

Gabapentin in the Treatment of Mental Illness: The Echo Chamber of the Case Series

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Background. Bipolar disorder is a common and debilitating psychiatric illness. Several antiepileptic drugs (AEDs) have been approved for the treatment of bipolar disorder. Gabapentin gained a large market share of AED use in the late 1990s in spite of a lack of randomized clinical trial (RCT) evidence and no labeled indication from the U.S. Food and Drug Administration for its use in psychiatric illness. This article describes the results of a literature review, the purpose of which was to examine the characteristics of studies conducted in humans concerning the efficacy of gabapentin in bipolar disorder. **Methods.** Publications relevant to this topic were identified based on a PUBMED search as well as an examination of references from a published systematic review and citations from relevant review articles. **Results.** The search located 29 studies published between 1997 and 2007, with the greatest number of articles published in 1998 and 1999. Of these 29 publications, 15 involved uncontrolled case series, while 6 were single case reports. The sample size in the studies was generally small, and often we could not identify the funding source. Despite the generally weak study design in the identified publications, the authors of the articles often commented on the promising nature of gabapentin therapy for bipolar disorder. However, 4 small, randomized trials in heterogeneous populations demonstrated little if any evidence of such efficacy. Nine letters to the editor demonstrated a similar pattern. **Conclusions.** The large number of case series concerning gabapentin is striking. The number of reports and their distribution in many different journals created a type of “echo chamber” effect, through which the sheer number of publications and citations may give legitimacy to the practice of using gabapentin for bipolar disorder. Although the case series were generally of poor quality, their publication in peer-reviewed journals may have been partially responsible for the widespread use of an ineffective medication. (*Journal of Psychiatric Practice* 2007;14(suppl 1):15-27)

KEY WORDS: gabapentin, bipolar disorder, case series, case studies, efficacy

Off-label use of medications generally refers to the clinical use of a medication or device by a provider for an indication that has not been approved by the U.S. Food and Drug Administration (FDA). Off-label use falls within the accepted practice of medicine, which gives physicians broad discretion to prescribe treatments according to their best clinical judgment. A designation of “off-label” does not necessarily mean that a medication or treatment is ineffective for the condition it is being used to treat; rather, it might be effective, but it has not been demonstrated to have efficacy and been approved by the FDA for that indication. When medications are under patent, additional randomized trials and regulatory approval are required to expand the conditions for which the medication is indicated.

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Pharmaceutical companies may not legally advertise or otherwise market their medications for indications other than those for which they have received FDA approval. In contrast, case reports, case series, and other observational studies examining the use of already licensed medications for new indications are routinely published in the clinical literature. Such studies and publications are generally considered part of the research process of discovering new uses for existing medications.

Recent literature and court cases have reflected concerns about the origin, intent, and quality of some of the literature and about inappropriate marketing activities addressing off-label indications for medications.¹⁻³ Studies of off-label use which appear in the peer-reviewed literature may use study designs that result in exclusion from systematic reviews of treatment efficacy, such as those conducted by the Cochrane Collaboration, the Drug Effectiveness Review Project, or the Evidence-Based Practice Centers sponsored by the Agency for Health Research and Quality (AHRQ). Without a contemporaneous control group and randomization, it is very difficult to assess the efficacy of an intervention, since improvement in the patient's condition may be due to chance, the natural history of the illness, or a nonspecific effect of treatment (placebo effect). Thus, case series and non-randomized prospective observational studies are generally excluded from systematic reviews assessing efficacy and not included in either the abstract or the full text of the review. Observational studies may be included in systematic reviews that examine adverse events and may also sometimes be included to provide information on the effect of a treatment in subpopulations for which no randomized trial evidence exists.

For some medications, off-label use has become much more common than use for the medication's approved indications—despite a lack of evidence of treatment efficacy for those off-label uses.⁴ Journalists and court cases have found that in some circumstances off-label use has been encouraged by pharmaceutical companies working through medical education companies. While some of the activities of medical education companies resemble conventional continuing medical education (CME), these companies may collaborate with researchers and influential clinicians to conduct and write case reports and case series, give grand rounds and CME lectures, and serve on speakers bureaus to promote off-label use of medications. An unknown number of articles may be written in whole or in part by employees of the educational company but the

authorship may be attributed to academics, a practice generally known as “ghost authorship.”⁵

Gabapentin (Neurontin) is an antiepileptic drug (AED) that was licensed in June 1993.⁶ The medication underwent a very rapid growth in sales in the late 1990s in spite of generally narrow FDA indications as an AED and a treatment for certain types of neuropathic pain such as postherpetic neuralgia. However, by 1999, the second most common use of gabapentin was for the treatment of psychiatric conditions,⁷ despite the absence of FDA indications for such conditions. In addition, no randomized trials were done in the 1990s that demonstrated efficacy for mental health indications, although multiple articles were published during the 1990s discussing the use of gabapentin for bipolar disorder. This wave of publications coincided with the rapid growth of off-label use of this agent.

Our group was funded by the Neurontin Executive Committee (a consortium of state attorneys general) to disseminate evidence-based information on the roles of AEDs, including gabapentin, in the treatment of bipolar disorder. A systematic review of the use of AEDs in bipolar disorder conducted by the Drug Effectiveness Review Project (DERP) found minimal acceptable evidence concerning the efficacy of gabapentin.⁸ The literature regarding gabapentin included a small number of negative randomized trials, and the review concluded that no acceptable evidence existed to support the use of gabapentin for bipolar disorder. The review did find evidence for the efficacy of three AEDs: carbamazepine, valproic acid/valproate, and lamotrigine. In order to better understand the reasons for growth in the prescribing of gabapentin by providers, we examined the characteristics of the published literature during the period this occurred. Once a study is published in the peer-reviewed literature, it can be cited and reproduced, giving the conclusions of the study an aura of authority that is perhaps not warranted by the quality of the research. Our qualitative review includes literature that is generally excluded from systematic reviews addressing efficacy; we are including this literature to better understand how provider behavior may be affected by weak, but widely disseminated, published literature.

METHODS

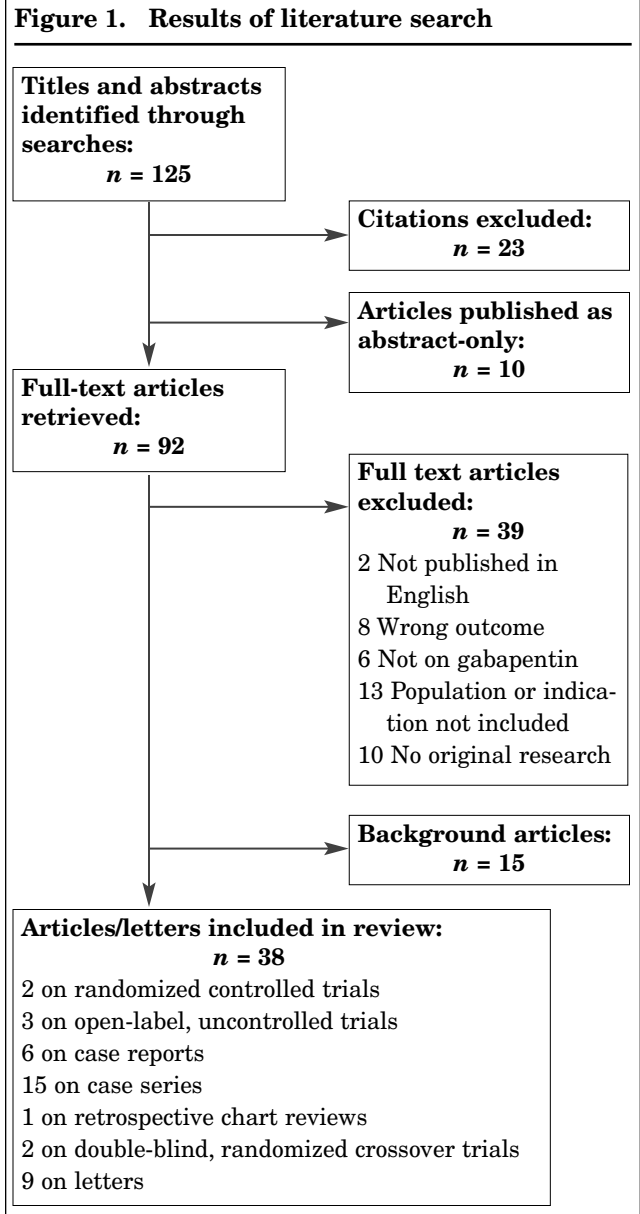
We searched for literature on PUBMED using Medical Subject Headings (MeSH) or key words for gabapentin and bipolar disorder. Our inclusion criteria were all English-language studies published between 1966 and

2007 that involved original research on humans examining the role of gabapentin in bipolar disorder. We supplemented the PUBMED searches with hand searches of recent review articles as well as searches of the Drug Industry Document Archive (DIDA) database through the University of California-San Francisco (UCSF) library. The DIDA database is a compendium of documents gathered as part of the discovery process during the litigation concerning gabapentin. Articles were reviewed for relevance to bipolar disorder and inclusion of original data addressing the efficacy of gabapentin in the treatment of bipolar disorder either as monotherapy or as an adjuvant to other treatments. The articles we identified were then abstracted into evidence tables by staff and these abstractions were then reviewed by a second author.

RESULTS

We found 29 articles in the peer reviewed literature during the time period examined. Only 4 of these studies were randomized trials, 2 of which were crossover trials. The remaining 25 articles were excluded from previous systematic reviews for the standard reason that they lacked an appropriate comparison group and it was therefore not possible to judge efficacy compared with existing treatments or placebo. The characteristics of the 29 articles are summarized in Appendix 1. Nineteen studies were conducted in the United States or Canada, and 10 in Europe. Figure 1 summarizes the results of the literature search.

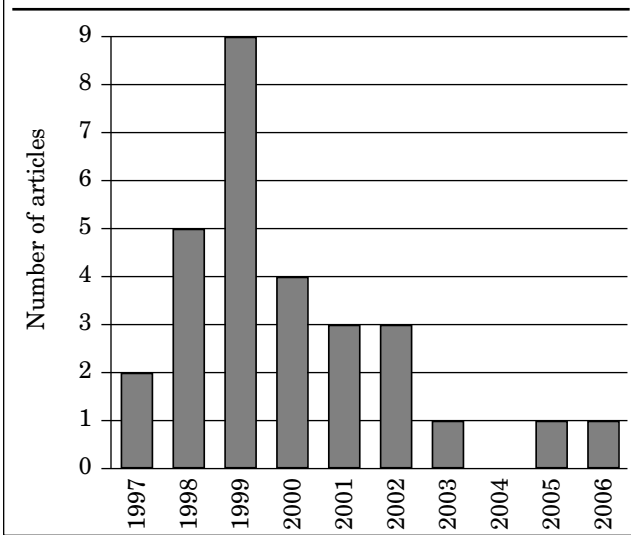
The temporal distribution of the articles is presented in Figure 2. The first articles appeared in 1997, with the most frequent publications in 1998 and 1999. Publication became less common after 2000, the year in which the first randomized controlled trial (RCT) was published demonstrating lack of efficacy of gabapentin as an adjunct to other AEDs in bipolar disorder.⁹ Only three articles were published after 2002, the year that Warner-Lambert’s fraudulent promotion of off-label uses for gabapentin became public. The most common type of study design was the case series (15 studies), in which patients were given gabapentin without blinding of the patients or providers and without comparison to any control group. Evidence of efficacy was inferred through improvement over time. Sample sizes in these case series were generally small, 18 patients on average (range 2–43); 8 of the 15 case series contained 20 or fewer subjects. The duration of follow-up was quite variable, sometimes even within the same study. Of the 29 studies, 22 reported less than



6 months of patient outcome data, which is short for a chronic disease such as bipolar disorder. Seventeen of the studies reported outcomes measures such as standard scales, while the others reported clinician impressions.

The conclusions presented in the articles were almost uniformly optimistic, with the exception of 3 of the 4 controlled studies. Appendix 1 includes conclusions as reported by the authors. While most of the articles did note the need for additional studies and randomized trials, there was little discussion concerning the inability to show causality and other possible

Figure 2. Number of articles published per year



explanations (e.g., natural history of the disease, effect of co-interventions, placebo effect) for the improvement that had been observed. Six studies were case reports of single patients. Several of the cases reported benefit of gabapentin in ameliorating the adverse effects of other medications, such as bruxism (teeth grinding) due to an antidepressant. Most of the case series and single case reports addressed the use of gabapentin as adjunctive therapy in patients who were taking other medications. The rationale for testing gabapentin in bipolar disorder varied among the studies and included the sometimes refractory nature of the illness, the usefulness of other AEDs (class effect), and the perceived modest incidence of adverse events with gabapentin.

Four randomized trials were published between 2000 and 2006.⁹⁻¹² The average number of patients in each trial was 55; only one trial⁹ studied more than 100 patients. The quality of this trial was considered fair; the other trials all had significant design or conduct problems and were rated as poor. The trials by Frye¹⁰ and Obrocea¹¹ both had crossover designs, which can be problematic in diseases which may be influenced by the order in which medications are provided, leading to attenuation of effect. Both of these small crossover trials found that gabapentin was not distinguishable from placebo. The fourth trial¹² was very small with only 25 randomized patients, and only half of the subjects were followed for the duration of the study. In spite of the high attrition and generally negative results, the author concluded that “gabapentin might provide some benefit on the long-term outcome of bipo-

lar disorder.”¹² These four trials provided no substantial evidence of the efficacy of gabapentin in the treatment of bipolar disorder, or in preventing recurrence of symptoms. Three of the four trials’ conclusions did match their results sections.

One article was a retrospective chart review without collection of information directly from patients.²⁹ We identified three prospective studies that did not have contemporaneous comparison groups.^{41,44,46}

Seventeen of the articles (58.6%) had unknown funding sources, 6 studies were funded by private foundations or internal university grants, 4 were reported to be funded by industry, and 2 by Canadian government agencies.

To understand the impact of the 29 articles published in the peer-reviewed literature, we used the ISI Web of Science to conduct citation searches. According to this reference database, all 29 studies were cited in other articles. The average number of citations was 35 per article. Even the most recent article, which was published in 2006, had been cited at least twice. Those cited most frequently were the randomized trials: Frey et al. 2000¹⁰ was cited 196 times, and Pande et al. 2000⁹ was cited 130 times. The 1,001 citations of the 29 articles appeared in 429 unique articles in 152 unique journals (any article could cite any number of the original 29 studies). The lead authors of the original 29 articles also co-authored articles that cited the original 29. For example, Grunze was an author or co-author of 20 of the 429 articles in which citations appeared, while Frye was an author or co-author of 19 of the 429 and McElroy was an author or co-author of 15 of them. In all, the authors of the original 29 articles appeared as authors 130 times for these 429 articles in which citations of the original studies appeared. More than half (15) of the 29 articles were originally published in only four journals: *Bipolar Disorder*, *Journal of Clinical Psychopharmacology*, *Journal of Affective Disorders*, and *Journal of Clinical Psychiatry*. The tracking of citations and authors done for this study indicated that a few authors, often writing together and appearing in a limited number of journals, can appear in other research for a much broader audience.

We did search the University of California at San Francisco’s digital archive of documents regarding the case of *United States of America ex. rel David Franklin vs Pfizer Inc and Parke Davis, Division of Warner-Lambert Co* (<http://dida.library.ucsf.edu>). These documents, which mostly date from the late 1990s, document pharmaceutical marketing strategies for gabapentin for multiple indications, including bipolar

disorder. We found authors of 8 of the 29 articles referenced in the archives, with involvement such as presence at a company-sponsored meeting, being a paid speaker, or a reference to working with ghostwriters. We were unable, based on these documents, to directly tie specific involvement or payment to specific publications.

In addition to the 29 peer reviewed articles, we identified an additional 9 letters to the editor published in journals that contained patient information.^{38,48-55} Three were case reports, while 6 were case series with a mean sample size of 24. Four letters were published in 1997; the most recent letter, which was a case report, appeared in 2006 and stated that “Gabapentin showed preliminary efficacy as an add-on mood stabilizer to divalproex for adults with mental retardation and bipolar mood disorder or schizoaffective disorder, bipolar type.”⁵¹

DISCUSSION

We identified a large number of studies reporting on the use of gabapentin in bipolar disorder that were published in the late 1990s and early in the current decade. The studies were characterized by small sample sizes, poor description of the patient populations, and relatively brief follow-up. Most of the studies did not report sponsorship or potential conflicts of interest by the authors. The DIDA database did indicate that the manufacturer of gabapentin at that time contracted with medical education companies in the late 1990s to produce peer reviewed publications on off-label use of the medication.⁷ The timing and type of publications we identified are consistent with just such a campaign.

The reduction in the number of publications examining the use of gabapentin in bipolar disorder in recent years may be due to a number of factors, such as the disclosure of the manufacturer’s fraudulent marketing scheme, lapsing of the contracts with medical education companies, or consensus in the academic psychiatry community regarding the lack of utility of gabapentin for these indications. The number of publications from European authors in recent years may reflect attempts to increase market share outside the United States.

The number of times this limited literature was cited is remarkable. Simple citation counts do not, of course, describe how the citation was used in this secondary literature and an examination of the 429 articles in which these citations appeared was beyond the scope of this review.

Case series and other observational study designs do have a role in the medical literature. Clinical observations, and their report in series of cases, are often the first way hypotheses are generated and transmitted to the research and the clinical communities. Case series may be useful in settings of initial reports of innovative treatment, hospital reports of outcomes, or multi-institutional registries. Although relatively little guidance has been published on quality grading of case series, readers are referred to one publication in this area by our group.⁵⁶ Characteristics of good case series reports include:

- A clearly defined question
- Well-described study population
- Use of validated outcome measures
- Appropriate statistical analyses
- Well-described results
- Discussion/conclusions supported by the data
- Acknowledgment of funding source if any.

The studies on gabapentin were limited, even as case series, in that they often did not describe the study population or patient selection. The discussion sections were also limited, and there was a lack of clarity concerning funding sources. Drawing inferences regarding treatment efficacy from pre-post case series may be especially fraught with difficulties in a chronic condition such as bipolar disorder, which is characterized by a waxing and waning clinical course. Yet limitations in drawing inferences from such small samples were often unacknowledged in these publications. Patients with bipolar disorder are also often taking a number of medications, including other AEDs or antipsychotic medications. Unless such co-interventions are carefully assessed and their equal distribution across the intervention and comparison groups is assured, treatment effect will be difficult to distinguish from improvement due to natural history, placebo effect, or the effect of the co-interventions. Use of contemporaneous controls and randomization are the only ways in which treatment effect can be assessed in these circumstances. In the case of gabapentin, RCTs were not conducted for some years after this agent began to be widely used for mental health indications, and the studies that were done were often small and sometimes of poor quality (Figure 1).

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

have given legitimacy to the practice of using gabapentin for bipolar disorder. Although pharmaceutical representatives visiting providers' offices are prohibited from distributing copies of articles addressing off-label use of their products, such practices did occur in the past,¹ and the large number of available publications may have made such practices easier. The citation of such publications during grand rounds or CME conferences by clinical experts who may have relationships with pharmaceutical companies is another potential route of dissemination. The case of gabapentin, a medication that has modest benefit for seizures and neuropathic pain, but which has been used for many other indications, is one of the most striking examples of coordinated off-label marketing. A recent settlement regarding olanzapine is another.⁵⁷ The clinical community knows about these activities only through the public availability of documents obtained in the discovery process of litigation. Other examples of the use of the medical publication system for off-label marketing purposes may exist but have not yet been similarly uncovered. While the fines from litigation were imposed on the pharmaceutical company (Warner-Lambert and Pfizer), the clinicians and faculty who were the authors of record of the reports should also bear responsibility. How many case reports or case series are needed to generate a hypothesis that must then be tested in an appropriately designed experiment—i.e., a clinical trial? Certainly not dozens. Since the journals in which these articles were published often did not require reporting of the source of funding for the research, readers are unable to judge for themselves whether industry sponsorship of the study would influence their opinion of the study conduct and conclusions. While major journals now require authors to report sources of funding for studies and potential competing interests such as industry consulting relationships, the specialty journals in which the literature on gabapentin for bipolar disorder was reported rarely did so. Journal reviewers and editors are also responsible in that the conclusions of the articles were essentially unchallenged. Regular repetition of a statement about the medication being “promising” and more study being needed may lead readers to focus on the “promising” part of the message. A more appropriate message in such circumstances might be: “We have observed apparent benefit in a preliminary uncontrolled case series. The next step required to demonstrate efficacy is an appropriately sized randomized controlled trial. Since multiple other agents are available for the treatment of bipolar disorder, at this

time we recommend that gabapentin be used only in the setting of a randomized trial among patients refractory to other agents.” We recognize that circumstances might arise in which patients are truly refractory to the multiple treatments available, and clinicians do need some flexibility to address such difficult clinical situations. The role of the research literature should be to encourage appropriate clinical use, not inappropriate prescribing in settings in which other efficacious treatments are available. Clinicians may prescribe medications off label for appropriate reasons, including lack of data or FDA evaluation in certain populations (e.g., children) or in patients whose illness is refractory to treatment or who are unable to tolerate other medications.

A cursory examination of the literature identified in this review reveals repeated references to a promising new treatment. Our more detailed examination demonstrates multiple poor quality observational studies which collectively represent an echo chamber encouraging utilization of the medication based on minimal evidence. The literature on gabapentin represents a cautionary tale for industry, researchers, and journal editors.

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Appendix 1. Summary of studies located by literature search

<i>Study</i>	<i>Study design</i>	<i>N</i>	<i>Adj?</i>	<i>Results</i>	<i>Author conclusions</i>
Pande et al. 2000 ⁹	Double-blind, placebo-controlled trial	117	Yes	Significantly greater decrease in total YMRS ¹³ in GP than placebo group (-9 vs. -6; $p < 0.05$). No difference between groups on HAM-D. ¹⁴	"The findings of this study did not demonstrate that GP is an effective adjunctive treatment when administered to outpatients with bipolar disorder."
Frye et al. 2000 ¹⁰	Double-blind, randomized, crossover trial	31	No	Response rates (CGI ¹⁵ ratings of much or very much improved): LTG, 52%; GP, 26%; and placebo, 23%.	"With respect to anticonvulsant dose and gender, there was no difference between the responders and the nonresponders. This controlled investigation preliminarily suggests the efficacy of LTG in treatment-refractory affectively ill patients."
Obrocea et al. 2002 ¹¹	Double-blind, randomized, crossover trial	45	No	CGI-BP ¹⁶ response rates higher for LTG than for GP or placebo (51% vs. 28% vs. 21%).	"LTG appeared most effective for male patients with fewer prior medication trials. GP monotherapy, although not better than placebo, appeared most effective in those with younger age and lower baseline weight. These preliminary data in a treatment refractory subgroup may help in the further definition of the range of clinical utility of these widely used anticonvulsants."
Vieta et al. 2006 ¹²	Double-blind RCT	25	Yes	Change from baseline in mean CGI-BP-M ¹⁷ scores between GP and placebo groups was statistically significant (-2.1 vs. -0.6, $p = 0.0046$). No significant differences between groups for YMRS, HAM-D, HAM-A ¹⁸ or PSQI. ¹⁹ PSQI-6 subscale (use of sleep medication) at 12 months was -1.1 for GP group vs. -0.6 for placebo group ($p = 0.0267$). No significant differences between groups for time from randomization to first new episode ($p = 0.6658$).	This trial "suggests that, despite lack of acute efficacy, treatment with GP might provide some benefit for the long-term outcome of bipolar disorder." "This is, to the best of our knowledge, the first 'pure' prophylactic study in bipolar disorder conducted to date."
Altschuler et al. 1999 ²⁰	Case series	28	Yes	72% of patients showed overall positive response (defined as CGI-BP score of much or very much improved).	"GP may thus emerge as an important addition to the anticonvulsants used for treating bipolar disorder....Future double-blind randomized studies are needed...."
Brannon and Roland 2000 ²¹	Case report	1	No	Bipolar symptoms resolved but patient developed anorgasmia 10 days after starting GP. Patient began valproate and anorgasmia resolved 12 days after discontinuing GP; bipolar symptoms remained under control.	"Initial reports of GP for mood stabilization are favorable....controlled studies are needed to clarify the role of GP in the treatment of bipolar disorder."
Brown and Hong 1999 ²²	Case report	1	Yes	Patient with bipolar I disorder on venlafaxine and valproate presented with bruxism. When placed on GP as adjunctive therapy (other medications continued) bruxism resolved within 4 weeks, improvement maintained out to 3 months.	"This case also suggests that GP may be a useful treatment for patients with antidepressant-induced bruxism... GP was prescribed to this patient on the basis of literature reports of efficacy in treating anxiety and mood symptoms. ... Larger controlled trials of GP in patients with iatrogenic, and possibly idiopathic bruxism are needed to substantiate this anecdotal observation."

Appendix 1. continued

<i>Study</i>	<i>Study design</i>	<i>N</i>	<i>Adj?</i>	<i>Results</i>	<i>Author conclusions</i>
Cabras et al. 1999 ²³	Case series	25	Taper*	76% of patients had a "positive response" as measured by improvement in CGI and BPRS ²⁴ scores.	"These data in 25 patients suggest that GP may have anti-manic efficacy in bipolar and schizoaffective disorders...The findings of our study must be regarded as preliminary and in need of replication in double-blind or placebo-controlled trials."
Carta et al. 2001 ²⁵	Case series	10	Yes	Number of patients with mood disorder recurrence decreased after being given medication. Improvement in scores on scales of anxiety, depression, and adjustment disorder.	"The present results suggest a possible role for GBP as a mood stabilizer and its usefulness as adjunctive therapy, at least in patients with ID...the present data seem to confirm the previous evidence reported in the open trials...."
Erfurth et al. 1998 ²⁶	Case series	14	Yes (6) No (8)	Mean BRMAS ²⁷ score declined from 37.7 to 7.8 on day 21 in the add-on group and from 27.8 to 9.0 in 4/8 patients finishing 21 days in the monotherapy group.	"It is suggested that GP monotherapy might be useful in selected patients to treat modest but not severe manic states. In addition, GP in conjunction with other effective mood stabilizers seems to be safe and efficacious in the treatment of severe mania."
Ghaemi and Goodwin 2001 ²⁸	Case series	21	Yes (13) No (8)	Based on CGI-BP scores, GP was moderately to markedly effective in 43% of patients for overall bipolar illness, in 38% for depressive symptoms, and in 25% for manic symptoms.	"GP, either alone or as an adjunct, appeared moderately effective in treating depression in this small, uncontrolled, heterogeneous sample of non-refractory bipolar spectrum illness."
Ghaemi et al. 1998 ²⁹	Retrospective study (chart review)	50	Yes	GP was moderately to markedly effective in 30% of patients, with statistically nonsignificant differences between patients with bipolar disorder type I, bipolar disorder type II and not otherwise specified, and unipolar major depressive disorder. 70% reported side effects, mainly sedation, with 16% of the total sample discontinuing treatment due to adverse events.	"GP appears to be somewhat effective as add-on treatment in a subgroup of patients with mood disorders in a naturalistic setting. Prospective, controlled studies are required to clarify these pilot data."
Grunze et al. 1998 ³⁰	Case report	1	Yes	Initially well tolerated, an increase of creatinine after several weeks of GP (2000 mg) was observed which was reversible after discontinuation of GP.	"It is suggested that the possibility of renal dysfunction should be kept in mind with the usage of GP."
Hamrin and Bailey 2001 ³¹	Case report	1	Yes	Improvement and stabilization of mood symptoms was remarkable within 3 weeks of start of treatment and remained so for 6 months of follow-up.	"Controlled studies are needed to evaluate the possible antimanic mood stabilizing and/or antidepressant properties of GP in youths."
Hardoy et al. 1999 ³²	Case series	16	Yes	4 case studies: in 2 cases, blepharospasm and other signs of tardive dyskinesia diminished until they completely remitted. In the other 2 cases, blepharospasm diminished markedly. Use of GP was accompanied by reduction of tardive dyskinesia in all but 2 of 12 consecutive patients.	"GP, whose mood stabilizing properties have been reported in several clinical reports, represents a more natural treatment in the setting of bipolar spectrum disorders...this agent could be of significant clinical utility in the management of tardive dyskinesia in psychotic patients with affective features of those with bipolar spectrum disorders."
Hatzimanolis et al. 1999 ³³	Case series	2	No	After 2 weeks of treatment a moderate improvement in mania symptoms in both patients was observed according to YMRS score.	"Our report suggests that the possible antimanic properties of GP should be investigated further."

Appendix 1. continued

<i>Study</i>	<i>Study design</i>	<i>N</i>	<i>Adj?</i>	<i>Results</i>	<i>Author conclusions</i>
Knoll et al. 1998 ³⁴	Case series	12	Yes	Response according to CGI score: 1 patient marked response; 7 moderate response; 2 mild response; 2 no response. Half of the patients chose to discontinue GP due to adverse effects.	"Given the severity and chronicity of these patients' illness, a moderate response must be considered a relative success. Controlled studies of GP are needed to clarify its role in the treatment of bipolar disorder."
McElroy et al., 1997 ³⁵	Case series	9	Yes	Eight patients showed moderate or marked improvement 1 to 3 months after the addition of GP; six of these patients displayed sustained anti-manic responses over subsequent periods of time.	"Adjunctive GP may have antimanic and mood-stabilizing effects in some patients with bipolar disorder and is generally well tolerated. Controlled studies of BP in bipolar disorder appear to be warranted."
Perugi et al., 2002 ³⁶	Case series	43	Yes	After 8 weeks, 18 patients were "responders" according to CGI scores: 8 showed marked improvement, 10 showed moderate improvement; 22 patients were deemed "nonresponders." Mean total HAM-D score showed significant reduction during 8 weeks of treatment; mean total YMRS score did not show a statistically significant reduction. Of the 18 responders, 17 maintained symptoms of remission for 4–18 months.	"The results of the present study replicate prior studies indicating that GP is an effective and well tolerated treatment in a large proportion of bipolar patients who are resistant to traditional mood stabilizers. More specifically, this drug appears to have antidepressant and anxiolytic properties." New finding from this study "is the suggestion that the utility of GBP in resistant bipolar disorder resides in its effectiveness against comorbid panic disorder and alcohol abuse."
Perugi et al., 1999 ³⁷	Case series	21	Yes	10 of 21 patients "responded" based on CGI scores. HAM-D mean change from 18.2 to 10.6 ($p = 0.0001$). YMRS change from 9.7 to 7.2 ($p = NS$).	"...GP appears to be an effective adjunctive treatment for drug-resistant bipolar mixed states...The major weakness of the data presented here is the lack of a control group. However, a placebo response or spontaneous remissions must be regarded as unlikely."
Schaffer and Schaffer 1997, ³⁸ 1999 ³⁹	Case series	18	Yes	39% (7/18) of original patients (Schaffer 1997 ³⁸) continued to experience benefit from maintenance GP treatment (for an average of 33 months).	"The results of this small open study suggest that GP may be effective as an augmenting agent in the maintenance phase of treatment of some bipolar spectrum patients." "The data from this small study is quite preliminary, and should be validated by the standard research design consisting of random assignment, comparison with control groups and blind ratings."
Sethi et al. 2003 ⁴⁰	Case series	7	Yes	All 7 patients experienced improvement in manic symptoms with minimal or no side effects.	"This case series suggests that controlled studies are warranted to examine GP's efficacy and side effects, particularly as an adjunctive medication, in geriatric mania...These cases also indirectly suggest that GP may help reduce the dosage requirement for antipsychotics to treat psychotic symptoms in mania; that is, it may have utility as an adjunctive medication."
Sokolski et al. 1999 ⁴¹	Open-label, uncontrolled trial	10	Yes	GP exerted potent early effect on initial, middle, and late insomnia. Depressive symptoms continued to improve with further treatment while manic symptoms stabilized at low levels; 9 subjects remained stabilized with no significant side effects for periods of 3–12 months.	"The results suggest that GP may be of benefit to bipolar patients who only partially respond to other mood stabilizers. A favorable side-effect profile and rapid action make this drug an attractive choice as an adjunctive therapy...This investigation is limited by an open-label design, which does not permit an unbiased evaluation of GP's efficacy. The magnitude and sus-

Appendix 1. continued

<i>Study</i>	<i>Study design</i>	<i>N</i>	<i>Adj?</i>	<i>Results</i>	<i>Author conclusions</i>
Soutullo et al. 1998 ⁴²	Case report	1	Yes	Patient showed marked response within 1 month and remained euthymic 7 months after addition of GP. YMRS score, which was 27 when GP was added, dropped to 9 after 1 month of treatment. YMRS score at month 4 was 15 and at month 7 was 6.	tained nature of the improvements, however, weigh against the likelihood of a placebo response.” “Controlled studies are needed to evaluate the possible anti-manic, mood stabilizing, and/or anti-depressant properties of GP in youth.”
Tran et al. 2005 ⁴³	Case report	1	Yes	Patient had moderate upper respiratory tract infection symptoms and somatic complaints 1 day after termination of GP. Symptoms gradually worsened until day 10 when she acutely developed severe mental status changes, severe somatic chest pain, and hypertension. When GP was reintroduced, patient returned to baseline within 2 days.	“GP is widely utilized currently for chronic treatment of recalcitrant migraines, bipolar illness, pain, and epilepsy. It has a wide therapeutic index with few side effects and drug interactions...Past reports have suggested that some withdrawal symptoms can present after 1–2 days upon abrupt discontinuation of GP...Unique to this case is that this geriatric patient developed debilitating withdrawal symptoms after a gradual, week-long taper...GP taper should follow a course similar to that of a benzodiazepine taper—slowly and over a period of weeks to months.”
Vieta et al., 2000 ⁴⁴	Open-label, uncontrolled trial	22	Yes	Of the 16 patients evaluated at 12 weeks, 8 showed improvement (defined as a decrease of at least 2 points in CGI-BP score), 3 showed modest improvement, and 4 showed no therapeutic effects (outcome of 1 patient not described). The most radical improvement was seen in one depressed patient with bipolar II disorder and severe agoraphobia and history of panic attacks. Significant improvement on depression subscale in mean CGI-BP scores. Using last observation carried forward analysis, differences remained significant for improvements in CGI-BP depression subscale; CGI-BP for manic symptoms showed globally minimal changes after treatment.	“GP may be a useful drug for the add-on treatment of bipolar patients with poor response to mood stabilizers. GP may improve depressive residual symptoms such as irritability, social withdrawal or anxiety. These results should be confirmed in randomized clinical trials...Depressive symptomatology improved more than manic or hypomanic features. With respect to specific areas, the main benefits of GP seemed to involve aspects like social functioning, irritability and anxiety, according to patients’ reports. However, patients did not rate its mood-stabilizing effects so markedly.”
Wang et al., 2002 ⁴⁵	Case series	22	Yes	Overall, 53% mean decrease in HAM-D ratings; mean CGI-S decreased from 4.4 to 3.0; YMRS scores were unchanged. 12 patients were responders; 8 patients were remitters. In nonresponders, HAM-D decreased 24%.	“Open adjunctive GP was effective and well tolerated in patients with mild to moderate bipolar depression. This open pilot study must be viewed with caution, and randomized controlled studies are warranted...Adjunctive GP was uncommonly well-tolerated, and may be beneficial in bipolar depression. However, the significance and generalizability of our findings to other patients are limited by the small sample size, open treatment design, and lack of a randomized, parallel control group...Contrary to prior studies, GP responders compared with non-responders had longer, not shorter, durations of illness.”

Appendix 1. continued			
Study	Study design	N	Adj? Results
Young et al. 1999 ⁴⁶	Open label, uncontrolled trial	37	Yes Patients experienced significant reduction in depressive and manic symptoms. Patients entering study during a depressive episode showed significant decrease in depressive symptoms over 12 weeks. Subgroup of manic patients had significant reduction of manic symptoms over 12 weeks, which was maintained over 6 months. Subgroup analysis in depressed group to determine effect of GP on mood versus anxiety symptoms (using HAM-D) showed significant overall reduction in both anxiety and mood clusters from baseline to 12 weeks.
Young et al. 1997 ⁴⁷	Case series	15 Yes (11) No (4)	Significant but modest reduction from baseline in HAM-D scores after 6 weeks. Eight subjects responded (3 marked, 5 partial) and 7 subjects did not respond to GP treatment. One subject had worse depression after treatment and this subject was the only one to experience hypomania.
<p>Author conclusions</p> <p>“These findings are consistent with others establishing the efficacy of GP in both phases of bipolar disorder.” “Limitations: Small sample size and the use of an uncontrolled design limit interpretation of results”</p> <p>“Anecdotal reports suggest that GP may have acute and longer term prophylactic efficacy in bipolar disorder. Our clinical series adds to this by providing clinical data to support its acute antidepressant effects, at least in a subgroup of patients...longer follow-up of patients who initially present in the depressed phase of bipolar disorder and are treated with GP is needed to clarify continued efficacy of this drug in depression and whether it leads to longer term mood stabilization.”</p>			
<p>Legend:</p> <p><i>Adj</i> = adjunctive treatment <i>BPRS</i>: Brief Psychiatric Rating Scale; <i>BRMAS</i>: Bech-Rafaelson Mania Assessment Scale; <i>CGI</i>: Clinical Global Impressions <i>CGI-BP</i>: Clinical Global Impressions Scale for Bipolar Illness <i>CGI-BP-M</i>: Clinical Global Impressions Scale for Bipolar Illness, Modified; <i>CGI-I</i>: Clinical Global Impressions of Improvement Scale; <i>CGI-S</i>: Clinical Global Impressions Severity Scale <i>GP</i>: gabapentin; <i>HAM-A</i>: Hamilton Anxiety Rating Scale <i>HAM-D</i>: Hamilton Rating Scale for Depression; <i>ID</i>: intellectual disability <i>LTG</i>: lamotrigine; <i>NS</i>: not significant; <i>PSQI</i>: Pittsburgh Sleep Quality Index; <i>YMRS</i>: Young Mania Rating Scale</p>			