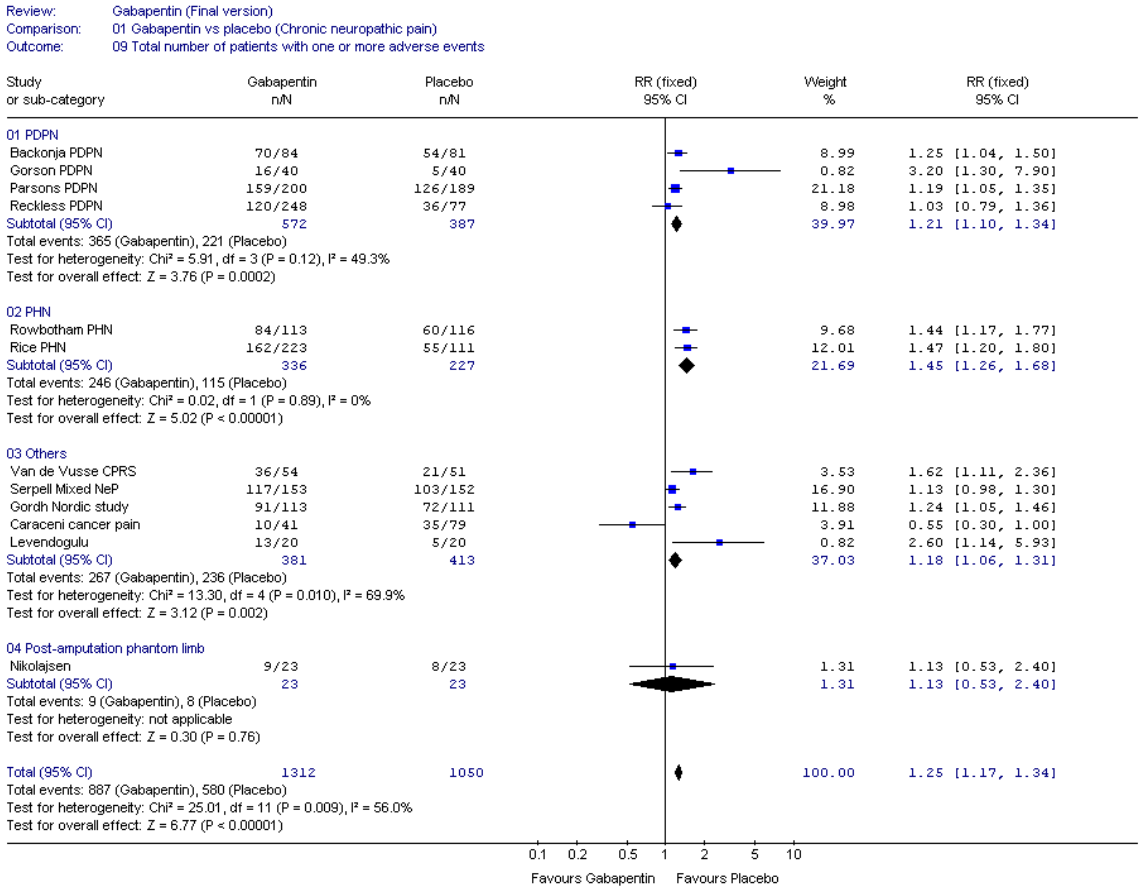
Edema
# of trials = 5; G =77/631 (12.2%) and P = 17/511 (3.3%)
RR with 95% CI = 3.80(2.33, 6.47); ARI = 8.9%, NNH = 11

All CNS adverse events
# of trials = 2; G =122/448 (27.2%) and P = 39/266 (14.7%)
RR with 95% CI = 2.30(1.66, 3.185); ARI = 12.5%, NNH = 8

Specific adverse events (Outcome 08)
Forrest plot follows on next page …


Review: Gabapentin (Final version)
Comparison: 01 Gabapentin vs placebo (Chronic neuropathic pain)
Outcome: 08 Specific Adverse events
Study or sub-category
Gabapentin n/N
Placebo n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
01 Dizziness
Blackonja PDPN 20/84 4/81 5.05 4.82 [1.72, 13.49]
Gorsen PDPN 1/40 1/40 1.24 1.00 [0.06, 15.44]
Rowbotham PHN 27/113 6/116 7.34 4.62 [1.98, 10.76]
Rice PHN 72/223 11/111 18.20 3.26 [1.80, 5.89]
Van de Vusse CPRS 20/54 2/51 2.55 9.44 [2.32, 38.39]
Serpell Mixed NeP 37/153 12/152 14.92 3.06 [1.66, 5.64]
Gordh Nordic study 39/113 9/111 11.25 4.26 [2.17, 8.37]
Caraceni cancer pain 8/79 0/41 0.81 8.93 [0.53, 150.88]
Parsons PDPN 38/200 16/189 19.11 2.39 [1.36, 4.21]
Hahn 9/15 5/11 7.15 1.32 [0.61, 2.85]
Arnold 19/75 7/75 8.67 2.71 [1.21, 6.07]
Kimos 7/25 2/25 2.40 3.50 [0.90, 15.23]
Levendoglu 3/20 1/20 1.24 3.00 [0.34, 26.45]
Subtotal (95% CI) 1194 1023 100.00 3.35 [2.64, 4.24]
Total events: 300 (Gabapentin), 75 (Placebo)
Test for heterogeneity: Chi² = 12.20, df = 12 (P = 0.43), I² = 1.6%
Test for overall effect: Z = 9.98 (P < 0.00001)
02 Somnolence
Blackonja PDPN 19/84 5/81 9.65 3.66 [1.44, 9.35]
Gorsen PDPN 4/40 0/40 0.95 9.00 [0.50, 161.86]
Rowbotham PHN 31/113 6/116 11.22 5.30 [2.30, 12.22]
Rice PHN 42/223 7/111 17.71 2.99 [1.39, 6.43]
Van de Vusse CPRS 15/54 3/51 5.05 4.72 [1.45, 15.35]
Serpell Mixed NeP 22/153 8/152 15.21 2.73 [1.26, 5.94]
Caraceni cancer pain 19/79 4/41 9.96 2.47 [0.90, 6.77]
Parsons PDPN 31/200 8/189 15.59 3.66 [1.73, 7.76]
Hahn 12/15 2/11 4.37 4.40 [1.22, 15.81]
Arnold 19/75 3/75 5.60 6.00 [1.94, 19.52]
Kimos 7/25 2/25 3.79 3.50 [0.80, 15.23]
Subtotal (95% CI) 1061 892 100.00 3.74 [2.70, 5.02]
Total events: 220 (Gabapentin), 48 (Placebo)
Test for heterogeneity: Chi² = 9.48, df = 10 (P = 0.97), I² = 0%
Test for overall effect: Z = 8.75 (P < 0.00001)
03 Confusion
Blackonja PDPN 7/84 1/81 33.54 6.75 [0.88, 53.65]
Gordh Nordic study 16/113 2/111 66.46 7.86 [1.85, 33.38]
Subtotal (95% CI) 197 192 100.00 7.49 [2.29, 24.50]
Total events: 23 (Gabapentin), 3 (Placebo)
Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%
Test for overall effect: Z = 3.33 (P = 0.0009)
04 Ataxia
Rowbotham PHN 0/113 0/116 9.93 17.45 [1.02, 298.77]
Van de Vusse CPRS 8/54 0/51 10.34 16.07 [0.95, 271.51]
Hahn 7/15 3/11 69.66 1.71 [0.57, 5.17]
Kimos 1/25 0/25 10.06 3.00 [0.13, 70.30]
Subtotal (95% CI) 207 203 100.00 4.89 [1.96, 12.19]
Total events: 24 (Gabapentin), 3 (Placebo)
Test for heterogeneity: Chi² = 5.00, df = 3 (P = 0.17), I² = 40.0%
Test for overall effect: Z = 3.40 (P = 0.0007)
05 Light headedness
Arnold 11/75 1/75 100.00 11.00 [1.46, 83.08]
Subtotal (95% CI) 75 75 100.00 11.00 [1.46, 83.08]
Total events: 11 (Gabapentin), 1 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.32 (P = 0.02)
06 Imbalance
Gorsen PDPN 3/40 0/40 100.00 7.00 [0.37, 131.28]
Subtotal (95% CI) 40 40 100.00 7.00 [0.37, 131.28]
Total events: 3 (Gabapentin), 0 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.30 (P = 0.19)
07 Memory and cognitive impairment
Kimos 4/25 1/25 100.00 4.00 [0.48, 33.33]
Subtotal (95% CI) 25 25 100.00 4.00 [0.48, 33.33]
Total events: 4 (Gabapentin), 1 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
08 Drowsiness
Gorsen PDPN 6/40 0/40 100.00 13.00 [0.76, 223.33]
Subtotal (95% CI) 40 40 100.00 13.00 [0.76, 223.33]
Total events: 6 (Gabapentin), 0 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
09 Sedation
Levendoglu 3/20 0/20 100.00 7.00 [0.38, 127.32]
Subtotal (95% CI) 20 20 100.00 7.00 [0.38, 127.32]
Total events: 3 (Gabapentin), 0 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.31 (P = 0.19)
10 Fatigue
Gorsen PDPN 4/40 0/40 100.00 9.00 [0.50, 161.86]
Subtotal (95% CI) 40 40 100.00 9.00 [0.50, 161.86]
Total events: 4 (Gabapentin), 0 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
11 Aesthenia
Rice PHN 13/223 4/111 25.97 1.62 [0.54, 4.85]
Parsons PDPN 22/200 8/189 40.00 2.60 [1.19, 5.69]
Arnold 6/75 5/75 24.31 1.20 [0.38, 3.76]
Levendoglu 5/20 2/20 9.72 2.50 [0.55, 11.41]
Subtotal (95% CI) 518 395 100.00 1.99 [1.19, 3.35]
Total events: 46 (Gabapentin), 19 (Placebo)
Test for heterogeneity: Chi² = 1.42, df = 3 (P = 0.70), I² = 0%
Test for overall effect: Z = 2.61 (P = 0.009)
13 Lethargy
Van de Vusse CPRS 11/54 1/51 100.00 10.39 [1.39, 77.62]
Subtotal (95% CI) 54 51 100.00 10.39 [1.39, 77.62]
Total events: 11 (Gabapentin), 1 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.20 (P = 0.02)
14 Headache
Serpell Mixed NeP 14/153 21/152 51.08 0.66 [0.35, 1.25]
Gordh Nordic study 10/113 20/111 48.92 0.49 [0.24, 1.00]
Subtotal (95% CI) 266 263 100.00 0.57 [0.38, 1.18]
Total events: 32 (Gabapentin), 41 (Placebo)
Test for heterogeneity: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%
Test for overall effect: Z = 1.19 (P = 0.23)
15 Nausea/vomiting
Gordh Nordic study 9/113 10/111 80.14 0.79 [0.32, 1.92]
Levendoglu 0/20 2/20 19.86 0.20 [0.01, 3.92]
Subtotal (95% CI) 133 131 100.00 0.67 [0.29, 1.55]
Total events: 8 (Gabapentin), 12 (Placebo)
Test for heterogeneity: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
16 Weight gain
Arnold 6/75 0/75 35.80 13.00 [0.75, 226.73]
Kimos 1/25 0/2 64.20 0.35 [0.02, 6.74]
Subtotal (95% CI) 100 77 100.00 4.88 [0.98, 27.97]
Total events: 7 (Gabapentin), 0 (Placebo)
Test for heterogeneity: Chi² = 3.50, df = 1 (P = 0.06), I² = 71.4%
Test for overall effect: Z = 1.70 (P = 0.09)
17 peripheral edema
Rowbotham PHN 11/113 4/116 21.56 2.82 [0.93, 8.61]
Rice PHN 10/223 0/111 9.64 10.50 [1.13, 304.10]
Parsons PDPN 33/200 7/189 39.31 4.46 [2.02, 9.83]
Arnold 12/75 6/75 32.77 2.00 [0.79, 5.05]
Levendoglu 3/20 0/20 2.73 7.00 [0.38, 127.32]
Subtotal (95% CI) 631 511 100.00 3.88 [2.33, 6.47]
Total events: 77 (Gabapentin), 17 (Placebo)
Test for heterogeneity: Chi² = 3.75, df = 4 (P = 0.44), I² = 0%
Test for overall effect: Z = 5.20 (P < 0.00001)
18 All nervous sysytem (combined)
Parsons PDPN 83/200 33/189 78.75 2.38 [1.67, 3.38]
Reckless PDPN 39/248 6/77 21.25 2.02 [0.89, 4.58]
Subtotal (95% CI) 449 266 100.00 2.30 [1.66, 3.18]
Total events: 122 (Gabapentin), 39 (Placebo)
Test for heterogeneity: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%
Test for overall effect: Z = 5.03 (P < 0.00001)
0.001 0.01 0.1 1 10 100 1000
Favours gabapentin
Favours Placebo

Total number of patients with adverse events (Outcome 09)



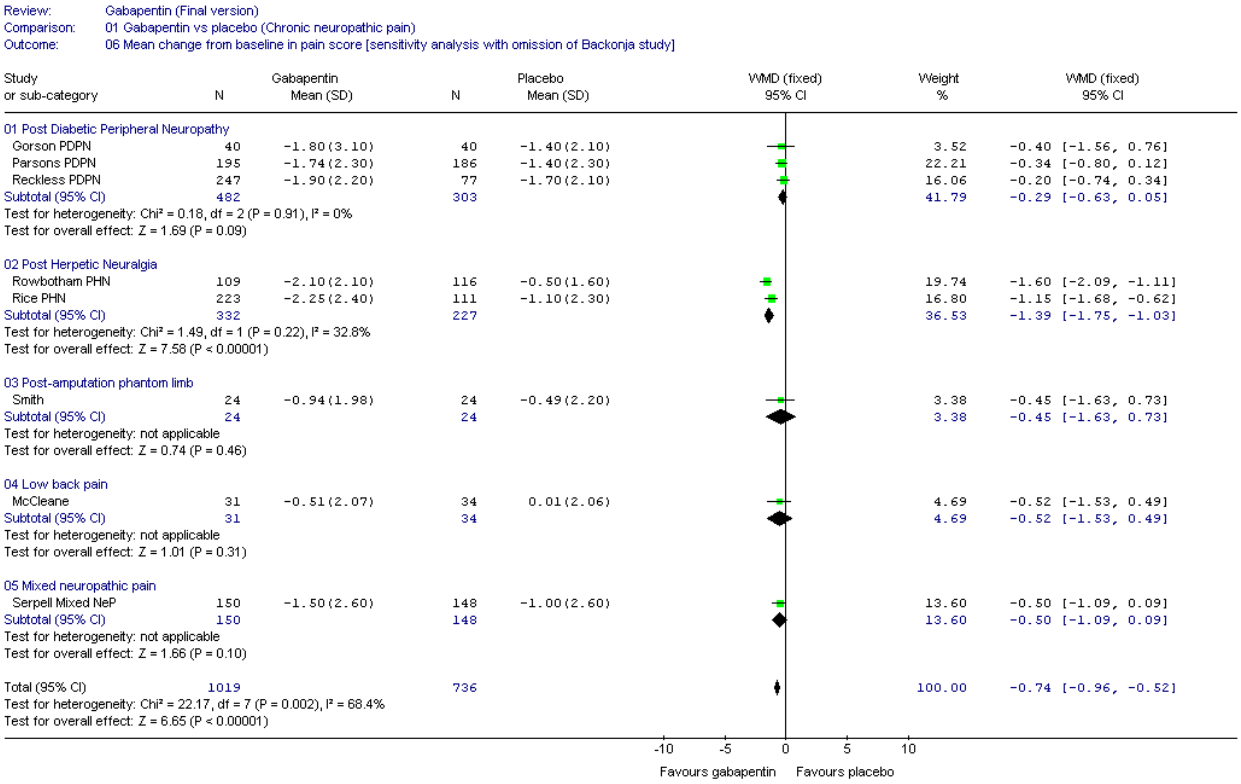
Summary

Number of trials = 12; G =887/1312 (67.6%) and P = 580/1050(55.2%)
RR with 95% CI = 1.25(1.17, 1.34)
ARI (absolute risk increase) = 12.4%, NNH = 8; favours placebo

SENSITIVITY ANALYSIS No. 1: NRS/VAS pain score (Outcome 06)

(omission of Backonja 1998 trial as potentially biased estimate due to unblinding)

Mean change from baseline in NRS/VAS pain score (Outcome 06)



Summary

Number of trials = 8; G = 1019 and P = 736

WMD (weighted mean difference) with 95% CI = -0.74(-0.96, -0.52); favours gabapentin

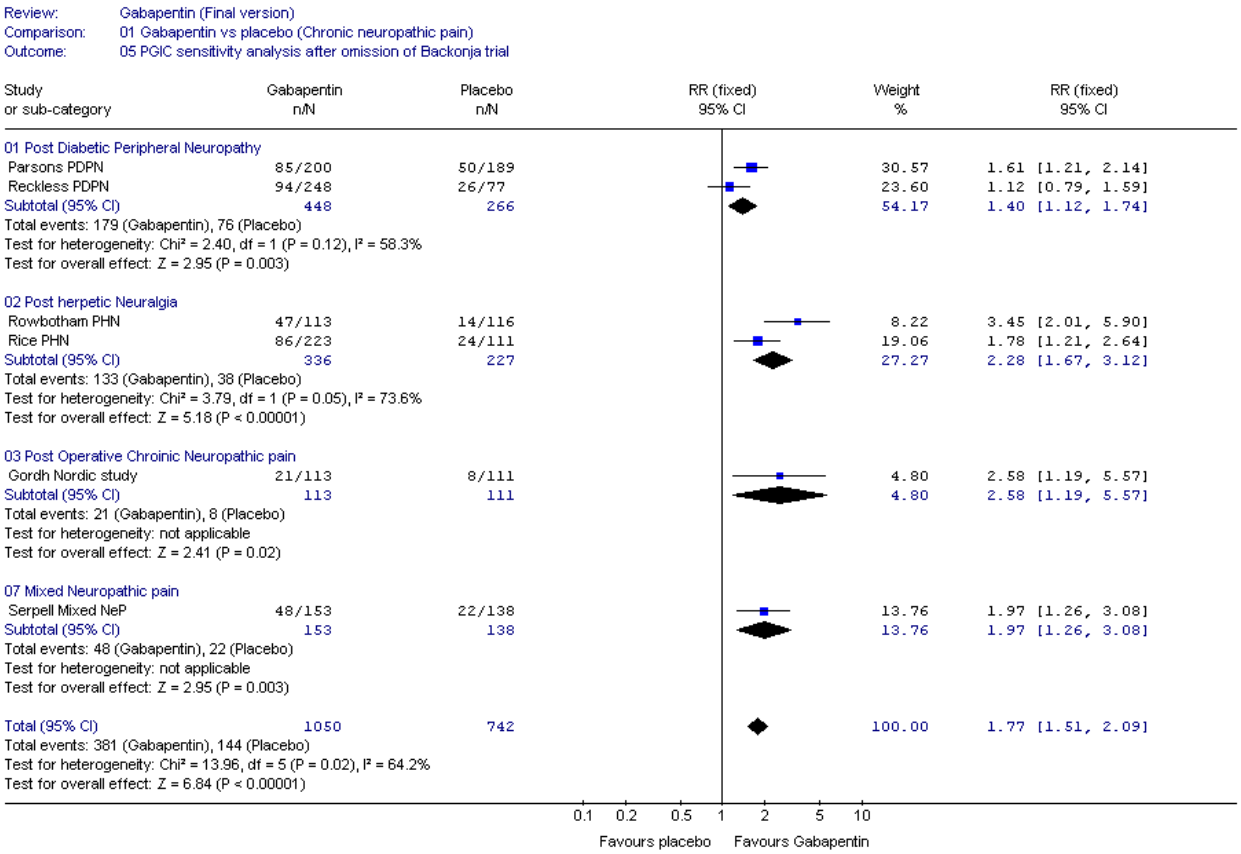
There is significant heterogeneity present when PDPN trials and PHN trials are combined.

WMD for change in pain score is slightly lower with Backonja 1998 removed.

SENSITIVITY ANALYSIS No. 2: PGIC (Outcome 05)

(omission of Backonja as potentially biased estimate due to unblinding)

PGIC (7 point scale) moderately or much improved as a pre defined outcome (Outcome 5)



Summary

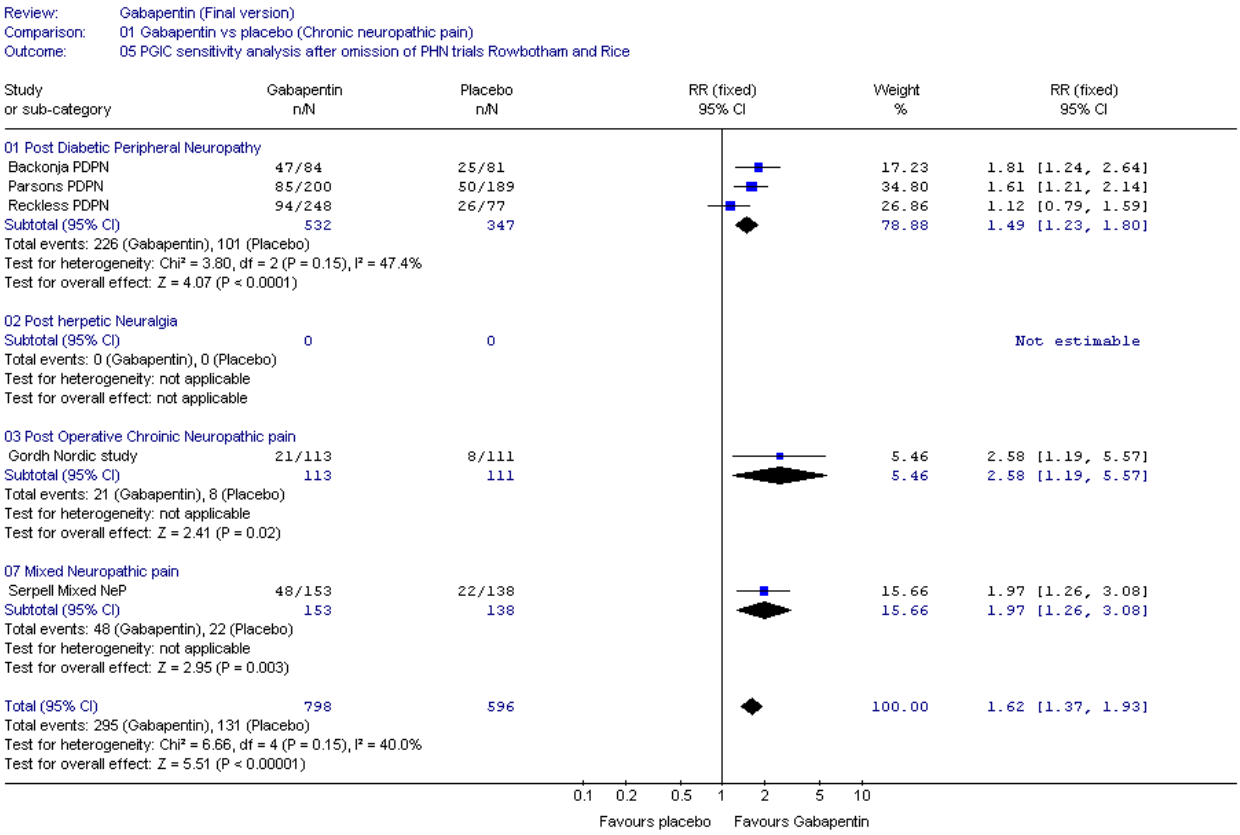
Number of trials = 6; G = 381/1050 (36.3%) and P = 144/742(19.4%)
RR with 95% CI = 1.77(1.51, 2.09)
ARR (absolute difference) = 16.9%, NNT = 6; favours gabapentin

Overall results heterogeneity is significant and may be due to the lower effect size of PDPN trials than the effect size for trials for other pain conditions.

SENSITIVITY ANALYSIS No. 3: PGIC (Outcome 5)

(omission of PHN trials Rowbotham and Rice – to segregate PHN from other pain conditions)

PGIC (7 point scale) moderately or much improved as a pre defined outcome (Outcome 5)



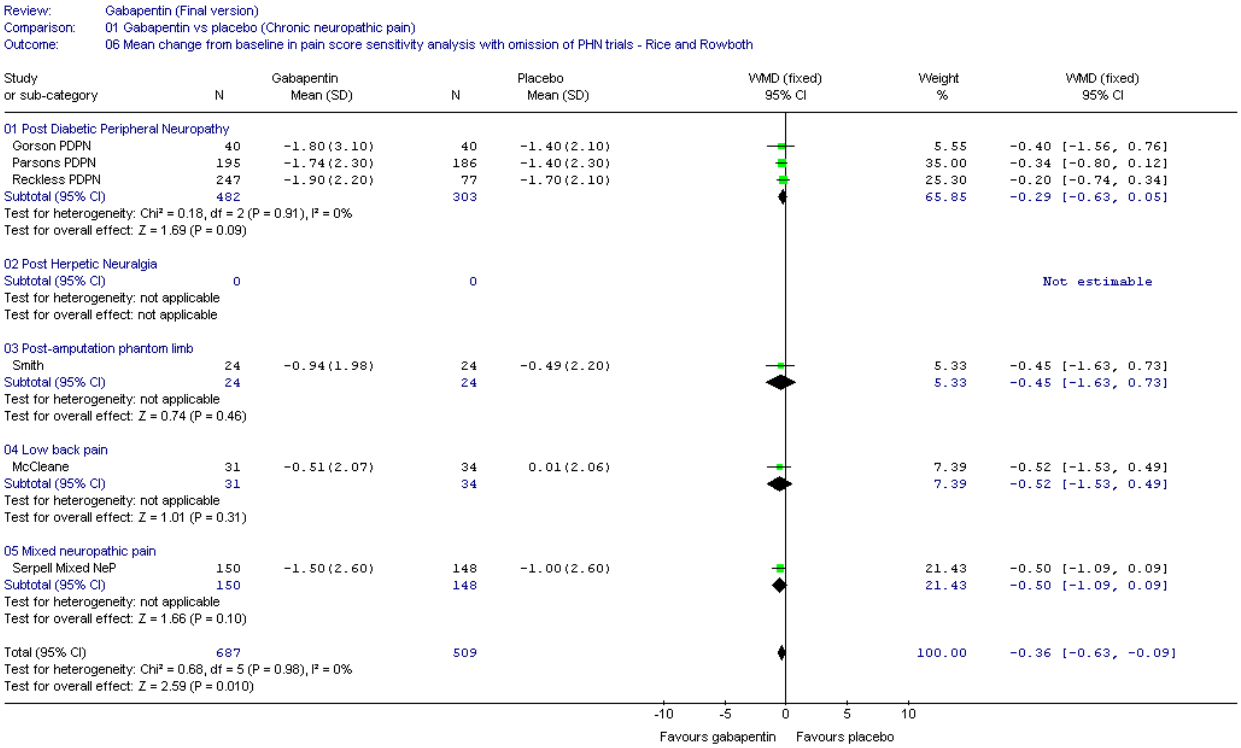
Summary

Number of trials = 5; G =295/798 (37.0%) and P = 131/596(22%)
RR with 95% CI = 1.62(1.37, 1.93)
ARR (absolute difference) = 15%, NNT = 6.7; favours gabapentin

SENSITIVITY ANALYSIS No. 4: NRS/VAS pain score (Outcome 06)

(omission of PHN trials Rowbotham and Rice – to segregate PHN from other pain conditions)

Mean change from baseline in NRS/VAS pain score (Outcome 06)



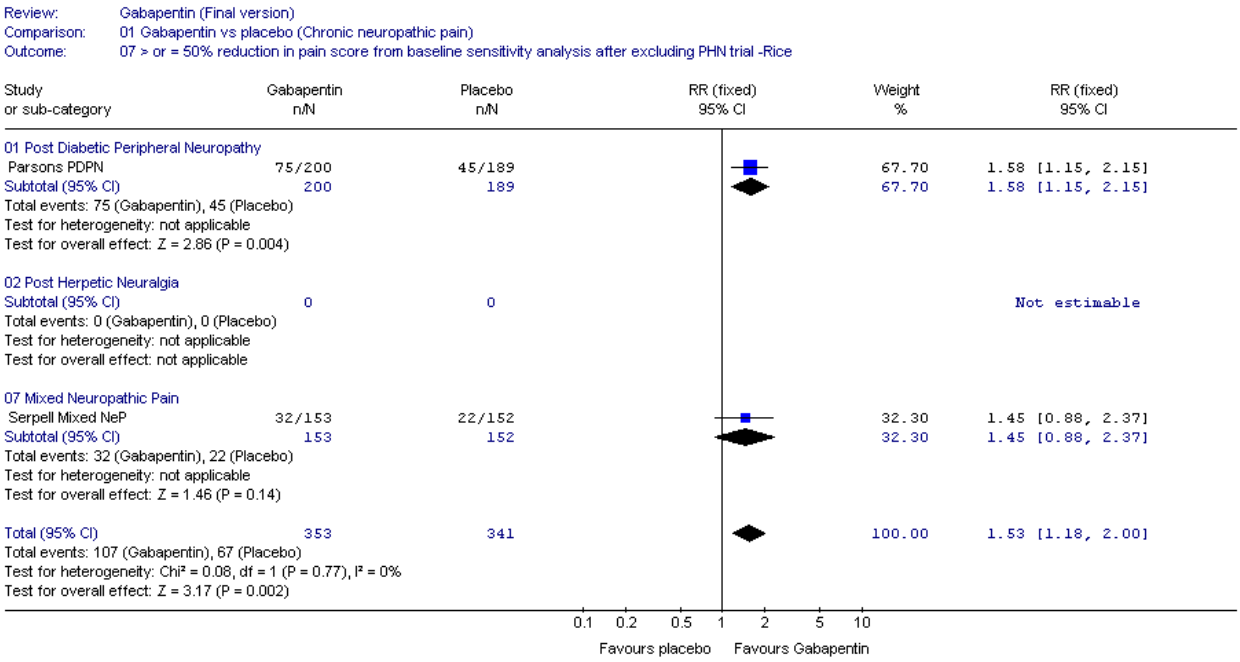
Summary

Number of trials = 6; G = 687 and P = 509
WMD with 95% CI = -0.36(-0.63, -0.09); favours gabapentin

There is no significant heterogeneity present when PHN trials are omitted.
Estimate of WMD is lower without 2 PHN trials.

SENSITIVITY ANALYSIS No. 5: ≥ 50% reduction in NRS/VAS pain score (Outcome 07)
(omission of PHN trials Rice – to segregate PHN from other pain conditions)

> 50% reduction in NRS/VAS pain score from baseline (Outcome 07)



Summary
Number of trials = 2; G =107/353 (30.3%) and P = 67/341(19.6%)
RR with 95% CI = 1.53(1.18, 2.00)
ARR (absolute difference) = 10.7%, NNT = 9; favours gabapentin

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT – Summary tables for Forrest plot analysis: gabapentin vs. placebo

Dr. Thomas L. Perry, August 8, 2008

Thomas L. Perry M.D.

Thomas L. Perry, M.D., FRCPC

GABAPENTIN VS PLACEBO TRIALS
Dr. Thomas L. Perry, August 8, 2008

Included trials:

A) Painful Diabetic Peripheral Neuropathy (PDPN): 4 trials

1. Backonja PDPN (Study 945-210; also published 1998)

Outcome	Gabapentin 900 to 3600mg/day	Placebo	Comments
Screened	Screened 232; randomized 165		
Randomized	84	81	
Mortality	0/84	0/81	
Total number of patients with 1 or >SAE	3/84	2/81	
Total withdrawals	14/84	16/81	
WDAE	7/84	5/81	
Global function	NR	NR	
Mean baseline to end point diff in pain score	-2.6 (2.5) N = 82	-1.4(1.7) N = 80	
50% reduction in pain score from baseline	NR	NR	Not a pre-specified endpoing
PGIC	47/84	25/81	
Total number of patients with 1 or >adverse events	70/84	54/81	
Specific AE Dizzness Somnolence Confusion	 20/84 19/84 7/84	 4/81 5/81 1/81	

Total numbers of AEs in gabapentin and placebo groups is not reported

2. Gorson PDPN (No study number; published 1999 and unpublished report)

Outcome	Gabapentin 900mg/day	Placebo	Comments
Screened	126 screened; 53 randomized		Published report N = 40 patients
Randomized	53 Phase I G = 19	53 phase I P = 21	
Mortality	0/53	0/53	
Total number of patients with 1 or > SAE	0/53	0/53	
Total withdrawals	NR	NR	
WDAE	4/53	4/53	
Global function	NR	NR	
Mean baseline to end point diff in pain score	-1.8 (3.1) N = 40	-1.4(2.1) N = 40	
> 50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	non-equivalent scale
Total number of patients with 1 or >adverse events	16/40	5/40	Reported in usable form only for this denominator
Specific AE Drowsiness Imbalance Fatigue Dizziness	 6/40 3/40 4/40 1/40	 0/40 0/40 0/40 1/40	Reported in usable form only for this denominator

Total numbers of AEs in gabapentin and placebo groups is not reported

3. Parsons PDPN (Study 945-1008; unpublished only 2005)

Outcome	Gabapentin 3600mg/day	Placebo	Comments
Screened	724 screened; 389 randomized		
Randomized	200	189	
Mortality	1/200	1/189	
Total number of patients with 1 or >SAE	15/200	15/189	
Total withdrawals	64/200	54/189	
WDAE	25/200	17/189	
Global function	NR	NR	
Mean baseline to end point diff in pain score	-1.74 (2.3) N = 195/200	-1.4 (2.3) N = 186/189	Reported difference in detailed study summary table: -0.34(-0.77, 0.09) p = 0.12
50% reduction in pain score from baseline	75/200	45/189	
PGIC	85/200	50/189	
Total number of patients with 1 or >adverse events	159/200	126/189	
Specific AE All nervous system Dizziness Somnolence Aesthenia (weakness) Peripheral edema	 83/200 38/200 31/200 22/200 33/200	 33/189 15/189 8/189 8/189 7/189	

Total adverse events G =521; Pbo = 326

4. **Reckless PDPN (Study 945-224; unpublished only 2000)**

Outcome	Gabapentin 600mg/day	Gabapentin 1200mg/day	Gabapentin 2400mg/day	ALL GBP groups	Placebo	Comments
Screened	Screened 432; randomized 325					
Randomized	82	82	84	248	77	
Mortality	0/82	0/82	0/84	0/248	0/77	
Total number of patients with 1 or >SAE	5/82	2/82	3/84	10/248	4/77	
Total withdrawals	12/82	6/82	19/84	37/248	12/77	
WDAE	8/82	3/82	11/84	22/248	8/77	
Global function	NR	NR	NR	NR	NR	
Mean baseline to end point diff in pain score (LOCF)	-1.4 (2.0) N = 82	-2.2 (2.2) N = 82	-2.1 (2.5) N = 83	-1.9(2.2) N = 247	-1.7(2.1) N = 77	
50% reduction in pain score from baseline	NR	NR	NR	NR	NR	Not a pre-specified outcome
PGIC	22/82	36/82	36/83	94/248	26/77	
Total number of patients with 1 or >adverse events	40/82	35/82	45/84	120/248	36/77	
Specific AE Nervous system (combined)	10/82	10/82	19/84	39/248	6/77	

Calculation for 3 gabapentin groups together
Weighted mean change = [114.8 +180.4 +174.3] / 247 =469.5 / 247 = 1.9
Weighted mean SD of change = [164 +180.4 +207.5] / 247 + 551.9 / 247 = 2.23

Total numbers of AEs in gabapentin and placebo groups not reported

B) Post-herpetic neuralgia (PHN): 2 trials

5. Rowbotham PHN (Study 945-211; also published 1998)

Outcome	Gabapentin 3600mg/day or maximum tolerated dose	Placebo	Comments
Screened	292 screened; 229 randomized		
Randomized	113	116	
Mortality	0/113	1/116	
Total number of patients with 1 or > SAE	10/113	5/116	
Total withdrawals	24/113	21/116	
WDAE	21/113	14/116	
Global function	NR	NR	
Mean baseline to end point diff in pain score	-2.1 (2.1) N = 109/113	-0.5 (1.6) N = 116	
50% reduction in pain score from baseline	NR	NR	
PGIC	47/113	14/116	
Total number of patients with 1 or >adverse events	84/113	60/116	
Specific AE Dizziness Somnolence Ataxia Peripheral edema	 27/113 31/113 8/113 11/113	 6/116 6/116 0/116 4/116	

Total numbers of AEs in gabapentin = 278 and placebo group = 151 (page 1/16 in detailed study summary)

6. Rice PHN (Study 945-295; also published 2001)

Outcome	Gabapentin 1800mg/day	Gabapentin 2400mg/day	OVERALL GBP group	Placebo	Comments
Screened	411 screened; 334 randomized				
Randomized	115	108	223	111	
Mortality	0/115	1/108	1/223	0/111	
Total number of patients with 1 or >SAE	3/115	1/108	4/223	1/111	
Total withdrawals	22/115	23/108	45/223	17/111	
WDAE	15/115	19/108	34/223	7/111	
Global function	NR	NR	NR	NR	
Mean baseline to end point diff in pain score	- 2.2(2.5) N =115	- 2.3(2.1) N =108	-2.25(2.4) N = 223	-1.1(2.3) N = 111	
50% reduction in pain score from baseline	37/115	37/108	74/223	16/111	
PGIC	44/115	42/108	86/223	24/111	
Total number of patients with 1 or >adverse events	81/115	81/108	162/223	55/111	
Specific AE Dizziness Somnolence Peripheral edema Asthenia	 36/115 20/115 6/115 7/115	 36/108 22/108 12/108 6/108	 72/223 42/223 18/223 13/223	 11/111 7/111 0/111 4/111	

Total AEs G1800 =180; G 2400=206; Pbo = 112 (pg 6 of 18)
Calculation for both GBP groups together; weighted mean change= [253 +248.4] / 223 =501.4 / 223=2.25
Weighted mean SD of change = [287.5 + 248.4] / 223 = 535.9 / 223 = 2.4
Used end of treatment SD for imputation

C) Post-operative chronic neuropathic pain: 1 trial

7. GORDH Nordic study POPP (Study 945-271; unpublished only 2003)

Outcome	Gabapentin 2400mg/day	Placebo	Comments
Screened	159 screened; randomized 120; exposed to G 113; exposed to placebo 111		
Randomized	G/P =61	P/G = 59	
Mortality	0/113	0/111	
Total number of patients with 1 or >SAE	2/113	3/111	
Total withdrawals 2/120 during wash out accounted in Pbo group	11/113	9/111	
WDAE	7/113	4/111	
Global function	NR	NR	
Mean baseline to end point diff in pain score Pain intensity score	Overall results at the end of treatment NR Reported at end of Rx 1 and Rx 2 so cannot be used		
50% reduction in pain score from baseline	NR	NR	Not a pre-specified outcome comparable to other studies
PGIC	21/113	8/11	
Total number of patients with 1 or >adverse events	91/113	72/111	
Specific AE Dizziness and vertigo Malaise & tiredness Headache (inc migraine) Nausea /vomiting Confusion	 39/113 31/113 18/113 8/113 16/113	 9/111 17/111 20/111 10/111 2/111	

Total numbers of AEs in gabapentin = 241 and placebo group = 168

D) Mixed neuropathic pain: 2 trials

8. Serpell (Study 945-430-306; also published 2002)

Outcome	Gabapentin 900 to 2400mg/day	Placebo	Comments
Screened	351 screened; 307 randomized (2 withdrew prior to drug)		
Randomized	153	152	
Mortality	0/153	0/152	See detailed discussion of mortality/SAE in detailed study summary
Total number of patients with 1 or >SAE	2/153	2/152	
Total withdrawals	32/153	41/152	
WDAE	24/153	25/152	
Global function	NR	NR	
Mean baseline to end point diff in pain score	-1.5 (2.6) N =150 SD end of RX used =2.6	-1.0 (2.6) N = 148 SD end of RX used =2.6	
>50% reduction in pain score from baseline	32/153	22/152	
PGIC	48/153	22/138	
Total number of patients with 1 or >adverse events	117/153	103/152	
Specific AE Somnolence Dizziness	 22/153 37/153	 8/152 12/152	

Total AEs : G = 336 and P = 223 (Table pg 2)

9. Gilron (No study number; published 2005)

Outcome	Gabapentin 3200mg/day	Morphine 120mg/day	G 2400mg/day + Morphine 60mg/day	Placebo (Lorezapam 1.6mg/day)
Screened	86 screened 57 randomized			
Total randomized	57 of which 41 completed all 4 treatment periods			
Randomized during Period A Period B Period C Period D Total in each group=	 13 11 11 13 48	 16 10 13 10 49	 14 13 9 11 47	 14 12 10 8 44
Mortality	NR	NR	NR	NR
Total number of patients with 1 or >SAE	NR	NR	NR	NR
Total withdrawals = 16	4/48	5/49	6/47	1/44
WDAE *inferred from close reading of p. 1328 under "Subjects" and "Primary Outcome"	0/48	0/49	3/47	0/44
Global function	NR	NR	NR	NR
Mean change from baseline in pain score Baseline mean = 5.72 (1.74); N = 57(SD – calculated as SE of 0.23 x root 57) – values taken from p. 1328 of Gilron)Primary outcome was mean pain scores in each group at maximal tolerated dose (p. 1327) – the change from baseline can only be estimated from figures and is therefore not meta-analysable.	NR	NR	NR	NR
>50% reduction in pain score from baseline	NR	NR	NR	NR
PGIC Reporting of best 3/6 categories of a 6-point scale is not suitable for meta-analysis with best 2/7 of the conventional PGIC scale.	NR	NR	NR	NR
Total number of patients with 1 or >adverse events ** not reported numerically – impossible to calculate accurately for meta-analysis	NR	NR	NR	NR
Specific AE [at max tolerated dose]*** ***Provided as % without providing denominators at week 4 in each Rx group – also active placebo comparator (lorazepam) invalidates comparisons for specific outcomes used in meta-analysis.	NR	NR	NR	NR

Total numbers of AEs in gabapentin and placebo groups is not reported

E) Cancer Neuropathic Pain: 1 trial

10. Caraceni (Study 945-420-276; also published 2004)

Outcome	Gabapentin 600 to 1800mg/day	Placebo	Comments
Screened	691 screened; randomized 121		Patients on stable dose of opioid and additional opioid as needed.
Randomized	80 (79 received drug)	41	
Mortality	1/79	0/41	
Total number of patients with 1 or >SAE	1/79	0/79	
Total withdrawals	21/79	10/41	
WDAE	6/79	3/41	
Global function	NR	NR	
Mean baseline to end point diff in pain score {Global pain score) VAS/NRS	NR	NR	
>50% reduction in pain score from baseline Pain intensity difference	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	10/41	35/79	
Specific AE Somnolence Dizziness Headache	 19/79 8/79	 4/41 0/41	

Total numbers of AEs in gabapentin and placebo groups is not reported

F) Spinal Cord injury neuropathic pain: 2 trials

11. Rintala (no study number, published 2002)

Outcome	Gabapentin 3600 mg/day	Amitriptyline 150mg/day	Active Placebo (Diphenhydramine 75mg/day)	Comments
Screened	50 screened; randomized 38 22/38(58%)completed all 3 phases			
Randomized and exposed to drug	32	34	31	
Mortality	NR	NR	NR	
Total number of patients with 1 or >SAE	NR	NR	NR	
Total withdrawals/exposed	6/32	6/34	3/31	Do not use active placebo arm for TW
WDAE	5/32	4/34	2/31	Do not use active placebo arm for WDAE
Global function	NR	NR	NR	
Mean baseline to end point diff in pain score^ Data cannot be used ^ Not reported as ITT with LOCF	Data cannot be used	Data cannot be used	Data cannot be used	
50% reduction in pain score from baseline	NR	NR	NR	
PGIC	NR	NR	NR	
Total number of patients with 1 or >adverse events	NR	NR	NR	
Specific AE Absolute numbers not reported but presented as % of side effect reports	NR	NR	NR	

See calculation of exposed/withdrawals in detailed study table

12. Levendoglu (no study number, published 2004)

Outcome	Gabapentin 900 to 3600mg/day	Placebo	Comments
Screened	Screened= ? ; randomized = 20		
Randomized	20	20	
Mortality	NR	NR	
Total number of patients with 1 or >SAE since \	NR	NR	
Total withdrawals	0/20	0/20	
WDAE	0/20	0/20	
Global function	NR	NR	
Mean baseline to end point diff in pain score (not reported consistently with other studies)	NR	NR	Reporting is not consistent with any other study, not meta-analysable
>50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	13/20	5/20	
Specific AE Asthenia (weakness) Sedation Dizziness (vertigo) Edema	 5/20 3/20 3/20 3/20	 2/20 0/20 1/20 0/20	

Total # of AEs G = 17 and P = 6

F) Complex Regional pain Syndrome – type 1: 1 trial

13. van de Vusse A (no study number; ublished 2004)

Outcome	Gabapentin 1800mg/day	Placebo	Comments
Screened	151 screened; 58 randomized		P=50/56 exposed, completed, G=49/53 exposed, completed; 46 completed crossover
Randomized	G/P=29	P/G=29	
Total withdrawals = 12 2 during wash out (numerator/exposed to drug)	4/53	6/56	
WDAE (numerator/exposed to drug)	3/53	0/56	
Mortality	NR	NR	
Total number of patients with 1 or >SAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score VAS/NRS mean (SD)	NR	NR	Completer analysis with unsatisfactory presentation of numerical outcomes, which cannot be meta-analysed.
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	36/54	21/51	
Specific AE Dizziness Somnolence Lethargy Ataxia	 20/54 15/54 11/54 8/54	 2/51 3/51 1/51 0/51	

G) Post-amputation phantom limb or residual limb pain: 3 trials

14. Bone (no study number; published 2002) – provides no usable data for meta-analysis

Outcome	Gabapentin 2400mg/day or maximum tolerated dose	Placebo	Comments
Screened	33 screened; randomized 19		
Randomized	G/P =10	P/G = 9	
Total withdrawals	Not interpretable	Not interpretable	
WDAE	NR	NR	
Mortality	NR	NR	
Total number of patients with 1 or >SAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score Mean (SD)	Data cannot be used as reported	Data cannot be used as reported	Unusable because of reporting
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	NR	NR	
Specific AE (denominators not reported Somnolence Dizziness Headache Nausea	 7 2 2 1	 2 1 1 1	Unusable because of reporting

15. Smith (no study number; published 2005)

Outcome	Gabapentin 3600 mg/d	Placebo	Comments
Screened	78 screened; 24 randomized to cross over (P/G=13, G/P=11)		
Randomized & exposed to drug	24	24	As reported in text
Mortality	NR		
Number of patients with 1 or more SAEs	NR		
Total withdrawals	0/24	0/24	
WDAE	0/24	0/24	
Global function	NR	NR	
Mean baseline to end point difference in pain score: Phantom limb pain Residual limb pain	 -0.94 (1.98) -1.22 (2.56)	 -0.49 (2.20) -0.74 (1.94)	Use phantom limb pain, which has higher numeric values at baseline and endpoint for both G and P: (more sensitive indicator) – differences for phantom limb or residual limb pain (G vs P) are similar and immaterial to results of meta-analysis.
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or > AE	NR	NR	

Total AE not reported.

16. Nikolajsen (no study number; published 2006)

Outcome	Gabapentin 2400mg/day	Placebo	comments
Screened	**? screened; 46 randomized; 12 withdrew; 41 "evaluable" (?LOCF)**		
Randomized	**23**	**23**	
ITT-LOCF population at first scheduled assessment, 1 week	**21/23**	**20/23**	
Mortality	**NR**	**NR**	**G = 1 death > 2 months after end of treatment, <u>not</u> reasonably ascribable to treatment**
SAEs	**NR**	**NR**	
Total withdrawals during 30 day medication phase	**7/23**	**5/23**	
WDAE	**2/23**	**2/23**	
Global function	**NR**	**NR**	
Mean baseline to end point diff in pain score (back pain at rest, LOCF)	**NR**	**NR**	**Pain reported only as group <u>median</u> scores derived from patient mean pain scores. Cannot use results for meta-analysis.**
50% reduction in pain score from baseline	**NR**	**NR**	
PGIC	**NR**	**NR**	
Total AE (patients with AE)	**9/23**	**8/23**	
Specific AE	**NR**	**NR**	

Total AE: not reported

H) Fibromyalgia: 1 trial

17. Arnold (no study number; published 2007)

Outcome	Gabapentin 300mg/day or to 2400mg/day	Placebo	Comments
Screened	252 screened; randomized 150		
Randomized	75	75	
Total withdrawals	18/75	13/75	
WDAE	12/75	7/75	
Mortality	NR	NR	
Total number of patients with 1 or >SAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score Mean (SD)	NR	NR	
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	NR	NR	
Specific AE Somnolence Dizziness Light headedness Edema Aesthenia Weight gain	 18/75 19/75 11/75 12/75 6/75 6/75	 3/75 7/75 1/75 6/75 5/75 0/75	

Total Adverse events were not reported

I) Painful HIV-associated neuropathy: 1 trial

18. Hahn (no study number; published 2004)

Outcome	Gabapentin 400mg/day to 2400mg/day	Placebo	Comments
Screened	Screened not reported; randomized 26		
Randomized	15	11	
Total withdrawals	1/15	1/11	
WDAE	1/15	0/11	
Mortality	NR	NR	
Total number of patients with 1 or >SAE	1/15	0/11	
Global function	NR	NR	
Mean baseline to end point diff in pain score Mean (SD)	NR	NR	
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	NR	NR	
Specific AE Somnolence Dizziness Ataxia	 12/15 9/15 7/15	 2/11 5/11 3/11	

Total Adverse events were not reported

J) Chronic pain of masticatory muscles: 1 study

19. Kimos (no study number; published 2007)

Outcome	Gabapentin 300mg/day to 4200mg/day	Placebo	Comments
Screened	Screened 79; randomized 50		
Randomized	25	25	
Total withdrawals	6/25	8/25	
WDAE	NR	NR	
Mortality	NR	NR	
Total number of patients with 1 or >SAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score Mean (SD)	NR	NR	
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or >adverse events	NR	NR	
Specific AE Somnolence Dizziness Memory and cognitive impairment Ataxia Weight gain	 7/25 7/25 4/25 1/25 1/25	 5/25 2/25 1/25 0/25 0/25	

Total Adverse events were not reported

K) Chronic low back pain: 1 study

20. McCleane (no study number; published 2001)

Outcome	Gabapentin 1200mg/day	Placebo	comments
Screened	? screened; 80 randomized; 65 evaluable; 8 dropped out (not reported by group); 7 failed to complete pain scores		
Randomized	40	40	
ITT-LOCF population	31	34	
Mortality	NR	NR	
SAEs	NR	NR	
Total withdrawals	NR	NR	Reported only for all patients, not by treatment group
WDAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score (back pain at rest, LOCF)	-0.51 (2.07), N=31/40	+0.01 (1.98), N=34/40	Table reports means at baseline and week 8 endpoint, SD for difference calculated as mean of (SDbaseline + SDendpoint) for G, P
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total AE (patients with AE)	NR	NR	
Specific AE	NR	NR	Unclear whether reported AE are number of patients or number of AE; therefore not used.

Total AEs: G =19; Pbo = 13

Excluded from analysis of gabapentin vs. placebo

21. Morello 1999: Active comparator trial No Placebo CONTROL

22. Dallocchio 2000: Active comparator trial No Placebo CONTROL; Open label so include only for Mortality, SAE and AE analysis

23. Chandra 2006: Active comparator trial NO Placebo CONTROL

24. GOMEZ- PEREZ 2004: No Placebo CONTROL so EXCLUDE

25. Tai, Rao 2007: EXCLUDE from analysis (see Dr. Perry's comments in detailed study summary table)

End of Appendix

* * * * *

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT – Forrest plots for gabapentin vs. active comparator

Dr. Thomas L. Perry, July 30, 2008

Thomas L. Perry M.D.

Thomas L. Perry, M.D., FRCPC

Gabapentin project – Forrest plots for gabapentin vs. active comparator
Dr. Thomas L. Perry, July 28th 2008

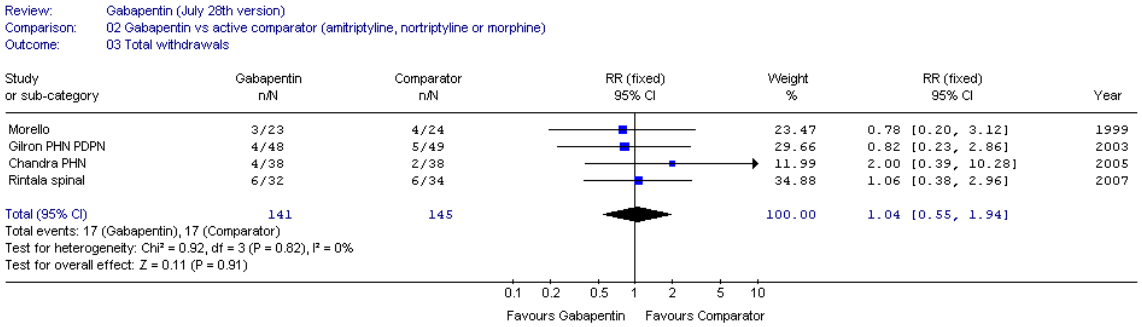
5 DBRCTs meet criteria for meta-analysis:

Dallocchio is an active comparator trial (gabapentin vs. amitriptyline) which is open label; randomization is questionable – Excluded from analysis
Data from 4DBRCTS – Morello (gabapentin vs. amitriptyline), Gilron (gabapentin vs. morphine), Chandra (gabapentin vs. Nortriptyline) and Rintala (gabapentin vs. amitriptyline) were used when available as an ITT with LOCF analysis

For the following outcomes data were not reported or data as reported in the publication could not be used for meta-analysis: mortality (Outcome 01 for gabapentin/placebo comparison); **number of patients with 1 or more SAEs** (Outcome 02 for G/P comparison); **PGIC** (Outcome 05 in G/P comparison; **mean change from baseline in pain scores** (NRS/VAS scale, Outcome 06 in G/P comparison).

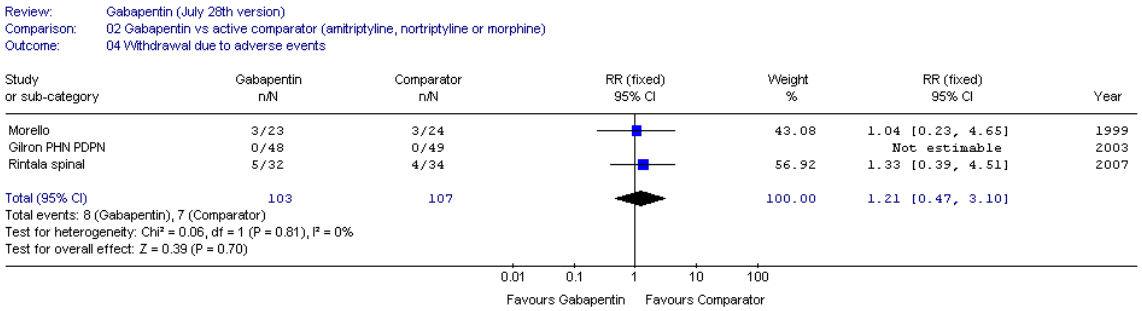
For the following outcomes, data were available for meta-analysis:

Total withdrawals (Outcome 03)



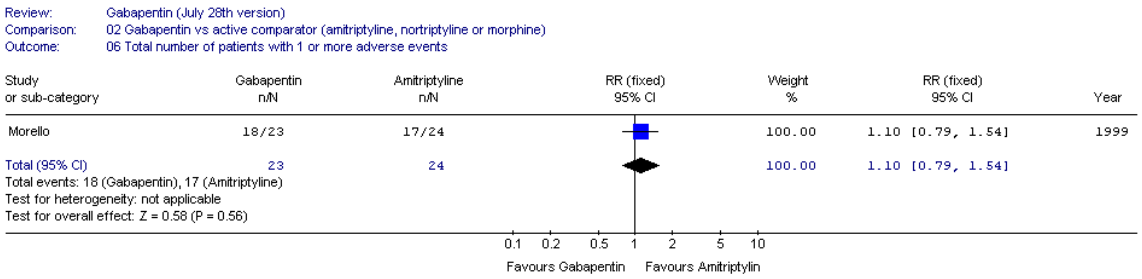
G = 17/141(12.1%) vs. active comparator = 17/145(11.7%)
RR 1.04 (0.55, 1.94); not statistically significant between treatment groups

Withdrawal due to adverse events (Outcome 04)



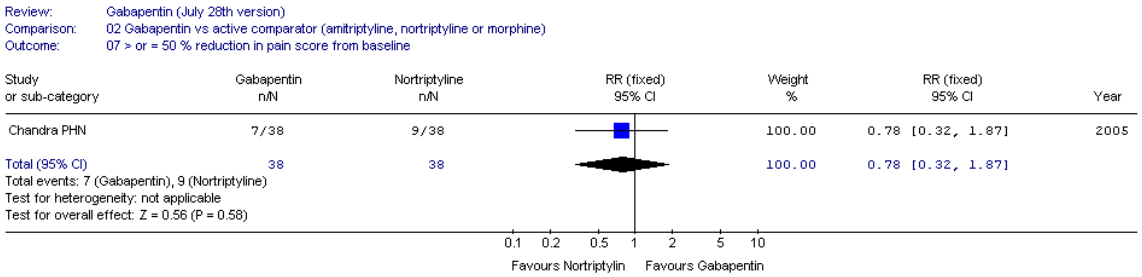
G = 8/103(7.8%) vs. active comparator = 7/107(6.5%)
RR 1.21(0.47, 3.10); not statistically significant between treatment groups

Total number of patients with with adverse events (Outcome 09 in G/P analysis)



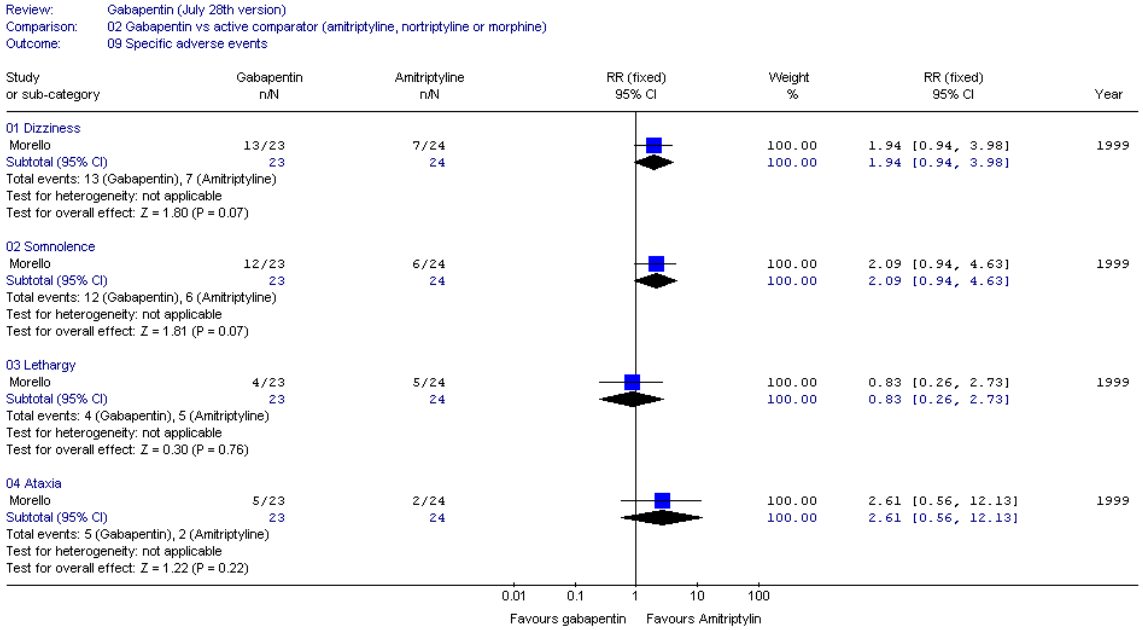
G = 18/23(78.3%) vs. active comparator = 17/24(70.4%)
RR 1.10(0.79, 1.54); not statistically significant between treatment groups

> 50% reduction in pain score from baseline (Outcome 07)



G = 7/38(18.4%) vs. active comparator = 9/38(23.7%)
RR 0.78 (0.32, 1.87); not statistically significant between treatment groups

Specific adverse events (Outcome 08 in G/P analysis)



No significant difference between treatment groups

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August 8, 2008

APPENDIX – GABAPENTIN PROJECT – Summary tables for Forrest plot analysis: gabapentin vs. active comparator

Dr. Thomas L. Perry, July 28, 2008

Thomas L. Perry M.D.

Thomas L. Perry, M.D., FRCPC

GABAPENTIN VS. ACTIVE COMPARATOR TRIALS
Dr. Thomas L. Perry – July 28, 2008

5 DBRCTS identified

a) EXCLUDED: Dallocchio 2000 is an active comparator trial but **open label** and randomization is questionable – excluded from meta-analysis.

b) INCLUDED: 4 trials:

Morello 1999 – PDPN (Published data only)

Outcome	Gabapentin 900 - 1800mg/day	Amitriptyline 25 - 75mg/day	Comments
Screened	**28 screened; 25 cross over**		**No placebo control**
Randomized & exposed to drug	**G/A 12/11 = 23**	**A/G 13/11 = 24**	
Mortality	**NR**		
Number of patients with 1 or more SAEs	**NR**		
Total withdrawals	**3/23**	**4/24**	
WDAE	**3/23**	**3/24**	
Global function	**NR**	**NR**	
Mean baseline to end point difference in pain score	**NR**	**NR**	**Cannot be used.** Numerical pain scale differs from all other studies; not ITT analysis**.**
50% reduction in pain score from baseline	**NR**	**NR**	
PGIC **Note:** "At least moderate relief" (top 3/6 categories) on "Global Rating of Pain Relief" might otherwise be usable, but is only reported for **completers** of both arms, not directly comparable with Study No. 15 (Gilron) – presented only for **interest.**	**NR** **"at least moderate relief" as best 3/6 on "GRPR"** **11/21** **(crossover completers)**	**NR** **"at least moderate relief" as best 3/6 on "GRPR"** **14/21** **(crossover completers)**	**Cannot be used.** 6-point "GRPR" categorical score not comparable with PGIC. Analysis not ITT (only shown for **completers**) therefore not comparable with 6-point score in Study No. 15 (Gilron).
Total number of patients with 1 or > AE	**18/23**	**17/24**	
Specific AE **Somnolence** **Dizziness (includes postural hypotension)** **Ataxia** **Lethargy (asthenia)**	 **12/23** **13/23** **5/23** **4/23**	 **6/24** **7/24** **2/24** **5/24**	

Total adverse events not reported.

GILRON 2005 - MIXED NEUROPATHIC PAIN (Published data only)

Outcome	Gabapentin ≤ 3200mg/day	Morphine ≤ 120mg/day	Comments
Screened	**86 screened 57 randomized**		**(G + M) and Lorazepam (active placebo) arm not shown – see Study No. 15 summary for results.**
Total randomized	**57 of which 41 completed all 4 treatment periods**		
Randomized and exposed to drug during: **Period A** **Period B** **Period C** **Period D** **Total exposed to drug in each group**	 **13** **11** **11** **13** **48**	 **16** **10** **13** **10** **49**	
Mortality	**NR**	**NR**	
Number of patients with 1 or more SAEs	**NR**	**NR**	
Total withdrawals	**4/48**	**5/49**	**From G, M arms**
WDAE	**0/48**	**0/49**	***inferred from close reading of p. 1328 under "Subjects" and "Primary Outcome"**
Global function	**NR**	**NR**	
Mean change from baseline in pain score	**NR**	**NR**	**Cannot be used.** Primary outcome was mean pain scores in each group at maximal tolerated dose (p. 1327) – the change from baseline can only be estimated from figures and therefore is not meta-analysable.
>50% reduction in pain score from baseline	**NR**	**NR**	
PGIC **Note:** "At least moderate relief" (top 3/6 categories)on Global Pain Relief Scale ("GPRS") is calculable for patients **exposed** to G, M but cannot be compared with Study No. 2 (Morello) which reports only on **completers**. Presented for **interest**.	**NR** **"at least moderate relief" as best 3/6 on "GPRS"** **27/48**	**NR** **"at least moderate relief" as best 3/6 on "GPRS"** **35/49**	**Cannot be used.** Reporting of best 3/6 categories of a 6-point scale is not suitable for meta-analysis with best 2/7 of the conventional PGIC scale. Best 3/6 on "GPRS" is calculable for patients **exposed** to G, M, but not comparable with Study No. 2 (Morello) which reports only **completers**.
Total number of patients with 1 or > AE	**NR**	**NR**	**Not reported numerically – impossible to calculate accurately for meta-analysis**
Specific AE (at max tolerated dose)	**NR**	**NR**	**Provided as % without providing denominators at week 4 in each Rx group – also active placebo comparator (lorazepam) invalidates comparisons for specific outcomes used in meta-analysis.**

Total adverse events not reported

CHANDRA 2006 – PHN (Published data only)

Outcome	Gabapentin 2700mg/day	Nortriptyline 150mg/day	Comments
Screened	110 screened; 76 randomized		ITT with LOCF in G = 34 and NT = 36
Randomized	38	38	
Mortality	NR	NR	
Number of patients with 1 or more SAEs	NR	NR	
Total withdrawals	4/38	2/38	
WDAE	NR	NR	
Global function	NR	NR	
Mean baseline to end point diff in pain score	Data cannot be used	Data cannot be used	See detailed study summary.
50% reduction in pain score from baseline	7/38	9/38	Suitable for meta-analysis (although not apparently a pre-defined outcome)
PGIC	NR	NR	
Total number of patients with 1 or > AE	Data cannot be used	Data cannot be used	See detailed study summary.
Specific AE	Data cannot be used	Data cannot be used	See detailed study summary.

Total adverse events data cannot be used (See detailed study summary).

RINTALA 2002 - SPINAL CORD INJURY NEUROPATHIC PAIN (Published data only)

Outcome	Gabapentin 3600 mg/day	Amitriptyline 150mg/day	Comments
Screened	50 screened; randomized 38		Diphenhydramine (active placebo) arm not shown – see Study No. 19 summary for results. 22/38(58%) completed all 3 phases (G, A, D)
Randomized (phase1/2/3) and exposed to drug	13/9/10 =32	12/12/10 = 34	
Mortality	NR	NR	
Number of patients with 1 or more SAEs	NR	NR	
Total withdrawals	6/32	6/34	Use data
WDAE	5/32	4/34	Use data
Global function	NR	NR	
Mean baseline to end point diff in pain score	Not reported as ITT with LOCF		Data cannot be used
50% reduction in pain score from baseline	NR	NR	
PGIC	NR	NR	
Total number of patients with 1 or > AE	NR	NR	
Specific AE Absolute numbers not reported but presented as % of side effect reports	NR	NR	

Total adverse events not reported

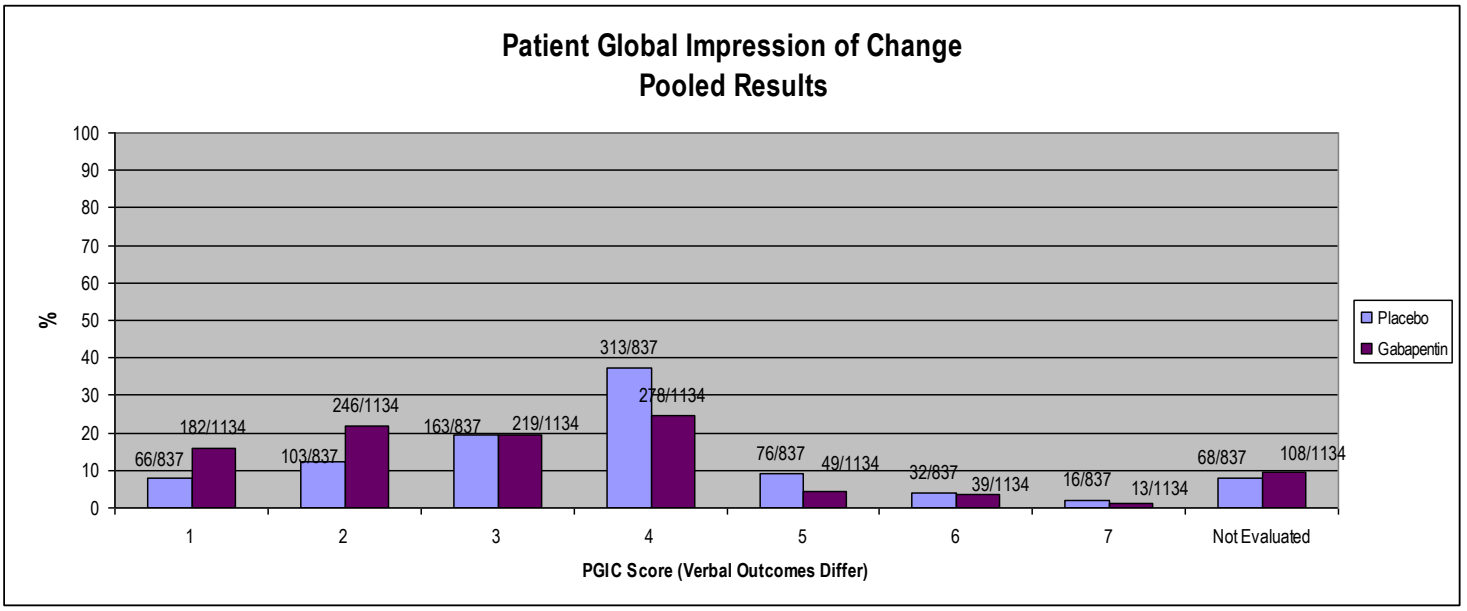
Patient Global Impression of Change: Histograms of Data

The following document contains histograms, representing the results from Patient Global Impression of Change (PGIC) on a 7-point ordinal scale. The first histogram pools the results for all 7 trials in which PGIC was a pre-specified endpoint. Individual histograms for each of these 7 trials follow.

Backonja (945-210), Rowbotham (945-211), and Gordh (945-271) used the following seven-point scale:
1 = Much Improved; 2 = Moderately Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Moderately Worse; 7 = Much Worse.

Reckless (945-274), Rice (945-295), Serpell (945-430-306), and Parsons (945-1008) employed the following seven-point scale:
1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse.

The denominators shown represent the number of patients who were randomized to and received at least 1 dose of placebo or gabapentin (true ITT denominators). For certain trials, the reported number of patients who completed PGIC evaluations was not consistent with the number of patients who received a given treatment. Patients for whom PGIC evaluations at "endpoint" are reported as missing, plus any other patients missing from the true ITT denominator for each study (placebo or gabapentin groups) comprise the "Not Evaluated" category.

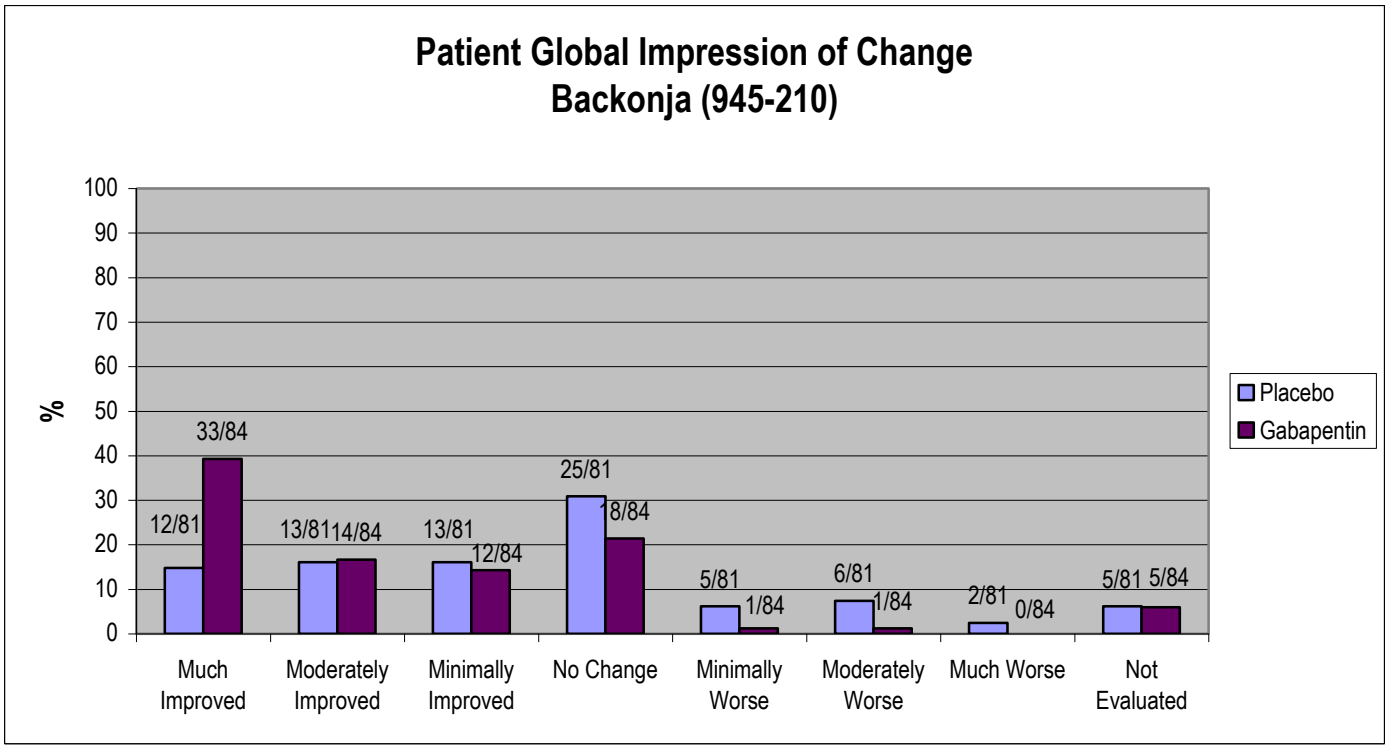


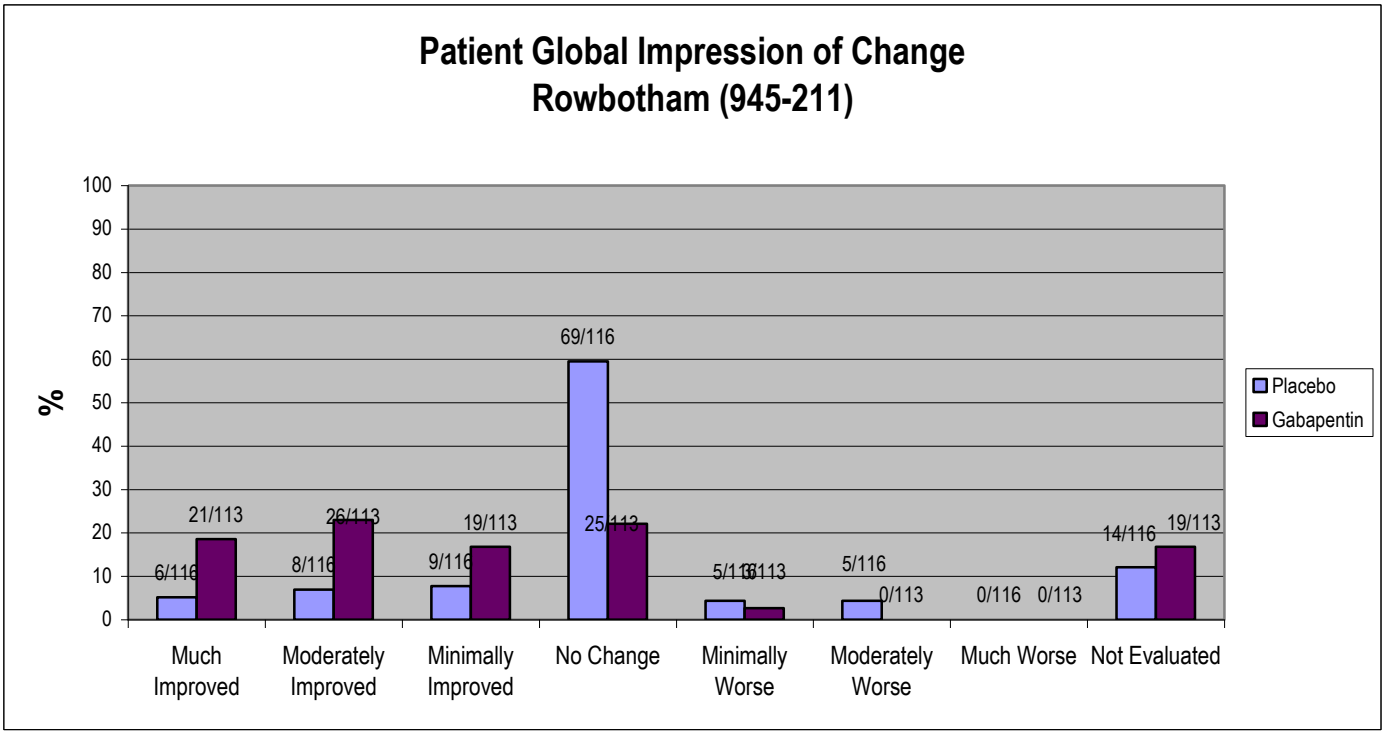
PGIC Score (Verbal Outcomes Differ)	% Placebo*	% Gabapentin*	Absolute Difference % Gabapentin - % Placebo*
1	7.89	16.0	8.16
2	12.3	21.7	9.39
3	19.5	19.3	-0.162
4	37.4	24.5	-12.9
5	9.08	4.3	-4.76
6	3.82	3.4	-0.384
7	1.91	1.15	-0.765
Not Evaluated	8.12	9.52	1.40

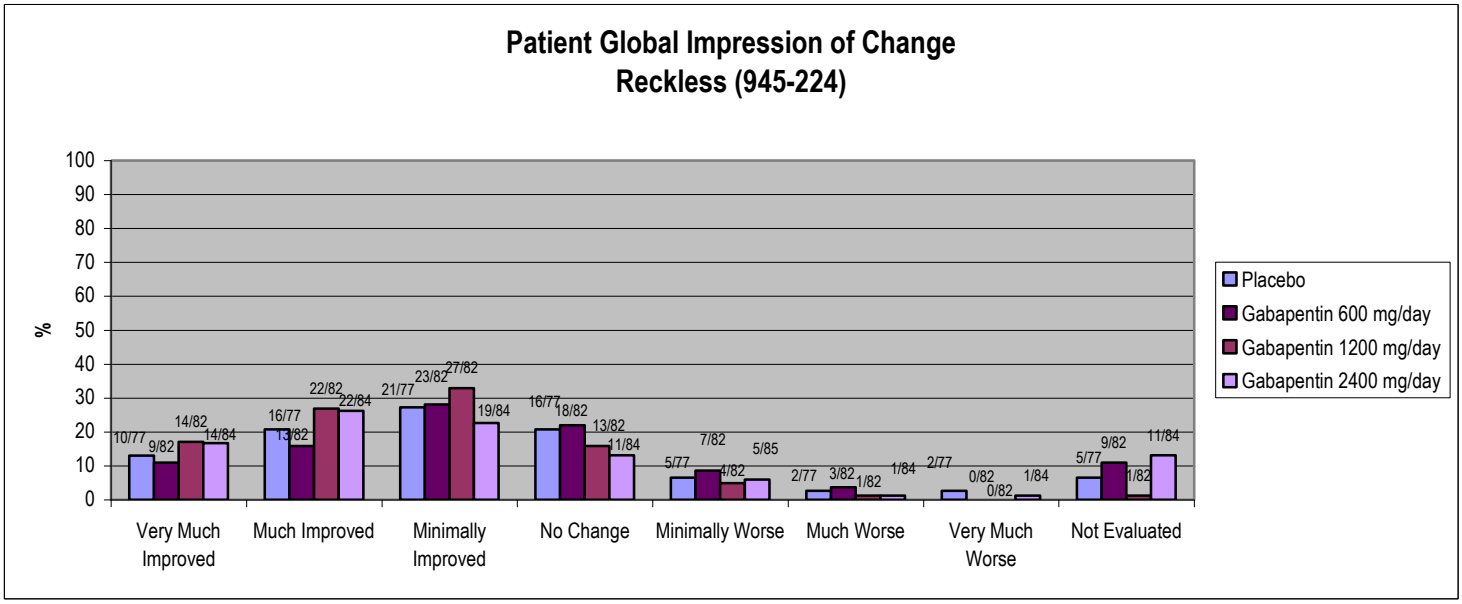
*rounded to three significant figures

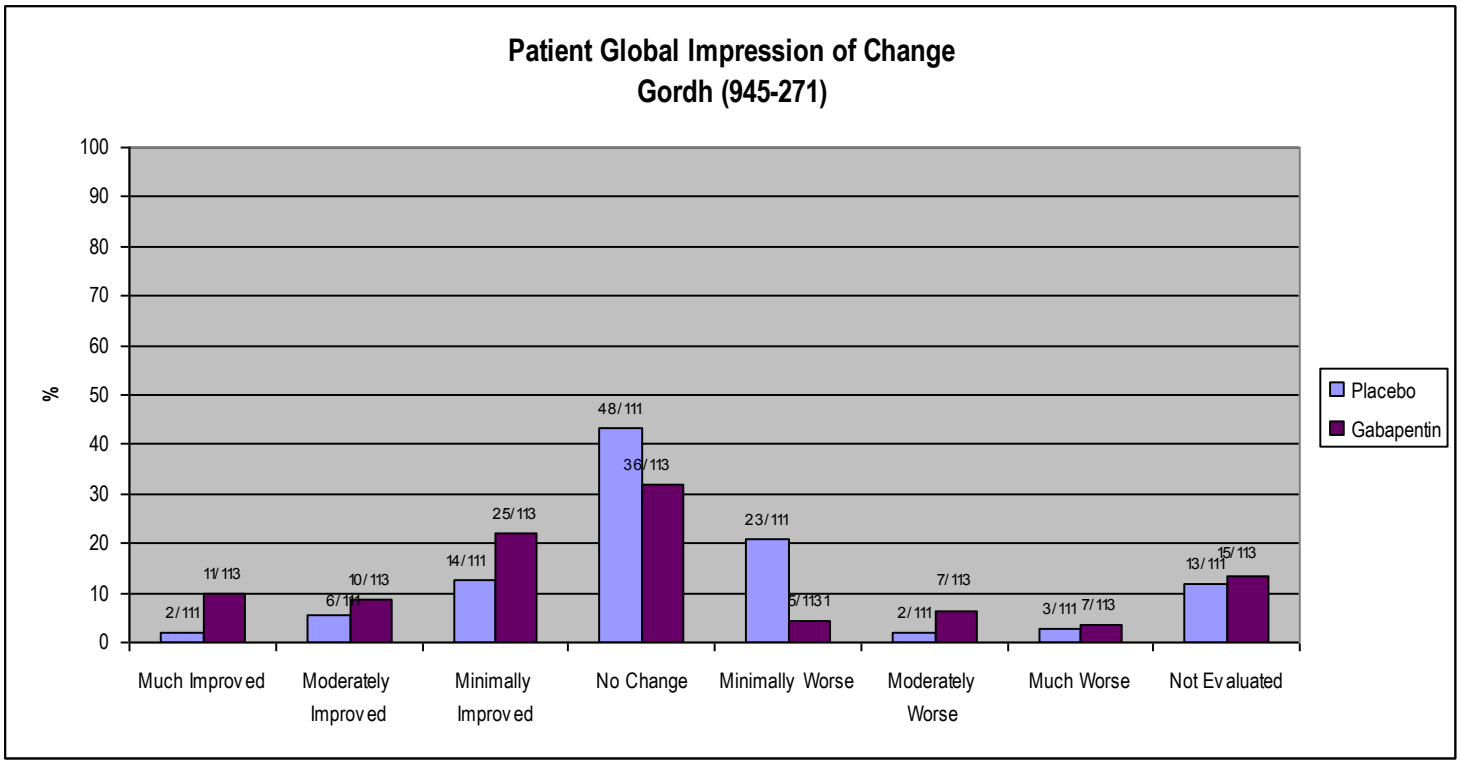
Because the studies reported on 2 slightly different 7-point scales, the pooled histogram shows along the horizontal axis the number of patients classified by 7 numerical outcomes (see previous page) and the category "Not Evaluated", for placebo (light blue) and gabapentin (maroon).

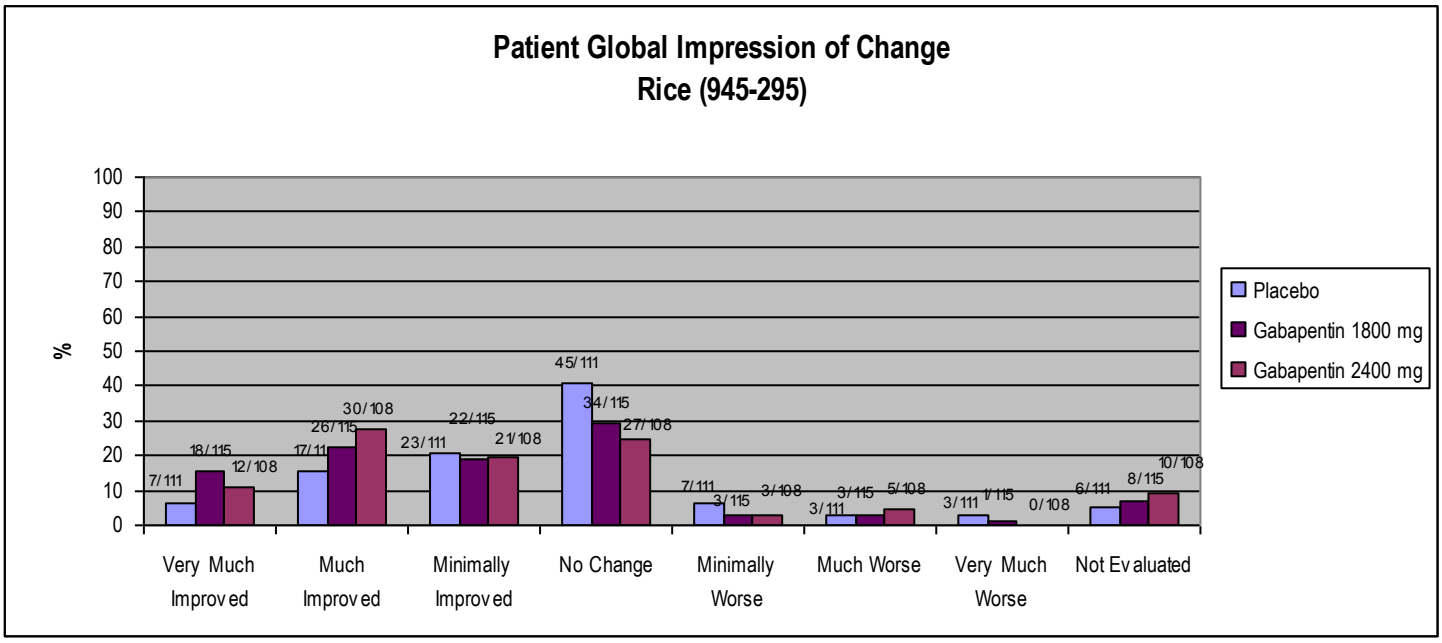
The table below the pooled histogram shows the percentage of patients classified at study "endpoint" (LOCF) for each of the same 8 categories (7 numerical categories as well as "Not Evaluated") for placebo and gabapentin. The absolute difference between the two percentages is also shown in the extreme right column. Statistical significance of the differences has not been tested, as the pre-specified outcome subjected to meta-analysis was the number (and percentage) of patients reporting the rating "moderately or much improved" (equivalent to "much or very much improved"), comprising the best 2 categories on the 7-point PGIC. The individual studies typically report tests of statistical significance for the overall pattern of the 7-point scores for the comparison gabapentin vs. placebo and/or for the best 2 categories, but not for each category.

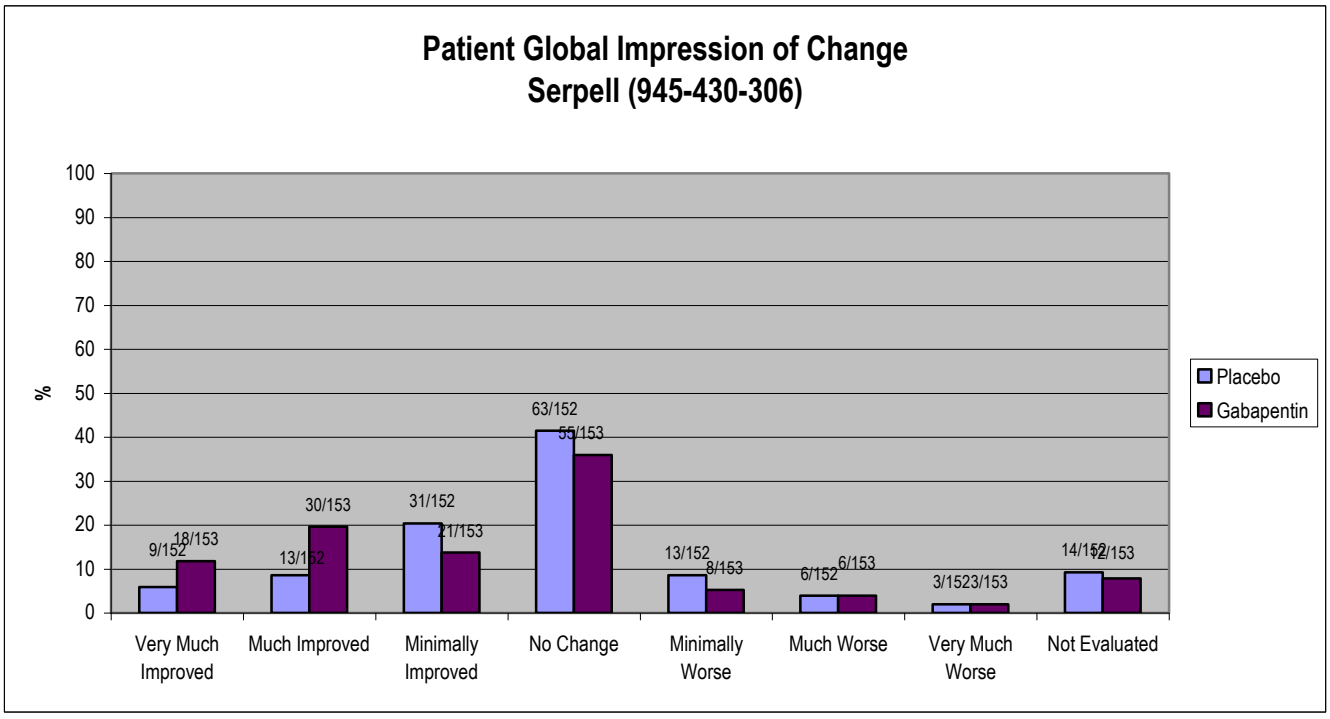

Patient Global Impression of Change
Backonja (945-210)
%
100
90
80
70
60
50
40
30
20
10
0
12/81
33/84
13/81
14/84
13/81
12/84
25/81
18/84
5/81
1/84
6/81
1/84
2/81
0/84
5/81
5/84
Much Improved
Moderately Improved
Minimally Improved
No Change
Minimally Worse
Moderately Worse
Much Worse
Not Evaluated
Placebo
Gabapentin

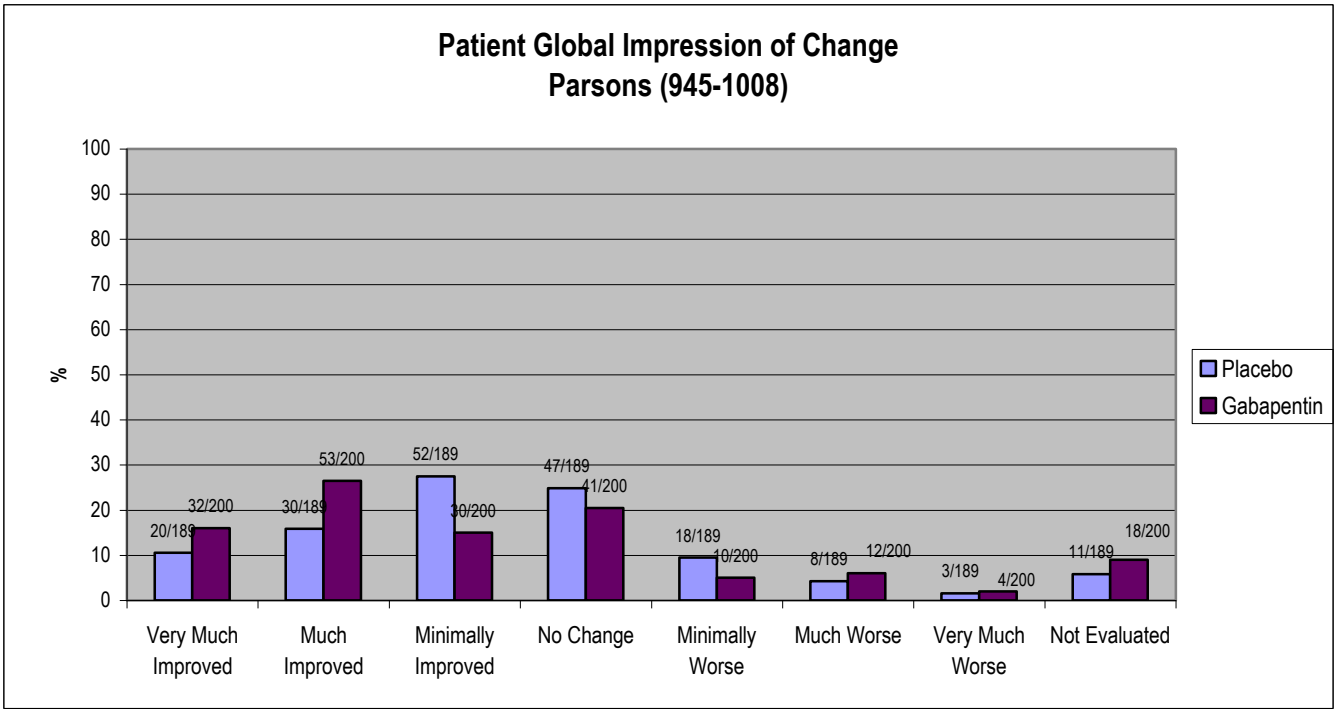

Patient Global Impression of Change
Rowbotham (945-211)
%
100
90
80
70
60
50
40
30
20
10
0
6/116
21/113
8/116
26/113
9/116
19/113
69/116
25/113
5/116
0/113
0/116
0/113
14/116
19/113
Much Improved
Moderately Improved
Minimally Improved
No Change
Minimally Worse
Moderately Worse
Much Worse
Not Evaluated
Placebo
Gabapentin


Patient Global Impression of Change
Reckless (945-224)
%
100
90
80
70
60
50
40
30
20
10
0
10/77
9/82
14/82
14/84
16/77
13/82
22/82
22/84
21/77
23/82
27/82
19/84
16/77
18/82
13/82
11/84
5/77
7/82
4/82
5/85
2/77
3/82
1/82
1/84
2/77
0/82
0/82
1/84
5/77
9/82
1/82
11/84
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Much Worse
Very Much Worse
Not Evaluated
Placebo
Gabapentin 600 mg/day
Gabapentin 1200 mg/day
Gabapentin 2400 mg/day


Patient Global Impression of Change
Gordh (945-271)
%
100
90
80
70
60
50
40
30
20
10
0
2/111
11/113
6/111
10/113
14/111
25/113
48/111
36/113
23/111
5/113 1
2/111
7/113
3/111
7/113
13/111
15/113
Much Improved
Moderately Improved
Minimally Improved
No Change
Minimally Worse
Moderately Worse
Much Worse
Not Evaluated
Placebo
Gabapentin


Patient Global Impression of Change
Rice (945-295)
%
100
90
80
70
60
50
40
30
20
10
0
7/111
18/115
12/108
17/111
26/115
30/108
23/111
22/115
21/108
45/111
34/115
27/108
7/111
3/115
3/108
3/111
3/115
5/108
3/111
1/115
0/108
6/111
8/115
10/108
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Much Worse
Very Much Worse
Not Evaluated
Placebo
Gabapentin 1800 mg
Gabapentin 2400 mg


Patient Global Impression of Change
Serpell (945-430-306)
%
100
90
80
70
60
50
40
30
20
10
0
9/152
18/153
13/152
30/153
31/152
21/153
63/152
55/153
13/152
8/153
6/152
6/153
3/152
3/153
14/152
12/153
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Much Worse
Very Much Worse
Not Evaluated
Placebo
Gabapentin


Patient Global Impression of Change
Parsons (945-1008)
%
100
90
80
70
60
50
40
30
20
10
0
20/189
32/200
30/189
53/200
52/189
30/200
47/189
41/200
18/189
10/200
8/189
12/200
3/189
4/200
11/189
18/200
Very Much Improved
Much Improved
Minimally Improved
No Change
Minimally Worse
Much Worse
Very Much Worse
Not Evaluated
Placebo
Gabapentin