Drug Class Review
on
Antiepileptic Drugs in Bipolar Mood Disorder and Neuropathic Pain

Final Report

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Francine Goodman, PharmD, BCPS
Peter Glassman, MBBS, MSc
Qiufei Ma, MA
Margaret Maglione, MPP
Shannon Rhodes, MPH
Cony Rolón, BA
Marika Suttorp, MS

Produced by
Southern California Evidence-based Practice Center
RAND
1700 Main Street, PO Box 2138
Santa Monica, CA 90407

Paul Shekelle, MD, PhD, co-Director
Sally Morton, PhD, co-Director

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INTRODUCTION

Antiepileptic drugs (AEDs) have been used in the treatment of bipolar disorder and neuropathic pain since the 1960s after they became available for the treatment of epilepsy. In addition to their established uses for various seizure types, they are now approved by the Food and Drug Administration for the treatment of trigeminal neuralgia (carbamazepine), postherpetic neuralgia (gabapentin), mania (divalproex), migraine (divalproex), and bipolar I disorder with depression, mania, hypomania, or mixed episodes (lamotrigine). There has been a dramatic increase in the use of AEDs in both bipolar disorder (particularly with valproate) and neuropathic pain (particularly with gabapentin).

Bipolar disorder is a spectrum of symptoms characterized by cycles of manic or hypomanic episodes and may include depressive episodes. Psychotic features, which are mood-congruent, and dysphoria may also be present. The major types of bipolar disorder are bipolar I disorder (classic manic episodes only or classic manic-depression), bipolar II disorder (hypomania-depression), and bipolar disorder not otherwise specified. About 5% to 15% of individuals with bipolar I disorder have rapid cycling (four or more episodes per year), which is associated with a poorer prognosis. Manic episodes are marked by abnormally and persistently elevated, expansive, or irritable moods. Patients may not necessarily dislike the symptoms of mania, however, and they may be reluctant to receive or continue treatment directed at reducing those symptoms. Major depressive episodes are characterized by depressed mood, severe loss of interest or pleasure in activities, and a constellation of other diagnostic signs and symptoms including recurrent thoughts of death, suicidal ideation, or suicide attempts. In one review of 31 studies of 9389 patients with bipolar disorder, it was estimated that the lifetime prevalence of suicide ranged from 9% to 60% (weighted mean, 18.9%).[1]

The incidence of bipolar I disorder is estimated to be relatively low, between 2 and 21 per 100,000 per year.[2] However, due to its chronic, recurrent nature, bipolar I disorder is a highly prevalent condition. The incidence of bipolar II disorder is higher than that of bipolar I disorder. Estimates of the prevalence of neuropathic pain are not available.[3] Both bipolar disorder and neuropathic pain tend to have chronic courses and both can have a profound impact on the interpersonal relationships, social activities, and occupational functioning of afflicted individuals.[4, 5]

Neuropathic pain has been defined as pain caused by a lesion of the peripheral or central nervous system (or both) manifesting with sensory symptoms and signs.[6] Since neuropathic pain may be caused by any disease or injury to the nervous system, it is a broad category comprising numerous, heterogeneous types of painful disorders each with their own spectra of causes, presentations, durations, and pain characteristics. Its exact pathophysiologic mechanisms and the processes involved in the development of persistent, chronic pain are still poorly understood. Traditionally, neuropathic pain has been classified by the underlying disease (e.g., diabetic neuropathy, postherpetic neuralgia) or site of the lesion (e.g., peripheral nerve, spinal cord). The diagnosis of neuropathic pain has been supported by objective documentation of a lesion whose anatomic location was consistent with the findings on neurologic examination; however, a lesion cannot always be detected. Neuropathic pain is typically manifested by positive and negative sensory signs and symptoms, and the pain may be spontaneous or stimulus-evoked. Spontaneous pain includes a constant burning sensation or intermittent or paroxysmal shooting, lancinating, or

electric shock-like pain, and often both constant and intermittent pains are present. Dysesthesias (abnormal and unpleasant sensations) and paresthesias (abnormal but not unpleasant sensations) include numbness, itching, tingling, or crawling sensations. Hyperalgesia (increased pain response to a stimulus that normally evokes pain) and allodynia (pain evoked by a stimulus that does not normally induce pain) are often seen in patients with chronic neuropathic pain.

All the AEDs are capable of depressing abnormal neuronal discharge in the central nervous system. Their exact mechanisms of action, however, remain uncertain. Several mechanisms have been proposed, such as potentiation of gamma-aminobutyric acid–mediated inhibition, inactivation of sodium or calcium channels, or blockade of N-methyl-D-aspartate (NMDA) receptor sites. The sodium channel–blocking action of the AEDs may reduce ectopic discharges from injured nerve endings and dorsal root ganglion neurons.

A number of clinical practice guidelines on bipolar disorder and neuropathic pain recommend AEDs (Table 1).

Table 1. Clinical practice guideline recommendations on antiepileptic drugs

		Recommendations				
Practice Guideline	**Indication**	**CBZ**	**GBP**	**LTG**	**OXC**	**VPA**
Bipolar disorder						
APA[7]	Acute Mania/Mixed	✓	—	—	✓	✓
	Acute Bipolar Depression	—	—	✓	—	—
	Acute Rapid Cycling	—	—	✓	—	✓
	Maintenance	✓	—	✓	✓	✓
BAP[2]	Acute Mania/Mixed	✓	—	—	—	✓
	Acute BP Depression	—	—	✓	—	✓
	Rapid Cycling	—	—	✓	—	✓
	Maintenance	✓	—	✓	✓	✓
Neuropathic pain						
Expert Panel[3]	Neuropathic Pain	✓	✓	✓	—	—
IRF for RSD / CRPS[8]	RSD / CRPS	✓	✓	—	—	—
SIGN[9]	Painful diabetic neuropathy	—	✓	—	—	—
WSMA[10]	Neuropathic pain, certain types	—	✓	—	—	—
AAPMR[11]	Chronic nonmalignant pain	AEDs in general				
AMDA[12]	Chronic pain in LTC	AEDs in general				
APA–MSS on HIV / AIDS[13]	HIV-related neuropathies	AEDs used; not supported by published evidence				

Organization Abbreviations:
APA, American Psychiatric Association
BAP, British Association of Psychopharmacology
IRF, International Research Foundation;
SIGN, Scottish Intercollegiate Guidelines
WSMA, Washington State Medical Association
AAPMR, American Academy of Physical Medicine and Rehabilitation;
AMDA, American Medical Directors Association; MSS, Medical Specialty Society; Network
Drugs:
CBZ, Carbamazepine; GBP, Gabapentin; LTG, Lamotrigine; OXC, Oxcarbazepine; VPA, Valproic acid / Valproate
Others:
RSD, Reflex Sympathetic Dystrophy; CRPS, Complex Regional Pain Syndrome
HIV, Human immunodeficiency virus; AIDS, Acquired immunodeficiency syndrome
LTC, Long-term care

Response to conventional therapies in both bipolar disorder and neuropathic pain has typically been suboptimal and limited by drug-related toxicities. Often, multimodal approaches using combinations of pharmacologic and nonpharmacologic therapies are used. In bipolar disorder, a

combination of antidepressive, antimanic, and mood stabilizing agents is advocated to treat and prevent recurrences of mood episodes. In neuropathic pain, the available therapies used alone are often inadequate to completely relieve pain, perhaps because multiple pathophysiologic mechanisms are involved. Therefore, combination therapy consisting of agents from different drug classes has been suggested.[3]

Since newer AEDs have become available, there has been increasing interest to evaluate their efficacies and safety in bipolar disorder and neuropathic pain to determine whether they can improve on the effectiveness, tolerability, and safety of existing therapies. It has also become important to determine whether the use of the newer AEDs over older ones (carbamazepine, phenytoin, valproate) is justified. There is a perception that the AEDs have different spectra of activity in bipolar disorder and may have different efficacies against the various types or symptoms of neuropathic pain. Their relative efficacies in the treatment of these two disorders, as monotherapy or in combination with another AED or other agent, remain unclear. Therefore, the objective of this report is to evaluate the comparative effectiveness, safety, tolerability, and response predictors of AEDs in the treatment of bipolar disorder and neuropathic pain. The AEDs covered in this report are carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, tiagabine, topiramate, valproate/valproic acid/divalproex, and zonisamide.

Scope and Key Questions

The primary goal was to compare the effectiveness and adverse event profiles of AEDs in the treatment of bipolar mood disorder and neuropathic pain. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. For adult outpatients with bipolar disorder or neuropathic pain do antiepileptic drugs (AEDs) differ in effectiveness?

    a. In head-to-head comparisons (one AED compared to another), what is the relative effectiveness of AEDs in reducing symptoms, maintaining remissions, and improving functional capacity when used to treat adult outpatients with bipolar disorder and neuropathic pain?

    b. In trials comparing AEDs to other types of drugs or to placebo, do the results suggest that one AED is more effective than another?

2. For adult outpatients, do AEDs differ in safety or adverse events?

    a. In head-to-head comparisons, what is the relative safety of AEDs in terms of adverse events and tolerability?

b. In trials comparing AEDs to other types of drugs or to placebo and in observational studies, do the results suggest that one AED is associated with fewer adverse events or is better tolerated than another?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one AED is more effective or associated with fewer adverse events?

METHODS

Literature Search

To identify articles relevant to each key question, a librarian searched the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects (DARE), Medline/PubMed (1966–2004), and Embase (1974–2004). We also checked reference lists of included review articles. In electronic searches for efficacy trials, we combined terms for AEDs, bipolar or mood disorder, neuropathic pain, randomized clinical trials (RCTs), systematic reviews, and meta-analyses. For adverse event studies, we combined terms for AEDs, adverse effects, and various types of observational studies. All searches were limited to English language and human studies. (See Appendix B for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

One reviewer assessed studies for inclusion in this report using the following criteria, which were developed by the Oregon Evidence-based Practice Center research team with input from the Participating Organizations:

Population. We included studies that involved adult outpatients with one of the following indications:

a. Bipolar Disorder as diagnosed by validated DSM (*Diagnostic and Statistical Manual of Mental Disorders*) criteria. We excluded trials that included heterogeneous patient populations unless data was presented separately for patients with bipolar disorder or manic episodes.

b. Neuropathic or mixed nociceptive/neuropathic pain (of any duration). Since there is no single diagnostic test that is pathognomonic for neuropathic pain, any studies in which the pain was described by the author in terms that suggested a neuropathic or neurogenic nature or a combination of neuropathic and nociceptive pain were included in this report. Neuropathic pain included but were not limited to the following types:

Central/Post-stroke neuropathic pain
Complex regional pain syndrome
Neuropathy associated with low back pain
Painful diabetic neuropathy
Peripheral nerve injury pain
Phantom limb pain

Polyneuropathy
Postherpetic neuralgia
Spinal cord injury–related pain
Trigeminal neuralgia

Other pain syndromes, such as back pain and fibromyalgia, were not included unless they were described as neuropathic in nature. We attempted to include all trials in which the results at the study end point were wholly or at least partly based on data from outpatients. We excluded studies that involved only inpatients as well as studies that entailed admission of outpatients to hospital either upon initiation or during the course of the study as part of the protocol (but studies in which inpatients were discharged for outpatient follow-up were included). In cases where clinical setting was not reported, the article was included if an outpatient setting was implied by wording (e.g., subjects "returned for visits"), the nature of the patients' condition, the duration of the study, or other factors. If, after reviewing all outpatient trials, there were no comparative trials of one AED versus another (i.e., head-to-head trials), then we made an exception and included head-to-head trials performed in hospitalized patients. We made this post hoc decision as we judged that some data comparing the two drugs, albeit in a somewhat different patient population, was better than no data. Studies that reported efficacy results in a manner that did not allow treatment comparisons (i.e., older placebo-controlled studies which reported findings for only the active treatment) were also excluded.

For safety analyses, we also included systematic reviews and observational studies involving patients with any diagnosis, since adverse events may occur independent of medical disorders.

Drugs. At least one of the treatment groups had to consist of one or more of the following interventions alone or in combination, and the efficacy and safety outcomes had to be distinguished for the individual AED: carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, tiagabine, topiramate, valproate/valproic acid/ divalproex, and zonisamide. We excluded studies in which an AED was compared to itself (e.g., dose or formulation comparisons). When a study evaluated sodium valproate or valproic acid, we referred to the agent as *valproate*, but we used *divalproex* if it was the agent studied.

Outcomes. For assessing effectiveness of the AEDs, we included studies that reported one or more of the following as primary, secondary, or tertiary outcome measures:

Bipolar Disorder: These we designated as scores on symptom rating scales, responder rates, remission, relapse or recurrence, speed and duration of response and remission, use of other medications for acute episodes, functional capacity (quality of life, work productivity) danger to self (suicide attempts and completions), and hospitalization. A number of rating scales were used to measure improvement in symptoms. The abbreviations of the rating scales are defined for each trial in their individual tabulated summary in Evidence Tables 1-3. The abbreviations to the rating scales as they appeared in fair-quality reports are shown in Table 2.

Table 2. Psychiatric Rating Scales

Abbreviation*	Rating Scale
BPRS	Brief Psychiatric Rating Scale
B-R MRS	Bech-Rafaelsen Mania Rating Scale
CGI-BP	Clinical Global Impression for Bipolar Disorder
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
DSS	Depressive Syndrome Scale
GAS	Global Assessment Scale
HAM-D	Hamilton Depression Rating Scale, 17-item or not specified
HDRS	Hamilton Depression Rating Scale, 21-item
HRSD	Hamilton Rating Scale for Depression
ISS	Internal state scale
Life Chart	Life Chart for Recurrent Affective Illness
MADRS	Montgomery-Asberg Depression Rating Scale
MRS	Mania Rating Scale
PNSS	Positive and Negative Syndrome Scale
PSR	Psychiatric Status Rating
YMRS	Young Mania Rating Scale

* Actual abbreviation used in reports; note that there were several abbreviations used for the Hamilton Depression Rating Scale (HAM-D, HDRS, and HRSD).

We used the author's definition of response, remission, recurrence, or relapse. Where these terms were not defined, we used an outcome measure that most closely approximated the outcome, such as Kaplan-Meier estimates of survival for assessing remission, and "breakthrough depression" for relapse. DSM-IV-TR criteria specify that a *recurrence* is indicated by either a shift in the polarity of the mood episode or an interval between episodes of at least 2 months without manic symptoms. The term *relapse* is not mentioned.

The Global Assessment Scale (GAS) was used as a measure of functional capacity in bipolar trials. The GAS evaluates the patient's global functioning, taking into account behavioral disturbances, distress levels, impulsivity, reality testing, self-care, and social functioning.

For hospitalization, we looked for rates of hospitalization due to events relevant to efficacy or safety of treatment, such as psychiatric episodes or adverse events.

Neuropathic Pain: These were designated as pain intensity and pain relief as measures of response, speed and duration of response, relapse, use of rescue medications, and functional capacity. Whenever possible, we reported, as a measure of the clinical relevance of treatment effects, the responder rates of at least 50% or 30% pain relief relative to baseline or a change of at least 2 points from baseline on an 11-point Likert Numerical Rating Scale. However, these were not a requirement for inclusion of a trial. At least 50% pain relief reflects at least moderate improvement in pain intensity and has been the standard for comparing analgesics. Although it has not been a standard for comparing analgesic effects of AEDs, a number of trials used 50% pain relief or a measure of moderate improvement as outcome measures. Farrar, et al. evaluated 10 trials involving patients with neuropathic pain (6 trials), low back pain (2 trials), osteoarthritis (1 trial) and fibromyalgia (1 trial) and showed that a clinically important improvement in pain corresponds with a smaller relative degree of change, at least 30% pain relief, or a change of at least 2 points from baseline on an 11-point Likert numerical rating scale for pain intensity.[14] For complex regional pain syndrome type 1, a relative pain reduction of 50% or more and an absolute pain reduction of at least 3 cm on the Visual Analog Scale (VAS) has been shown to be predictive of "successful" treatment.[15] It is

interesting to note that responder rates for the more stringent but often used threshold, at least 50% pain relief, may underestimate the proportion of patients who will experience a clinically important improvement in pain (i.e., if one were to use at least 30% pain relief). Most trials evaluating the analgesic effects of AEDs in neuropathic pain have used the VAS or 11-point numerical pain rating scales. It should be noted that these pain scales were not developed to assess specific qualities of neuropathic pain and may be better at measuring nociceptive pain. The Short-Form McGill Pain Questionnaire (SF-MPQ) evaluates various characteristics of pain, some of which may be applicable to neuropathic pain qualities (such as shooting, stabbing, and hot-burning pain). A neuropathic pain scale has been developed but not fully validated.

Safety Outcomes: These were designated as overall adverse event reports; withdrawals due to adverse events; serious adverse events; and specific adverse events or adverse events that resulted in withdrawal (e.g., dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, and hyperammonemia).

Design. For effectiveness, we included RCTs and good-quality systematic reviews or meta-analyses that involved human subjects and whose titles, abstracts, and full texts were published in English. We excluded articles that did not report original research data (e.g., editorials, certain letters, duplicate publications) as well as studies that were reported only as abstracts. For safety, we included RCTs involving the target diagnoses, good-quality systematic reviews of adverse events in patients with any diagnosis, as well as long-term (at least 1-year) observational, retrospective or prospective, cohort studies that included at least two AEDs in patients with any diagnosis. We included case-control studies only if two or more drugs were compared individually and a specific adverse event of interest was evaluated. We included studies that used large administrative or prescription databases as long as they met the inclusion criteria for cohort or case-control studies.

In the first stage of study selection, titles and abstracts were identified for full-text retrieval if they met the inclusion criteria. In the second stage, the same inclusion criteria were applied to the full-text articles. Studies that were not published or available in full reports were excluded.

Data Abstraction

Data were abstracted by one of the authors **(FG)** and checked for accuracy by two reviewers **(MM, QFM)** trained in the critical assessment of evidence. The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intent-to-treat results if available. Where studies consisted of an open-label nonrandomized phase followed by a blinded randomized phase, only the results from the randomized portion were included for assessing effectiveness in this report. For crossover trials, the overall results were used to assess effectiveness.

Quality Assessment

We assessed the quality of included study reports in terms of both internal and external validity. For assessing internal validity, we evaluated the adequacy of the randomization method; the adequacy of allocation concealment; maintenance of blinding; the similarity of compared groups at baseline and the author's explanation of the effect of any differences between groups in important confounders or prognostic characteristics; specification of eligibility criteria; maintenance of comparable groups (i.e., reporting of dropouts, attrition, crossover, adherence, and contamination); the overall proportion of subjects lost to follow-up and important differences between treatments; use of intent-to-treat analysis; post-randomization exclusions; and consideration of all important outcomes. We defined loss to follow-up as the number of patients excluded from efficacy analyses, expressed as a proportion of the number of patients randomized.

For assessing external validity, we recorded the number screened, eligible, and enrolled; the use of run-in and washout periods or highly selective criteria; the use of standard care in the control group; the source of funding; and overall relevance.

The grading of the overall quality of a study was based on the methods of the U.S. Preventive Services Task Force[16] and the U.K. National Health Service Centre for Reviews and Dissemination.[17] Trials that had a substantial methodological shortcoming in one or more of the above listed categories were rated poor quality; trials that met all criteria were rated good quality; and the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses; the validity of results of some fair quality studies may be likely, probable, or unlikely. "Poor quality" studies were not discussed in the report because the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. When more than one publication was available on an included trial, the combination of quality elements from all publications results on the same group of patients (e.g., trial extensions or subanalyses), then the publication with the more comprehensive data was cited as the main trial in the text. All included studies were summarized in evidence and quality assessment tables (Evidence Tables 1-7 and Quality Tables 1-7) and trials rated at least fair were discussed in more detail in the text.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met all of the seven predefined criteria, poor if they had a serious methodological flaw; and fair for all others.

Trials that were initially deemed to be poor quality by one of the authors **(FG)** were subsequently reviewed by at least one other senior investigator **(PG, PS)**, who made the final determination about study quality.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the study. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Systematic reviews were evaluated on the comprehensiveness of sources considered, search strategy used, use of standard appraisal of included studies, use of explicit and relevant selection criteria, validity of conclusions, recency, and relevance. Good-quality systematic reviews were recent, used explicit and relevant selection criteria, used comprehensive sources and search strategies, and reached conclusions supported by their data. Fair-quality reviews were recent, relevant reviews that lacked comprehensive sources and search strategies. Systematic reviews not judged as fair or good quality were not included in this report.

Data Synthesis

For the assessment of effectiveness of AEDs for both bipolar disorder and neuropathic pain, we determined that the trials were too heterogeneous to pool quantitatively via meta-analysis. The observed heterogeneity ranged from differences in the measures used, for example studies used different scales or metrics (continuous versus dichotomous outcomes), to the range of follow-up times employed across the studies. When we categorized the studies into homogeneous subgroups, the numbers of studies available for pooling in the different subgroups were too small to warrant meta-analysis. Thus, the studies are only discussed qualitatively in terms of effectiveness. In terms of safety, we did pool studies quantitatively as discussed below.

Meta-Analysis of Adverse Event Data

We aggregated the more commonly documented (or expected) adverse events using patient-level data and, in a separate analysis, using event-level data. The use of patient-specific data can underestimate prevalence and/or eliminate low-level signals of events that might occur rarely because the inclusion criteria for the studies are more limited. On the other hand, since an individual could potentially have one or more different adverse events and multiples of the same type of adverse event over the course of a trial, an event-level analysis may cause an overstatement of prevalence (e.g., find high proportional adverse event rates in comparison with the trial population). The methods and results of the event-level aggregate analysis may be found in Appendix A. Note that for the event-level analysis, since there were a number of less common outcomes and less clinically specific measures (e.g., infections or fatigue), we listed adverse events using more general clinical categories (e.g., metabolic, hematologic, central nervous system).

In the patient-level analysis, we included only trials that specifically reported events at the patient level. The listed adverse events, such as diarrhea, headache, nausea, and rash, were extracted. To avoid double counting patients, no collapsing of events was done. For instance, in the event-level analysis, we combined diarrhea and nausea into a category called “other GI.” The patient-level analysis kept the categories separate. This prevented overestimation of the number of patients having an adverse event.

An odds ratio was calculated for those subgroups that just had one trial. For subgroups of events that had at least two trials, at least one event in the medication group, and at least one event in the placebo group, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to either estimate an odds ratio for a single study or to perform the pooling if meta-analysis was warranted, rather than applying the usual asymptotic methods that assume

normality. Asymptotic methods require corrections if zero events are observed, and generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analysis using the statistical software package StatXact.[18]

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with AEDs (the intervention group) is larger than the odds associated with being in the comparison (placebo; lithium; or other AED as appropriate) group. We note that if no events were observed in the comparison group, but events were observed in the intervention group, the odds ratio is infinity and the associated confidence interval is bounded from below only. We report the lower bound of this confidence interval. If no events were observed in either group, the odds ratio is undefined, which we denote as "Not calculated (NC)" in the results tables. We did not observe any subgroups of studies for which no events for the intervention group were reported but events were observed for the comparison group.

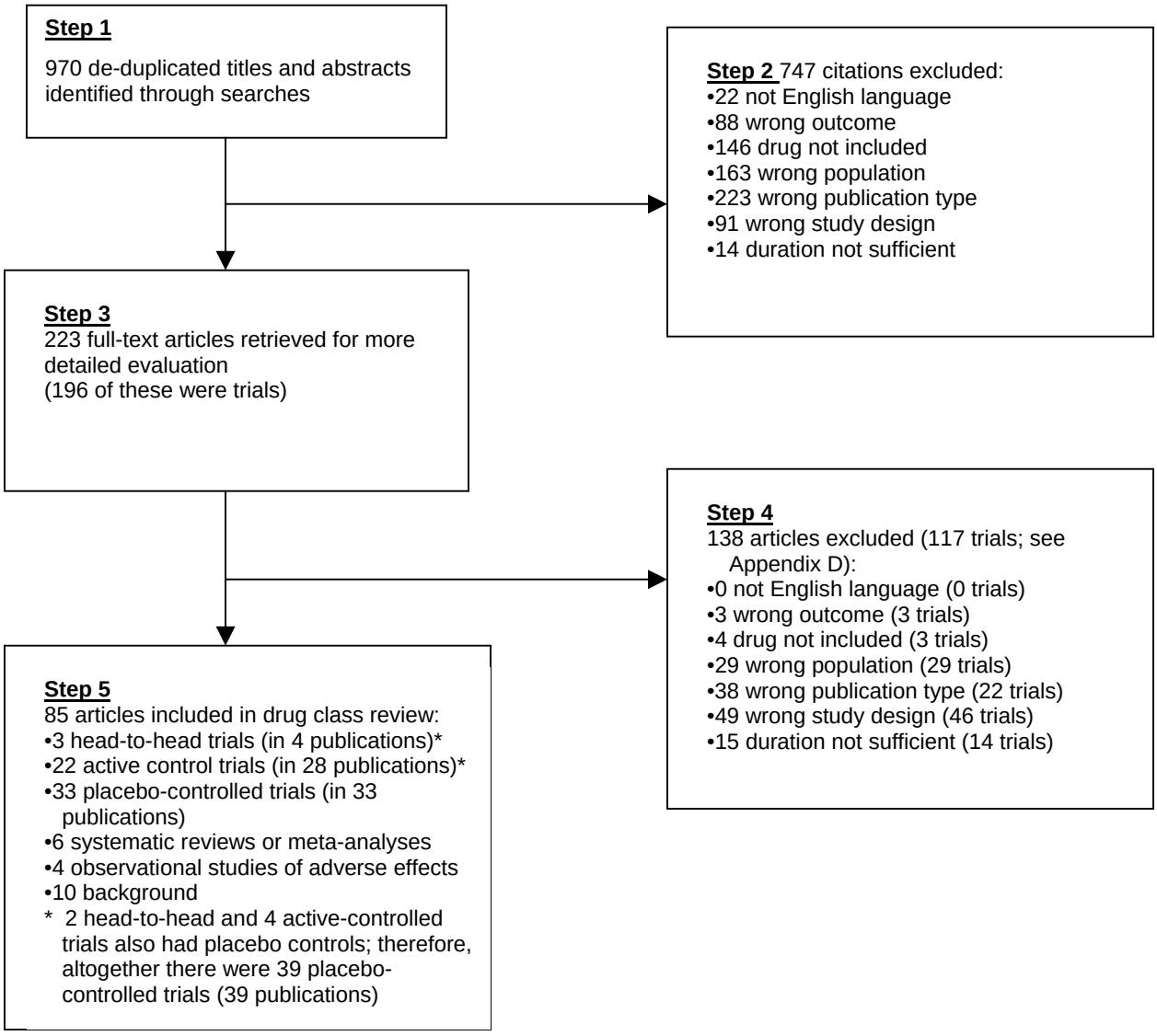
Since only one of the bipolar disorder trials directly compared adverse events between AEDs, we assessed the comparison of AED versus placebo, and AED versus lithium for bipolar disorder. We looked for overlap between the confidence intervals of the pooled odds ratios (or single study odds ratio if only one trial was available) for each AED. If the confidence intervals overlapped, then we could not conclude that the odds between AEDs were significantly different.

RESULTS

Overview

Searches identified 970 de-duplicated citations: 542 from the Cochrane Library, 350 from Medline/PubMed, 39 from Embase, 27 from reference lists, and 12 from 4 pharmaceutical company dossiers submitted by Abbott Laboratories, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, and Ortho-McNeil Pharmaceutical, Inc. We included 85 reports: 65 papers on 58 RCTs, 6 systematic reviews, 4 long-term (> 1 year) observational safety studies, and 10 background articles. Of the 27 articles identified from reference lists, 3 were included, and none of the articles from company dossiers were included. A total of 884 articles were excluded for the reasons listed in Figure 1. Appendix D lists the excluded trials.

Figure 1. Results of literature search



Of the 58 included RCTs (3 head-to-head, 22 active control, and 33 placebo-controlled; total 65 publications), 21 (28 publications) dealt with bipolar disorder and 37 (37 publications) pertained to neuropathic pain. For the 6 systematic reviews, the numbers were 3 for bipolar disorder, 2 for pain, and 1 for safety.

The internal validity of the 21 bipolar RCTs was rated poor or fair; there were no good-quality RCTs. Most of the trials did not describe the methods of randomization or allocation concealment or did not use or report an adequate allocation concealment method. Many trials did not have similar groups at baseline. Eligibility criteria were not described in either of 2 publications on 1 head-to-head trial.[19, 20] Many trials did not report or did not use methods to mask the outcome assessor. Most of the trials described a method for masking the care provider and patient, and were described as double-blind trials. Eight of the trials had high (20% or greater) withdrawal rates.[21-28] Nine trials did not use intent-to-treat analysis.[20]

External validity of the trials or their subgroup analyses was often limited by selective patient populations[19, 20, 22, 28-36] or small sample size (number randomized was less than 40 per treatment group).[19, 20, 23, 26, 29, 30, 36-38] Run-in periods on study treatment (either active drug or placebo) may have resulted in selective populations because patients who experienced adverse events during the run-in period may have not been eligible for randomization[33, 35, 38-40]or placebo responders were excluded.[42] Only 2 trials reported both the numbers of patients screened and eligible;[23,30] the remainder did not report one or both of these figures.

All of the 37 RCTs on neuropathic pain were rated poor or fair in internal validity. Many trials did not report the methods of randomization and allocation concealment as well as masking of outcome assessor, care provider, and patient (although the trials may have been described as double-blind). Many trials, while described as randomized, did not have similar treatment groups at baseline. Many trials did not describe eligibility criteria for entry into the trial. Intent-to-treat analysis was not used in 20 trials[42-61] and could not be determined in 4 trials.[62-65] Applicability of the trial results to adult outpatients with neuropathic pain was limited because most trials were small;[43-47, 49-53, 55-58, 65-69] two trials had selective populations;[49,55] and two large trials[70,71] introduced the possibility of selection bias by excluding patients who had inadequate responses or intolerance to previous treatment with gabapentin. Most trials did not report the number of patients who were screened or eligible.[43-46, 48, 50-52, 54-56, 65, 67-69, 72-75] In addition to these published trials, we found a summary of an unpublished placebo-controlled trial in a systematic review.[76] We excluded this trial because it was not published in full and its internal and external validity could not be fully assessed.

The quality of 2 observational studies on adverse events of AEDs was considered to be poor because selection was biased,[77] loss to follow-up was not clear,[77,78] ascertainment techniques were not adequate,[78] or statistical analysis of potential confounders was not performed.[78] Another 2 observational studies on adverse events were rated fair in internal validity because loss to follow-up was not clear,[79,80] ascertainment techniques were not adequately described,[80] or ascertainment methods were inadequate[79] or could not be determined.[80]

Key Question 1.
For adult outpatients with bipolar disorder or neuropathic pain do AEDs differ in effectiveness?

1a. Bipolar Disorder

Systematic reviews

There were three good-quality systematic reviews that evaluated AEDs in the acute treatment or maintenance therapy of bipolar disorder. These studies are abstracted in the Systematic Review Table 1, and the results are summarized in Table 3.

Table 3. Summary of systematic reviews of AEDs in bipolar disorder

Reference (Quality)	Treatment Phase No. of AED trials (N)	Outcome Measure(s)	Carbamazepine	Valproate
Poolsup (2000)[81] (Good)	Acute Mania 5 (397)	Psychotic symptoms, BPRS	= Lithium	= Lithium
		Global symptoms, CGI	= Lithium	—
		Responder rate	= Lithium	= Lithium
Macritchie (2004)[82] (Good)	Maintenance 1 (372)	Recurrence rate, any mood episode	—	= Lithium > Placebo
		Recurrence rate, manic episodes	—	= Placebo
		Recurrence rate, depressive episodes	—	= Lithium > Placebo
		Time to recurrence	—	= Lithium = Placebo
		Functional capacity, GAS	—	= Lithium = Placebo
Tondo (2003)[83] (Good)	Maintenance, rapid cycling 16 (1856) total; see text for N of meta-analyses	Recurrence rate	= Lithium	—
		Non-improvement rate	= Lithium	—

AED, Antiepileptic drug; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression rating scale; GAS, Global Assessment Scale (a measure of global functioning); = Lithium or = Placebo, no statistically significant difference between AED and either lithium or placebo; > Placebo, AED was statistically superior to placebo

In acute mania, both carbamazepine and valproate were not statistically different from lithium in terms of responder rate and improvement in symptoms.[81]

In the maintenance therapy of bipolar disorder, valproate was similar to lithium in preventing recurrences of any mood episode and depressive episodes, in time to recurrence, and in global functioning as assessed by the Global Assessment Scale (GAS).[82] Valproate was superior to placebo in preventing any mood episode and depressive episodes, but was not statistically different from placebo in preventing manic episodes, time to recurrence, and GAS scores.

In the maintenance therapy of rapid cyclers, meta-analyses to compare the effects of specific treatments were performed as part of a systematic review of 16 trials evaluating carbamazepine, lamotrigine, topiramate, valproate, lithium, or placebo in rapid cycling versus non–rapid cycling patients.[83] A meta-analysis could be performed on only three open-label studies and 1 blinded RCT comparing carbamazepine (with or without other agents except lithium) and lithium (with or without other agents except carbamazepine) using recurrence rate. The results showed no statistically significant differences between the two agents. A meta-analysis of two trials

comparing the two agents using non-improvement rate also showed no statistically significant treatment difference. There was also no indication of a significant interaction effect of diagnostic subtype by treatment. Overall, there was no clear advantage for any treatment or superiority of AEDs (carbamazepine, lamotrigine, topiramate, valproate) over lithium based on pooled crude recurrence and non-improvement rates.

Head-to-head trials

We reviewed five head-to-head trials (six publications)[19, 20, 29, 84-86] for possible inclusion and none of the reports met eligibility criteria for trials in outpatient populations. Two trials were excluded because they were the wrong publication type (conference abstracts)[84,86] and one trial was excluded because of study design (non-DSM diagnostic criteria).[85] Two trials (for which original data were published in three reports)[19, 20, 29] did not meet our entry criteria because the patients were hospitalized for the study duration.

Because we found no head-to-head trials in outpatients, we evaluated the inpatient trials. One was a double-blind trial (2 publications)[19,20] that was rated fair in quality because it did not report eligibility criteria or use intent-to-treat analyses for efficacy. This trial evaluated a heterogeneous patient population consisting of patients with DSM-IV diagnosis of bipolar disorder (most with rapid cycling) or unipolar disorder. The results of this trial are summarized here. The other trial was not double-blind and did not report allocation concealment; it was rated poor in quality.[29] The generalizability of the results of these two trials to a bipolar outpatient community population may be limited. The three publications on these two trials are summarized in Evidence Table 1 and Quality Table 1.

The first of the two publications on the same trial was a double-blind, double-dummy, double-crossover RCT comparing lamotrigine, gabapentin, and placebo monotherapy in 38 patients with refractory bipolar and unipolar disorders, 92% of whom had rapid cycling disorder.[20] Response was defined as a score of much or very much improved on the Clinical Global Impressions Scale for Bipolar Illness after 6 weeks of treatment. In 31 evaluable trial completers, overall responder rates for lamotrigine, gabapentin, and placebo were 52%, 26%, and 23%, respectively. Lamotrigine was superior to both gabapentin in terms of overall responders. Responder rates were similar between treatment groups for manic episodes (44%, 20%, and 32%) and depressive episodes (45%, 26%, and 19%). In addition, lamotrigine was associated with a significantly greater reduction in depression scores (HAM-D difference: –7.7 points; $p = 0.015$) relative to gabapentin. There were no treatment differences in other ratings (Young Mania Rating Scale [YMRS], Speilberger State Anxiety Scale, and Brief Psychiatric Rating Scale [BPRS]). The results should be considered preliminary given the small sample size, selective population of refractory patients, and diagnostically heterogeneous patient population. Other outcome measures of interest (i.e., remission, speed and duration of response or remission, use of other medications, relapse and recurrence, functional capacity, and danger to self) were not evaluated.

The second report presented an extension of the first trial and evaluated possible clinical response predictors to lamotrigine and gabapentin in the original 31 patients plus an additional 14 with bipolar or unipolar mood disorder.[19] Responder rates were again higher on lamotrigine (51%) than gabapentin (28%) or placebo (21%). There was no statistically significant difference in response between gabapentin and placebo. The subgroup analyses are discussed in section *3a. Bipolar disorder*.

The other head-to-head trial was a poor-quality, single-blind randomized trial that compared carbamazepine and valproate in 30 patients with bipolar disorder (DSM-III-R) and YMRS scores of ≥ 20.[29] After 4 weeks of therapy, valproate was superior to carbamazepine in the reduction of YMRS scores (calculated difference, carbamazepine minus valproate: 12; p = 0.023). There was no statistically significant difference in rates of response (> 50% decrease in YMRS total score from baseline to end point) between carbamazepine (53.3%) and valproate (73.3%).

Based on the fair-quality, preliminary evidence discussed above, lamotrigine may possibly be superior to gabapentin in patients with bipolar disorder with predominantly rapid cycling or unipolar disorder. There was no evidence that gabapentin was more effective than placebo. In patients with bipolar disorder with recent mania, valproate may be superior to carbamazepine; however, the evidence for this comparison is poor.

Active control trials

A total of 54 citations on active control mood trials were reviewed for eligibility, 14 trials (20 publications) were included in this report (Evidence Table 2),[21-28, 30-34, 37, 39, 40, 88, 89, 90] and 7 fair-quality trials (9 publications)[21, 22, 26, 28, 33, 39, 40, 87,90] are discussed here. The quality of these 7 trials was rated fair because they used an intent-to-treat or modified intent-to-treat analysis, but methods of randomization or allocation concealment were often not reported, treatment groups may not have been similar at baseline, blinding methods were not reported, and/or loss to follow-up could not be determined. There were no good-quality trials and the remaining 7 trials were of poor quality primarily because of lack of either blinding or high loss to follow-up. The applicability of results to an outpatient community population was limited in a number of trials because maintenance therapy trials may have initially hospitalized patients for stabilization of symptoms,[21,87] a selective sample population was studied, (e.g., rapid cyclers, milder forms of bipolar disorder, AED responders),[22,28, 33, 39] or the sample size was small.[23, 26] Of the 14 included trials, 8 were multicenter,[22, 24, 28, 34, 39, 40, 87, 90,]12 double-blind,[22, 23, 25-28, 30, 34, 39, 40, 87, 90] 1 open-label,[24] 1 crossover,[27] 8 double-dummy,[23, 25, 26, 28, 30, 34, 40, 90] and 3 included a placebo control in addition to the active control.[22, 39, 40] The design, results, and quality of the included trials are summarized in Evidence Table 2 and Quality Table 2.

In the 7 fair-quality trials discussed here, carbamazepine (2 trials),[26,90] divalproex (1 trial in 2 publications),[22,33] or lamotrigine (2 trials),[39,40] was compared with lithium or both lithium and placebo, and 2 trials (in 3 publications) compared divalproex with olanzapine.[21, 28,87]

Response: Symptom Rating Scales

Improvement in symptoms was evaluated in 5 of the 7 fair-quality trials (Table 4). Divalproex was compared with olanzapine in 2 trials (three publications),[21, 28, 87] and divalproex and lamotrigine were each compared with lithium in 1 trial[22] and 2 trials,[39,40] respectively.

Table 4. Change in symptom intensity in patients with bipolar disorder (active-control trials)

Trial	Interventions	Duration	Diagnosis N	Symptom Scale	Change in Scores from Baseline, mean	Interpretation of Results
Acute Therapy						
Tohen (2002)[87]	Divalproex vs. Olanzapine	3 wk	BPI-M/Mx 251	YMRS (11-item)	-10.4 vs. -13.4	DVP < OLN
				HDRS (21-item)	-3.46 vs. -4.92	DVP = OLN
Zajecka (2002)[28]	Divalproex vs. Olanzapine	3 wk	BPI-M 120	MRS	-14.9 vs. -16.6	DVP = OLN
				BPRS	-8.1 vs. -10.2	DVP = OLN
				HAM-D	-6.7 vs. -8.1	DVP = OLN
				CGI-S	-0.8 vs. -1.0	DVP = OLN
Maintenance Therapy						
Tohen (2003)[21]; extension of Tohen (2002)[87]	Divalproex vs. Olanzapine	47 wk	BPI–M/Mx 251	YMRS (11-item)	-12.5 vs. -15.4	DVP < OLN
				HDRS (21-item)	-1.59 vs. –3.78	DVP = OLN
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52 wk	BPI-M 372	MRS	3.1 vs. 3.0 vs. 3.4	DVP = LI = PBO
				DSS	3.9 vs. 5.7 vs. 6.1	DVP = LI = PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76 wk	BPI-M/HM 175	MRS	1.79 vs. -0.04 vs. 2.3	LTG < LI LTG = PBO LI > PBO
				HAM-D (17-item)	2.05 vs. 2.68 vs. 3.92	LTG = LI LTG > PBO LI = PBO
				CGI-S	0.37 vs. 0.44 vs. 0.56	LTG = LI = PBO
				CGI-I	0.79 vs. 0.8 vs. 0.95	LTG = LI = PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76 wk	BPI-D 463	MRS	0.7 vs. 0.7 vs. 1.1	LTG = LI = PBO
				HAM-D (17-item)	2.5 vs. 2.9 vs. 4.9	LTG = LI LTG > PBO LI > PBO
				CGI-S	0.7 vs. 0.4 vs. 0.3	LTG = LI LTG > PBO LI > PBO
				CGI-I	2.6 vs. 2.5 vs. 2.5	LTG = LI = PBO

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state;
Symptom scale: BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical global impression of improvement; CGI-S, Clinical global impression of symptoms; DSS, Depressive Syndrome Scale; HAM-D and HDRS, Hamilton Depression Rating Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale
Interpretation of results / Drugs: DVP, Divalproex; LI, Lithium; LTG, Lamotrigine; OLN, Olanzapine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); <, Inferior to ($p < 0.05$)

Divalproex vs. Olanzapine

No indirect comparisons between AEDs could be made on the basis of olanzapine-controlled trials because only divalproex was compared with this atypical antipsychotic in the fair-quality trials. There was conflicting evidence on the relative efficacy of divalproex and olanzapine. One large trial showed that divalproex was inferior to olanzapine in improving manic symptoms during acute and maintenance therapy of bipolar I disorder with recent mania or mixed episodes.[21,87] Another, smaller trial showed that divalproex was not statistically different from olanzapine on any symptom scale in the acute treatment of mania.[28] This was the only fair-quality active control trial to measure antipsychotic effects of an AED.

Divalproex vs. Lithium

One long-term (52-week) maintenance trial showed no statistically significant treatment differences between divalproex and lithium in 372 patients with bipolar I mania in terms of changes in scores on the MRS, Depressive Syndrome Scale (DSS), and Global Assessment Scale (GAS).[22] There were a number of limitations to this trial. Design-related biases favored recruitment and retention of patients with milder illness and may have diminished the power of the study to detect treatment differences. A high dropout rate produced a study population of less severely affected patients than those usually encountered in clinical practice. The practical difficulties in conducting maintenance therapy trials in patients with bipolar disorder have been discussed in detail by the authors of the RCT.[93]

Lamotrigine vs. Lithium

Lamotrigine showed mixed results on the Mania Rating Scale (MRS) in two 76-week trials comparing lamotrigine with lithium and placebo. In patients with bipolar I mania/hypomania (DSM-IV), lamotrigine was inferior to lithium in terms of improvement on MRS scores.[39] The mean change (SD) from baseline was 1.79 (5.67) for lamotrigine and –0.04 (2.75) for lithium (calculated difference, 1.83; $p = 0.03$). These results indicated a lesser overall degree of worsening of manic symptoms with lithium. However, in patients with bipolar I depression, there was no statistically significant treatment difference between the same agents in terms of improvement in MRS scores: 0.7 (3.8) vs. 0.7 (3.4).[40]

For the remaining symptom rating scales, the 17-item Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression for Severity of illness (CGI-S), and for Improvement (CGI-I), the results showed no statistically significant treatment difference between lamotrigine and lithium in either population.

The comparisons of efficacy between lamotrigine and lithium in this trial were confounded by the use of open-label lamotrigine as stabilization therapy prior to randomization of patients to double-blind treatment. Patients may have withdrawn from the trial during the open-label phase because of lack of efficacy (or adverse events), thereby causing an enriched enrollment of lamotrigine responders to the double-blind phase. The opposing results may have also been related to differences in study populations and study designs.

Divalproex vs. Lamotrigine: Indirect Comparisons

Based on the results of the lithium-controlled maintenance trials discussed above, it is difficult to indirectly derive relative treatment effects for divalproex and lamotrigine. Both agents seem to be no better than lithium in improvement on symptom rating scales. Therefore, they appear to be comparable to each other in this respect with the exception that lamotrigine may be less effective than divalproex on the MRS in patients with bipolar I mania.

Response: Responder Rate

Only one fair-quality trial reported responder rate;[87] therefore, no indirect comparisons between the AEDs can be made based on this outcome measure.

Remission

Five fair-quality trials reported remission rates in patients with bipolar disorder, four in which carbamazepine, divalproex, or lamotrigine was compared with lithium,[22, 26, 39, 40] and one (reported in two publications) in which divalproex was compared with olanzapine (Table 5).[21,87]

Table 5. Remission rates of patients with bipolar disorder (active control trials)

Trial	Interventions	Duration (wk)	Diagnosis N	Measure of Remission Rate	Remission Rate (%)	Interpretation of Results
Coxhead (1992)[26]	Carbamazepine vs. Lithium	52	BP (DSM-III) 31	Proportion of patients remaining relapse-free at end of study	47 vs. 44	CBZ = LI
Hartong (2003)[90]	Carbamazepine vs. Lithium	103	BP (DSM-III-R) 144	Proportion of patients who completed 2 y without episode	32.0 vs. 36.4	CBZ = LI†
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Proportion of patients remaining in study*	48 vs. 42 vs. 41	DVP = LI = PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	Proportion of patients remaining in study†	43 vs. 47 vs. 15	LTG = LI LTG > PBO LI > PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-D 463	Proportion of patients remaining in study†	36 vs. 40 vs. 25	LTG = LI LTG > PBO LI > PBO
Tohen (2002)[87]	Divalproex vs. Olanzapine	3	BPI-M/Mx 251	Symptomatic remission (end point (YMRS total score ≤ 12)	34 vs. 47	DVP < OLN
Tohen (2003);[21] double-blind, randomized trial extension of Tohen (2002)[87]	Divalproex vs. Olanzapine	47	BPI-M/Mx 251	Symptomatic mania remission (end point total YMRS ≤ 12)	45.5 vs. 56.8	DVP = OLN
				Syndromal mania remission (DSM-IV criteria; see text)	38.2 vs. 50.8	DVP = OLN
				Symptomatic remission of both mania and depression (end point total YMRS ≤ 12 and HDRS ≤ 8)	30.9 vs. 30.9	DVP = OLN
				Syndromal remission of both mania and depression (DSM-IV criteria; see text)	27.6 vs. 29.8	DVP = OLN

* Proportion of patients remaining in study at 52 weeks according to Kaplan-Meier survival estimate for time to any affective episode; these were patients who had not experienced a recurrence of any affective episode.

† Proportion of patients remaining in study at 76 weeks according to Kaplan-Meier survival estimate for time to intervention for any mood episode; these were patients who were not given therapeutic intervention for a mood episode

Diagnosis: BP, Bipolar disorder (not subcategorized); BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state

Measure of remission rate: HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale

Interpretation of results / Drugs: CBZ, Carbamazepine; DVP, Divalproex; LI, Lithium; LTG, Lamotrigine; OLN, Olanzapine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); <, Inferior to ($p < 0.05$); †, post hoc statistical analysis; $p = 0.656$ (statistical analysis not reported in publication)

Based on different measures of remission in patients with different types of bipolar disorder, carbamazepine, divalproex, and lamotrigine were each found to be not statistically different from lithium. Indirect comparisons of these AEDs based on their treatment effects relative to lithium suggest they are similar in terms of remission rates, as defined by the original authors, in patients

with bipolar disorder. Remission rates during acute therapy were better on olanzapine than on divalproex; however, there were no differences in remission rates between these two agents during maintenance therapy.

Speed and duration of response or remission

Four fair-quality trials (5 publications) assessed various measures of speed or duration of *remission*.[21, 22, 39, 40, 87] No fair-quality active control trials reported speed or duration of *response*. A single trial compared divalproex with olanzapine using different measures of time to remission during acute[87] and maintenance therapy.[21] Divalproex and lamotrigine have been compared with lithium on the basis of duration of remission in 1 trial[22] and 2 trials, respectively.[39,40] Therefore, indirect comparisons of the AEDs are possible based on remission duration using the lithium-controlled trials only. The measure of the duration of remission was the time to relapse or recurrence, as defined by the original authors, or time *to intervention* for return of mood symptoms.

The trial that compared divalproex (mean serum concentration of valproate, 84.8 mcg/ml) and lithium (titrated to serum concentrations of 0.8 to 1.2 mEq/l) showed no treatment difference in the time to intervention (addition of drug or electroconvulsive therapy) for any mood episode.[22] This outcome measure was used in the primary efficacy analysis, and no treatment difference was detected between either of the active treatments and placebo. These results may have been due to a high dropout rate, lower planned recruitment rate into the lithium group (randomization ratio for divalproex, lithium, and placebo was 2:1:1, which reduced the power for lithium-placebo comparisons), selection of milder forms of bipolar disorder by requiring two consecutive GAS scores > 60, and possible bias caused by requiring that remission of mania be achieved within 3 months of the manic episode (28 of 199 patients [14.1%] who failed to achieve randomization into the maintenance phase of the trial were excluded for not meeting this requirement). As a result, the trial lacked sufficient power to adequately test the primary outcome measure (0.3 as opposed to the planned power of > 0.8), and the results may be considered inconclusive.

The two trials that compared lamotrigine and lithium (titrated to serum concentrations of 0.8 to 1.1 mEq/l in both trials) showed no treatment differences in the time to intervention for any mood episode.[39,40]

Based on the results discussed above, an indirect comparison based on relative efficacy to lithium (titrated to similar serum concentrations in all three trials) suggests that neither divalproex nor lamotrigine is better than the other in terms of duration of remission in bipolar disorder.

Use of other medications for acute episodes

Two trials that evaluated maintenance therapy with either lamotrigine, lithium, or placebo used the time to intervention (pharmacotherapy or electroconvulsive therapy) for any mood episode as the primary efficacy measure.[39,40] A third trial assessed additional use of sertraline or paroxetine after the start of maintenance therapy with divalproex, lithium or placebo.[33] As mentioned previously, the comparisons between lamotrigine and lithium were confounded by open-label treatment with lamotrigine prior to randomization to double-blind maintenance therapy;

therefore, the results for additional therapy requirements must be interpreted with caution. No statistical analyses were performed for any of the comparisons between AED and lithium and the types of therapies varied between trials. Therefore, it is difficult to make indirect comparisons of the AEDs.

Relapse and Recurrence

Four fair-quality active control trials (in 5 publications) evaluated AEDs (carbamazepine, divalproex, or lamotrigine) with lithium,[26,90] and one trial compared divalproex with olanzapine[21] in terms of relapse or recurrence rates during double-blind maintenance therapy (Table 6).

Table 6. Recurrence rates in patients with bipolar disorder (active control trials)

Trial	Interventions	Duration (wk)	Diagnosis N	Definition of Recurrence	Recurrence Rate (%)	Interpretation of Results
Coxhead (1992)[26]	Carbamazepine vs. Lithium	52	BP (DSM-III) 31	Relapse (not defined)	40 vs. 50	CBZ = LI†
Hartong (2003)[90]	Carbamazepine vs. Lithium	103	BP (DSM-III-R) 144	Recurrence of an episode of (hypo)mania or major depression (DSM-III-R)	42.0 vs. 27.3	CBZ = LI†
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52 wk	BPI–M 372	Occurrence/relapse of mania or depression	24 vs. 31 vs. 38	DVP = LI DVP > PBO LI = PBO
				Manic episode (MRS ≥ 16 or hospitalization)	18 vs. 21 vs. 22	DVP = LI = PBO
				Depressive episode requiring antidepressant or premature discontinuation from study because of symptoms	6 vs. 10 vs. 16	DVP = LI DVP > PBO LI = PBO
Gyulai (2003);[33] additional analyses from Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI–M 372	Depressive relapse: need for treatment or early discontinuation for depression	27 vs. 26 vs. 28	DVP = LI = PBO†
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	Intervention for a mood episode	47 vs. 39 vs. 70	LTG = LI† LTG > PBO† LI = PBO†
Tohen (2003)[21]	Divalproex vs. Olanzapine	47	BPI-M/Mx 251	Symptomatic relapse / recurrence into an affective episode (YMRS ≥ 15, HDRS ≥ 15) Syndromal recurrence into an affective episode (DSM-IV criteria)	Symptomatic: 56.5 vs. 42.4 Syndromal: 65.0 vs. 64.5	DVP = OLN

Diagnosis: BP, Bipolar disorder, not subcategorized; BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state. **Definition of recurrence:** HDRS, Hamilton Depression Rating Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale. **Interpretation of results / Drugs:** DVP, Divalproex; LI, Lithium; OLN, Olanzapine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); †, post hoc statistical analyses; see text for p-values (statistical analyses not reported in publication)

Since none of the fair-quality trials reporting this outcome defined the terms using DSM criteria,[21, 22, 26, 33, 39] and because all the trial results pertained to return of mood symptoms after starting maintenance therapy (without describing whether there was a shift in polarity or the interval between occurrences of manic symptoms), it was not possible to distinguish between *relapse* and *recurrence.* Therefore, this report uses *recurrence* whether the author used *relapse* or *recurrence,* in keeping with the preferred term used in DSM criteria for bipolar disorder.

No statistical analyses on *recurrence* rates were reported in three of the four trials that compared the three AEDs with lithium. Post hoc statistical analyses reveal no significant differences between lithium and either carbamazepine ($p = 0.576$ in one trial[26] and $p = 0.136$ in the second trial)[90] or lamotrigine ($p = 0.459$).[39] The second trial that compared carbamazepine and lithium showed a different pattern of recurrence between the two agents.[90] The risk of recurrence of an episode on carbamazepine was fairly constant over the 2-year study period (about 40% per year). In comparison, most recurrences on lithium occurred in the first 3 months. Post hoc subgroup analyses suggested that patients who had started lithium during an acute episode had a risk of recurrence of about 40% in the first 3 months. Thereafter, the risk of recurrence was less than 10% per year during lithium maintenance therapy. These results should be interpreted with caution since the trial did not use an intent-to-treat analysis, a high proportion of patients (34.7%) were not included in analyses, and the subgroup analyses were not planned a priori.

The remaining trial showed no significant difference between divalproex and lithium.[22] Additional analyses from this trial, published separately, did not report statistical analyses;[33] however, a post hoc analysis again shows no statistically significant difference between divalproex and lithium ($p = 0.979$).

Therefore, indirect comparisons of carbamazepine, divalproex, and lamotrigine, based on the lack of treatment differences relative to lithium, suggest that the three AEDs are similar in terms of recurrence rates.

Functional capacity (quality of life, work productivity)

Three trials assessed GAS scores during maintenance therapy of patients with recent manic episodes (Table 7).

Table 7. Changes in Global Assessment Scale (GAS) scores in patients with bipolar disorder (active control trials)

Trial	Interventions	Duration (wk)	N	Change in GAS Score	Interpretation of Results
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI–M 372	Center Effects model: -4.7 vs. -7.8 vs. -5.7	DVP = LI = PBO
				Mania Subtype model: -4.7 vs. -10.8 vs. -6.2	DVP > LI DVP = PBO LI < PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI–M/HM 175	-3.19 vs. -3.85 vs. -5.63	LTG = LI = PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI–D 463	-2.8 vs. -4.1 vs. -6.9	LTG = LI LTG > PBO LI > PBO

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state;
Interpretation of results / Drugs: DVP, Divalproex; LI, Lithium; LTG, Lamotrigine; OLN, Olanzapine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); <, Inferior to ($p < 0.05$)

All of these trials compared the AED (divalproex in one trial and lamotrigine in two trials) with lithium and placebo. Individual scores for employment (i.e., work productivity) were not reported. Quality of life is not assessed by GAS and was not an outcome measure for any of the fair-quality active control trials. A higher GAS score indicates a better level of function.

One trial analyzed the changes in GAS scores using a Center Effects model (analysis of variance model that included effects for treatment, center, and treatment-center interaction) and a Mania Subtype model (included effects for treatment, mania type [depressive versus elated], and their interaction). With the Center Effects model, the changes in GAS scores for divalproex, lithium, and placebo were –4.7, –7.8, and –5.7, respectively.[22] There were no statistically significant treatment differences. In the Mania Subtype model, divalproex treatment was associated with significantly less worsening in GAS scores in comparison with lithium (change in GAS score for divalproex, lithium, and placebo: –4.7, –10.8, and –6.2, respectively; $p = 0.001$for divalproex vs. lithium; $p = 0.03$ for lithium versus placebo). The analysis of the interaction between treatment and mania subtype indicated lithium provided an inferior prophylactic effect in terms of GAS scores among patients without depression during the index manic episode.

The trial that compared lamotrigine, lithium, and placebo showed no statistically significant treatment differences between lamotrigine and lithium in changes in GAS scores in either patients with mania or depression as most recent episode.[39,40]

Therefore, indirect comparisons of divalproex (using a Center Effects model) and lamotrigine, based on treatment differences relative to lithium, suggest that neither AED is superior to the other in improving functional capacity, as measured by the GAS. Divalproex may be associated with less worsening in functional capacity as compared with lamotrigine in patients without depression during an index manic episode (using a Mania Subtype model).

Danger to self (suicide attempts and completions)

Only one fair-quality active control trial assessed frequency of suicide attempts during maintenance therapy with divalproex, lithium, or placebo.[33] Therefore, no indirect comparisons of AEDs can be made.

Hospitalization

One trial reported that the rates of admission for relapse during maintenance treatment with carbamazepine and lithium were 33.3% (5 / 15) and 31.2% (5 / 16), respectively.[26] No statistical analysis was performed in this study for this outcome. A post-hoc analysis yields a p-value of 0.90 for a chi-squared test of independence between drug and the rate of admission for relapse, and the confidence intervals for the rates are 11.8% to 61.6% for carbamazepine and 11.0% to 58.7% for lithium, respectively.

In a trial comparing divalproex, lithium, and placebo for maintenance therapy, the rates of hospitalization for depression were 1.6% (3 / 187), 2.2% (2 / 91), and 6.4% (6 / 94), respectively (no statistical analyses).[33] A post-hoc analysis yields a p-value of 0.10 for a chi-squared test of independence between drug and the rate of hospitalization for depression. This indicates that there was no difference between the three treatments. We calculated a p-value of 0.66 for divalproex versus lithium (and 0.07 for divalproex versus placebo), again showing no significant difference.

Our post-hoc analyses suggest that, based on comparisons with lithium, carbamazepine and divalproex are similar in rates of hospitalization for mood episodes during maintenance therapy.

Placebo-controlled trials

We reviewed 32 citations on placebo-controlled trials, including 2 that presented results on one trial that also had an AED control (head-to-head trial) and 11 with additional active controls. A total of 9 placebo-controlled trials (1 also with AED control,[20] 3 with active controls (4 publications),[22,23,39,40] and 5 with only placebo control)[35, 36, 38, 41, 94] were included in this report. Of these, 6 trials (3 with active control[22, 39, 40] and 3 with only placebo control)[35, 41, 94] were rated as fair quality because they used an intent-to-treat or modified intent-to-treat analysis but did not report the methods of randomization or allocation concealment, or had unequal distribution of baseline patient characteristics or did not report them. These fair-quality trials are discussed here. The remaining trials were poor quality because they did not use either adequate blinding methods or intent-to-treat analysis, or did not report randomization methods plus baseline patient characteristics were either not similar or not reported. All 9 included trials were double-blind, 6 were multicenter,[22, 35, 39-41, 94] 2 used a double dummy,[40,41] and 1 was a crossover design.[36] The methods, results, and quality of the included trials are summarized in Evidence Table 3 and Quality Table 3.

Response: Symptom Rating Scales

There were 6 fair-quality placebo-controlled trials that reported changes in symptom scores: 1 involving divalproex,[22] 1 assessing gabapentin (as add-on therapy to lithium and/or valproate),[41] and 4 assessing lamotrigine.[35, 39, 40, 94] Results are displayed in Table 8.

For reducing mania symptoms, none of the trials—for either acute or maintenance therapy—reported a superiority of any of the three AEDs over placebo. In fact, the primary efficacy analysis for the 10-week gabapentin trial showed add-on gabapentin to be inferior to placebo for changes in YMRS scores (–6.5 vs. –9.9, respectively; difference –3.34; 95% CI: –6.35 to –0.32; p = 0.03). A post hoc analysis postulated that the apparent benefit of placebo over gabapentin was due to a greater number of lithium dosage changes in the placebo group than the gabapentin group during the 2-week placebo open-label lead-in phase.

The results with lamotrigine were consistent, in that one acute treatment trial in patients with bipolar I depression[94] and 2 maintenance therapy trials (one in patients with recent bipolar I depression[40] and the other in patients with bipolar I mania/hypomania)[39] all reported no statistically significant difference between lamotrigine and placebo on the MRS.

For antidepressive effects, indirect comparisons of the AEDs from placebo-controlled trial results suggest there is a differential treatment effect. Long-term (52-week) divalproex treatment of patients with recent mania[22] and short-term (10-week) add-on gabapentin treatment of patients with bipolar I mania, hypomania, or mixed symptoms[41] did not report statistically significant benefits compared with placebo on DSS and HAM-D scales, respectively. In contrast, two long-term (76-week) trials with lamotrigine showed better results on lamotrigine than placebo on the 17-item HAM-D in patients with bipolar-I mania/hypomania[39] or bipolar I depression.[40] Two other trials, one evaluating acute therapy (7-week) and the other maintenance therapy (26-week), however, showed no statistically significant difference on either the 17- or 31-item HAM-D in patient populations with bipolar I depression[94] or rapid cycling,[35] respectively. In the acute therapy trial, lamotrigine 200 mg improved depressive symptoms as measured on the MADRS, whereas a dose of 50 mg was not statistically different from placebo.

Thus, lamotrigine maintenance therapy improved depressive, but not mania/hypomania, symptoms, gabapentin acute therapy had no effect on either symptom complex, and divalproex maintenance therapy, which was tested in mania only, had no effect.

No indirect comparisons between the three AEDs could be made for improvement in CGI-S or CGI-I because these outcome measures were only evaluated with lamotrigine.

Table 8. Change in symptom intensity in patients with bipolar disorder (placebo-controlled trials)

Trial	Interventions	Duration (wk)	Diagnosis N	Symptom Scale	Change in Scores from Baseline, mean	Interpretation of Results
Acute Therapy						
Pande (2000)[41]	Gabapentin vs. Placebo (Add-on)	10	BPI-M/HM/Mx 117	YMRS	-6.5 vs. -9.9	GBP < PBO
Calabrese (1999)[94]	Lamotrigine 50 mg/d vs. Lamotrigine 200 mg/d vs. Placebo	7	BPI-D 195	MRS	0.9 vs. 0.3 vs. -0.5	LTG50 = LTG200 = PBO
				HAM-D (17-item)	-9.3 vs. –10.5 vs. –7.8	LTG50 = LTG200 = PBO
				HAM-D (31-item)	-14.2 vs. –15.7 vs. –12.1	LTG50 = LTG200 = PBO
				MADRS	-11.2 vs. –13.3 vs. –7.8	LTG50 = PBO LTG200 > PBO
				CGI-S	-1.0 vs. –1.2 vs. -0.7	LTG50 = PBO LTG200 > PBO
				CGI-I	3.0 vs. 2.6 vs. 3.3	LTG50 = PBO LTG200 > PBO
Maintenance therapy						
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	MRS	3.1 vs. 3.0 vs. 3.4	DVP = LI = PBO
				DSS	3.9 vs. 5.7 vs. 6.1	DVP = LI = PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	MRS	1.79 vs. -0.04 vs. 2.3	LTG < LI LTG = PBO LI > PBO
				HAM-D (17-item)	2.05 vs. 2.68 vs. 3.92	LTG = LI LTG > PBO LI = PBO
				CGI-S	0.37 vs. 0.44 vs. 0.56	LTG = LI = PBO
				CGI-I	0.79 vs. 0.8 vs. 0.95	LTG = LI = PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-D 463	MRS	0.7 vs. 0.7 vs. 1.1	LTG = LI = PBO
				HAM-D (17-item)	2.5 vs. 2.9 vs. 4.9	LTG = LI LTG > PBO LI > PBO
				CGI-S	0.7 vs. 0.4 vs. 0.3	LTG = LI LTG > PBO LI > PBO
				CGI-I	2.6 vs. 2.5 vs. 2.5	LTG = LI = PBO
Calabrese (2000)[35]	Lamotrigine vs. Placebo	26	RC 182	MRS	Data not shown	LTG = PBO
				HAM-D (17-item)	Data not shown	LTG = PBO
				CGI-S	Data not shown	LTG = PBO

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state; RC, Rapid cycling
Symptom scale: BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical global impression of improvement; CGI-S, Clinical global impression of symptoms; DSS, Depressive Syndrome Scale; HAM-D and HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale. For all of these scales, scores increase with symptoms severity.
Interpretation of results / Drugs: GBP, Gabapentin; LI, Lithium; LTG, Lamotrigine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); <, Inferior to ($p < 0.05$)

Response: Responder Rate

Two placebo-controlled trials assessed responder rates with either gabapentin[41] or lamotrigine.[94] Neither agent was significantly better than placebo in terms of the responder rate. Indirect comparisons of the AEDs were not possible because of differences between trials in type of episodes (manic, hypomanic, or mixed versus depressive) of bipolar I disorder and definitions of

response ("much improved" or "very much improved" on Clinical Global Impression of Change [CGIC][41] versus CGI-I).[94]

Remission

One trial compared divalproex with lithium and placebo[22] and three trials compared lamotrigine with lithium and placebo[39,40] or placebo only[35] in terms of remission rates (Table 9).

Table 9. Remission rates in patients with bipolar disorder (placebo-controlled trials)

Trial	Interventions	Duration (wk)	Dx N	Measure of Remission Rate	Remission Rate (%)	Interpretation of Results
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Proportion of patients remaining in study*	48 vs. 42 vs. 41	DVP = LI = PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	Proportion of patients remaining in study†	43 vs. 47 vs. 15	LTG = LI LTG > PBO LI > PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-D 463	Proportion of patients remaining in study†	36 vs. 40 vs. 25	LTG = LI LTG > PBO LI > PBO
Calabrese (2000)[35]	Lamotrigine vs. Placebo	26	RC 182	Clinically stable without relapse for 6 mo	41 vs. 26	LTG > PBO

* Proportion of patients remaining in study at 52 weeks according to Kaplan-Meier survival estimate for time to any affective episode; these were patients who had not experienced a recurrence of any affective episode.

† Proportion of patients remaining in study at 76 weeks according to Kaplan-Meier survival estimate for time to intervention for any mood episode; these were patients who were not given therapeutic intervention for a mood episode.

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; RC, Rapid cycling

Interpretation of results / Drugs: DVP, Divalproex; LI, Lithium; LTG, Lamotrigine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$)

The trial comparing divalproex with placebo (and lithium) showed no treatment effect; however, this trial lacked sufficient power to detect a true difference, as discussed previously.[22] In contrast, all trials comparing lamotrigine with placebo showed a superiority of lamotrigine over placebo in patients with bipolar I mania/hypomania,[39] depression,[40] or rapid cycling.[35] It is difficult to make indirect comparisons between the AEDs because of the inconclusive results shown in the divalproex trial. There was consistent evidence, however, that showed better remission rates with lamotrigine than placebo across different clinical presentations of bipolar disorder.

Speed and duration of response/remission

Although one trial defined response to treatment, the time to and duration of response were not evaluated.[94]

Time to remission was not evaluated by any of the fair-quality placebo-controlled trials.

Four placebo-controlled trials, including one involving divalproex[22] and three involving lamotrigine,[35, 39, 40] evaluated treatments using different measures for duration of remission (Table 10).

Table 10. Duration of remission in patients with bipolar disorder (placebo-controlled trials)

Trial	Interventions	Duration (wk)	Dx N	Measure of Remission Duration	Remission Duration (95% CI), d	Interpretation of Results
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Time to 50% relapse of any mood episode	275 (167 to NC) vs. 189 (88 to NC) vs. 173 (101 to NC)	DVP = LI = PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	Median time to intervention for any mood episode	141 (71 to > 547) vs. 292 (123 to > 547) vs. 85 (37 to 121)	LTG = LI LTG > PBO LI > PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-D 463	Median time to intervention for any mood episode	200 (146 to 399) vs. 170 (105 to NC) vs. 93 (58 to 180)	LTG = LI LTG > PBO LI > PBO
Calabrese (2000)[35]	Lamotrigine vs. Placebo	26	RC 182	Median survival time to additional pharmacotherapy for emerging mood symptoms (Kaplan-Meier estimate)	126 (NR) vs. 84 (NR)	LTG = PBO

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; RC, Rapid cycling
Remission duration: NC, Not calculable; NR, Not reported
Interpretation of results / Drugs: DVP, Divalproex; LI, Lithium; LTG, Lamotrigine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$)

Results with divalproex showed no treatment benefit relative to placebo.[22] As mentioned previously, this study lacked sufficient power to detect a moderate sized difference.

All trials with lamotrigine showed it to be superior to placebo in duration of remission, despite differences in measures of remission duration, types of bipolar disorder, and lengths of treatment.[35, 39, 40]

Indirect comparisons between divalproex and lamotrigine cannot be made because of the inconclusive divalproex results.

Use of other medications for acute episodes

One fair-quality trial comparing divalproex and placebo assessed the proportion of patients who required additional selective serotonin reuptake inhibitors [SSRIs] for treatment of depressive symptoms in patients with recent bipolar I mania.[33] Three trials compared lamotrigine and placebo in patients with bipolar mania/hypomania, depression, or rapid cycling in terms of the proportion of each treatment group that required additional drug or electroconvulsive therapy.[35, 39, 94] No indirect comparisons of the AEDs could be made because only one[40] of the trials performed statistical analyses on the additional therapy results.

Relapse and Recurrence

One fair-quality placebo-controlled trial compared divalproex with placebo and lithium,[22,33] and another trial compared lamotrigine with placebo and lithium[39] in terms of recurrence in patients with bipolar I disorder with recent mania or hypomania (see Table 6). Statistical analyses were performed in one trial, which showed divalproex to be superior to placebo for recurrence of mania or depression and recurrence defined as either depressive episode requiring antidepressant or premature discontinuation because of symptoms.[22] There was no significant difference between divalproex and placebo for recurrence of manic episodes. A post hoc analysis for the other trial shows that lamotrigine is superior to placebo in reducing the proportion of patients who experience recurrence, defined as intervention for a mood episode ($p = 0.009$). Therefore, indirect comparisons of divalproex and lamotrigine, based on treatment differences relative to placebo, suggest that the two AEDs are similar in reducing recurrence of mood episodes (i.e., mania or depression).

A third trial compared lamotrigine and placebo as maintenance therapy for 26 weeks in 182 patients with rapid cycling,[35] a type of bipolar disorder that is typically less responsive to treatment. Recurrence, defined as additional pharmacotherapy required for emerging symptoms of a mood episode, occurred in 45 (50%) of 90 lamotrigine-treated patients versus 49 (56%) of 87 placebo patients. No statistical analysis was reported. A post hoc analysis shows there is no significant difference between lamotrigine and placebo ($p = 0.399$).

Functional capacity (quality of life, work productivity)

Four trials assessed improvement in GAS scores;[22, 35, 39, 40] however, one of these trials[35] did not report the data. These trials are displayed in Table 11. One trial did not show a superiority of divalproex over placebo as maintenance therapy in patients with recent bipolar I mania.[22] Again, these results were inconclusive because the trial lacked sufficient power to detect a moderate sized difference.

Results of trials comparing lamotrigine with placebo or lithium and placebo were mixed. One trial in 372 patients with recent mania/hypomania[39] and another trial in 182 patients with rapid cycling[35] both showed no significant treatment differences between lamotrigine and placebo. A third trial in 463 patients with recent bipolar I depression showed significantly lesser degrees of worsening on GAS scores with lamotrigine (-2.8) than placebo (–6.9; calculated difference: 4.1; $p < 0.05$).[40]

It is difficult to make indirect AED comparisons because of the inconclusive results with divalproex. Furthermore, the results varied with lamotrigine and the trials differed in treatment duration, sample size, and diagnosis of index mood episode.

Table 11. Changes in Global Assessment Scale (GAS) scores in patients with bipolar disorder (placebo-controlled trials)

Trial	Interventions	Duration (wk)	Dx N	Change in GAS score from baseline to end point	Interpretation of Results
Bowden (2000)[22]	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Center Effects model: -4.7 vs. -7.8 vs. –5.7	DVP = LI = PBO
				Mania Subtype model: -4.7 vs. -10.8 vs. -6.2	DVP > LI DVP = PBO LI < PBO
Bowden (2003)[39]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	-3.19 vs. -3.85 vs. -5.63	LTG = LI = PBO
Calabrese (2003)[40]	Lamotrigine vs. Lithium vs. Placebo	76	BPI-D 463	-2.8 vs. -4.1 vs. -6.9	LTG = LI LTG > PBO LI > PBO
Calabrese (2000)[35]	Lamotrigine vs. Placebo	26	RC 182	Data not reported	LTG = PBO

Diagnosis: BPI, Bipolar I disorder; –D, With recent depressive episode; –HM, With recent hypomania; –M, With recent mania; –Mx, With recent mixed state; RC, Rapid cycling
Interpretation of results / Drugs: GBP, Gabapentin; LI, Lithium; LTG, Lamotrigine; PBO, Placebo; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$); <, Inferior to ($p < 0.05$). A higher GAS score indicates a higher level of function.

Danger to self (suicide attempts and completions)

One trial comparing divalproex with lithium and placebo[33] and three trials comparing lamotrigine with placebo[35, 40, 94] reported suicide attempts or suicide deaths. There were no remarkable differences between either of the AEDs and placebo for both suicide outcomes; however, the numbers of events (0 to 2 patients per treatment group) were too small to make any meaningful treatment comparisons.

Five trials also reported suicidal ideation or suicidality scores on depression rating scales (Schedule for Affective Disorders-Change Version [SADS-C] or HAM-D item 3). One trial compared divalproex with lithium and placebo[33] and the remaining four trials compared lamotrigine with lithium and placebo[39, 40, 94] or placebo alone.[35] In the trials involving lamotrigine, the rates of suicidality were similar or not significantly different between treatment groups according to the authors. No statistical analysis was performed in the trial involving divalproex; therefore, we cannot make indirect comparisons between divalproex and lamotrigine.

Hospitalization

In a trial comparing divalproex, lithium, and placebo for maintenance therapy, the rates of hospitalization for depression were 1.6% (3 / 187), 2.2% (2 / 91), and 6.4% (6 / 94), respectively.[33] No statistical analysis was performed in this study for this outcome. A post-hoc analysis yields a p-value of 0.10 for a chi-squared test of independence between drug and the rate of hospitalization for depression. This indicates that there was no difference between the three treatments. We calculated a p-value of 0.07 for divalproex versus placebo (and 0.66 for divalproex versus lithium), again showing no significant difference. Two trials comparing lamotrigine with placebo reported no hospitalizations due to adverse events, where mood-related events were counted as adverse events,[94] or hospitalizations due to mood-related events or adverse events.[35] Based on indirect comparisons, divalproex and lamotrigine are similar in rates of hospitalization.

Summary

There were 3 good-quality systematic reviews, one fair-quality head-to-head trial, 7 fair-quality active control trials, and 6 fair-quality placebo-controlled (including 3 also active control) trials upon which to base indirect comparisons of AEDs.

The systematic reviews allowed indirect comparisons of carbamazepine and valproate based on their effectiveness relative to lithium. The findings suggest that carbamazepine and valproate are similar in improving psychotic symptoms (BPRS) and responder rate in patients with acute mania. In rapid cycling patients, there was no clear advantage for any AED (carbamazepine, lamotrigine, topiramate, and valproate) in reducing pooled crude recurrence or non-improvement rates.

Fair-quality, preliminary data from a head-to-head trial suggest that lamotrigine is better than gabapentin and that gabapentin is no better than placebo in a diagnostically mixed population of refractory patients with mostly rapid cycling.

Indirect comparisons of the AEDs based on the results of 3 fair-quality lithium-controlled trials suggest that divalproex may be more effective than lamotrigine in improving manic symptoms during maintenance therapy of patients with bipolar I mania, but head-to-head trials are needed to confirm this. Divalproex and lamotrigine appear to be similar in improving depressive symptoms, global impressions of symptom severity, duration of remission, and functional capacity, with the exception that divalproex may be associated with less worsening of functional capacity than lamotrigine in patients without depression during an index manic episode. Indirect comparisons of the results of lithium-controlled trials suggest that carbamazepine, divalproex, and lamotrigine have similar effects on remission rates and recurrence rates based on relative comparisons of each AED with lithium. Carbamazepine and divalproex are associated with similar rates of hospitalization for mood episodes during maintenance therapy, based on comparisons of these agents with lithium. No indirect comparisons of the AEDs were possible for responder rate, use of additional therapies, and danger to self.

On the basis of treatment effects relative to placebo (4 trials), lamotrigine maintenance therapy improved depressive symptom scores while long-term divalproex and short-term gabapentin did not. Acute therapy with lamotrigine (2 trials) does not appear to share an advantage over divalproex and gabapentin as was seen with lamotrigine maintenance therapy. Divalproex, gabapentin, and lamotrigine appear to have similar effects on reducing manic symptoms; this finding contradicts the indirect comparisons based on active control trial results, which suggested divalproex might be better than lamotrigine for mania. Divalproex (1 trial) and lamotrigine (2 trials) are similar in rates of hospitalization. No indirect comparisons of the AEDs could be made for CGI-S and CGI-I scores, responder rate, remission rates, speed and duration of response, time to remission, duration of remission, use of additional therapies, relapse and recurrence, functional capacity, and danger to self (suicide attempts and completions).

Comparisons with divalproex were largely hindered by inconclusive results from a trial that compared the agent with lithium and placebo; this trial lacked statistical power sufficient to detect a clinically important difference.[22] Indirect AED comparisons must be interpreted with

caution because they are based on different measures of the outcomes in patient populations who manifested different types of index mood episodes and were treated for various periods of time.

1b. Neuropathic Pain

Systematic reviews

Two good-quality systematic reviews provided evidence on the effectiveness or safety of the AEDs in neuropathic pain.[95,96] One systematic review allowed indirect comparisons of AEDs and is discussed below. The other systematic review evaluated gabapentin only and is not discussed in further detail here. Both systematic reviews are summarized in Systematic Review Table 2.

The systematic review that allowed AED comparisons evaluated 23 randomized trials (N = 1074) of 6 AEDs in acute or chronic (including cancer) pain management.[96] The AEDs were carbamazepine (12 trials), phenytoin, (6 trials), valproate (2 trials), gabapentin (2 trials), and clonazepam (1 trial). The results for clonazepam, which was not an AED of interest, are not presented in this report. Six of the trials were active-control, 16 were placebo-controlled, and 1 included both active and placebo controls. The acute pain conditions were postoperative pain and acute postherpetic neuralgia. The chronic pain conditions were trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia, and other pain syndromes. Data for only neuropathic pain types are presented here. The original authors of the trials defined the index of effectiveness and there was variability in the outcome measures across trials. In some trials, it was the number of patients improved while in other trials it was the number of patients pain-free at the end of the study. In the systematic review, no weighting was applied to the different indices.

The effectiveness odds ratios and relative risks for the AEDs are presented by neuropathic pain type in Table 12. Doses and durations of treatment of the AEDs differed across trials. Numbers-needed-to-treat (NNTs) relative to placebo for effectiveness in any neuropathic pain were 2.5 (95% CI: 2.0 to 3.4) for carbamazepine and 3.7 (2.6 to 4.9) for gabapentin (time periods for NNTs not specified).[96] There was no clear advantage of one agent over the other. Numbers-needed-to-harm (NNH) were also calculated and are presented under *Key Question 2. For adult outpatients, do AEDs differ in safety or adverse events.*

Table 12. Relative effectiveness of AEDs compared with placebo in neuropathic pain

Interventions	No. of trials	Range of doses, mg/d†	Range of durations, wk†	Odds Ratio (OR) or Relative Risk (RR)	95% CI
Trigeminal neuralgia					
Carbamazepine	4	100–2400	0.4–184	OR 4.83	3.39–6.89
Lamotrigine	1	Up to 400	2	OR 2.36	0.49–11.34
Diabetic neuropathy					
Carbamazepine	1	200–600	2	RR 1.47	1.10–1.97
Phenytoin	2	300	5–23	RR 2.80	1.59–4.93
Gabapentin	1	Up to 3600	8	RR 1.81	1.25–2.62
Postherpetic neuralgia					
Gabapentin	1	Up to 3600	8	RR 3.57	2.09–6.11
Central spinal cord injury pain					
Valproate	1	1200–2400	3	RR 1.50	0.50–4.52
Central stroke pain					
Carbamazepine	1	800	4	OR 7.78	0.78–77.93

Source: Wiffen, 2004[96]
† Across trials

Three trials included in the systematic review compared phenytoin or a combination of carbamazepine and clomipramine with active controls.[96] Indirect comparisons of the AEDs were not possible because the control therapies (intramuscular gold, buprenorphine, or transcutaneous electrical nerve stimulation) differed between trials and the effects of carbamazepine could not be distinguished from that of clomipramine.

Head-to-head trials

We reviewed 1 randomized head-to-head trial and included that trial in this report.[43] It was rated poor quality because it did not use intent-to-treat analysis and did not meet any of the quality assessment criteria. This trial showed a calculated difference of 0.57 points between carbamazepine and phenytoin in the change in pain scores from baseline to 6 months (as measured on a 10-point numerical rating scale) in 11 evaluated veterans with painful neuropathy due to thiamine deficiency. No statistical analysis was performed. Its results and quality are summarized in Evidence Tables 4 and Quality Table 4.

Active control trials

We reviewed 13 randomized active control trials for eligibility and included 8 in this report. Of these 8 trials, 6 were double-blind,[42,44-47,97] 6 were crossover,[42, 44-47, 97] 1 was multicenter,[42] 1 was open-label,[69] and 2 included double dummies.[44,47] Most of the trials did not report the methods of randomization and allocation concealment, 4 had similar groups at baseline[42, 44, 47, 97] (the remainder either did not have similar groups at baseline or did not report baseline patient characteristics), all except 1 trial[98] reported attrition rates, and all had acceptable rates of loss to follow-up with the exception of one trial[46] that did not report losses to follow-up. None were rated good quality and 7 of the 8 trials were rated poor quality because intent-to-treat analysis was not performed (5 trials),[42,44-47] blinding was not reported (2 trials),[46,69] or eligibility criteria were not specified (1 trial).[97] The remaining trial was rated fair quality because it lacked intent-to-treat analysis.[44] External validity was limited by small sample size (< 40 patients per treatment group) in 7 trials[44-47, 69, 97, 98] and 2 trials evaluated selective populations (Fabry's disease,[97]

recalcitrant trigeminal neuralgia).[42] In addition, 5 of the trials used comparators (combination nortriptyline-fluphenazine,[45] tocainide,[46] pimozide,[42] prednisolone,[98] and aspirin or multivitamin)[97] that are not considered to be standard of care.

The fair-quality trial was a double-blind, double-dummy, crossover trial.[44] Analysis of data from 19 of 25 randomized patients revealed no statistically significant differences between gabapentin (900 to 1800 mg daily) and amitriptyline (25 to 75 mg daily) for any outcome measure (pain intensity scores at end of treatment, global pain scores, and change in pain scores from baseline).

Since the remaining trials were less than fair quality, no indirect comparisons of AEDs could be made. The results and quality of all of these trials are summarized in Evidence Table 5 and Quality Table 5.

Placebo-controlled trials

We reviewed 39 randomized placebo-controlled trials and 28 met criteria for inclusion in this report; the remaining 11 were excluded. All of the 28 included trials were double-blind, [48-52, 54-63, 65-68, 70, 72-75, 99-101] 15 were crossover,[48, 50, 52, 53, 55, 56, 59, 60, 62, 63, 66, 68, 99-101] and 8 were multicenter.[50, 55, 67, 70, 72-75] Methods for randomization and allocation concealment were not reported in 15 trials[51, 52, 55, 57- 60, 62, 63, 65, 68, 73, 75, 99, 100] and 20 trials, [48-52, 54, 55, 58, 59, 60, 62, 65, 66, 68, 72, 74, 75, 99-101,]respectively, and 1 trial did not have adequate allocation concealment.[61] However, 7 trials reported adequate methods for both.[53, 56, 57, 63, 67, 70, 73] Groups were similar at baseline in 12 trials,[48, 52, 53, 56, 57, 62, 65, 66, 72-74, 100] not similar in 8 trials, [50, 54, 58, 61,67, 70, 75, 101,] and in 9 trials, data on patient characteristics were either not reported[51, 55, 59, 60, 63, 68, 99] or not presented by treatment group.[49, 51] Seventeen trials did not report masking of the outcome assessor, [49, 51, 53-55, 61, 63,65-67, 70, 73-75, 99-101] but most reported masking or method of masking the care provider and patient. Most (21) of the trials had acceptable rates of loss to follow-up, [48-52, 55-57, 59- 61, 63, 65, 66, 68, 70, 72-74, 99, 101] 6 trials had a high rate,[53, 54, 58, 67,75, 100] and the remaining 1 trial did not report data to determine loss to follow-up.[62] One trial used an unconventional statistical method, called a "closed" sequential design, to limit the duration of the trial.[99]

None of the trial reports were rated good quality because they did not meet all of the quality assessment criteria, and 15 were rated poor quality because intent-to-treat analysis was not used (13 trials,[48-53, 55-61] including 1 trial that also appeared to have an inadequate method of concealing treatment allocation)[61] or not reported (2 trials),[62,63] groups were dissimilar at baseline and the method of randomization was not reported (1 trial),[75] the loss to follow-up rate was high (1 trial),[100] or a combination of these reasons. The 13 remaining trials were fair quality and are included in the discussion here. The results and quality of the included trials are summarized in Evidence Table 6 and Quality Table 6.

In addition to the 28 included trials, we found results of an unpublished, manufacturer-sponsored multicenter, double-blind, placebo-controlled trial (Study 945-224 or “PDN II” by Reckless, et al., 2000) that was conducted in the United Kingdom, European Union, and South Africa. This trial was summarized in a poor-quality systematic review[76] that included 4 other trials[70,72-74] which were performed in the U.S. or U.K. and which are also reported here. There was no statistically significant difference between gabapentin (600, 1200, or 2400 mg/day) and placebo in the mean change in pain scores from baseline (primary efficacy variable). However, there

were significant treatment differences in responder rate with only the 1200-mg dose, as well as for some other secondary measures. Although the trial met eligibility criteria for population, drugs, outcomes, and design, it was excluded because a full-text article had not been published.

We also found two trials that evaluated gabapentin in patients with back pain. One was a randomized, double-blind, placebo-controlled trial that showed nominal or no substantial analgesic effect with gabapentin in 80 patients with low back pain.[102] The other trial was a randomized, double-blind, placebo-controlled crossover trial that showed small but statistically significant improvements in pain and mobility in 30 adults suffering from chronic posttraumatic ligamentous back pain.[103] Both trials did not meet inclusion criteria because patients with neuropathic pain were excluded from the trials.

Response: Symptom Rating Scales

Among the 13 fair-quality trials, the most commonly used pain rating tools for measuring changes in pain intensity in the total patient cohort during study treatment were, for the primary efficacy variable, the 11-point Likert scale (5 trials) [56,70,72, 73, 74,] and, as a secondary efficacy variable, a VAS, either part of the SF-MPQ (6 trials)[57,68, 70,72, 73,74,] and/or as a separate scale (4 trials).[54,66, 68,101] Five of six trials that evaluated the SF-MPQ also used the Likert scale[70,72,73,74] or VAS.[57] These trials showed consistent relative treatment effectiveness with the SF-MPQ and either the Likert scale or VAS; therefore, only the Likert scale or VAS scores were presented for these five trials in Table 13. The one remaining trial that used the SF-MPQ showed a significant treatment difference between gabapentin and placebo with the SF-MPQ but insignificant results with the VAS.[68] The changes in scores on either the VAS or 11-point Likert pain scales are shown for the 10 trials reporting these variables for the total patient cohort in Table 13.

Table 13. Mean change in VAS or 11-point Likert scores in neuropathic pain (placebo-controlled trials)

Trial	Interventions* Duration	N	Pain Scale	Change in Scores from Baseline, mean	Difference (AED – Placebo)	Interpretation of Results
Diabetic neuropathy						
Backonja (1998)[72]	Gabapentin 900 to 3600 vs. Placebo 8 wk	165	11-point Likert, average daily pain	–2.5 vs. –1.4	–1.1	Not reported for change in pain scores; see text
Gorson (1999)[68]	Gabapentin 300 to 900 vs. Placebo 6 wk	40	10-cm VAS, average daily pain	–1.8 vs. –1.4	–0.4	GBP = PBO (GBP > PBO on SF-MPQ; see text)
Kochar (2004)[57]	Valproate 500 x 1 wk then 1000 vs. Placebo 3 mo	43	VAS, pain at 3 mo	–3.00 vs. 0.29 (calculated)	–3.29 (calculated)	Not reported for change in pain scores; see text
Postherpetic neuralgia						
Rowbotham (1998)[73]	Gabapentin 300 to 3600 vs. Placebo 8 wk	229	11-point Likert, average daily pain	–2.1 vs. –0.5	–1.6	GBP > PBO
Rice (2001)[74]	Gabapentin 1800 vs. 2400 vs. Placebo 7 wk	334	11-point Likert, average daily pain	–2.2 vs. –2.2 vs. –1.0	–1.2 vs. –1.2	GBP > PBO
Mixed neuropathic syndromes						
Serpell (2002)[70]	Gabapentin 900 to 2400 vs. Placebo 8 wk	307	11-point Likert, average daily pain	–1.5 vs. –1.0	–0.5	GBP > PBO
McCleane (1999)[54]	Lamotrigine titrated from 25 to 200 vs. Placebo 8 wk	100	0–10 VAS, mean change in average weekly overall pain	–0.01 vs. 0.03	–0.04	LTG = PBO
McCleane (1999)[101]	Phenytoin 15 mg/kg i.v. vs. 0.9% Saline (placebo) over 2 h 1 dose	20	11-point VAS at 2 h, overall pain	–1.37 vs. 0	–1.37	No statistical analysis for difference
Phantom limb pain						
Bone (2002)[66]	Gabapentin 300 to 2400 vs. Placebo 6 wk	19	100-mm VAS pain intensity difference from baseline†	3.2 vs. 1.6	1.6	GBP > PBO
Central post-stroke pain						
Vestergaard (2001)[56]	Lamotrigine titrated from 25 to 200 vs. Placebo 8 wk	30	11-point Likert, median daily pain in last week of treatment	–2 vs. 0	–2	LTG > PBO

GBP, Gabapentin; NA, Not applicable; PBO, Placebo; rCRS, Relative categorical rating scale (relative to baseline); SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, Visual analog scale; >, Superior to ($p < 0.05$)
All doses given orally except as indicated.
* Doses shown in mg/d unless otherwise specified.
† 100-mm VAS was reported as the pain scale; however, results appear to be measured in cm.
‡ Dosage titration depended on presence or absence of concomitant enzyme inducing drugs.

Six of the 13 fair-quality trials compared gabapentin with placebo in a variety of neuropathic pain disorders, including diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain syndromes, and phantom limb pain. All of the trials showed gabapentin to be superior to placebo except in diabetic neuropathy, where 1 of 2 trials showed no significant difference between gabapentin and placebo in improving VAS pain scores. In one fair-quality trial evaluating gabapentin 1800 and 2400 mg/day versus placebo in postherpetic neuralgia, no additional benefit could be shown with the higher dose (2400 mg/day) over the lower dose (1800 mg/day).[74]

In the study reporting no difference, the authors speculated that the 3-week washout period before crossover of study treatments may have been too short, as the scores on VAS and the McGill Pain Questionnaire (MPQ) did not return to baseline in those patients who received gabapentin before they crossed over to placebo.[68] In addition, the dose of gabapentin (900 mg/day) was lower than in trials reporting a benefit. Although there was no treatment difference in terms of reduction in VAS scores, there was a treatment difference when pain was measured using the SF-MPQ (difference in reduction in score: 6.7; $p = 0.03$).

In the second trial evaluating gabapentin and placebo in diabetic neuropathy, the difference in pain scores *at study end point* was shown to be significantly better with gabapentin (–1.2; 95% CI: –1.9 to –0.6; $p < 0.001$).[72] This analysis did not take into account baseline pain scores, which were similar (6.4 for gabapentin and 6.5 for placebo). Statistical analysis of the difference in the *change in pain scores from baseline to study end point* between the two treatment groups was not reported.

The remaining fair-quality placebo-controlled trials evaluated AEDs other than gabapentin. One trial showed that valproate was superior to placebo in the treatment of painful diabetic neuropathy based on the difference at the 3-month end point using the SF-MPQ (–8.10), VAS (–3.0), and VAS for present pain intensity (–1.28) ($p < 0.001$ for each test).[57] Differences between treatment groups based on the changes in scores from baseline were not provided.

A randomized, double-blind, placebo-controlled trial in patients with symptom-based diagnoses of neuropathic pain showed no statistically significant differences between lamotrigine and placebo in terms of changes in either overall pain or specific neuropathic pain qualities (i.e., burning pain, numbness, pins and needles, shooting pain, and skin sensitivity) as measured using 0 to 10 VAS scores. The authors suggested that the insignificant results did not exclude a possibility that lamotrigine at doses higher than 200 mg daily will produce analgesic effects either for overall pain or for specific subtypes of neuropathic pain.

One trial involving patients with central post-stroke pain showed lamotrigine to be better than placebo.[56]

Two other trials also evaluated the efficacy of lamotrigine but are not shown in Table 13 because they did not report results based on the Likert scale or VAS for the total cohort. A placebo-controlled trial of lamotrigine in 42 patients with HIV-related distal sensory polyneuropathy did not show a statistically significant treatment difference in terms of reduction in Gracely Pain Scale scores using intent-to-treat analysis (calculated difference, lamotrigine minus placebo): -0.059 ($p = 0.65$).[67] In subgroup analyses, only patients *without* prior exposure to neurotoxic antiretroviral agents showed a significant benefit of lamotrigine over placebo in reducing pain

scores. These results were contradicted by results of analyses obtained in a subsequent, larger study (N = 227) in a similar patient population by the same primary author.[75] In the follow-on trial, there was no significant difference between lamotrigine and placebo (data not reported) using the Gracely Pain Scale, the primary efficacy measure, in 172 analyzed patients with HIV-related distal sensory polyneuropathy. In subgroup analyses, only patients *with* prior neurotoxin exposure benefited from lamotrigine therapy based on either Gracely Pain Scale or VAS. The discrepancy in results was postulated to be due to the small sample size and high dropout rate (13/42, 31.0%) in the former study. Additional information on the subgroup analyses is discussed under section *3b. Neuropathic pain.*

Reductions in mean overall VAS pain scores were seen with a 2-hour intravenous infusion of phenytoin in patients with mixed neuropathic pain syndromes; however, no statistical analyses were reported (Table 13).[101]

The last fair-quality trial evaluated the efficacy of carbamazepine (not shown in Table 13). In this trial, which used an unconventional statistical method called a “closed” sequential design, 8 (88.9%) of 9 patients with trigeminal neuralgia preferred carbamazepine over placebo ($p < 0.05$).[99] (This study used a "closed" sequential design to limit the duration of the trial. The probability of a preference for carbamazepine was based on the assumptions that the response rates would be 80% for carbamazepine and 40% for placebo. A design was then chosen such that if the preference path crossed an outside boundary, then the null hypothesis would be rejected with $p = 0.05$.)

The 11-point Likert scale was used in 4 placebo-controlled trials evaluating gabapentin[70-74] and 1 trial with lamotrigine;[56] therefore, the clinical relevance of the changes in pain rating scores could be assessed using the threshold criteria validated by Farrar, et al. in patients with various types of chronic pain.[14] Farrar showed that reductions in pain scores from baseline of about 2 points or about 30% on the 11-point pain intensity numerical rating scale were clinically important. The criteria for clinically important changes in pain scores were met in 3 of the 4 fair-quality gabapentin trials[72] and the single lamotrigine trial[56] for doses showing significant treatment effects.[73, 74] The trial evaluating gabapentin in mixed neuropathic syndromes showed absolute and relative reductions in pain scores of 1.5 points and 21%, respectively, and therefore, did not meet the criteria for clinically important improvements in pain scores.[70] The responder rate (> 50% decrease in pain) also did not show a significant treatment difference. However, gabapentin was significantly better than placebo in the patients reporting “much” or “very much improved” on the Patient’s Global Impression of Change (PGIC) and in certain quality of life domains.

Indirect comparisons of the AEDs were difficult because of the differences in outcome measures, types of neuropathic pain, routes of administration, and durations of therapy. The dimensions of the VAS varied between trials (e.g., 100-mm, 11-point, or 0 to 10 VAS) or were not specified. Based on the overall findings for any type of neuropathic pain, gabapentin and valproate are both better than placebo while lamotrigine showed contradictory results, with 2 trials showing no significant difference and 1 trial showing superiority of lamotrigine over placebo for the total cohort results. Results with lamotrigine were also inconsistent in subgroup analyses of two trials. Carbamazepine also showed a beneficial effect, albeit with an unconventional statistical method. The response with phenytoin was inconclusive. The evidence of the effectiveness of gabapentin

is better documented than with other AEDs. Therefore, limited indirect comparisons suggest that gabapentin (6 trials) and valproate (1 trial) are similar in reducing neuropathic pain; however, lamotrigine (3 trials) showed inconsistent effects, when each of the agents was compared with placebo. Carbamazepine and phenytoin are more difficult to compare against the other AEDs.

Response: Responder Rate

Response was defined by authors as ≥ 50% reduction in pain scores from baseline in 2 trials[70, 74] and as at least moderate improvement on Clinician's Global Impression of Change (CGIC) or PGIC in 1 trial.[72] We applied these definitions to the other trials in which response was not explicitly defined but for which data was reported that fit these definitions. In addition, we included one trial that provided dichotomous data on measures that approximate overall response, namely the proportions of patients who experienced reduction in pain scores and who rated treatment to be of significant benefit. In total, responder rates were available in 8 of the 13 fair-quality trials (Table 14).

Six of these trials compared gabapentin with placebo. Based on responder rates, 2 trials showed that gabapentin was superior to placebo.[72,74] Gabapentin was numerically better than placebo in another 2 trials (no statistical analyses).[73,101] Finally, 2 trials showed no significant difference between gabapentin and placebo in terms of the responder rates as defined by the authors.[68,70]

One of two trials that compared lamotrigine with placebo involved patients with symptom-based diagnoses of neuropathic pain.[54] There were no patients on lamotrigine who experienced 50% reduction in overall pain (responder rate for placebo was not reported), and the authors concluded that lamotrigine (up to 200 mg daily) lacked an analgesic effect.

The other trial evaluated the efficacy of lamotrigine (up to 200 mg daily) in patients with central post-stroke pain using a crossover design.[56] It defined response as pain reduction of 2 or more points but reported the responder rates for each treatment based on patients who achieved pain reduction of 2 or more points *lower than the corresponding comparator value*. Using this latter definition, the responder rates were 44.4% (12/27) for lamotrigine and 11.1% (11/27) for placebo. No statistical analysis was reported. A post hoc analysis reveals a p-value of 0.014. However, 11 (40.7%) of 27 patients showed no difference between treatment periods. Therefore, in contrast to the insignificant results in the first trial involving lamotrigine, this trial showed a significant benefit with lamotrigine in terms of responder rates. These results should be interpreted with caution since the definition of response was inconsistent in the publication, and 40.7% of the patients did not obtain a response on either treatment.

Using Farrar's criteria,[14] even reductions in pain scores as low as 30% are clinically important. The proportion of patients who achieved this smaller degree of pain improvement was reported for one fair-quality trial[74] in the authors' reply to comments.[71] The response rates for 30% reduction in pain for gabapentin 1800 mg and 2400 mg and placebo were 61/115 (53%), 59/108 (55%), and 32/111 (29%), respectively. The numbers-needed-to-treat (NNT) for 30% and 50% reduction, respectively, were 4.1 and 5.6 for gabapentin 1800 mg, and 3.88 and 5.04 for the 2400-mg dose each given for 7 weeks.

Overall responder rates were available for gabapentin in 5 fair-quality trials while 2 trials provided these results for lamotrigine and 1 trial for single-dose, intravenous phenytoin. It is difficult to make indirect comparisons between the AEDs in terms of responder rates since the definitions of response varied between the trials for the different agents, and the AEDs have not been compared in patients with the same types of neuropathic pain, except in populations with mixed types of neuropathic pain. In two trials that had similar patient populations (mixed neuropathic pain types / symptom-based diagnoses) and outcome measures (50% reduction in pain on either an 11-point Likert scale or 0 to 10 VAS), the results showed a lack of analgesic effect over placebo for both gabapentin and lamotrigine.

Table 14. Responder rates in patients with neuropathic pain (placebo-controlled trials)

Trial	Interventions Duration (Dose in mg/d)	N	Definition of Response	Responder Rate	Interpretation of Results
Diabetic neuropathy					
Backonja (1998)[72]	Gabapentin 900 to 3600 vs. Placebo 8 wk	165	At least moderate improvement on CGIC	39/81 (48.1%) vs. 16/75 (21.3%) (p = 0.001)	GBP > PBO
			At least moderate improvement on PGIC	60% vs. 33% (p = 0.001)	GBP > PBO
Gorson (1999)[68]	Gabapentin 300 to 900 vs. Placebo 6 wk	40	Patient Global Assessment, moderate or excellent pain relief	17 vs. 9 (p = 0.11)	GBP = PBO
Postherpetic neuralgia					
Rowbotham (1998)[73]	Gabapentin 300 to 3600 using a forced titration schedule vs. Placebo 8 wk	229	CGIC, moderately or much improved	39.5% vs. 12.9% (no statistical analysis)	Data inconclusive based on analysis
			PGIC, moderately or much improved	43.2% vs. 12.1% (no statistical analysis)	Data inconclusive based on analysis
Rice (2001)[71, 74]	Gabapentin 1800 vs. Gabapentin 2400 vs. Placebo 7 wk	334	≥ 50% reduction in mean pain score from baseline	32% vs. 34% vs. 14% (p = 0.001)	GBP1800 > PBO GBP2400 > PBO
Mixed neuropathic pain syndromes					
Serpell (2002)[70]	Gabapentin 900 to 2400 vs. Placebo 8 wk	307	> 50% reduction in mean pain score from baseline on 11-point Likert scale	21% vs. 14% (p = 0.16)	GBP = PBO
McCleane (1999)[101]	Phenytoin 15 mg/kg i.v. vs. 0.9% Saline (placebo) over 2 h 1 dose	20	A reduction in pain scores	14/20 (70.0%) vs. 0 (0%) (no statistical analysis)	Data inconclusive based on analysis
			Rated treatment to be of significant benefit	8/20 (40.0%) vs. Not reported	Unable to determine
McCleane (1999)[54]	Lamotrigine titrated from 25 to 200 vs. Placebo 8 wk	100	50% reduction in overall pain on 0–10 VAS	0/36 (0%) vs. Not reported	LTG lacks an analgesic effect

Cont'd

Trial	Interventions Duration (Dose in mg/d)	N	Definition of Response	Responder Rate	Interpretation of Results
Central post-stroke pain					
Vestergaard (2001)[56]	Lamotrigine titrated from 25 to 200 vs. Placebo 8 wk	30	Pain reduction ≥ 2 relative to corresponding value for comparator treatment (11-point Likert scale)	12/27 (44.4%) vs. 3/27 (11.1%) 11/27 (40.7%) showed no difference between treatment periods	LTG > PBO[†]

CGIC, Clinician's Global Impression of Change; GBP, Gabapentin; PBO, Placebo; PGIC, Patient's Global Impression of Change; =, Not statistically different from ($p \geq 0.05$); >, Superior to ($p < 0.05$)
[†] Post hoc analysis; p = 0.014 (statistical analysis not reported in publication)

Speed and duration of response

We defined the speed of response in terms of the time to earliest significant ($p < 0.05$) treatment difference between AED and placebo (i.e., earliest significant "treatment effect") in the pain response measure. Of 6 placebo-controlled trials that reported data showing statistical analyses for response over time, 5 evaluated gabapentin,[66, 70, 72-74] 1 evaluated lamotrigine,[56] and 1 evaluated intravenous phenytoin.[101]

For gabapentin, the time to the earliest significant treatment effect was 1 to 2 weeks in diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain syndromes, as compared with 6 weeks in phantom limb pain. The longer response time in phantom limb pain may have been due to the trial's lack of sufficient power to detect an earlier treatment difference if a true difference existed, as the respective trial had a small sample size (N = 19).[66] The significant treatment effect was maintained for the remainder of the 6-to-8-week trials in all cases except for 1 trial[70] in which a significant response was shown from weeks 1 to 6 except for week 2 and no significant treatment difference was shown at weeks 7 and 8.

Intravenous phenytoin produced a significant treatment effect in mixed neuropathic pain syndromes as early as 45 minutes into the 2-hour infusion and a significant effect was maintained for 1 day following the completion of the infusion.[101]

One placebo-controlled crossover trial involving patients with central post-stroke pain presented pain scores by dose of lamotrigine, which was increased every 2 weeks from 25 mg to a maximum of 200 mg daily.[56] The earliest significant treatment effect based on the analyzed patients (N = 27) was seen at a dose of 200 mg, corresponding to weeks 7 to 8.

Indirect comparisons of the AEDs are limited by differences in frequencies of measurements, routes of administration, type of neuropathic pain, and manner of data presentation. Indirect comparisons suggest that, even at lower doses of a titration schedule, gabapentin (based on 5 trials) may have an earlier onset than lamotrigine (based on 1 trial).

None of the trials evaluated the long-term (≥ 1 year) duration of response.

Use of Rescue Medications

Four fair-quality trials reported rescue medication requirements during AED treatment for neuropathic pain. One trial showed no significant difference between gabapentin and placebo in the number of tablets (177 vs. 187) of combination codeine plus acetaminophen taken for phantom limb pain.[66]

Three trials compared lamotrigine and placebo. One trial showed no significant treatment effect with lamotrigine relative to placebo in terms of the number of patients who had increased (1 vs. 2) and decreased (both zero) requirements for concomitant analgesics at the end of the study for treatment of pain due to HIV-related distal sensory polyneuropathy.[67] The second trial showed no significant differences between lamotrigine and placebo in the mean change from baseline in the number of analgesic tablets used.[54] In the third trial, the median number of acetaminophen tablets (500 mg) taken during study treatment was zero, and there were no significant differences between the four 2-week lamotrigine dosing periods (25, 50, 100, and 200 mg).[56]

Indirect comparisons from the 1 gabapentin trial and the 3 lamotrigine trials, based on the lack of treatment differences relative to placebo, suggest that neither gabapentin or lamotrigine is better in reducing concomitant analgesic use.

Functional capacity (quality of life, work productivity)

Measures of functional capacity, including quality of life, work productivity, or both, were evaluated in 7 fair-quality placebo-controlled trials: 5 evaluated gabapentin in the treatment of diabetic neuropathy (1 trial),[72] postherpetic neuralgia (2 trials),[73, 74] mixed neuropathic pain syndromes (1 trial),[70] and phantom limb pain (1 trial);[66] and 2 trials compared lamotrigine with placebo, one in patients with symptom-based diagnoses of neuropathic pain[54] and the other in patients with central post-stroke pain.[56]

In all 5 gabapentin trials except for the one involving patients with phantom limb pain, gabapentin showed a significant benefit over placebo in sleep interference scores (3 trials)[72-74] and in 1 to 5 domains (range among 4 trials) of the Short-form–36 (SF-36) health-related quality of life questionnaire.[70,72-74] Greater improvements were seen with gabapentin than placebo in the following SF-36 domains: bodily pain (4 trials), mental health (3 trials), vitality (3 trials), physical functioning, role-emotional, role-physical, and social functioning (1 trial each).

In the trial on phantom limb pain, there was no significant difference between gabapentin and placebo in either sleep interference or the Barthel Index, a rating tool that assesses a patient's ability to perform activities of daily living.[66] The results may have been due to the small sample size (N = 19).

The two trials comparing lamotrigine and placebo showed no significant treatment differences in either the mean changes from baseline in 0 to 10 VAS scores for mobility, mood, sleeping, and quality of life,[54] or the mean degree to which pain affected daily activities.[56]

Therefore, there is fair-quality evidence that gabapentin reduces pain-related sleep interruptions and improves some domains of quality of life, with more consistent effects being shown for bodily pain, mental health, and vitality. However, these beneficial effects were not shown in a

small, fair-quality trial involving patients with phantom limb pain. There was fair-quality evidence that lamotrigine therapy does not result in improvements in functional capacity relative to placebo. Indirect comparisons of gabapentin and lamotrogine, based on treatment effects relative to placebo in 4 of 5 trials involving gabapentin and 2 trials involving lamotrogine, suggest that gabapentin is better than lamotrigine in improving functional capacity in patients with neuropathic pain. While one trial evaluated the extent to which pain interfered with daily activities,[56] there is a lack of evidence that AED therapy results in improvement in the patient's physical abilities to perform daily or work-related activities.

Relapse

None of the fair-quality placebo-controlled trials evaluated relapse rates either during or as an open-label extension of treatment following a double-blind phase.

Summary

A good-quality systematic review showed that the numbers-needed-to-treat (NNTs) for effectiveness in any neuropathic pain were 2.5 (95% CI: 2.0 to 3.4) for carbamazepine and 3.7 (2.6 to 4.9) for gabapentin.[96] There was no evidence that one agent was better than the other.

There were no head-to-head trials of at least fair quality and only one fair-quality active-control trial, which showed no significant differences in pain reduction between gabapentin and amitriptyline.

Most of the fair-quality placebo-controlled trials evaluating the efficacy of gabapentin in neuropathic pain showed evidence of some beneficial effects across various types of neuropathic pain in terms of improvement in symptom rating scores, responder rates, speed of response, duration of response, use of rescue medications, sleep interference, and certain domains of quality of life questionnaires. Only a few trials evaluated AEDs other than gabapentin (carbamazepine, lamotrigine, or phenytoin) with placebo. Benefit from AED therapy has not been shown for functional capacity in terms of physical abilities. None of the trials evaluated long-term (≥ 1 year) duration of response or relapse rates.

Because there were differences in neuropathic pain disorders, outcome measures, and durations of therapy between the trials, along with a predominance of gabapentin trials, it was difficult to make indirect comparisons of the AEDs for any of the outcomes of interest. Limited indirect comparisons based on treatment differences relative to placebo suggest that gabapentin (6 trials) and valproate (1 trial) are similar in reducing neuropathic pain, whereas lamotrigine (3 trials) showed inconsistent effects. It is difficult to make indirect comparisons between the AEDs in terms of responder rates since the definitions of response varied between the trials for the different agents, and the AEDs have not been compared in patients with the same types of neuropathic pain, except in populations with mixed types of neuropathic pain. In two trials that had similar patient populations (mixed neuropathic pain types / symptom-based diagnoses) and outcome measures (50% reduction in pain on either an 11-point Likert scale or 0 to 10 VAS), the results showed a lack of analgesic effect over placebo for both gabapentin and lamotrogine. Indirect comparisons of the two AEDs based on treatment effects relative to placebo suggest that gabapentin (4 trials) is better than lamotrigine (2 trials) in improving functional capacity in

patients with neuropathic pain; however, in 1 trial, gabapentin did not show a beneficial effect over placebo. Neither gabapentin nor lamotrigine reduce requirements for rescue medications, based on lack of treatment differences with the AEDs relative to placebo. However, these indirect comparisons should be interpreted with caution because of methodologic differences between trials and the lack of head-to-head trials.

There is more fair-quality evidence based on intent-to-treat analyses to support using gabapentin than there is with other AEDs in patient populations with diabetic neuropathy, postherpetic neuralgia, and mixed neuropathic pain syndromes. Two trials involving lamotrigine did not find it to be significantly better than placebo in reducing symptom-diagnosed neuropathic pain or pain related to HIV polyneuropathy; however, there was conflicting data that it may have analgesic properties in a subgroup of patients with HIV polyneuropathy. One trial showed a significant analgesic effect of lamotrigine in patients with central post-stroke pain. No trials of at least fair quality were found for trigeminal neuralgia.

A large trial evaluating gabapentin in postherpetic neuralgia did not show additional efficacy with doses greater than 1800 mg/day.[74]

Key Question 2. For adult outpatients, do AEDs differ in safety or adverse events?

We included adverse event data for the AEDs from 3 systematic reviews, 28 controlled clinical trials evaluating their use in bipolar disorder and neuropathic pain, as well as 2 observational studies for bipolar disorder and any other diagnosis. Since the indication for the AEDs may influence the quantity and quality of the adverse events as well as withdrawals due to adverse events, the safety evidence is presented by disease.

2a. Bipolar disorder

Systematic review

We found one good-quality systematic review that provided comparative data on the adverse events of carbamazepine relative to lithium. This systematic review is summarized in Systematic Review Table 1. We also found a systematic review that addressed a specific adverse event of interest (rash) in patients with bipolar disorder. We excluded this article because the results of the analysis may have been biased since only company-sponsored trials were included, a comprehensive literature search for other trials was not performed, and eligibility criteria for inclusion of the trials in the analysis were not given.

Overall adverse events

The good-quality systematic review evaluated two RCTs and showed no statistically significant difference between carbamazepine and lithium in the risk of adverse events during acute (4-week) treatment of mania.[81] The pooled analysis (N = 139) showed that the rate difference for adverse events between the two treatments was –0.14 (95% CI: –0.30 to 0.01) and the relative risk of adverse events was 0.71 (95% CI: 0.49 to 1.02; $p > 0.05$). Although there was no statistically significant difference between treatments, there may be a clinically relevant difference in the rate of adverse events in favor of lithium. The same systematic review also

showed no treatment difference between valproate and lithium in the relative risk of adverse events (rate difference 0.08; 95% CI: –0.05 to 0.20; RR 1.09; 95% CI: 0.95 to 1.26; N = 105). These findings indirectly suggest that carbamazepine and valproate have similar risks of adverse events, since neither was statistically different from a common comparator treatment, lithium.

Head-to-head trials

One fair-quality head-to-head trial provided safety data based on evaluable patients.[20] Further details on this trial are summarized in Evidence Table 1 and Quality Table 1.

Overall adverse events

In the head-to-head, double-blind, randomized crossover trial comparing lamotrigine, gabapentin, and placebo in 38 randomized patients with refractory bipolar or unipolar disorder with mostly rapid cycling, there was no significant difference between treatments in the proportion of patients experiencing no major adverse events.[20] The most common adverse events were ataxia, diarrhea, diplopia, fatigue, headache, and rash. The numbers of patients experiencing each type of adverse event were too small for meaningful analysis. Lamotrigine was associated with the only case of rash, which progressed to toxic epidermal necrolysis and required the patient to be admitted to an intensive care burn unit. Weight change was also observed and is discussed under specific adverse events below.

Withdrawals due to adverse events

One patient was withdrawn from lamotrigine due to serious rash (toxic epidermal necrolysis).[20] The number of withdrawals was too small to determine treatment differences.

Serious adverse events

One patient developed a rash in week 15 during continuation treatment with lamotrigine (after completion of the 6-week blinded trial) and it progressed to toxic epidermal necrolysis. The patient needed admission to an intensive care burn unit and fully recovered.

Specific adverse events or withdrawals due to specific adverse events: dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, hyperammonemia, and weight gain

Dizziness was not reported as a common adverse event.

As mentioned above, 1 (3.2%) of 31 patients developed rash during continuation therapy with lamotrigine, whereas no patients developed rash on gabapentin or placebo.

Lamotrigine was associated with weight loss (mean change from baseline to 6 weeks, –0.96 kg) while gabapentin was associated with weight gain (1.83 kg; calculated difference, –2.79 kg; p = 0.024; based on 31 evaluable patients). There were no significant differences between lamotrigine and placebo (–0.40 kg) and between gabapentin and placebo. This data should be interpreted with caution, since it was not based on the randomized patients.

Active control trials

We reviewed but excluded 2 active control safety trials in bipolar disorder. One trial was excluded because a mixed population of patients with bipolar disorder (DSM-III) and major depression were included and results for bipolar patients were not presented separately.[104] The other trial was excluded because it was available only as a conference abstract.[105]

All 7 of the fair-quality active-control efficacy trials (9 publications) reported adverse events. These compared carbamazepine,[26,90] divalproex,[22,33] or lamotrigine[39,40] with lithium or lithium and placebo, or divalproex with olanzapine.[21, 28, 87] Two of the three publications on two trials that compared divalproex with olanzapine involved acute therapy for bipolar I mania or mania and mixed state; the third publication and all of the remaining trials evaluated maintenance therapy. Since there was no clear pattern distinguishing between acute and long-term adverse events, the results for acute and maintenance therapy with divalproex or olanzapine are discussed together below. These trials are summarized in Evidence Table 2 and Quality Table 2.

Overall adverse events

None of the 7 fair-quality active control trials (9 publications) reported overall rates of adverse events.[21, 22, 26, 28, 39, 40, 87]

In comparison with lithium, carbamazepine was associated with a higher frequency (difference in rates of at least 10%) of increased appetite.[90] Neither of the trials involving carbamazepine performed statistical analyses for adverse event rates. The adverse events occurring at a significantly greater frequency on divalproex in comparison with lithium were sedation,[22] infection,[22] and tinnitus.[22] Relative to lithium, lamotrigine was more frequently associated with headache.[39]

The adverse events that occurred more frequently on divalproex than olanzapine were nausea,[21,87] nervousness,[21] rectal disorder,[21] and decreased platelet count.[87] Compared with divalproex, olanzapine was associated with a higher rate of akathisia,[21] increased appetite,[21,87] dry mouth,[21,87] edema,[28] neck rigidity,[87] rhinitis,[28] somnolence,[21,28, 87] tremor,[87] sleep disorder,[87] speech disorder,[28,87] tongue edema,[87] weight gain,[21,28] increased alanine aminotransferase/serum glutamic-pyruvic transferase (ALT/SGPT),[87] and abnormal liver function test result.[21]

The adverse events reported more than once in any trial were nausea with divalproex; diarrhea with lithium; and increased appetite, dry mouth, somnolence, speech disorder, weight gain, and increased liver function test result (or ALT/SGPT) with olanzapine. Overall, there were no consistent patterns to the adverse events reported for either AEDs or active comparators. Based on indirect comparisons relative to lithium, carbamazepine, divalproex, and lamotrigine seem to differ in the types of adverse events commonly reported during maintenance therapy.

Changes in certain laboratory values and QT interval on electrocardiographs were seen with divalproex,[28] lithium,[39,40] or olanzapine;[21, 28, 87] however, indirect comparisons of the AEDs were not possible because laboratory tests were not reported for other AEDs.

Withdrawals due to adverse events

A total of 6 fair-quality active control trials (7 publications) reported rates of withdrawals due to adverse events. Four trials compared maintenance therapy with carbamazepine (2 trials)[26,90] or lamotrigine (2 trials)[39,40] versus lithium or lithium and placebo, and another 2 trials compared divalproex with olanzapine (as acute and maintenance therapy in 1 trial[21,87] and acute therapy in 1 trial.)[28] Since no other AEDs were compared against olanzapine, the results of the latter 2 trials could not be used to make indirect comparisons of the AEDs. In addition, 1 trial comparing divalproex with lithium and placebo reported withdrawals due to intolerance or noncompliance and could not be included in indirect comparisons of the AEDs because it used a different outcome measure.[22]

In one trial involving carbamazepine, withdrawals due to adverse events occurred in 13.3% (2/15) of carbamazepine-treated patients and 0% (0/16) of lithium-treated patients.[26] The absolute numbers of events were low and no statistical analyses were done. In another trial, the rates of withdrawal were similar between carbamazepine and lithium with rates of 8.0% (4/50) and 11.4% (5/44), respectively (no statistical analyses).[90] One of the two trials involving lamotrigine showed that lamotrigine was better tolerated than lithium in patients with a recent manic episode, with rates of withdrawal due to adverse events of 5% (3/59) and 24% (11/46), respectively ($p = 0.01$).[39] The other trial showed no significant difference between lamotrigine and lithium (or placebo) in patients with a recent depressive episode.[40] It is difficult to indirectly compare the AEDs because of inconsistent results between trials or the small numbers of patients assessed in the trials.

Among the adverse events or most frequent adverse events leading to withdrawal for any study treatments were rash,[26,90] weight loss with decreased sodium levels,[90] and severe general malaise with increased gamma-glutamyltransferase level[90] with carbamazepine; and mania,[39] somnolence,[39] nausea,[40] tremor,[40] and non-serious rash[40] with lamotrigine. None of the divalproex trials reported the nature of adverse events that led to withdrawal. There was no consistency between trials in the types of adverse events that led to withdrawal during maintenance treatment with lamotrigine. Withdrawals due to rash during maintenance therapy occurred in 13.3% (2/15) of patients in one trial[26] and 4.0% (2/50) in another trial[90] with carbamazepine, and 4% (7/169) with lamotrigine;[40] the rates of withdrawal due to rash on lithium in the corresponding trials were 0% (0/16), 0% (0/44), and 1% (1/120), respectively. The rate of rash with lamotrigine must be interpreted with caution because the trial involved an open-label lamotrigine run-in phase during which patients who developed rash may have been discontinued from the trial prior to randomization to maintenance therapy.[40]

Serious adverse events

One fair-quality trial reported the frequency of serious adverse events that occurred during acute therapy with divalproex (5/63, 7.9%) or olanzapine (2/57, 3.5%).[28] No statistical analysis was performed in this trial for this outcome. A post-hoc analysis yields a p-value of 0.30 for a chi-squared test of independence between drug and serious adverse events, and the confidence intervals for event rates are 2.6% to 17.6% for divalproex and 0.4% to 12.1% for olanzapine, respectively. The serious adverse events on divalproex were abnormal electrocardiogram results, anticholinergic syndrome, catatonic reaction, psychotic depression, and somnolence. For olanzapine, the serious adverse events were depression and fatal diabetic ketoacidosis. Of the 7

serious adverse events, somnolence (on divalproex) and diabetic ketoacidosis (on olanzapine) were considered to be possibly or probably related to the study drug.

Specific adverse events or withdrawals due to specific adverse events: dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, hyperammonemia, and weight gain

Dizziness was not a reported adverse event in 2 trials that compared either divalproex or lamotrigine with lithium. In a third trial, the frequency of dizziness was not significantly different between lamotrigine (8%, 14/169) and lithium (11%, 13/120).[40] Relative to lithium, divalproex was associated with a higher frequency of sedation,[22] whereas there was no significant difference in the frequency of somnolence between lamotrigine and lithium.[40,87] Rash was not reported as a common adverse event in the trials evaluating divalproex in comparison with lithium. There was no significant difference between lamotrigine and lithium in the frequency of rash.[39,40] Divalproex was associated with a decrease in platelet count, but the change was not significantly different from that seen on lithium.[22] There was no indication of thrombocytopenia in the fair-quality trials evaluating lamotrigine and lithium. Weight gain (undefined) occurred more frequently on divalproex (21%, 39/187) than lithium (13%, 12/94) in patients with bipolar I disorder with recent mania; however, the difference was not statistically significant.[22] Similar results were shown in another trial in patients with bipolar I disorder with recent mania/hypomania, where weight gain of ≥ 7% over baseline occurred at comparable rates on lamotrigine (11%, 19/169) relative to lithium (10%, 12/120).[39] In patients with bipolar I disorder with recent depression, the proportions of patients experiencing weight gain of ≥ 7% were also similar (7% and 10% for lamotrigine and lithium, respectively). However, in this trial, lamotrigine was associated with weight loss (2.2 kg) while lithium was associated with weight gain (1.2 kg; $p < 0.01$).[40]

In comparison with olanzapine, divalproex was not associated with a significantly different frequency of dizziness[21,87] or rash.[21] Somnolence,[21, 28, 87] and increased alanine aminotransferase/serum glutamic-pyruvic transferase[87] or abnormal liver function test[21] were less common on divalproex, whereas thrombocytopenia[21,87] was more common on divalproex. A decrease in platelet count was observed on divalproex while a small increase in platelet count occurred on olanzapine.[28] The frequency of weight gain (undefined) was less common on divalproex (10%) than olanzapine (25%) in one trial,[28] but weight gain of ≥ 7% was not significantly different between divalproex and olanzapine in 2 other trials.[21,87] One trial showed a significantly smaller increase in weight on divalproex (1.22 kg) than olanzapine (2.79 kg).[21]

One trial reported severe general malaise with increased gamma-glutamyltransferase levels in 1 (2.0%) of 50 patients treated with carbamazepine; this adverse event led to withdrawal from the trial.[90] None of the remaining lithium-controlled trials reported hepatotoxicity with either active drugs or placebo, and no fair-quality trials reported hyperammonemia.

Placebo-controlled trials

Adverse events were reported in all 6 fair-quality placebo-controlled trials. Of these, 3 had both active and placebo controls[22, 39, 40] and 3 used a placebo control only.[41] These trials are summarized in Evidence Table 3 and Quality Table 3.[35,94]

Overall adverse events

One trial reported overall adverse event rates for lamotrigine 50 and 200 mg (both 79%) and placebo (92%).[94]

Relative to placebo, adverse events that occurred more frequently on divalproex were tremor, weight gain, and alopecia.[22] Rash[40] and headache[94] occurred more commonly on lamotrigine than placebo. There were no adverse events experienced more frequently on placebo than AED in the fair-quality trials.

Four trials reported that there were no remarkable changes in laboratory test values in either AED or placebo groups.[35, 39, 40, 94] The other two trials did not report abnormalities in laboratory values.[22]

Withdrawals due to adverse events

One trial did not report a significant difference between divalproex and placebo in terms of withdrawals due to adverse events.[22] Another 3 trials showed no significant differences between lamotrigine and placebo for the same outcome.[39, 35, 40] The remaining 2 trials did not report statistical analyses for differences in the rate of withdrawals due to adverse events between either gabapentin or lamotrigine and placebo.[41,94]

Serious adverse events

Serious adverse events occurred in 6 (10.3%) of 58 gabapentin-treated patients and 5 (8.5%) of 59 placebo-treated patients.[41] In 3 gabapentin cases, the serious adverse events started in the single-blind placebo lead-in phase and in another 2 cases, during the lead-in phase before randomization. Another trial reported incomplete data for serious adverse events by treatment group.[94] In a third trial, 1 (1.1%) of 92 lamotrigine-treated patients and 2 (2.3%) of 88 placebo-treated patients experienced serious adverse events.

Serious adverse events experienced on gabapentin were manic reaction, manic depressive reaction, psychosis, and cervical carcinoma.[41] Lamotrigine 50 mg/day was associated with attempted suicide, suicidal ideation, worsening depression, and psychotic episode, while lamotrigine 200 mg/day was associated with suicidal ideation. One patient on lamotrigine (25 to 200 mg/day) experienced a syndrome of dehydration, faintness, migraine, shortness of breath, and tachycardia.[35] Serious adverse events reportedly occurring while on placebo included: basal cell carcinoma,[35] manic reaction,[41] pericarditis,[41] suicide,[94] attempted suicide,[94] and benign skull tumor.[35]

Specific adverse events or withdrawals due to specific adverse events: dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, hyperammonemia, and weight gain

Dizziness was reported in 19% of patients on acute add-on therapy with gabapentin,[41] 8% to 10% on either acute or maintenance therapy with lamotrigine,[35, 40, 94] and 3% to 14% on placebo.[39] There was no statistically significant difference between lamotrigine and placebo in two trials[40,94] and no statistical analyses were performed in another two trials, one comparing the same agents[35] and the other trial comparing gabapentin and placebo.[41]

Sedation was reported in 42% of patients treated with divalproex and 35% of placebo patients.[22] Somnolence occurred in 24.1% of gabapentin-treated patients[41] and 5% to 9% of lamotrigine-treated patients.[39, 40, 94] There was no significant difference between either AED and placebo (6% to 12%) for this adverse event.[22, 39, 40, 94]

Neither maintenance divalproex nor acute add-on gabapentin therapy was reported to cause rash. The frequency of rash on lamotrigine ranged from 3% to 14% of patients, and rates of rash on placebo (2% to 14%) also varied.[35, 39, 40, 94] The comparative results with lamotrigine were inconsistent. Rash was more common on lamotrigine than placebo in one maintenance trial (difference: 4.8%; 95% CI: 1.2 to 9.0),[40] but other trials either showed no significant difference between lamotrigine and placebo as acute[94] or maintenance therapy[39] or no statistical analyses were performed.[35]

There were no reports of hepatotoxicity, thrombocytopenia, or hyperammonemia in any of the fair-quality placebo-controlled trials.

Weight gain (undefined) was more common on divalproex (21%) than placebo (7%; $p = 0.004$).[22] Weight gain was not reported among common adverse events in one placebo-controlled trial that evaluated acute add-on gabapentin therapy.[41] Weight gain of ≥ 7% from baseline occurred in 7% to 11% of patients treated with lamotrigine and 2% to 6% on placebo. The results are difficult to compare because no statistical analyses were performed.[39,40] The mean change in weight from baseline to study end point ranged from –2.2 to 1.1 kg on lamotrigine and –0.3 to 1.2 on placebo among three trials.[35, 40, 94] There was either no significant difference between lamotrigine and placebo for this outcome[40,94] or statistical analyses were not done.[35]

Meta-analysis of specific adverse events: bipolar disorder

The patient-level adverse event analysis included 12 trials and evaluated 8 types of specific adverse events (diarrhea, dizziness, headache, nausea, rash, somnolence, tremor, and weight gain), whereas the event-level analysis included 15 trials and assessed 9 categories of adverse events (cardiac, central nervous system, other gastrointestinal, hematologic, infectious disease, liver, muscular pain, rash or skin, and metabolic). The results of our meta-analysis of specific adverse events at a patient level are shown in Tables 15, 16, and 17, and the results at an event level are presented in Appendix A and corresponding Tables 15A, 16A and 17A.

Table 15 presents our statistical analysis of the one small trial that compared carbamazepine with valproate. In this analysis, carbamazepine was significantly more likely than valproate to be associated with dizziness; however, the confidence interval was wide.

Table 15. Adverse Event Analysis at Patient Level, Mood: AED vs. AED

		Carbamazepine		Valproate			
Adverse Events	# of studies	# of patients with event	Sample size	# of patients with event	Sample size	Pooled OR	95% CI
Dizziness[29]	1	9	15	1	15	15.50	(1.53, 826.43)
Rash [29]	1	1	15	0	15	Inf	(0.03, Inf)

CI, Confidence interval; Inf, Infinity; OR, Odds ratio (odds of carbamazepine / odds of valproate)

In Table 16, three AEDs (carbamazepine, divalproex, and lamotrigine) are assessed against a common comparator, lithium. The numbers of trials and patients are small, and the 95% confidence intervals are wide. Thus, the lack of statistically significant evidence for a specific adverse event cannot be taken to mean that an AED did not cause that adverse event. Lamotrigine (2 trials), but not divalproex (1 trial), was significantly less likely than lithium to be associated with diarrhea. Lamotrigine (1 trial), but not carbamazepine (2 trials) and divalproex (1 trial), was also associated with a significantly lower odds of tremor compared with lithium.

Table 16. Adverse Event Analysis at Patient Level, Mood: AED vs. Lithium

			Lithium		Intervention Groups			
Adverse Events	Drug	# of studies	# of patients with event	Sample size	# of patients with event	Sample size	Pooled OR	95% CI
Depression	Carbamazapine[23]	1	1	27	1	27	1.00	(0.01, 81.48)
Depression	Divalproex//Valproate	0	NR	NR	NR	NR	NC	NC
Depression	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Diarrhea	Carbamazapine	0	NR	NR	NR	NR	NC	NC
Diarrhea	Divalproex[22]	1	42	94	65	187	0.66	(0.39, 1.13)
Diarrhea	Lamotrigine[39,40]	2	32	166	15	228	0.30	(0.14, 0.59)
Headache	Carbamazapine	0	NR	NR	NR	NR	NC	NC
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Lamotrigine[39,40]	2	25	166	42	228	1.27	(0.71, 2.28)
Nausea	Carbamazapine[25]	1	1	14	0	14	0.00	(0.0, 39.00)
Nausea	Divalproex[22]	1	41	94	79	187	0.95	(0.56, 1.61)
Nausea	Lamotrigine[39,40]	2	33	166	32	228	0.65	(0.37, 1.16)
Rash	Carbamazapine[23, 90, 92]	3	0	97	7	135	Inf	(0.93, Inf)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Somnolence	Carbamazapine	0	NR	NR	NR	NR	NC	NC
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Lamotrigine[39,40]	2	22	166	21	228	0.66	(0.33, 1.32)
Tremor	Carbamazapine[25,92]	2	7	40	0	72	0.00	(0.0, 0.30)
Tremor	Divalproex[22]	1	38	94	77	187	1.03	(0.61, 1.77)
Tremor	Lamotrigine[40]	1	20	120	9	169	0.28	(0.11, 0.68)
Weight gain	Carbamazapine[26]	1	5	16	0	15	0.00	(0.0, 1.01)
Weight gain	Divalproex[22]	1	12	94	39	187	1.80	(0.86, 3.99)
Weight gain	Lamotrigine	0	NR	NR	NR	NR	NC	NC

CI, Confidence interval; Inf, Infinity; NC, Not calculable; NR, Not reported; OR, Odds Ratio (odds of antiepileptic drug / odds of lithium)

In Table 17, data are pooled comparing AEDs (divalproex, gabapentin, and lamotrigine) with placebo. The numbers of trials and patients are small, and the 95% confidence intervals are wide. In general, the same cautions as mentioned for Table 16 apply. Lamotrigine (4 trials), and not gabapentin (1 trial), was more likely than placebo to be associated with headache. Divalproex (1 trial), and not lamotrigine (1 trial), was associated with significantly higher odds of tremor as compared with placebo.

Table 17. Adverse Events Analysis at Patient Level, Mood: AED vs. Placebo

			Placebo		Intervention Groups			
Adverse Events	Drug	# of studies	# of patients with event	Sample size	# of patients with event	Sample size	Pooled OR	95% CI
Diarrhea	Divalproex[22]	1	28	94	65	187	1.25	(0.71, 2.24)
Diarrhea	Gabapentin[41]	1	7	59	9	58	1.36	(0.41, 4.66)
Diarrhea	Lamotrigine[39, 40, 94]	3	26	255	21	357	0.53	(0.28, 1.02)
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Gabapentin[41]	1	7	59	6	58	0.86	(0.22, 3.21)
Headache	Lamotrigine[35, 39, 40, 94]	4	62	343	220	773	1.59	(1.14, 2.25)
Nausea	Divalproex[22]	1	29	94	79	187	1.64	(0.94, 2.89)
Nausea	Gabapentin	0	NR	NR	NR	NR	NC	NC
Nausea	Lamotrigine[39,40]	2	21	190	32	228	1.23	(0.66, 2.35)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Gabapentin	0	NR	NR	NR	NR	NC	NC
Rash	Lamotrigine[35,94]	2	9	153	63	545	2.23	(1.06, 5.28)
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Gabapentin[41]	1	7	59	14	58	2.35	(0.80, 7.51)
Somnolence	Lamotrigine[39, 40, 94]	3	21	255	27	357	0.93	(0.49, 1.79)
Tremor	Divalproex[22]	1	12	94	77	187	4.76	(2.38, 10.26)
Tremor	Gabapentin	0	NR	NR	NR	NR	NC	NC
Tremor	Lamotrigine[40]	1	6	121	9	169	1.08	(0.33, 3.79)
Weight gain	Divalproex[22]	1	7	94	39	187	3.26	(1.36, 9.03)
Weight gain	Gabapentin	0	NR	NR	NR	NR	NC	NC
Weight gain	Lamotrigine	0	NR	NR	NR	NR	NC	NC

CI, Confidence interval; NC, Not calculable; NR, Not reported; OR, Odds Ratio (odds of antiepileptic drug / odds of placebo)

The only consistent finding was a higher likelihood of tremor with divalproex than lamotrigine, based on the data from lithium- and placebo-controlled trials. However, the 95% confidence intervals overlapped in both analyses (0.61 to 1.77 for divalproex and 0.11 to 0.68 for lamotrigine, AED versus lithium; and 2.38 to 10.26 for divalproex and 0.33 to 3.79 for lamotrigine, AED versus placebo). Therefore, we cannot definitely conclude that there is a difference between divalproex and lamotrigine in their association with tremor.

Observational studies

One long-term (> 1 year) cohort study provided data on suicide risk with carbamazepine, divalproex, and lithium in patients with bipolar disorder. The evidence and quality of this report are summarized in Evidence Tables 7 and Quality Tables 7.

Specific adverse events or withdrawals due to specific adverse events: suicide risk

This fair quality study used a large computerized prescription database to retrospectively identify a cohort of 20,638 patients with bipolar disorder.[79] All were members of 2 large integrated health plans in California and Washington between January 1, 1994 and December 31, 2001. Patients were 14 years or older, had at least 1 outpatient diagnosis of bipolar disorder (DSM-IV), and at least 1 filled prescription for carbamazepine, divalproex, or lithium. The follow-up period for each patient (mean, 2.9 years) started with the first qualifying prescription and ended with death, disenrollment from the health plan, or end of the study period. An account of patients lost to follow-up was not reported.

Suicide attempts diagnosed in emergency departments were more frequent during periods of exposure to divalproex than to lithium (unadjusted rates, 31.3 vs. 10.8 per 1000 person-years; $p < 0.001$). Similar relationships were shown for the other main outcome measures: suicide attempt resulting in hospitalization (10.5 vs. 4.2 per 1000 person-years; $p < 0.001$) and suicide death (1.7 vs. 0.7 per 1000 person-years; $p = 0.04$). After adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs, the hazard ratio for divalproex relative to lithium was 2.7 (95% CI: 1.1 to 6.3; $p = 0.03$) for suicide death, indicating an almost three-fold higher risk of fatal suicide on divalproex compared with lithium. The hazard ratios for the other outcome measures for divalproex were 1.7 (95% CI: 1.2 to 2.3; $p = 0.002$) for suicide attempts resulting in hospitalization and 1.8 (1.4 to 2.2; $p < 0.001$) for emergency department–diagnosed suicide attempts.

Hazard ratios for carbamazepine relative to lithium were less consistent and stable (range: 1.4 to 2.9), showing a statistically significant result only for suicide attempts leading to hospitalization (2.9; 95% CI: 1.9 to 4.4; $p < 0.001$). The results for combination treatment and no treatment, each relative to lithium, were also inconsistent. Comparing the hazard ratio estimates and confidence intervals for valproate (1.7; 1.2 to 2.3) and carbamazepine (2.9; 1.9 to 4.4) for suicide attempts leading to hospitalization, one cannot conclude there is a difference between the two agents for this outcome.

Data were further analyzed for possible confounding factors, such as confounding by indication (where the differences in suicide risk could have reflected differences in preexisting illness severity or other factors affecting suicide risk). The distribution of initial mood stabilizer prescriptions from 1994 to 2001 showed a shift from lithium to divalproex. This trend was consistent with changes in prescribing behavior seen in other settings over that time period, and suggested that, overall, the selection of mood stabilizer was influenced more by temporal trends than by characteristics of individual patients. An analysis for time-dependent risk differences between divalproex and lithium showed consistent results for risk of suicide attempts and less consistent risk differences for suicide deaths. A subgroup analysis of patients who switched

between divalproex and lithium evaluated the hypothesis that patients with higher suicide risk were more likely to be switched from one class of mood stabilizer to another. It revealed little differences in risk between switching from divalproex to lithium and vice versa. Therefore, it appeared that any medication switch was associated with a higher, roughly two-fold risk of suicide attempt.

Although this cohort study was well designed and attempted to adjust for possible confounders, like other observational studies based on large databases, the ascertainment of cases depended on the accuracy and completeness of the prescription, diagnostic, and medical records, and the sensitivity and specificity of the search by diagnostic codes. Drug exposures may have been inaccurate because prescription claims do not necessarily reflect patient adherence to medications and assumptions were made about combining discontinuous periods of prescriptions to arrive at exposure estimates. These limitations should apply equally to the main treatment groups and not produce systematic bias;[106] however, adjustments could not be made for potential differences in case mix. These limitations should be considered when reviewing the conclusions of these studies.

Summary

One systematic review, 1 head-to-head trial, 7 active-control trials, 6 placebo-controlled trials, and 1 cohort study provided data on adverse events in patients with bipolar disorder.

For overall adverse events, indirect evidence from a systematic review suggests that carbamazepine and valproate are associated with similar rates of adverse events, when they are each compared with lithium. One head-to-head trial showed that lamotrigine and gabapentin were not significantly different in the number of patients with no major adverse events. Data from active- and placebo-controlled trials suggest that the nature of adverse events may differ between carbamazepine, divalproex, and lamotrigine. Relative to either lithium or placebo, carbamazepine was associated with a higher frequency of increased appetite; divalproex was more often associated with nausea, sedation, infection, tinnitus, tremor, weight gain, and alopecia; and lamotrigine had more frequent reports of rash and headache. Overall, there was little consistency to the patterns of adverse events reported for each AED.

Indirect comparisons of the AEDs based on active control trials could not be made with regards to withdrawals due to adverse events. Indirect evidence from the placebo-controlled trials suggest that the rate of withdrawals due to adverse events are similar for divalproex (1 trial) and lamotrigine (3 trials).

No indirect comparisons of the AEDs could be made for serious adverse events. The nature of the serious adverse events for any particular AED showed no consistency.

For specific adverse events, one head-to-head trial provided direct evidence that lamotrigine may be associated with weight loss whereas gabapentin was associated with weight gain. The difference in weight between treatments was relatively small (2.79 kg). This data should be interpreted with caution, since they are considered preliminary and were based on the evaluable and not randomized patients. Indirect comparisons based on active- and placebo-controlled trials could be attempted for somnolence, thrombocytopenia, and weight gain. The indirect

comparisons suggest that somnolence is more common on divalproex than lamotrigine. Thrombocytopenia was reported with divalproex, whereas it was not reported with the other AEDs. Weight gain occurred more frequently on divalproex than placebo. In contrast, lamotrigine may be associated with weight loss or no significant change in weight. In our pooled patient-level analyses comparing AEDs to a common comparator (placebo or lithium), we could not reach strong conclusions about differences between AEDs in terms of specific adverse events because data for AEDs were often based on one trial. There is consistent, but not conclusive, evidence that divalproex is more often associated with tremor than lamotrigine.

A fair-quality cohort study showed a higher suicide risk with divalproex and inconsistent risk with carbamazepine relative to lithium. We could not conclude that there was a difference in risk of suicide attempts leading to hospitalization between carbamazepine and divalproex.

2b. Neuropathic pain

Systematic reviews

Of the two good-quality systematic reviews of AEDs in neuropathic pain,[95,96] the one that allowed indirect comparisons of AEDs provided pooled analyses on adverse events and calculated numbers-needed-to-harm (NNHs) for minor and major adverse events.[96] Minor adverse events included symptoms such as drowsiness, dizziness, constipation, nausea, and ataxia. Major adverse events were those that led to withdrawal from the trial. Adverse event data from the trials (5 placebo-controlled trials for carbamazepine, 2 for gabapentin, and 2 for phenytoin) were combined for each agent regardless of the type of neuropathic pain. This systematic review is summarized in Systematic Review Table 2.

Overall adverse events

We considered the data on minor harm to approximate overall adverse events of the AEDs. The NNHs (95% CI) for minor harm were similar between carbamazepine (3.7; 2.4 to 7.8), gabapentin (2.5; 2.0 to 3.2), and phenytoin (3.2; 2.1 to 6.3).

Withdrawals due to adverse events

The NNHs for major harm were not statistically significant for any drug relative to placebo (data not reported).

Head-to-head trials

The head-to-head trial in patients with painful thiamine deficiency neuropathy did not provide data on adverse events.[43]

Active control trials

One active control trial of at least fair quality provided adverse event data from a total of 23 patients who received gabapentin and 24 patients who received amitriptyline in a crossover design.[44] The gabapentin and amitriptyline were similar in terms of overall proportion of patients experiencing adverse events (17/23, 73.9% vs. 18/24, 75.0%); withdrawals due to adverse events

(2/23, 8.7% vs. 1/24, 4.2%); and early crossovers due to adverse events (1/23, 4.3% vs. 1/24, 4.2%). The most common adverse events were sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia, and lethargy. Of specific adverse events, weight gain was less common on gabapentin (0/24, 0%) than amitriptyline (6/24, 25.0%). Gabapentin was better than amitriptyline in terms of pruritus at week 1 (rates not reported; $p < 0.03$) but was not statistically different from amitriptyline at week 4 (1/23, 4.3% vs. 3/24, 12.5%). Indirect comparisons between AEDs could not be made because there were no other fair-quality active control trials.

Placebo-controlled trials

Safety data were reported in all 13 fair-quality placebo-controlled trials. Of these, 6 evaluated gabapentin therapy of 6 to 8 weeks duration,[66, 68, 70, 72-74, 76] 4 evaluated lamotrigine given for 8 to 14 weeks,[54, 56, 67, 75] 1 evaluated carbamazepine given for 3 days,[99] 1 evaluated a single dose of intravenously administered phenytoin,[101] and 1 evaluated a 3-month course of valproate.[57] For one of the trials that evaluated lamotrigine, the only safety data reported were withdrawals due to adverse events.[54] These trials are summarized in Evidence Table 6 and Quality Table 6.

The dosing regimens of the AEDs varied between trials. Of the 6 gabapentin trials, 4 titrated doses according to clinical response and tolerability,[72] 2 compared 2 or 3 fixed doses,[72] and 1 used a forced titration schedule,[107] where doses were increased to a maximum of 3600 mg/day or until the patient developed intolerable adverse effects, regardless of efficacy at lower doses. The overall dosage range of gabapentin across the 6 trials was 300 to 3600 mg/day. Lamotrigine was slowly titrated, starting at 25 mg daily or every other day, then increasing the dose at various rates across the different trials. The titration period lasted for 6 to 7 weeks depending on the trial and stable or maintenance doses were given for 2, 4, or 8 weeks. Maximum daily doses ranged from 200 to 300 mg in 3 trials that did not indicate adjustment for concomitant enzyme inducing drugs;[54,56,67,] or 400 or 600 mg depending on the absence or presence, respectively, of enzyme-inducing drugs.[75] Carbamazepine was initiated and maintained at 600 mg/day. Phenytoin was given as a 15 mg/kg bolus intravenously over 2 hours. The dose of valproate was 500 mg for 1 week then 1000 mg for 3 months.[57]

Overall adverse events

The overall rate of adverse events was reported in 5 trials, including 3 with gabapentin,[68, 70, 74] 1 with lamotrigine,[56] and 1 with parenteral phenytoin.[101] For gabapentin, the overall rates of adverse events were 63.2% at doses of 300 to 900 mg/day,[68] 70.4% at 1800 mg/day,[74] 75.0% at 2400 mg/day,[74] and 76.5% at 900 to 2400 mg/day.[70] The corresponding rates for placebo were 19.0%, 49.5%, 49.5%, and 67.8%. Therefore, the proportion of patients reporting adverse events was higher on gabapentin. Only one trial performed statistical analyses; it showed a significantly higher rate of adverse events with gabapentin (63.2%) than placebo (19.0%; $p < 0.001$).[68]

The overall rate of adverse events with lamotrigine was 57% and 60% with placebo (no statistically significant difference).[56]

With the single intravenously administered dose of phenytoin, all (100%) of the 20 patients experienced at least 1 adverse event during active treatment while none did so on placebo treatment.

Statistically significant differences between AED and placebo in the frequency of common adverse events were reported in one trial involving patients with diabetic neuropathy. It showed that, compared with placebo, gabapentin was associated with a significantly higher rate of somnolence and dizziness.[72] Another, small trial did not detect a statistically significant difference between the two treatments.[66] The remaining trials either did not report adverse event rates by treatment[67, 68, 99] or did not perform statistical analyses of the adverse event data for gabapentin,[70, 73, 74] lamotrigine,[56] phenytoin,[101] or valproate.[57] All 3 of the trials involving gabapentin reported that somnolence and dizziness were reported at higher rates (no statistics) on the active drug relative to placebo. Pain was the only adverse event reported at a higher frequency on placebo than gabapentin (no statistics).[73]

One trial reported that no abnormalities were detected on liver function tests, urinalyses, or complete blood counts.[99] The other 9 trials did not report laboratory adverse events.

Withdrawals due to adverse events

Four of the 13 placebo-controlled trials reported no withdrawals due to adverse events during double-blind treatment. The AED in these trials were carbamazepine (1 trial),[99] gabapentin (2 trials),[66, 68] or phenytoin (1 trial).[101]

Among 4 trials, the rate of withdrawals due to adverse events ranged from 8.3% to 18.6% with gabapentin therapy and 0% to 16.4% with placebo.[70, 72-74, 76] The rates were generally comparable in both treatment groups; no statistically analyses were reported. The adverse events that led to discontinuation of gabapentin were dizziness (reported in 3 trials), somnolence (3 trials), abdominal pain, abnormal thinking, asthenia, body odor, confusion, diarrhea, headache, hypesthesia, and nausea (1 trial each). There was some overlap with types of adverse events that led to discontinuation of placebo: somnolence (3 trials), constipation, dizziness, dyspepsia, flatulence, and infection (1 trial each). One trial did not report this information for placebo.[74]

Four trials involving lamotrigine showed inconsistent comparative rates for withdrawals due to adverse events, with two trials finding similar rates for lamotrigine (range: 6.7% to 12%) as compared with placebo (range 9.1% to 12%)[54,75] and two other trials showing higher rates on lamotrigine (range: 10% to 30%) versus placebo (0% in both trials) (no statistical analyses).[56, 67,] The adverse events that led to withdrawal of lamotrigine were rash (5 cases) and gastrointestinal infection (1 case) in one trial (n = 20 for lamotrigine)[67]; mild rash, severe headache, and severe pain (1 case each) in the second trial (n = 30 for lamotrigine)[56]; and nausea (3 cases), rash (2 cases), and bad taste of tablets (1 case) in the third trial (n = 50 for lamotrigine)[54]. In the fourth trial, the most common adverse events (≥ 10% of patients in either treatment group) that led to discontinuation of lamotrigine (n = 150) were rash (2 cases), nausea (1 case), and headache (1 case).[75]

Valproate was similar to placebo in rates of withdrawals due to adverse events, with 1 case reported among 22 valproate-treated patients (4.5% vs. 0.0%).[57] Increased liver function tests (bilirubin and liver transaminases) was the reason for discontinuation of valproate.

Indirect comparisons of gabapentin (4 trials) and lamotrigine (4 trials), based on the rates of withdrawals due to adverse events in comparisons with placebo, suggest that gabapentin may be

better tolerated than lamotrigine. However, the lamotrigine results were inconsistent. Data for lamotrigine were limited to a small number of cases and valproate (1 trial) could not be indirectly compared with the other two AEDs because it was associated with only a single withdrawal due to an adverse event. The data also suggest that the more consistently reported adverse events leading to withdrawal of gabapentin were dizziness and somnolence. In comparison, the adverse event more likely to limit tolerability of lamotrigine was rash. [54, 56, 67,75]

Serious adverse events

Serious adverse events were reported in 4 of the 13 placebo-controlled trials in neuropathic pain, and all of them involved gabapentin.[68, 70, 73, 74] The rate of serious adverse events with gabapentin was low, ranging from 0% to 2.6% among the 4 trials. The corresponding rate with placebo ranged from 0% to 1.3%. Indirect comparisons of the AEDs could not be made since serious adverse events were not reported for other AEDs.

Specific adverse events or withdrawals due to specific adverse events: dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, hyperammonemia, and weight gain

Dizziness was reported more commonly with gabapentin (range: 23.8% to 36.8%) than placebo (4.9% to 10.5%) in 5 trials;[66, 70, 72-74] however, a statistically significant difference was reported in one trial[72] and not performed in the other trials. "Imbalance" occurred in 15.8% of gabapentin-treated patients in another trial; however, the corresponding rate on placebo was not provided.[68] A trial comparing carbamazepine with placebo also reported dizziness as a common adverse event, but reported only the rate for placebo (22.2%).[99] Light-headedness occurred in 100% of 20 patients at the end of 2-hour infusions of phenytoin and none of the patients during placebo infusions.[101] Indirect comparisons of the AEDs in terms of the prevalence of dizziness during therapy cannot be made because of the lack of frequency rates with carbamazepine and differences in routes of administration and dosing regimens (loading dose of intravenously administered phenytoin versus slow titration of orally administered gabapentin).

Somnolence was another common adverse event reported more frequently on gabapentin (range: 10.5% to 27.4%) than placebo (5.2% to 6.3%) among 5 trials.[66, 70, 72-74] In another trial, drowsiness was also mentioned as a common adverse event on gabapentin therapy (31.6%); however, the frequency of this adverse event was not reported for placebo.[68] Sedation occurred at similar rates with valproate (4.5%) and placebo (0.0%) in one trial.[57] Somnolence was not reported as a common adverse event with carbamazepine, lamotrigine, and phenytoin.

The frequency of rash on lamotrigine relative to placebo was inconsistent across 3 trials. In one trial, mild-to-moderate morbilliform rashes were reported in 5 (25.0%) of 20 patients during lamotrigine therapy while none of the patients developed skin rash during treatment with placebo.[67] In the second trial, the frequency of rash was the same on lamotrigine and placebo (2/30, 6.7% for each treatment period).[56] In the third trial, the rates of rash were similar between lamotrigine (21/150, 14%) and placebo (9/77, 12%), and no serious rashes occurred.[75] The only other trial that reported rash evaluated phenytoin. In a double-blind, crossover trial, skin rash occurred in 2 (10.0%) of 20 patients who received loading doses of phenytoin by intravenous infusion and was not reported in any of the patients after saline (placebo) infusions.[101]

A small trial reported 1 case of hepatotoxicity among 22 valproate-treated patients (4.5%); this adverse event led to discontinuation of therapy.[57] This trial also reported no cases of weight gain or thrombocytopenia on valproate. There were no reported adverse events in the placebo group.

Meta-analysis of specific adverse events: neuropathic pain

The patient-level analysis of adverse events reported in neuropathic pain trials included 7 trials and evaluated 6 adverse events (diarrhea, dizziness, headache, nausea, rash, and somnolence). The event-level analysis included 9 placebo-controlled trials and evaluated 7 adverse event categories (central nervous system/psychiatric, hematologic, infections, liver, metabolic/endocrine, other gastrointestinal, and rash or skin). Table 18 summarizes the findings of the patient-level analysis and the event-level analysis is presented in Appendix A and the corresponding Table 18A.

Table 18 presents the results of our pooled analyses of the small number of placebo-controlled trials. Gabapentin (4 trials), but not lamotrigine (1 trial) was associated with a significantly higher likelihood of dizziness as compared with placebo. The 95% confidence intervals overlapped; therefore, we cannot conclude that the odds of dizziness were different for the two agents.

Table 18. Adverse Events Analysis at Patient Level: Pain, AED vs. Placebo

			Placebo		Intervention Groups			
Adverse Events	Drug	# of studies	# of patients with event	Sample size	# of patients with event	Sample size	Pooled OR	95% CI
Diarrhea	Divalproex	0	NR	NR	NR	NR	NC	NC
Diarrhea	Gabapentin[65, 70, 72, 74]	4	15	371	32	487	1.83	(0.94, 3.73)
Diarrhea	Lamotrigine[75]	1	7	77	16	150	1.19	(0.44, 3.60)
Dizziness	Divalproex	0	NR	NR	NR	NR	NC	NC
Dizziness	Gabapentin[65, 70, 72, 74]	4	28	371	135	487	4.40	(2.81, 7.07)
Dizziness	Lamotrigine[61]	1	4	22	3	24	0.65	(0.08, 4.40)
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Gabapentin[65, 70, 72]	3	25	260	26	264	1.03	(0.55, 1.92)
Headache	Lamotrigine[61,75]	2	10	99	18	174	1.01	(0.42, 2.57)
Nausea	Divalproex	0	NR	NR	NR	NR	NC	NC
Nausea	Gabapentin[65, 70, 72]	3	19	260	23	264	1.21	(0.61, 2.42)
Nausea	Lamotrigine[61,75]	2	12	99	21	174	1.05	(0.46, 2.47)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Gabapentin	0	NR	NR	NR	NR	NC	NC
Rash	Lamotrigine[61, 67, 75]	3	9	121	28	194	2.00	(0.87, 5.05)
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Gabapentin[65, 70, 72, 74]	4	21	371	89	487	3.66	(2.19, 6.37)
Somnolence	Lamotrigine	0	NR	NR	NR	NR	NC	NC

CI, Confidence interval; CNS, Central nervous system; GI, Gastrointestinal; Inf, Infinity; NR, Not reported; OR, Odds ratio (odds of antiepileptic drug / odds of placebo)

Observational studies

There were no long-term controlled cohort studies evaluating adverse events in patients with neuropathic pain.

Summary

Safety data in patients with neuropathic pain were available from indirect comparisons based on results of 1 good-quality systematic review and 13 fair-quality published placebo-controlled trials. Indirect comparisons could not be made using data from 1 fair-quality active control trial. Based on the results of the systematic review, carbamazepine, gabapentin, and phenytoin are similar in the overall rate of adverse events. Indirect comparisons from the placebo-controlled trials were limited due to a paucity of data with AEDs other than gabapentin for each outcome measure of safety. Indirect comparisons of gabapentin (4 trials) and lamotrigine (4 trials), based on the rates of withdrawals due to adverse events in comparisons with placebo, suggest that gabapentin may be better tolerated than lamotrigine. However, the lamotrigine results were inconsistent. The nature of adverse events leading to withdrawal seems to differ between gabapentin and lamotrigine. Dizziness and somnolence due to gabapentin seemed to be more consistently reported as reasons for intolerance, whereas rash was a consistent reason for discontinuation of lamotrigine. These findings should be interpreted with caution due to the small number of reported cases. Our pooled analysis of specific adverse events suggested that gabapentin is more likely than lamotrigine to be associated with dizziness; however, we cannot definitely conclude that there is a difference between these two agents in this respect.

2c. Other diagnoses

Observational studies

A total of 54 observational studies that reported adverse events of AEDs were screened for eligibility and 4 met entry criteria.[77-80] One was discussed in regard to suicide risk under section *2a. Bipolar disorder, Observational studies*.[79] Of the remaining 3 studies, 2 were poor-quality cohort studies)[77,78] and one was a fair-quality, case-control study comparing five AEDs.[80] One trial used a selective patient sample,[77] all 3 trials did not report losses to follow-up, one trial did not adequately describe ascertainment methods,[80] one trial used potentially unreliable ascertainment methods,[78] and in another trial the adequacy of the ascertainment methods could not be determined.[80] Two trials analyzed the results for potential confounders.[77,80] These studies are summarized in Evidence Table 7 and Quality Table7, and the fair-quality study is discussed here.

Specific adverse events or withdrawals due to specific adverse events: Stevens-Johnson syndrome and Toxic Epidermal Necrolysis

The fair-quality, case-control study with comparative data for five AEDs was conducted in hospitals in France, Germany, Italy, and Portugal.[80] There were 352 cases of Stevens-Johnson syndrome or toxic epidermal necrolysis with onset before hospitalization and 1579 matched, hospitalized controls. The univariate relative risk of Stevens-Johnson syndrome or toxic epidermal necrolysis for 8 or fewer weeks of use was 57 (95% CI: 16 to 360) for phenobarbital,

91 (26 to infinity) for phenytoin; 120 (34 to infinity) for carbamazepine, 25 (5.6 to infinity) for lamotrigine, and 24 (5.9 to infinity) for valproate. The multivariate relative risk for phenobarbital was 59 (95% CI: 12 to 302). The univariate relative risk for more than 8 weeks of use was 6.2 (2.4 to 17.0) for phenobarbital; 1.2 (0 to 5.4) for phenytoin, 0.4 (0.02 to 2.1) for carbamazepine, and 7.0 (2.4 to 21.0) for valproate. The multivariate risk for long-term use was 2.1 (0.5 to 9.3) for phenobarbital and 2.0 (0.3 to 15.0) for valproate (neither were significant). Short-term use of other AEDs was a potential confounder for an association with valproate. Therefore, the risks of these serious skin reactions appear to be increased for short-term (≤ 8-week) use of phenobarbital, phenytoin, and carbamazepine. The numbers for lamotrigine were too small for meaningful analysis.

Summary

Specific adverse event data were available from 1 fair-quality case-control study in patients treated with AEDs for unreported diagnoses. The rate of Stevens-Johnson syndrome / toxic epidermal necrolysis appears to be increased for short-term (≤ 8-week) use of phenobarbital, phenytoin, and carbamazepine. Risk with valproate was potentially confounded by use of other AEDs. The numbers for lamotrigine were too small for comparison.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one AED is more effective or associated with fewer adverse events?

3a. Bipolar disorder

Systematic reviews

There were no data available to perform subgroup analyses in the good-quality systematic review comparing valproate, lithium, and placebo in the maintenance therapy of bipolar I disorder with recent mania.[82]

Head-to-head trials

There were no head-to-head trials with subgroup analyses in an outpatient population. We therefore evaluated the 2 head-to-head trials (3 publications) conducted in inpatient populations.[19, 20, 29] One of these trials presented post hoc analyses of subgroup response predictors.[19] These trials are summarized in Evidence Table 1 and Quality Table 1.

Patient characteristics

The head-to-head trial in a hospitalized inpatient population was a fair-quality trial that evaluated possible clinical response predictors to lamotrigine and gabapentin in 45 patients with bipolar or unipolar mood disorder.[19] Overall responder rates were higher on lamotrigine (51%) than gabapentin (28%) or placebo (21%). Univariate analyses and linear regression reported that response to lamotrigine may be better in male patients with fewer trials of prior medications. A better response to gabapentin appeared to occur in younger patients with lower baseline weight; however, there was no statistically significant difference in response between gabapentin and placebo. These results should be considered preliminary because of the post hoc subgroup

analyses, the small and selective (treatment-refractory) study population, and the heterogeneous patient diagnoses.

Active control trials

Two of the fair-quality active control trials performed a priori subgroup analyses to determine response predictors.[33] Another trial performed post hoc sensitivity analyses for subgroups treated with lithium but not for the carbamazepine treatment group, and therefore, the findings were not relevant to the key question.[90] All of these trials are summarized in Evidence Table 2 and Quality Table 2.[87]

Patient characteristics

One trial showed no demographic factors to be predictors of a differential response between divalproex and lithium.[33]

Other medications

No fair-quality active control trials performed subgroup analyses by other medications.

Co-morbidities

One trial reported that among patients with bipolar I disorder with recent mania and who had previous psychiatric hospitalization, divalproex was associated with a longer time to depressive relapse than lithium.[33]

Patients who had acute mania without psychosis showed a significantly greater improvement on YMRS scores on olanzapine than divalproex (difference in change from baseline: 5.4; $p < 0.001$).[87] There was no treatment difference in the subgroup with psychotic features.

Placebo-controlled trials

Subgroup analyses were performed in 1 of the 3 fair-quality placebo-controlled trials. The trial[35] is summarized in Evidence Table 3 and Quality Table 3.

Patient characteristics

No subgroup analyses were performed based on age, gender, racial groups, or gender.

Subgroup analyses by bipolar subtype were performed in one trial that compared lamotrigine and placebo maintenance therapy in patients who had bipolar I or II disorder with rapid cycling. The bipolar II subgroup had a consistently better response with lamotrigine than placebo maintenance therapy in terms of the time to premature discontinuation for any reason, proportion of patients who were stable without relapse for 6 months, and GAS scores.[35] The time to relapse (primary efficacy measure) was also longer on lamotrigine in the bipolar II subgroup; however, the difference between treatments did not reach the level of statistical significance (17 vs. 7 weeks; calculated difference: 10 weeks; $p = 0.073$). There was no significant difference for any of these

outcomes in the bipolar I subgroup. According to the authors, this finding was unexpected, since lamotrigine had previously been shown to be effective in bipolar I disorder. A high placebo response rate was observed in bipolar I patients and may be a possible confounder or an indication of other possible confounders. The factors accounting for different responses between the two bipolar subtypes need further clarification.

Other medications

No subgroup analyses were performed based on other medications.

Co-morbidities

No subgroup analyses were performed based on co-morbidities.

Summary

One head-to-head, two active-control, and one placebo-controlled trial provided evidence from subanalyses on the factors that predict a differential treatment response in patients with bipolar disorder. Based on preliminary results of a fair-quality head-to-head trial, male patients with fewer trials of prior medications achieved better responses on lamotrigine, and younger patients with lower baseline weight seemed to predict response to gabapentin; however, this agent was no better than placebo. Previous psychiatric hospitalization predicted a better response on divalproex than lithium in time to depressive relapse. Acute mania without psychosis was a negative predictor for divalproex relative to olanzapine, with smaller improvement seen on YMRS scores on the AED. Finally, the bipolar II subtype was a consistent predictor of better response on lamotrigine versus placebo in patients who have bipolar I or II disorder with rapid cycling. Because the outcomes differed and only two AEDs were evaluated against three different comparators, no indirect comparisons of the AEDs were possible for subgroup response predictors in patients with bipolar disorder. There seemed to be no consistency in the factors predicting response for lamotrigine and divalproex, each of which was evaluated in two trials.

3b. Neuropathic pain

Systematic reviews

The good-quality systematic review of AEDs in acute and chronic pain did not perform subgroup response analyses.

Head-to-head trials

The one poor-quality head-to-head trial in neuropathic pain did not perform subgroup analyses.

Active control trials

The one fair-quality active control trial in neuropathic pain did not perform subgroup analyses.

Placebo-controlled trials

Analyses for potential subgroup response predictors were conducted in 3 of the 13 placebo-controlled trials in neuropathic pain. These trials are summarized in Evidence Table 6 and Quality Table 6.

Patient characteristics

In one fair-quality trial evaluating gabapentin relative to placebo in a population with mixed neuropathic pain syndromes, no significant differences (p = 0.29) were found when data were analyzed (a priori) by five categories of pain (back pain, complex regional pain syndrome, postherpetic neuralgia, postoperative pain, and other pain).[70]

Other medications

A protocolled subgroup analysis by exposure to neurotoxic antiretroviral therapy (stavudine / d4T, didanosine / ddI, or zalcitabine / ddC) was performed in a fair-quality trial that compared lamotrigine with placebo in 29 evaluable patients with HIV-related painful distal sensory polyneuropathy. Using a per-protocol analysis (completers), a significant treatment difference (calculated difference, lamotrigine minus placebo: –0.61; p = 0.03) was seen only in patients with no prior neurotoxin exposure for average Gracely pain scores.[67] No significant treatment differences were seen in patients with prior neurotoxin exposure for worst pain scores or in patients with prior exposure for either average or worst pain scores.

However, the opposite results were shown when the same primary author subsequently conducted a follow-on trial in a larger outpatient population (N = 227) and in which randomization was stratified according to the presence or absence of concomitant neurotoxic antiretroviral therapy.[75] In the stratum of patients receiving neurotoxic antiretroviral therapy, there was a nonsignificant, greater reduction in average Gracely pain scores on lamotrigine than on placebo (calculated difference, –0.17; p = 0.07). There were significant treatment differences in the slopes of the changes in average (p = 0.004) and worst (p = 0.002) pain scores in favor of lamotrigine over placebo, as well as for secondary outcome measures (VAS, Short-form McGill Pain Questionnaire [SF-MPQ], CGIC, and PGIC scores). In the stratum of patients without neurotoxic exposure, there was no significant difference in Gracely pain scores or secondary outcome measures, and the magnitude of reduction in pain scores for both lamotrigine (–0.30) and placebo (–0.27) were similar to that of lamotrigine in the neurotoxic stratum (–0.27). The authors attributed the discrepancy in results to the small sample size and high dropout rate in the first trial. Additional details of both trials are provided in Evidence Table 6 and Quality Table 6.

Co-morbidities

No fair-quality placebo-controlled trials analyzed co-morbidities as response predictors.

Summary

Data on subgroup response predictors during AED therapy for neuropathic pain were available from 3 fair-quality placebo-controlled trials. Type of neuropathic pain (back pain, complex regional pain syndrome, postherpetic neuralgia, postoperative pain, and other pain) were not

predictive of a differential treatment effect with gabapentin relative to placebo. Concomitant neurotoxic antiretroviral therapy appears to predict a better response to lamotrigine in the treatment of HIV-related distal sensory polyneuropathy; however, the robustness of this association is questionable, as a previous smaller trial showed contradictory results. No indirect comparisons of the AEDs could be made based on subgroup response factors

SUMMARY AND DISCUSSION

There was a lack of good-quality head-to-head trials and lack of good-quality trials overall. We found admissible randomized trials on only some of the AEDs of interest. At least one fair-quality trial each was available for carbamazepine, valproate, gabapentin, lamotrigine, and phenytoin for either bipolar disorder or neuropathic pain. There were two poor-quality trials each for topiramate (active control[37] and placebo-controlled)[100] and phenytoin (placebo-controlled)[36,62] (summarized in Evidence Tables 2, 3, and 6 and Quality Tables 2, 3, and 6, but not discussed in the text), and no randomized trials that met inclusion criteria were found for levetiracetam, oxcarbazepine, tiagabine, vigabatrin, and zonisamide. Four observational studies evaluated carbamazepine,[78-80] valproate/divalproex,[78-80] phenytoin,[80] or vigabatrin[77] (one trial included lamotrigine but no data was available).[80] Two of these studies were fair quality[79,80] and the other two were poor quality (not discussed in the text).[78,77] These four studies were summarized in Evidence Table 7 and Quality Table 7.

One of the limitations of this review was the inclusion of only published trials. Some data from an unpublished trial, which showed gabapentin to be no better than placebo for the primary efficacy variable (change in pain score) in patients with painful diabetic neuropathy, was available from a poor-quality systematic review.[76] We are aware from another review article that three major efficacy trials evaluating topiramate in painful diabetic neuropathy did not report an analgesic effect.[108] These trials were not referenced in the review article nor were they found by our literature search, and we presume they are unpublished. Rather than being able to conclude that there is evidence of lack of efficacy with topiramate in painful diabetic neuropathy, we can only say that we found no published evidence to support using topiramate for neuropathic pain (or bipolar disorder).

The criterion to evaluate outpatient trials limited the scope of our review for bipolar disorder to mainly maintenance therapy trials, since most of the inpatient trials dealt with acute therapy. We made an exception to the criterion and evaluated two trials in inpatients after we found no head-to-head trials in outpatients and consulting with an expert in psychiatry. Even with the inclusion of these two trials, we found the overall quality of trials evaluating AEDs in bipolar disorder to be poor to fair.

Our findings are summarized below.

Comparative effectiveness of AEDs in bipolar disorder

There were no head-to-head trials and no good-quality trials in outpatient populations. We found 3 good-quality systematic reviews, 1 fair-quality head-to-head trial (reported in 2 papers) in inpatients, and 7 active control trials and 6 placebo-controlled trials (including 3 with active controls) of fair quality in outpatients. Most relative treatment effects were based on indirect

comparisons of carbamazepine, divalproex, gabapentin, and lamotrigine using lithium as the standard. No evidence of at least fair quality was found on the other AEDs of interest. No AED comparisons could be made in terms of use of other medications and danger to self. Head-to-head trials of at least fair quality are needed to confirm our indirect comparisons. The findings are summarized by treatment phase.

Acute manic episodes: Indirect comparisons from 1 good-quality systematic review showed that carbamazepine and valproate are similar in effectiveness, based on lack of differences relative to lithium. There was also evidence from 1 poor-quality head-to-head trial that valproate is superior to carbamazepine in improving manic symptoms; however, this finding should be considered inconclusive. One fair-quality placebo-controlled trial showed that gabapentin is not effective as add-on therapy. In 1 fair-quality placebo-controlled trial, lamotrigine was not effective in improving mania symptoms in patients with bipolar I disorder with recent depressive episode.

Acute depressive episodes: One fair-quality trial showed that lamotrigine 200 mg is efficacious in improving depressive symptoms, whereas a dose of 50 mg showed no treatment benefit. There were no trials of at least fair quality for other AEDs.

Acute rapid cycling: Results of one fair-quality head-to-head trial suggested that lamotrigine is superior to gabapentin and gabapentin is no better than placebo in terms of responder rates; however, these results were not based on an intent-to-treat analysis and are preliminary.

Maintenance therapy, bipolar I disorder with recent mania or depression: Indirect comparisons from 3 fair-quality lithium-controlled trials and 4 placebo-controlled trials showed that lamotrigine is not more efficacious than divalproex in reducing mania symptoms and may be similar to or better than divalproex in reducing depressive symptoms. Indirect comparisons from 4 fair-quality active-control trials suggested that carbamazepine, divalproex, and lamotrigine are similar in achieving remission, based on lack of treatment differences with lithium. Based on indirect comparisons from 3 fair-quality placebo-controlled trials, lamotrigine is similar to or better than divalproex in achieving remission. Three fair-quality lithium- and placebo-controlled trials, based on indirect comparisons of the AEDs relative to controls, showed that lamotrigine is similar to or better than divalproex in duration of remission. Results of 4 fair-quality lithium-controlled trials suggested that carbamazepine, divalproex, and lamotrigine are similar in terms of recurrence rates, based on indirect comparisons of the AEDs. These results were partly supported by 2 placebo-controlled trials that also found divalproex and lamotrigine to be similar in preventing recurrence. Three lithium- and placebo-controlled trials showed inconsistent relative treatment effects between divalproex and lamotrigine in terms of functional capacity. Divalproex was similar to lamotrigine in improving GAS scores based on treatment differences relative to lithium, but divalproex may be better than lamotrigine in terms of preventing worsening of functional capacity in patients without depression during an index manic episode. Lamotrigine was better than divalproex in terms of effects on functional capacity when the AEDs were compared with placebo. Two fair-quality active-control trials suggested that carbamazepine and divalproex are similar in terms of hospitalization for mood episodes, based on lack of treatment differences between each AED and lithium. There was indirect evidence from 3 fair-quality placebo-controlled trials that divalproex and lamotrigine are similar in rates of hospitalization. Results with divalproex, however, were inconclusive because of methodological weaknesses in one trial.

In patients with rapid cycling, a good-quality systematic review showed no clear advantage for any AED (carbamazepine, lamotrigine, topiramate, and valproate) in reducing pooled crude recurrence or non-improvement rates. In a fair-quality placebo-controlled trial, lamotrigine was no better than placebo in improving scores on clinical global impression of symptoms, depression or mania rating scales, and global assessment scale (a reflection of functional capacity). No indirect comparisons of AEDs could be made using an active agent or placebo as a standard comparator.

Comparative effectiveness of AEDs in neuropathic pain

We obtained evidence from 1 good-quality systematic review and 13 placebo-controlled trials of fair quality, most involving gabapentin. There was 1 poor-quality head-to-head trial and one fair-quality active control trial, but no other fair-quality active control trials to make indirect comparisons of AEDs. The good-quality systematic review showed that the numbers-needed-to-treat (NNTs) for effectiveness in any neuropathic pain were 2.5 (95% CI: 2.0 to 3.4) for carbamazepine and 3.7 (2.6 to 4.9) for gabapentin.[96] There was no evidence that one agent was better than the other.

There is fair-quality evidence from placebo-controlled trials that gabapentin is effective in neuropathic pain, specifically painful diabetic neuropathy and postherpetic neuropathy. The evidence for mixed neuropathic pain syndromes is less robust, with reductions in pain falling short of thresholds for clinically relevant changes and responder rates no better than those of placebo. One small (N = 43) fair-quality trial provided evidence that valproate is effective for painful diabetic neuropathy;[57] however, there were no other fair-quality trials to validate these findings. Only carbamazepine had fair-quality evidence to support its use in trigeminal neuralgia. Lamotrigine was effective in central post-stroke pain but did not show an analgesic effect in the total cohorts of patients with symptom-based diagnoses of neuropathic pain or HIV-related distal sensory polyneuropathy. Subgroup analyses, however, showed inconsistent results in HIV-related polyneuropathy. Intravenously administered phenytoin showed some benefit in acute treatment of neuropathic pain. It was difficult to make indirect comparisons of the AEDs for any of the outcomes of interest because of methodological differences. When the overall treatment responses observed in fair-quality placebo-controlled trials are considered, gabapentin (6 trials) and valproate (1 trial) have been shown to have beneficial analgesic effects whereas the effects of lamotrigine (3 trials) are inconsistent in neuropathic pain.

Fair-quality placebo-controlled trials suggested that gabapentin (5 trials) may have an earlier onset than lamotrigine (1 trial), based on indirect comparisons. Based on lack of treatment differences relative to placebo, neither gabapentin (1 trial) nor lamotrigine (3 trials) is better in reducing concomitant analgesic use. Based on indirect comparisons, gabapentin (4 of 5 trials) is better than lamotrigine (1 trial) in improving functional capacity in patients with neuropathic pain. Better quality head-to-head trials and longer-term studies are needed, as well as additional subgroup analyses to explore the relationships between clinical factors and possible analgesic effects of lamotrigine.

Most of the fair-quality evidence documents the efficacy of gabapentin in neuropathic pain. We found little or no evidence of at least fair quality to support the use of other AEDs for neuropathic pain. However, a difference in amount of data is not evidence that one AED is better

than any other. We also noted that, in a population of patients with painful diabetic neuropathy or postherpetic neuralgia, the magnitude of improvement in pain with gabapentin seems to be slightly more than the threshold for clinically relevant changes defined by Farrar, et al.[14] The population data show that pain relief with gabapentin is modest at best, although we recognize that individuals may experience significant pain relief. When given in fixed doses, gabapentin also appeared to have a relatively flat dose-response curve, with a lack of additional benefit from 2400-mg over 1800-mg doses. When titrated to response, doses up to 3600 mg of gabapentin were reported to be necessary for adequate pain relief.

Comparative safety of AEDs in bipolar disorder

We evaluated 1 good-quality systematic review and 1 head-to-head trial, 6 active control trials, 6 placebo-controlled trials, all of fair quality, as well as 1 fair-quality cohort study. In the head-to-head trial, lamotrigine and gabapentin were not significantly different in the number of patients with no major adverse events. Indirect comparisons based on the systematic review suggest that carbamazepine and valproate may have similar risks of adverse events overall. Divalproex (1 trial) and lamotrigine (3 trials) are similar in terms of rates of withdrawals due to adverse events, based on indirect comparisons of the AEDs relative to placebo. However, the nature of adverse events leading to withdrawal was notable for lamotrigine, which was associated with toxic epidermal necrolysis in one patient. Serious adverse events were low and did not allow AED comparisons. For specific adverse events, indirect comparisons of AEDs could not be made for dizziness. Indirect comparisons based on data from 3 lithium-controlled trials suggest that divalproex may be associated with a higher frequency of sedation/somnolence than lamotrigine. Rash was reported with lamotrigine and carbamazepine, and not with gabapentin or valproate; however, the numbers are too small to allow comparisons of the AEDs. Lamotrigine caused weight loss while gabapentin (1 head-to-head trial) and divalproex (1 placebo-controlled trial) caused weight gain. Neither lamotrigine nor gabapentin was significantly different from placebo in terms of weight changes. Indirect comparisons were limited and suggested that the adverse event spectra of divalproex and lamotrigine differ (headache, rash, and weight loss or gain with lamotrigine versus weight gain and adverse events affecting the nervous system, digestive system, and platelet count with divalproex). Based on our pooled analyses comparing the AEDs to a common comparator (placebo or lithium), we could not reach strong conclusions about differences between AEDs in terms of specific adverse events, although there is consistent, but not conclusive, evidence that divalproex is more often associated with tremor than lamotrigine. Based on the findings of the cohort study, divalproex is associated with a higher rate of suicide deaths and attempts than lithium. We could not conclude there was a significant difference between divalproex and carbamazepine for these outcomes.

Comparative safety of AEDs in neuropathic pain

Evidence on the adverse events and tolerability of the AEDs were found in 1 good-quality systematic review, 1 active control trial, and 13 placebo-controlled trials of fair quality. In the good-quality systematic review, the numbers-needed-to-harm for minor adverse events appear to be similar for carbamazepine, gabapentin, and phenytoin. Tolerability also appears to be similar for the three AEDs. Indirect comparisons of gabapentin (4 trials) and lamotrigine (4 trials), based on the rates of withdrawals due to adverse events in comparisons with placebo, suggest that

gabapentin may be better tolerated than lamotrigine. However, the lamotrigine results were inconsistent. Indirect comparisons were otherwise limited and inconclusive.

Comparative safety of AEDs in other diagnoses

The results of 1 fair-quality case-control study suggest that the risks of serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) may be increased for phenobarbital, phenytoin, and carbamazepine in the first 8 weeks of therapy.

Subgroup response predictors

Patient characteristics. Fair-quality evidence was available from 1 head-to-head trial in patients with bipolar or unipolar disorder. Male patients with fewer trials of prior medications seemed to respond better to lamotrigine, while younger patients with lower baseline weight seemed to respond better to gabapentin. However, gabapentin was no better than placebo. These results are preliminary and inconclusive.

The bipolar II disorder subtype with rapid cycling responded better to lamotrigine than placebo maintenance therapy, whereas there was no treatment differential for the bipolar I subgroup. These results are questionable because of potential unknown confounding factors.

There were 2 fair-quality placebo-controlled trials in patients with neuropathic pain. Indirect comparisons of the AEDs were not possible.

Other medications. Two fair-quality placebo-controlled trials evaluated subgroup responses in patients with HIV-related distal sensory polyneuropathy; however, indirect comparisons of the AEDs were not possible.

Co-morbidities. There were no subgroup analyses based on co-morbidities.

Conclusion

There is a paucity of good-quality data on the effectiveness, safety, and tolerability of AEDs in the management of bipolar disorder and neuropathic pain. We found no clear evidence of superior effectiveness of one AED over another, although there was fair-quality evidence from randomized controlled trials that gabapentin is ineffective in the treatment of bipolar disorder. Indirect evidence suggests that there are clinically relevant differences between gabapentin and the AEDs that do have evidence of efficacy in bipolar disorder (carbamazepine, lamotrigine, and valproate / divalproex). For neuropathic pain, there was indirect evidence from overall results that gabapentin and valproate may be more effective than lamotrigine but there was no conclusive (i.e., head-to-head) evidence of differences between AEDs. Gabapentin is the most studied AED for this indication, and thus our conclusion that gabapentin is effective therapy for neuropathic pain is stronger than our conclusion for other AEDs. Limited comparative data on the safety and tolerability of the AEDs suggest that lamotrigine and divalproex may differ in their adverse event profiles but we did not detect clearly discernible differences in the rates of adverse events or withdrawals due to adverse events between any of the AEDs. The best quality evidence (from a systematic review) suggested that carbamazepine, gabapentin, and phenytoin

are similar in safety and tolerability in the treatment of neuropathic pain. No conclusive evidence could be obtained from analyses of subgroup response predictors.

Results for the key questions are summarized in Table 19.

Table 19. Summary of the Evidence by Key Question

Key Question 1: Efficacy	Overall Quality of Evidence	Conclusion
1a. Bipolar disorder	Poor	No head-to-head trials and no good-quality trials in outpatient populations. Three good-quality systematic reviews, 1 fair-quality head-to-head trial in inpatients, and 7 active control trials and 6 placebo-controlled trials of fair quality in outpatients. Except for a direct comparison of lamotrigine and gabapentin in one trial, all relative treatment effects were based on indirect comparisons The findings are summarized by treatment phase. *Acute manic episodes*: Indirect comparisons from 1 good-quality systematic review showed that carbamazepine and valproate are similar in effectiveness. One fair-quality placebo-controlled trial showed that gabapentin is not effective as add-on therapy. In 1 fair-quality placebo-controlled trial, lamotrigine was not effective in improving mania symptoms in patients with bipolar I disorder with recent depressive episode. *Acute depressive episodes*: One fair-quality trial showed that lamotrigine 200 mg is efficacious in improving depressive symptoms, whereas a dose of 50 mg showed no treatment benefit. There were no trials of at least fair quality for other AEDs. *Acute rapid cycling*: Preliminary results of one fair-quality head-to-head trial suggested that lamotrigine is superior to gabapentin and gabapentin is no better than placebo in terms of responder rates. *Maintenance therapy, bipolar I disorder with recent mania or depression*: Indirect comparisons from 3 fair-quality lithium-controlled trials and 4 placebo-controlled trials showed that lamotrigine is not more efficacious than divalproex in reducing mania symptoms and may be similar to or better than divalproex in reducing depressive symptoms. Indirect comparisons from 4 fair-quality active-control trials suggested that carbamazepine, divalproex, and lamotrigine are similar in achieving remission, based on lack of treatment differences with lithium. Based on indirect comparisons from 3 fair-quality placebo-controlled trials, lamotrigine is similar to or better than divalproex in achieving remission. Three fair-quality lithium- and placebo-controlled trials, based on indirect comparisons of the AEDs relative to controls, showed that lamotrigine is similar to or better than divalproex in duration of remission. Results of 4 fair-quality lithium-controlled trials suggested that carbamazepine, divalproex, and lamotrigine are similar in terms of recurrence rates, based on indirect comparisons of the AEDs. These results were partly supported by 2 placebo-controlled trials that also showed divalproex and lamotrigine to be similar in preventing recurrence. Three lithium- and placebo-controlled trials showed inconsistent relative treatment effects between divalproex and lamotrigine in terms of functional capacity. Two fair-quality active-control trials suggested that carbamazepine and divalproex are similar in terms of hospitalization for mood episodes, based on lack of treatment differences between each AED and lithium. There was indirect evidence from 3 fair-quality placebo-controlled trials that divalproex and lamotrigine are similar in rates of hospitalization. Results with divalproex, however, were inconclusive because of methodological weaknesses in one trial. In patients with rapid cycling, a good-quality systematic review showed no clear advantage for any AED (carbamazepine, lamotrigine, topiramate, and valproate) in reducing pooled crude recurrence or non-improvement rates. In a fair-quality placebo-controlled trial, lamotrigine was no better than placebo in improving scores on clinical global impression of symptoms, depression or mania rating scales, and global assessment scale (a reflection of functional capacity). No indirect comparisons of AEDs could be made.

1b. Neuropathic pain	Fair (gabapentin) Poor (other AEDs)	One good-quality systematic review and 13 fair-quality placebo-controlled trials, most involving gabapentin. The good-quality systematic review showed that the numbers-needed-to-treat (NNTs) for effectiveness in any neuropathic pain were 2.5 (95% CI: 2.0 to 3.4) for carbamazepine and 3.7 (2.6 to 4.9) for gabapentin. There was no evidence that one agent was better than the other. There is fair evidence that gabapentin is effective in neuropathic pain. One small fair-quality trial showed that valproate is effective for painful diabetic neuropathy. Only carbamazepine had fair-quality evidence to support its use in trigeminal neuralgia. Lamotrigine was effective in central post-stroke pain but did not show an analgesic effect in the total cohorts of patients with symptom-based diagnoses of neuropathic pain or HIV-related distal sensory polyneuropathy. Subgroup analyses showed inconsistent results in HIV-related polyneuropathy. Intravenously administered phenytoin showed some benefit in acute treatment of neuropathic pain. Fair-quality placebo-controlled trials suggested that gabapentin (5 trials) may have an earlier onset than lamotrigine (1 trial), based on indirect comparisons. Based on indirect comparisons, gabapentin (4 of 5 trials) is better than lamotrigine (1 trial) in improving functional capacity in patients with neuropathic pain.
Key Question 2: Safety	**Overall Quality of Evidence**	**Conclusion**
2a. Bipolar disorder	Fair	One good-quality systematic review; 1 head-to-head, 6 active control, and 6 placebo-controlled trials, all of fair quality; 1 fair-quality cohort study. In the head-to-head trial, lamotrigine and gabapentin were not significantly different in the number of patients with no major adverse events. Indirect comparisons based on the systematic review suggest that carbamazepine and valproate may have similar risks of adverse events overall. Divalproex (1 trial) and lamotrigine (3 trials) are similar in terms of rates of withdrawals due to adverse events, based on indirect comparisons of the AEDs relative to placebo. Serious adverse events were low and did not allow AED comparisons. For specific adverse events, indirect comparisons based on data from 3 lithium-controlled trials suggest that divalproex may be associated with a higher frequency of sedation / somnolence than lamotrigine. Rash was reported with lamotrigine and carbamazepine, and not with gabapentin or valproate; however, the numbers are too small to allow comparisons of the AEDs. Lamotrigine caused weight loss while gabapentin (1 head-to-head trial) and divalproex (1 placebo-controlled trial) caused weight gain. Indirect comparisons were limited and suggested that the adverse event spectra of divalproex and lamotrigine differ (headache, rash, and weight loss or gain with lamotrigine versus weight gain and adverse events affecting the nervous system, digestive system, and platelet count with divalproex). Based on our pooled analyses, there is consistent, but not conclusive, evidence that divalproex is more often associated with tremor than lamotrigine. Based on the findings of the cohort study, divalproex is associated with a higher rate of suicide deaths and attempts than lithium. We could not conclude there was a significant difference between divalproex and carbamazepine for these outcomes.
2b. Neuropathic pain	Fair / Poor	One good-quality systematic review, and 1 active control and 13 placebo-controlled trials of fair quality. In 1 good-quality systematic review, the numbers-needed-to-harm for minor adverse events appear to be similar for carbamazepine, gabapentin, and phenytoin. Tolerability also appears to be similar for the three AEDs. Indirect comparisons of gabapentin (4 trials) and lamotrigine (4 trials), based on the rates of withdrawals due to adverse events in comparisons with placebo, suggest that gabapentin may be better tolerated than lamotrigine. However, the lamotrigine results were inconsistent. Indirect comparisons were otherwise limited and inconclusive.
2c. Other diagnoses	Fair / Poor	The results of 1 fair-quality case-control study suggest that the risks of serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) may be increased for phenobarbital, phenytoin, and carbamazepine in the first 8 weeks of therapy.

Key Question 3: Subgroups	Overall Quality of Evidence	Conclusion
Patient characteristics	Poor	One fair-quality head-to-head trial, 2 fair-quality placebo-controlled trials in patients with bipolar disorder. Male patients with fewer trials of prior medications seemed to respond better to lamotrigine, while younger patients with lower baseline weight seemed to respond better to gabapentin. However, gabapentin was no better than placebo. These results are preliminary and inconclusive. Two fair-quality placebo-controlled trials in patients with neuropathic pain. Indirect comparisons of the AEDs were not possible.
Other medications	Poor	Two fair-quality placebo-controlled trials. Indirect comparisons of the AEDs were not possible.
Co-morbidities	Poor	No subgroup analyses.

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Appendix A. Meta-analysis of Specific Adverse Events at an Event Level

Methods

Extraction of Adverse Event Data at an Event Level

We identified only one trial on bipolar disorder that directly compared the relative frequency of adverse events of different AEDs. Therefore, we relied primarily on an indirect method of assessing this, by calculating the frequency of adverse events of AEDs compared with placebo (for both bipolar disorder and neuropathic pain trials), and of AEDs compared with lithium (for bipolar disorder trials only), and then comparing these frequencies across AEDs.

Each trial was examined to determine whether it reported data on adverse events. Crossover trials were excluded from the adverse event analysis, unless they reported events for each group before the crossover (which none of the trials did). Adverse events were recorded onto a spreadsheet that identified each trial group, the description of the adverse event as listed in the original article, and the number of subjects in each group. We then abstracted either the number of events or the number of patients, depending on how the trial chose to report events. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of patients having an adverse event.

Differences between trials in AED doses were not taken into account in this analysis because data were not available at different dosage levels. Most trials used a titrated dosage regimen and reported the most common adverse events that occurred at any dosage level during the treatment period. Dosage ranges for AEDs were generally comparable with those recommended for the respective agent.

If a report of a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume zero events occurred unless the trial report specifically stated that zero events were observed. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed.

After abstracting the data, we identified mutually exclusive subgroups of similar events, based on clinical expertise. For example, one subgroup was "other GI problems," consisting of all adverse events concerning this body system. When we subgrouped events, we again treated all observed events as having occurred in unique individuals. For example, we considered constipation, dyspepsia, and diarrhea as a single subgroup: For a trial that reported constipation events and dyspepsia events separately, we assumed the events that occurred in each category were unique and occurred in different individuals. The number of individuals who were at risk of being affected is the total number of patients in the trial's relevant group (medication or placebo).

For each adverse-event subgroup, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the medication groups in the relevant trials who were observed to have experienced the event and the total number of

patients in the medication groups in those trials. We then report the analogous counts for the placebo groups (or secondary medication groups) in the relevant trials.

Methods for calculating the odds ratios are the same as for the event-level analysis.

Results

Bipolar disorder

Tables 15A, 16A, and 17A summarize the results for the event-level analyses of adverse events in bipolar disorder trials. These tables correspond to in-text Tables 15, 16, and 17, which pertain to the patient-level adverse event analyses.

Table 15A presents our statistical analysis of the one small study that compared carbamazepine with valproate. In this analysis, carbamazepine was more likely than divalproex/valproate to be associated with central nervous system (CNS) and other gastrointestinal (GI) adverse events.

In Table 16A, AEDs are assessed against a common comparator, lithium. The number of trials and number of patients are small, and the 95% confidence intervals are very wide. Thus, the lack of statistically significant evidence for a specific adverse event cannot be taken to mean that an AED did not cause that adverse event. Carbamazepine and lamotrigine were less likely to be associated with CNS adverse events than lithium while divalproex was more likely to be associated with CNS adverse events than lithium. These results were statistically significant. These data conflict with the data in Table 15A, which suggest that carbamazepine was more likely to be associated with CNS/psychiatric adverse events than divalproex/valproate. All AEDs assessed (carbamazepine, divalproex, and lamotrigine) were less likely to be associated with "other GI" adverse events compared with lithium. Carbamazepine was associated with a greater likelihood of "rash or skin" adverse events than lithium. Carbamazepine, but not divalproex, was associated with significantly lower odds of metabolic adverse events compared with lithium; and divalproex, but not lamotrigine, was significantly more likely to be associated with "infectious disease" adverse events compared with lithium.

In Table 17A, data are pooled comparing AEDs with placebo. The number of trials and number of patients are small, and the 95% confidence intervals are wide. In general, the same cautions as mentioned for Table 16A apply. Still, some conclusions can be reached more specifically. All 3 AEDs assessed (divalproex, gabapentin, lamotrigine) were associated with statistically significantly more reports of CNS adverse events than placebo. Data are insufficient to reach a strong conclusion about whether differences between AEDs exist, but there is a suggestion that divalproex is associated with more CNS adverse events than gabapentin or lamotrigine. These data are consistent with the active control data suggesting that divalproex is associated with more CNS adverse events than lamotrigine (Table 16A). Divalproex, but not gabapentin or lamotrigine, was associated with a statistically significant increase in "other GI" adverse events compared with placebo. Divalproex, but not lamotrigine, was associated with a statistically significant increase in rash compared with placebo.

Table 15A. Adverse Event Analysis at Event Level, Mood: AED vs. AED

		Carbamazepine		Valproate			
Adverse Events	# of trials	# of patients with adverse events	Sample size	# of patients with adverse events	Sample size	Pooled OR	95% CI
CNS[1]	1	15	15	4	15	Inf	(6.77, Inf)
Liver[1]	1	1	15	1	15	1.00	(0.01, 84.46)
Other GI[1]	1	9	15	3	15	7.36	(1.03, 92,69)
Rash or skin[1]	1	1	15	0	15	Inf	(0.03, Inf)
Hematologic[1]	1	0	15	0	15	NC	NC

CI, Confidence interval; CNS, Central nervous system; GI, Gastrointestinal; Inf, Infinity; NR, Not reported; OR, Odds ratio (odds of carbamazepine / odds of divalproex)

Table 16A. Adverse Event Analysis at Event Level, Mood: AED vs. Lithium

			Lithium		Intervention Groups			
Adverse Events	Drug	# of trials	# of patients with events	Sample size	# of patients with events	Sample size	Pooled OR	95% CI
Cardiac	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Cardiac	Divalproex[2]	1	4	94	1	187	0.12	(0.01, 1.25)
Cardiac	Lamotrigine	0	NR	NR	NR	NR	NC	NC
CNS	Carbamazepine[3-7, 7-9]	7	150	255	118	285	0.51	(0.34, 0.77)
CNS	Divalproex[2]	1	83	94	182	187	4.79	(1.48, 18.18)
CNS	Lamotrigine[10, 11]	2	97	166	108	228	0.62	(0.40, 0.95)
Hematologic	Carbamazepine[12]	1	0	24	1	24	Inf	(0.03, Inf)
Hematologic	Divalproex	0	NR	NR	NR	NR	NC	NC
Hematologic	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Infectious dis	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Infectious dis	Divalproex[2]	1	12	94	51	187	2.55	(1.25, 5.58)
Infectious dis	Lamotrigine[10, 11]	2	35	166	48	228	1.00	(0.60, 1.69)
Liver	Carbamazepine[3-5, 5, 7]	4	1	148	6	149	6.21	(0.73, 292.44)
Liver	Divalproex	0	NR	NR	NR	NR	NC	NC
Liver	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Metabolic	Carbamazepine[3, 4, 7-9]	5	79	214	33	244	0.22	(0.13, 0.37)
Metabolic	Divalproex[2]	1	26	94	50	187	0.95	(0.53, 1.74)
Metabolic	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Muscular pain	Carbamazepine[4]	1	6	44	2	50	0.26	(0.02, 1.57)
Muscular pain	Divalproex	0	NR	NR	NR	NR	NC	NC
Muscular pain	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Other GI	Carbamazepine[3-5, 9]	3	52	186	26	185	0.38	(0.21, 0.69)
Other GI	Divalproex[2]	1	83	94	144	187	0.45	(0.20, 0.89)
Other GI	Lamotrigine[10, 11]	2	65	166	47	228	0.40	(0.25, 0.65)
Rash or skin	Carbamazepine[3-9, 12]	8	10	279	37	309	4.32	(2.00, 10.21)
Rash or skin	Divalproex[2]	1	7	94	30	187	2.37	(0.97, 6.66)
Rash or skin	Lamotrigine[10, 11]	2	9	166	14	228	1.14	(0.45, 3.06)

CI, Confidence interval; CNS, Central nervous system; Dis, Disease; GI, Gastrointestinal; NC, Not calculable; NR, Not reported; OR, Odds ratio (odds of antiepileptic drug / odds of lithium)

Table 17A. Adverse Events Analysis at Event Level, Mood: AED vs. Placebo

			Placebo		Intervention Groups			
Adverse Events	Drug	# of trials	# of patients with event	Sample size	# of patients with event	Sample size	Pooled OR	95% CI
CNS	Divalproex[2]	1	56	94	182	187	24.36	(8.99, 83.14)
CNS	Gabapentin[13]	1	19	59	37	58	3.66	(1.62, 8.57)
CNS	Lamotrigine[10, 11, 14, 15]	4	140	343	404	773	1.63	(1.23, 2.16)
Cardiac	Divalproex[2]	1	1	94	1	187	0.50	(0.01, 39.67)
Cardiac	Gabapentin	0	NR	NR	NR	NR	NC	NC
Cardiac	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Infectious disease	Divalproex[2]	1	18	94	51	187	1.58	(0.84, 3.09)
Infectious disease	Gabapentin	0	NR	NR	NR	NR	NC	NC
Infectious disease	Lamotrigine[10, 11, 14, 15]	4	72	343	150	773	0.88	(0.63, 1.25)
Metabolic	Divalproex[2]	1	14	94	50	187	2.08	(1.05, 4.34)
Metabolic	Gabapentin	0	NR	NR	NR	NR	NC	NC
Metabolic	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Muscular pain	Divalproex	0	NR	NR	NR	NR	NC	NC
Muscular pain	Gabapentin	0	NR	NR	NR	NR	NC	NC
Muscular pain	Lamotrigine[14, 15]	2	12	153	49	545	1.17	(0.58, 2.50)
Other GI	Divalproex[2]	1	57	94	144	187	2.17	(1.22, 3.84)
Other GI	Gabapentin[13]	1	7	59	9	58	1.36	(0.41, 4.66)
Other GI	Lamotrigine[10, 11, 14, 15]	4	89	343	219	773	1.10	(0.80, 1.52)
Rash or skin	Divalproex[2]	1	6	94	30	187	2.79	(1.09, 8.53)
Rash or skin	Gabapentin	0	NR	NR	NR	NR	NC	NC
Rash or skin	Lamotrigine[10, 11, 14]	3	15	255	24	357	1.12	(0.54, 2.36)

CI, Confidence interval; CNS, Central nervous system; GI, Gastrointestinal; NC, Not calculable; NR, Not reported; OR, Odds ratio (odds of antiepileptic drug / odds of placebo)

Neuropathic pain

Table 18A presents the results of our pooled event-level analyses of the small number of placebo-controlled trials. This table corresponds with in-text Table 18, which summarizes the patient-level analyses.

Statistically significant differences between AEDs in the rates of specific adverse events occurred in only one circumstance, where gabapentin was associated with more CNS/psychiatric events than lamotrigine.

Table 18A. Adverse Events Analysis at Event Level: Pain, AED vs. Placebo

			Placebo		Intervention Groups			
Adverse Events	Drug	# of trials	# of patients with events	Sample size	# of patients with events	Sample size	Pooled OR	95% CI
CNS/ psychiatric[16]	Divalproex	1	0	21	1	22	Inf	(0.02, Inf)
CNS/ psychiatric[17-20]	Gabapentin	4	79	371	272	487	4.63	(3.37, 6.41)
CNS/ psychiatric[21-23]	Lamotrigine	3	22	115	27	192	0.81	(0.41, 1.63)
Hematologic[16]	Divalproex	1	0	21	0	22	NC	NC
Hematologic	Gabapentin	0	NR	NR	NR	NR	NC	NC
Hematologic	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Infections	Divalproex	0	NR	NR	NR	NR	NC	NC
Infections[19]	Gabapentin	1	26	152	25	153	0.95	(0.49, 1.80)
Infections[22, 24]	Lamotrigine	2	7	99	18	170	1.41	(0.53, 4.18)
Liver[16]	Divalproex	1	0	21	1	22	Inf	(0.02, Inf)
Liver	Gabapentin	0	NR	NR	NR	NR	NC	NC
Liver	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Metabolic/ endocrine[16]	Divalproex	1	0	21	0	22	NC	NC
Metabolic/ endocrine	Gabapentin	0	NR	NR	NR	NR	NC	NC
Metabolic/ endocrine	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Other GI[16]	Divalproex	1	0	21	2	22	Inf	(0.18, Inf)
Other GI[17-20]	Gabapentin	4	40	371	65	487	1.60	(1.02, 2.53)
Other GI[21-23]	Lamotrigine	3	24	115	47	192	1.29	(0.71, 2.39)
Rash or skin	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash or skin[18]	Gabapentin	1	0	111	12	223	Inf	(1.43, Inf)
Rash or skin[20-23]	Lamotrigine	4	9	137	30	212	2.21	(0.97, 5.52)

CI, Confidence interval; CNS, Central nervous system; GI, Gastrointestinal; Inf, Infinity; NC, Not calculable; NR, Not reported; OR, Odds ratio (odds of antiepileptic drug / odds of placebo)

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Appendix B. Search Strategy and Update History

Cochrane Databases

First drug list

#1. (gabapentin or neurontin or depakote or (valproic next acid) or carbamazepine or tegretol or lamotrigine or lamictal or oxcarbazepine or trileptal) 1880
#2. (zonisamide or zonegran) 37
#3. (#1 or #2) 1899
#4. (#3 or anticonvulsive* or anti-convulsive* or antiepileptic* or anti-apileptic* or anticonvulsant* or anti-convulsant*) 2807
#5. (#4 and (bipolar or mood or antimanic or manic or depressive or depression or pain or neuralgi* or migraine*)) 748

Second drug list

#1. (levetiracetam or keppra or phenytoin or dilantin or tiagabine or gabitril or topiramate or topamax) 1117
#2. (depression or depressive or mood or bipolar or manic or antimanic or anti-manic or mania or antimania or anti-mania) 21439
#3. (pain or neuralgi* or headache) 35985
#4. (#1 and (#2 or #3)) 207

PubMed

First and second drug lists

#1 Search gabapentin OR neurontin OR depakote OR "valproic acid" OR carbamazepine OR tegretol OR lamotrigine OR lamictal OR oxcarbazepine OR trileptal OR zonisamide OR zonegran OR anticonvulsive* OR anti-convulsive* OR antiepileptic* OR anti-epileptic* Limits: English 18449
#2 Search #1 OR anticonvulsants Limits: English 89165
#3 Search levetiracetam OR keppra OR phenytoin OR dilantin OR tiagabine OR gabitril OR topiramate OR topamax Limits: English 12654
#4 Search #2 OR #3 Limits: English 90068
#5 Search depressive disorders OR bipolar disorder OR mood disorders OR mood OR antimanic OR manic OR depressive OR depression OR pain OR neuralgi* OR migraine* Limits: English 380912
#6 Search #4 AND #5 Field: All Fields, Limits: English, Human 6863
#7 Search #6 AND (randomi* OR randomized clinical trials OR randomized controlled trial[pt] OR meta analys* OR meta analysis OR meta analysis[pt] OR systematic review) Field: All Fields, Limits: English, Human 1472

Adverse events

#1 Search epidemiol* OR pharmacoepidemiolog* Limits: English, Human 479331
#2 Search observational OR prescription database evaluation* OR patient database evaluation* OR prescription event monitor* Limits: English, Human 13177
#3 Search spontaneous adverse drug reaction report OR Phase iv OR postmarketing surveillance OR cohort studies OR long-term OR odds ratio OR relative risk OR case-control Limits: English, Human 785214
#4 Search antiepileptic drug*/adverse effects Limits: English, Human 1423
#5 Search #1 AND (#2 OR #3) AND #4 Limits: English, Human 87
#6 Search anticonvulsants/adverse effects Limits: English, Human 4379
#7 Search #1 AND (#2 OR #3) AND #6 Limits: English, Human 179
#8 Search #7 NOT #6 Limits: English, Human 106 TOTAL NUMBER OF HITS: 193

Embase

First drug list

1 47396 gabapentin or neurontin or depakote or carbamazepine or tegretol or lamotrigine
2 48119 s1 or lamictal or oxcarbazepine or trileptal or zonisamide or zonegran
3 197580 anticonvulsive agent!
4 43131 anticonvulsive? or anti(2w)convulsive? or antiepileptic? or anti(2w)epileptic?
5 200384 1-4/+
6 265510 depression! or depression/ti,ab or depressive or mood disorder! or mood?(2n)disorder? or bipolar disorder! or bipolar/ti,ab
7 265610 s6 or manic depressive psychosis or antimanic or anti(2w)manic or antimania or anti(2w)mania
8 376100 pain! or neuralgia! or migraine or headache(2w)facial()pain
9 265610 6+7
10 3906 4*9
11 4995 4*8
12 327396 randomi?/ti,ab or randomized controlled trial? or systematic()review? or metaanaly? or meta(2w)analy?
13 373 10*12
14 531 11*12
15 775 13+14
16 392 rd (unique items)

Second drug list

s1 35686 levetiracetam or keppra or phenytoin or dilantin or tiagabine or gabitril or topiramate or topamax
s2 172309 depression! or depression/ti,ab or depressive or mood disorder! or mood?(2n)disorder? or bipolar disorder! or bipolar/ti,ab
s3 172388 s2 or manic depressive psychosis or antimanic or anti(2w)manic or antimania or anti(2w)mania
s4 227193 pain! or neuralgia! or migraine or headache(2w)facial()pain
s5 4086 1*(3+4)
s6 321 s5 and (randomi?/ti,ab or randomized controlled trial? or systematic()review? or metaanaly? or meta(2w)analy?)
s7 307 s6/eng
s8 307 s7/human
s9 15950 anticonvulsant? or anti(2w)convulsant?
s10 1853 9*(3+4)
s11 154 s10 and (randomi?/ti,ab or randomized controlled trial? or systematic()review? or metaanaly? or meta(2w)analy?)
s12 143 s11/eng
s13 70 12-7

Adverse events

s1 146691 anticonvulsive agent! or anticonvulsive therapy or anticonvuls?/ti,ab or anti(2w)convuls?/ti,ab or antiepileptic?/ti,ab or anti(2w)epileptic?/ti,ab
s2 56365 s1 and (adverse drug reaction! or side(2w)effect? or toxic? or drug response or adverse(2w)effect? or adverse(2w)event?)
s3 2518 anticonvulsant therapy/ae
s4 1169 s3 and (adverse drug reaction! or side(2w)effect? or toxic? or drug response or adverse(2w)effect? or adverse(2w)event?)
s5 56386 2+4
s6 4068 s5 and (epidemiol? or pharmacoepidemiolog?)
s7 43 s6 and (observational or prescription()database()evaluation? or patient()database()evaluation? or prescription()event() monitor? or spontaneous()adverse()drug()reaction()report?)

s8 467 s6 and (phase()iv or phase()4 or phase()four or postmarketing()surveillance or cohort? or long(2w)term or odds()ratio or relative()risk or case(2w)control)
s9 498 7+8
s10 452 s9/eng
s11 449 s10/human

Appendix C. Included Studies

1. Backonja, M.; Beydoun, A.; Edwards, K. R.; Schwartz, S. L.; Fonseca, V.; Hes, M.; LaMoreaux, L., and Garofalo, E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998; 280(21):1831-6.

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Appendix D. Excluded Studies

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Systematic Review Table 1. Bipolar Disorder

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Macritchie, 2004	To review the effectiveness of valproate, relative to placebo, other mood stabilizers, and antipsychotics, in the prevention and/or attenuation of acute episodes of bipolar disorder. To review patients' acceptability of long-term valproate treatment. To investigate the adverse effects of valproate treatment including general prevalence of adverse events. To determine overall mortality rates on valproate maintenance treatment.	Not reported	RCTs that compared valproate with placebo, alternative mood stabilizers (including lithium and carbamazepine), or neuroleptics, where the stated intent was the maintenance treatment of bipolar disorder. Males and female of all ages with a diagnosis of bipolar disorder however diagnosed, approximating ICD 10 Code F31 and DSM IV 296, but including ICD-9 manic-depressive psychosis and DSM-III and DSM-IIIR bipolar disorder.	372	1 double-blind, placebo-controlled, parallel-group RCT with an open phase and stabilization phase

Systematic Review Table 1. Bipolar Disorder

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Macritchie, 2004	1 study of patients with bipolar affective disorder (DSM-III-R) with at least one manic episode in the past 3 years	1 study of valproate (dose adjusted to reach serum concentration of 72 to 125 mcg/ml), lithium (dose adjusted to serum concentration of 0.8 to 1.2 mEq/l), or placebo for 52 wk	No treatment differences in time to occurrence of mood episode (primary efficacy measure of original study report). No significant treatment difference between divalproex and lithium in terms of the proportion of patients who left the study because of the occurrence of any mood episode (RRR 22%; RR 0.78; 95% CI: 0.52 to 1.17), a manic episode (RRR 15%; RR 0.85; 95% CI: 0.51 to 1.40), or a depressive episode (RRR 35%; RR 0.65; 95 % CI: 0.28 to 1.48). Kaplan-Meier survival analysis in the original study report showed a longer time to any mood episode in patients taking divalproex but the difference was not statistically significant (p = 0.06). Divalproex was superior to placebo in preventing recurrence of a mood episode (RRR 37%; RR 0.63; 95% CI: 0.44 to 0.90). Divalproex was better than placebo in preventing depressive episodes (RRR 60%; RR 0.40; 95% CI: 0.20 to 0.82) but was similar to placebo in preventing manic episodes (RRR 21%; RR 0.79; 95% CI: 0.20 to 0.82). These results are not robust since a Kaplan-Meier survival plot in the original study report showed no significant treatment difference in terms of the time to any mood episode (p = 0.33) and a sensitivity analysis also showed no significant treatment difference when all dropouts from the divalproex group and none of the placebo dropouts were counted as relapsers (RR 1.20; 95% CI: 0.89 to 1.62). No differences were found in the mean changes from baseline in the GAS scores between divalproex (–4.7) and lithium (–7.8) or between divalproex (–4.7) and placebo (–5.7).

Systematic Review Table 1. Bipolar Disorder

Author, year	Subgroups	Adverse events
Macritchie, 2004	Insufficient information in original study report to perform subgroup analyses	*Divalproex vs. lithium* Occurred more frequently on divalproex: sedation (RRI 58%; RR 1.58; 95% CI: 1.08 to 2.32) and infection (RRI 107%; RR 2.07; 95% CI: 1.16 to 3.68). Occurred less frequently on divalproex: thirst (RRR 62%; RR 0.38; 95% CI: 0.18 to 0.81) and polyuria (RRR 57%; RR 0.43; 95% CI: 0.22 to 0.82). *Divalproex vs. placebo* Tremor (RRI 223%; RR 3.23; 95% CI: 1.85 to 5.62), weight gain (RRI 187%; RR 2.87; 95% CI: 1.34 to 6.17), and alopecia (RRI 143%; RR 2.43; 95% CI: 1.05 to 5.65) were reported more frequently on divalproex than placebo. Divalproex-treated patients experienced larger decreases in platelet count (53 x 10^9/l ± 52.1 vs. 3.4 x 10^9/l ± 44.5; p = 0.001) and white cell count (1.1 x 10^9/l ± 2.0 vs. 0.3 x 10^9/l ± 2.2; p = 0.009) relative to placebo.

Systematic Review Table 1. Bipolar Disorder

Author, year	Comments
Macritchie, 2004	Summary of reviewers' conclusions: Findings are equivocal. Conclusions about the efficacy and acceptability of valproate relative to placebo and lithium cannot be made with confidence. With current evidence, patients and clinicians would probably wish to use lithium before valproate for maintenance treatment. Global functioning was assessed by the Global Assessment Scale (GAS) score, which is based on any behavioral disturbance, levels of distress, social functioning, self care, and impulsitivity and reality testing. One limitation is that individual scores were not reported for clinically relevant items such as employment, relationship stability, and effects of treatment on suicidality. The original study (Bowden, 2000) is also discussed under active controlled trials in this report.

Systematic Review Table 1. Bipolar Disorder

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Tondo, 2003	To estimate an overall effect of rapid cycling (RC) status on treatment response, and to examine the hypothesis that some treatments are more effective than others for RC patients.	Through September 2002	Studies that included patients with at least 4 recurrences of mania or depression within 1 y; treatment for at least 4 mo; at least 10 subjects/study; and outcomes that could be assessed as rates, based on proportions of subjets with recurrences or without substantial clinical improvement during treatment (typically < 50% reduction in morbidity) per average exposure time	1856	16 trials total, 25 treatment groups, average sample size 48.2 per condition, average quality rating 52.3. Meta-analysis of carbamazepine vs. lithium: 3 open-label studies and 1 blinded RCT (N = 207, total) Meta-analysis of carbamazepine vs. lithium in RC and non-RC patients: 1 open-label, 1 blinded RCT (N = 149)

Systematic Review Table 1. Bipolar Disorder

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Tondo, 2003	905 RC, 951 Non-RC	AEDs (611 patients for 1.27 y; 11 trials) Lithium (1142 patients x 5.9 y; 10 trials) Number of monotherapy / combotherapy trials: --Carbamazepine: 3 / 2 --Valproate: 1 / 2 --Lamotrigine: 2 / 1 --Topiramate: 0 / 1 Weighted average follow-up of 47.5 mo (7347 patient-years),	Crude rates (% / mo) of recurrence (2.31 vs. 1.20) and clinical non-improvement (1.93 vs. 0.49) were 2.9 times higher in RC vs. non-RC patients. Pooled RC / non-RC risk ratio (RR) for inferior treatment response: 1.40 (95% CI: 1.26 to .56; p < 0.0001). No clear advantage of any treatment nor AEDs over lithium. Meta-analysis of 4 RCTs comparing carbamazepine (+/- other agents except lithium) and lithium (+/- other agents except carbamazepine) in RC patients, RR (95% CI) --Recurrence rates: 0.93 (0.74 to 1.18); p = 0.54 --Non-improvement rates: 0.94 (0.81 to 1.08); p = 0.37 Meta-analysis of 2 RCTs comparing carbamazepine and lithium in both RC and non-RC patients, RR (95% CI) --Non-improvement rates: 1.10 (0.98 to 1.23); p = 0.10

Systematic Review Table 1. Bipolar Disorder

Author, year		Subgroups	Adverse events
Tondo, 2003	RC vs. Non-RC Patients Pooled recurrence rates, %/mo --Lithium 2.09 vs.1.33 --Carbamazepine 2.87 vs. 2.48 --Valproate 3.63 vs. Not applicable --Lamotrigine 8.57 vs. Not applicable --Topiramate Not applicable vs. Not applicable --All active agents 2.82 vs. 1.38 --Placebo 12.5 vs. Not applicable Pooled non-improvement rates, %/mo --Lithium 1.05 / 0.44 --Carbamazepine 3.23 vs. 1.75 --Valproate 0.503 vs. 0.901 --Lamotrigine 4.74 vs. 2.94 --Topiramate 11.9 vs. Not applicable --All active agents 1.57 vs. 0.48	---	Not reported

Systematic Review Table 1. Bipolar Disorder

Author, year	Comments
Tondo, 2003	Meta-analytic comparisons between carbamazepine and lithium may be confounded by the concomitant use of other agents and inclusion of studies with different designs. The pooled recurrence and non-improvement rates for different medications should be interpreted with caution; their stability is unknown and the rates may be based on a a few small studies of short duration.

Systematic Review Table 1. Bipolar Disorder

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Poolsup, 2000(81)	To resolve the apparent inconsistencies and to better define the position of lithium in relation to other pharmacotherapies	1966 to end of June 1999	RCTs dealing with lithium for acute mania; single- or double-blind design; provided efficacy data in terms of symptom improvement using Brief Psychiatric Rating Scale (BPRS) or improvement in global severity using Clinical Global Impression (CGI) or in terms of response rate	658	12 trials total: 11 double-blind placebo-controlled, 1 single-blind placebo-controlled 9 two-armed and 3 three-armed trials

Systematic Review Table 1. Bipolar Disorder

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Poolsup, 2000(81)	All trial patients had acute mania; otherwise not reported	Lithium vs. carbamazepine (3 RCTs) Lithium vs. valproate (1 RCT) Lithium vs. placebo vs. valproate (1 RCT) Remaining RCTs compared lithium with chlorpromazine, verapamil, haloperidol, lithium-haloperidol combination, risperidone, or placebo Treatment duration: 3 to 4 wk	Difference (95% CI) in outcome measures Lithium vs. Carbamazepine --Reduction in BPRS score: -2.04 (-9.59 to 5.51) --Reduction in CGI score: 0.44 (-0.78 to 1.67) --Response rate: 0.003 (-0.17 to 0.17); NNT not applicable Lithium vs. Valproate --Reduction in BPRS score: 2.0 (-4.53 to 8.53) --Response rate: 0.11 (-0.06 to 0.27); NNT not applicable

Systematic Review Table 1. Bipolar Disorder

Author, year	Subgroups	Adverse events
Poolsup, 2000(81)	---	Rate Difference (95% CI) for risk of adverse events Lithium vs. Carbamazepine: -0.14 (-0.30 to 0.01) Lithium vs. Valproate: 0.08 (-0.05 to 0.20)

Systematic Review Table 1. Bipolar Disorder

Author, year	Comments
Poolsup, 2000(81)	Three of the five AED RCTs were included in this report (Lerer, 1987, Small, 1991, Okuma, 1990) and two were excluded because DSM criteria were not used for diagnosis and the patients were hospitalized (Bowden, 1994, Freeman, 1992).

Systematic Review Table 2. Neuropathic Pain

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Wiffen, 2004(96)	To evaluate the analgesic effectiveness of AEDs in order to provide evidence-based recommendations for clinical practice	1966 to July 1999	RCTs that investigated the analgesic effects of AEDs in patients, with pain assessment as either the primary or a secondary outcome	1074 patients in 23 RCTs of 6 AEDs	6 active-controlled (4 parallel-group, 2 crossover) 16 placebo-controlled (5 parallel-group, 11 crossover) 1 both active- and placebo-controlled, crossover

Systematic Review Table 2. Neuropathic Pain

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Wiffen, 2004(96)	Adults 18 to 84 y of age with wide range of neuropathic pain types, including trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, central post-stroke pain, irritable bowel, and temporomandibular joint dysfunction	Oral agents except in one study, which used intravenous sodium valproate. Drugs evaluated: carbamazepine, clonazepam, gabapentin, phenytoin, and sodium valproate	One placebo-controlled trial in acute pain found no analgesic effect of sodium valproate. Three placebo-controlled trials of carbamazepine in trigeminal neuralgia had a combined NNT (95% CI) for effectiveness of 2.5 (2.0 to 3.4). One placebo-controlled trial of gabapentin in postherpetic neuralgia had an NNT of 3.2 (2.4 to 5.0). One RCT for each of the following drugs in diabetic neuropathy had NNTs of 2.3 (1.6 to 3.8) for carbamazepine, 3.8 (2.4 to 8.7) for gabapentin, and 2.1 (1.5 to 3.6) for phenytoin. There was no apparent advantage of gabapentin over other AEDs. About 66% (95% CI: 61% to 71%) of patients who take either carbamazepine or gabapentin can be expected to achieve good pain relief.	None evaluated

Systematic Review Table 2. Neuropathic Pain

Author, year	Adverse events	Comments
Wiffen, 2004(96)	NNHs (95% CI) for minor harm (adverse events), calculated by combining studies for each drug for any pain type, were 3.7 (2.4 to 7.8) for carbamazepine, 2.5 (2.0 to 3.2) for gabapentin, and 3.2 (2.1 to 6.3) for phenytoin. NNHs for major harm (withdrawals due to adverse events), were not statistically significant for any drug versus placebo.	This was a substantial update of the previous version of this meta-analysis. Date that 6 new studies were found but not yet included or excluded: 1 September 2003.

Systematic Review Table 2. Neuropathic Pain

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Mellegers, 2001(95)	To (1) assess the efficacy and effectiveness of gabapentin for neuropathic pain in different neuropathic conditions; (2) determine differential sensitivity of specific neuropathic pains to the drug; (3) document physicians' prescribing patterns in terms of highest dose achieved or rate of dose escalation; and (4) compare the incidence of side effects as a secondary outcome from both controlled and uncontrolled studies.	1966 to March 2001	Clinical trials in humans; controlled trials (randomized, RCTs, or nonrandomized, CCTs) and uncontrolled trials (case series or case reports); patients with any type of neuropathic pain; gabapentin administered for pain relief, alone or in conjunction with other drugs; outcome of pain relief	727 gabapentin-treated patients from 31 studies overall 267 gabapentin-treated patients from 4 placebo-controlled trials	2 active-controlled (1 open-label parallel-group; 1 double-blind crossover) 4 placebo-controlled (2 double-blind randomized; 2 with uncertain randomization, 1 crossover and 1 parallel-group) 30 uncontrolled studies

Systematic Review Table 2. Neuropathic Pain

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Mellegers, 2001(95)	Age not reported; various neuropathic pain syndromes: central pain, complex regional pain syndrome; mixed nociceptive and neuropathic pain; diabetic neuropathy; diabetic/other neuropathies; postherpetic neuralgia; trigeminal neuralgia; mixed neuropathic pain types	Drug comparisons: gabapentin vs. amitriptyline and gabapentin vs. placebo	Results here shown for controlled trials only, gabapentin vs. placebo Number of patients reporting moderate or excellent pain relief (4 RCTs), relative benefit (95% CI fixed): 2.5 (1.9 to 3.4) Visual Analogue Scale scores (2 RCTs), mean difference (95% CI fixed): -11.1 mm (-13.2 to -11.1) Short Form McGill Pain Questionnaire (2 RCTs), weighted final mean difference (95% CI): -5.89 (-6.20 to -5.59) Patients' Global Impression of Change (2 RCTs), relative benefit (95% CI): 2.44 (1.8 to 3.31) Clinicians' Global Impression of Change (2 RCTs): 2.65 Short Form-36 Quality of Life questionnaire (2 RCTs)	Differential symptom sensitivity analysis: all types of pain seemed to respond to gabapentin; however, there was considerable overlap because a patient frequently had more than one type of pain (allodynia, burning, lancinating/shooting pain).

Systematic Review Table 2. Neuropathic Pain

Author, year	Adverse events	Comments
Mellegers, 2001(95)	Total number of patients in RCTs who experienced >/=1 adverse event: unable to calculate because of missing data from 1 RCT Gabapentin (N = 256) vs. Placebo (N = 197) Withdrawals due to adverse events in RCTs: 27 (10.5%) vs. 12 (6.1%) Most common adverse events in RCTs Dizziness: 63 (24.6%) vs. 10 (5.1%) Somnolence: 51 (20.0%) vs. 11 (5.6%) Gastrointestinal complaints: 34 (13.2%) vs. 11 (5.6%) Sedation: 24 (9.3%) vs. 0 (0%) Ataxia: 19 (7.4%) vs. 0 (0%) Peripheral edema: 17 (6.6%) vs. 4 (2.0%) Headache: 13 (5.0%) vs. 3 (1.5%) Postural hypotension: 12 (4.7%) vs. not reported	Sensitivity analysis performed; tests for homogeneity done. Quality of each trial was assessed by 3 reviewers using the Jadad scoring system. Of 4 placebo-controlled trials, 2 were high quality (Backonja, 1998, Rowbotham, 1998) and two were low quality (Gorson, 1999, Tamez-Perez, 1998). Of 2 amitriptyline-controlled trials, 1 was high quality (Morello, 1999) and the other was low quality (Dallochio, 2000). Analyses of uncontrolled trials are not presented here.

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/ interventions
Frye, 2000(20) U.S. (Fair)	DB RCT with two crossovers Single center, National Institute of Mental Health (NIMH) Clinical Research Unit, inpatient setting Extension of this trial by Obrocea, 2002	Not explicitly listed. Refractory bipolar and unipolar affective illness confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (version 2.0), hospitalized in NIMH Clinical Research Unit. Illness did not respond to conventional agents	Lamotrigine (titrated from 25 to 500 mg/d over 5 to 6 wk, faster than current product labeling at the time of the study) vs. Gabapentin (titrated from 900 to 4800 mg/d) vs. Placebo for 6 wk	1-wk washout before crossover: taper old drug, titrate new drug	Levothyroxine; diuretic; triiodothyronine, clonazepam

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Frye, 2000(20) U.S. (Fair)	Clinical Global Impression scale modified for bipolar illness (CGI-BP), timing not reported. CGI-BP best estimate rating determined after completion of each 6-wk treatment phase	Age, mean (SD), y: 39.2 (9.4) Male / Female: 42% / 58% Ethnicity not reported	Bipolar I 36% Bipolar II 45% Unipolar 19% Rapid cycling 92% Nonrapid cycling 8% Prior treatment (N Refractory/N Exposed, %): Lithium 28/28 (100%) Valproic acid 21/26 (81%) Carbamazepine 14/20 (70%)	Number screened not reported / 38 eligible / 38 enrolled / 38 randomized	4 withdrawn / 0 lost to follow-up / 31 analyzed (3 not evaluable in all three phases and excluded from Cochran's *Q* analysis)

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Frye, 2000(20) U.S. (Fair)	Lamotrigine vs. Gabapentin vs. Placebo Responders (score of much or very much improved on Clinical Global Impressions Scale for Bipolar Illness) after 6 wk on each treatment: Mania, 44% vs. 20% vs. 32% (NSD) Depression, 45% vs. 26% vs. 19% (NSD) Overall, 52% vs. 26% vs. 23% (p = 0.031; post hoc Q differences: p = 0.011 for lamotrigine vs. gabapentin; p = 0.022 for lamotrigine vs. placebo; p = 0.700 for gabapentin vs. placebo)	Lamotrigine vs. Gabapentin Mean change in Hamilton Rating Scale score for Depression (HAM-D) from baseline to 6 wk: -6.1 vs. 1.6 (placebo result not reported) Calculated difference between mean changes: -7.7 Changes from baseline to 6 wk in Speilberger State Anxiety Scale, Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS): NSD (data not reported).	

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Frye, 2000(20) U.S. (Fair)	Not reported	Lamotrigine: Rash developed post-study in wk 15 during continuation treatment, progressed to toxic epidermal necrolysis; patient required hospitalization in an intensive care burn unit and fully recovered. Lamotrigine vs. Gabapentin vs. Placebo (N = 31) Weight change, mean (SD): -0.96 (3.11) vs. 1.83 (5.04) vs. -0.40 (2.97) kg (p = 0.024; for lamotrigine vs. gabapentin, p = 0.021; p > 0.05 for lamotrigine vs. placebo and for gabapentin vs. placebo) Common adverse effects: --Ataxia 3% vs. 10% vs. 0% --Diarrhea 6% vs. 6% vs. 13% --Diplopia 0% vs. 10% vs. 3% --Fatigue 0% vs. 10% vs. 3% --Headache 3% vs. 13% vs. 13% --Rash 3% vs. 0% vs. 0%	Lamotrigine vs. gabapentin Total Withdrawals : 3/38 (7.9%) vs. 1/38 (2.6%); 1 additional patient (treatment group not reported) withdrew due to nonresponse. Withdrawals due to adverse event: 3/38 (7.9%) vs. 1/38 (2.6%) (no statistical analysis) The gabapentin patient was the same as one of the lamotrigine patients; patient withdrew after developing edema on both drugs. Types of withdrawals due to adverse event: rash, edema on lamotrigine; edema on gabapentin.	Heterogeneous study population. Lamotrigine dose titrated at faster than currently recommended rates.

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/ interventions
Obrocea, 2002(19) (--) U.S. (Fair) Same trial as Frye 2000	DB RCT with two crossovers; extension of Frye, 2000; analyzed subgroup response predictors Single center, National Institute of Mental Health (NIMH) Clinical Research Unit, inpatient setting	Not explicitly listed. Refractory bipolar and unipolar affective illness confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (version 2.0), hospitalized in NIMH Clinical Research Unit. Illness did not respond to conventional agents	Lamotrigine (titrated from 25 to 500 mg/d over 5 to 6 wk, faster than current product labeling at the time of the study) vs. Gabapentin (titrated from 900 to 4800 mg/d) vs. Placebo for 6 wk	1-wk washout before crossover: taper old drug, titrate new drug	Levothyroxine; diuretic; triiodothyronine, clonazepam

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Obrocea, 2002(19) (--) U.S. (Fair) Same trial as Frye 2000	Clinical Global Impression scale modified for bipolar illness (CGI-BP), timing not reported. CGI-BP included Hamilton Depression Rating Scale (HAM-D); clinician and self prospective Life Chart Method (LCM), Young Mania Rating Scale (YMRS); Spielberger State Anxiety Scale; and Bunney-Hamburg ratings of depression and mania	N = 45 Age, mean (SD), y: 39.2 +/- 10.5 Male / Female: 40% / 60% Ethnicity not reported	Bipolar I 33% Bipolar II 44% Unipolar 22% Rapid cycling 74% Prior treatment (N Refractory or Intolerant / N Exposed, calculated %): --Lithium 34/40 (85.0%) --Valproate 23/35 (65.7%) --Carbamazepine 15/25 (60.0%) Hospitalizations, mean (SD) --Mania, bipolar: 0.9 (1.8) --Mania, unipolar: 0.0 (0.0) --Depression, bipolar: 3.6 (3.5) --Depression, unipolar: 2.6 (2.8)	Numbers screened and eligible not reported / 45 enrolled / 45 (?) randomized	Numbers withdrawn and lost to follow-up not reported / 38 to 40 analyzed depending on treatment group

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Obrocea, 2002(19) (--) U.S. (Fair) Same trial as Frye 2000	Lamotrigine vs. Gabapentin vs. Placebo Responder rate for CGI-BP much or very much improved All exposed to given drug: 20/39 (51%) vs. 11/40 (28%) vs. 8/38 (21%) (no statistical analysis) Exposed to all 3 phases of protocol (N = 36): 53% vs. 28% vs. 22% (p = 0.01; NSD for gabapentin vs. placebo) CGI ratings for depression showed a similar pattern (p = 0.03)	Predictors of response to lamotrigine (using CGI-BP overall degrees of improvement or deterioration): --Diagnosis of bipolar illness (r = -0.32; p = 0.49) --Male gender (r = 0.37; p = 0.022) --Exposure to fewer prior medication trials (r = -0.40; p = 0.015) --History of fewer prior hospitalizations for depression (r = -0.32; p = 0.050) Factors influencing amount of variance explained by the predictors (stepwise linear regression): --Number of prior medication trials (Beta coefficient = -0.369; p = 0.018) --Gender (Beta coefficient = 0.357; p = 0.021) Similar beta coefficients suggested that these variables had equal importance in predicting lamotrigine response. Adjusted R^2 showed that these variables explained 24% of the variance of CGI response.	Possible predictors of response to gabapentin --Duration of illness inversely correlated with response (r = -0.35; p = 0.028) --Weight at baseline inversely correlated with response (r = -0.44; p = 0.006) Stepwise linear regression analysis: --Age (Beta coefficient -0.492; p = 0.001) --Weight (Beta coefficient = -0.493; p = 0.001) Similar beta coefficients suggested that these variables were equally important in predicting response to gabapentin. Adjusted R^2 showed that these variables explained 37% of the variance of CGI response.

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Obrocea, 2002(19) (--) U.S. (Fair) Same trial as Frye 2000	Not reported	Not reported	Not reported	A post hoc test was used for specific paired comparisons.

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/ interventions
Vasudev, 2000(29) (--) India (Poor / Fair)	SB RCT Single-center, psychiatric inpatient setting	Bipolar disorder (DSM-III-R), Young Mania Rating Scale (YMRS) >/= 20	Carbamazepine titrated, 800 to 1600 mg/d Sodium valproate titrated, 800 to 2200 mg/d for 4 wk	None	Diazepam, promethazine

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Vasudev, 2000(29) (--) India (Poor / Fair)	YMRS weekly from day 0 to 28 for valproate and at days 0 and 10 then weekly to day 31 for carbamazepine (different schedules were used because a therapeutic dose of carbamazepine was reached at day 3)	Not reported	Not reported	Numbers screened and eligible not reported / 30 enrolled / 30 randomized	6 (20.0%) withdrew / 1 (3.3%) lost to follow-up / 30 analyzed

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Vasudev, 2000(29) (--) India (Poor / Fair)	Carbamazepine vs. Valproate YMRS total scores, mean change from baseline to day 28 (Primary Efficacy Measure; last observation carried forward): 20.8 vs. 32.8 (calculated difference: -12; p = 0.023)	Weekly analysis of change in YMRS scores Decrease in scores on YMRS --Week 1: Data not reported (NSD) --Week 2 and on: Valproate superior to carbamazepine (data not reported; p = 0.04) Response analysis > 50% decrease in YMRS total score from baseline to end point: 8/15 (53.3%) vs. 11/15 (73.3%) (NSD) YMRS individual items Valproate showed a numerically greater mean improvement vs. carbamazepine except for sleep.	Required rescue medication Week 1: NSD (data not reported) Week 2: 12/15 (80.0%) vs. 4/15 (26.7%) (p = 0.003) Average dose of rescue medication required, mg/d (estimated from Fig. 1 of article) Week 1 --Diazepam: 16 vs. 10 --Promethazine: 72 vs. 55 Week 2 --Diazepam: 8 vs. 1 --Promethazine: 40 vs. 10

Evidence Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Vasudev, 2000(29) (--) India (Poor / Fair)	Not reported	Carbamazepine vs. Valproate Experienced adverse events: 67% vs. 17% Adverse events more common on carbamazepine --Nausea/vomiting: 58.3% vs. 16.7% (p = 0.035) --Dizziness: 58.3% vs. 8.3% (p = 009) --Lethargy: 41.6% vs. 8.3% (no statistical analysis) --Ataxia / Tremors: 25% vs. 8.3% (no statistical analysis) --Rash: 8.3% vs. 0.0% (no statistical analysis) --Increased liver enzymes: 8.3% vs. 8.3% --Hematologic abnormalities: 0% vs. 0%	Total withdrawals: 3 vs. 3 Withdrawals due to adverse events: 1 vs. 0 (withdrawal on carbamazepine due to severe vomiting was temporary)	Unclear if care provider was the unblinded dosing psychiatrist. Medications were apparently not identical. Titration phases to therapeutic dose were of different durations (3 vs. 0 d on carbamazepine vs. valproate, respectively) and may have favored faster onset of effect with valproate, since a therapeutic (loading) dose of 20 mg/kg could be given on the first day. Drug exposure time and end point differed between treatment groups: 31 vs. 28 d.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Multicenter, open-label, long-term RCT Initially inpatient at psychiatric university hospitals then outpatient setting	Current episode of bipolar affective or schizoaffective disorder (ICD-9, World Health Organization, 1978; DSM was not a diagnostic criterion but patients were assessed with DSM); at least one former episode during the 3 y (schizoaffective patients) or 4 y (bipolar patients) preceding the index episode; no preventive treatment immediately before onset of present episode; age 18 to 65 y; no current alcohol or drug abuse. Patients in stable condition (Global Assessment Score (GAS) > 70 for at least 2 wk after discharge) entered the maintenance phase. Data presented for patients with bipolar disorder only.	Carbamazepine - mean dose 635 +/- 190 mg/d (between month 2 and study termination; dosing schedule not reported) vs. Lithium - mean dose 26.8 +/- 6.76 mmol/l (between month 2 and study termination; dosing schedule not reported) for 2.5 y

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	None	Antidepressants, neuroleptics, benzodiazepines	6-point psychopathology scale (1 = no disturbance, 6 = extremely severe recurrence) and 4-point Morbidity Index (0 = no symptoms, 3 = hospitalization) at beginning of maintenance phase, 3 times within first 3 months, every 8 to 12 weeks, then at 1, 2, and 2.5 years and between outpatient appointments as needed. Main outcomes of interest were criteria for failure: (a) Hospitalization; (b) Recurrence (psychopathology scale rating of 5 ("recurrence") or 6 ("extremely severe recurrence") of an affective episode (RDC criteria); (c) Recurrence and/or concomitant psychotropic medication (needed for at least 6 mo); (d) Recurrence and/or concomitant psychotropic medication and/or severe adverse events (prompting discontinuation)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Carbamazepine vs. Lithium Age, mean (SD), y: 42 (14) vs. 45 (14) Male / Female: 46% / 54% vs. 50% / 50% Ethnicity not reported	Carbamazepine (N = 70) vs. Lithium (N = 74) 91% of the ICD-9 diagnosed patients fulfilled the DSM-III-R criteria of a bipolar disorder (58% were pure "Bipolar," corresponding to Bipolar I (DSM-IV); 33% were "Bipolar NOS") Age at onset, mean (SD), y: 32.8 (12.8) vs. 35.4 (13.1) Suicide attempts (% of patients) None: 66% vs. 57% 1: 23% vs. 30% 2 or more: 11% vs. 13% Episodes of illness (%) 2: 22% vs. 8% 3-5: 34% vs. 51% 6 or more: 44% vs. 41% Hospitalization (%) 1-2: 34% vs. 29% 3-6: 57% vs. 62% 7 or more: 8% vs. 10%	Number screened not reported / 375 eligible / 175 enrolled / 144 randomized	41 withdrew / None lost to follow-up / 144 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Carbamazepine (N = 70) vs. Lithium (N = 74) (ITT Analysis) *Events (number of failures)* Hospitalization: 14 vs. 13 Recurrence: 20 vs. 17 Recurrence and/or concomitant medication : 27 vs. 22 (p = 0.041) Recurrence and/or concomitant medication and/or severe adverse events: 36 vs. 26 (p = 0.007)	Kaplan-Meier estimates of survivor functions (ITT Analysis) were similar for hospitalization and recurrence, and showed a higher cumulative proportion of patients remaining well on lithium than carbamazepine for recurrence/concomitant medication and recurrence/concomitant medication/severe adverse events. Similar results were found when DSM-III-R diagnoses of "Bipolar Disorders" (including "Bipolar Disorder NOS") were used.	Frequencies of treatment failures / per-protocol completers Hospitalization: 14/40 (35%) vs. 13/60 (22%) (p = 0.17) Recurrence: 20/43 (47%) vs. 17/60 (28%) (p = 0.06) Recurrence/concomitant medication: 27/46 (59%) vs. 22/60 (37%) (p = 0.03) Recurrence/concomitant medication/severe adverse events: 36/55 (65%) vs. 26/64 (41%) (p = 0.01)	Amount of concomitant medication (antidepressants, neuroleptics, benzodiazepines), arithmetic means of Defined Daily Doses (agreed upon standard doses, often close to the manufacturer-recommended average daily doses) At 1 y: 1.60 vs. 1.27 At 2 y: 1.24 vs. 0.90 At 2.5 y: 1.38 vs. 1.67 (NSD for each analysis) About 70% of patients did not receive additional medication.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Monitored	Carbamazepine vs. Lithium Adverse events leading to withdrawal, n Carbamazepine: exanthema [allergic skin rashes] (6), enlarged lymph nodes with exanthema (1), diarrhea (1), hepatopathy (1) Lithium: acne and weight gain (1), psoriasis (1), nausea (1), disturbance of potency (1) Pattern of withdrawals due to adverse events: 7/9 withdrawals in carbamazepine group occurred in the first 4 mo vs. 4/4 withdrawals in lithium group occurred after 3, 4, 5, and 25 mo. Adverse events more frequent on lithium Slight tremor (12% vs. 37%; p < 0.002) Polydipsia (6% vs. 32%; p < 0.001) Polyuria (10% vs. 29%; p = 0.009) Diarrhea (10% vs. 28%; p = 0.015) Adverse event more frequent on carbamazepine Pruritus (20% vs. 7%; p = 0.046) Suicides: 1 committed and 1 attempted suicide (both on carbamazepine)	Carbamazepine vs. Lithium Total withdrawals: 27/70 (38.6%) vs. 14/74 (18.9%) Withdrawals due to adverse events: 9/70 (12.9%) vs. 4/74 (5.4%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Greil, 1997 (--) Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Open-label design.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	Same as Greil, 1997; supplemental evaluation using DSM-IV terminology and post hoc "classical" and "nonclassical" subgroups Outpatient setting	Same as Greil, 1997; bipolar I, II or NOS (DSM-IV) required prophylactic treatment	Same as Greil, 1997

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	None	Same as Greil, 1997	Kaplan-Meier surivivor estimated. Fisher exact test, Tarone-Wave statistics test. Mantel-Haenszel statistics. Main outcomes: Hospitalization; recurrence; recurrence and/or concomitant psychotropic medication (antidepressants and/or neuroleptics) for at least 6 mo; recurrence and/or concomitant psychotropic medication and/or side effects prompting discontinuation of treatment; and recurrence and/or subclinical recurrence

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	Not reported	Not reported	Numbers screened, eligible, and enrolled were not reported / 171 randomized	40/171 (23.4%) withdrew / None lost to follow-up / 171 (ITT) or 80 (Per-Protocol) analyzed (see Kleindienst, 2002)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	*Classical bipolar subgroup (ITT analysis)* Carbamazepine (N = 32) vs. Lithium (N = 35) Hospitalizations: Lithium was superior to carbamazepine using Kaplan-Meier survival estimates (p = 0.005); cumulative survival at 30 mo (estimated from figure): 50% vs. 78% Lithium superior to carbamazepine for other failure criteria (data not reported) Recurrence: p = 0.010 Recurrence/concomitant medication: p = 0.002 Recurrence/concomitant medication/severe adverse events: p < 0.001 Recurrence/subclinical recurrence: p < 0.001	*Nonclassical bipolar subgroup* Carbamazepine (N = 53) vs. Lithium (N = 51) Hospitalizations: NSD using Kaplan-Meier survival estimates (p = 0.075); cumulative survival at 30 mo (estimated from figure): 70% vs. 60% NSD was found for the other failure criteria	Carbamazepine and Lithium Risk for treatment failure compared with a classical bipolar patient with one (at least 2) nonclassical diagnostic feature(s) Hospitalization: 0.54 (0.40) (p < 0.05) and 1.42 (2.52) (p < 0.05) Recurrence: 0.75 (0.40) (p < 0.1) and 1.34 (2.20) (p < 0.1) Recurrence/concomitant medication: 0.88 (0.53) and 1.42 (1.89) (p < 0.1) Recurrence/concomitant medication/severe adverse events: 0.91 (0.51) and 1.50 (1.98) (p < 0.05) Recurrence/subclinical recurrence: 0.76 (0.82) and 1.35 (2.43) (p < 0.05)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	Not reported	Not reported	Total withdrawals: 28/85 (32.9%) vs. 12/86 (14.0%) (before suffering recurrence; p = 0.004)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Greil, 1998 (--) Germany, Switzerland MAP Study (Poor)	There were numerous threats to internal validity: classification of patients into classical and nonclassical bipolar subgroups was done post hoc; nonclassical subgroup analysis may have been underpowered; no statistical adjustment for multiple comparisons; open-label design.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	Same as Greil, 1997	Same as Greil, 1997, except that this report describes patients with bipolar II disorder or bipolar disorder NOS according to DSM-IV (these patients were originally classified as bipolar disorder NOS under DSM-III-R)	Same as Greil, 1997

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	None	Same as Greil, 1997	Global psychopathology rating scale (1 = no disturbance, 4 = subclinical recurrence, 5 = recurrence, or 6 = extremely severe recurrence). Main outcomes of interest were criteria for failure: (a) Hospitalization; (b) Recurrence (psychopathology scale rating of 5 or 6 of an affective episode (RDC criteria); (c) Recurrence and/or concomitant psychotropic medication for at least 6 mo; (d) Recurrence and/or concomitant psychotropic medication and/or adverse events prompting discontinuation; and (e) recurrence and/or subclinical recurrence (score of 4, 5, or 6). Surval Analysis (Kaplan-Meier estimates of the survivor functions) 2.5 years period.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	Age, mean, y: 41 Female: 60% Ethnicity not reported	Not reported	Not reported/Not reported/Not reported/57 (This study describes patients with bipolar II disorder or bipolar disorder not otherwise specified (NOS) (DSM-IV), who were previously classified as bipolar disorder NOS under DSM-III-R). Thus, this is a subgroup of the population described in Greil, 1997	18 withdrew / Number lost to follow-up not reported / 57 analyzed in ITT survival analyses; number not reported for per-protocol completer analysis

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	Carbamazepine vs. Lithium *Frequency of failures/completers for failure criteria, relative risk (RR)* Hospitalization: 3/18 (17%) vs. 7/21 (33%), RR = 0.50 (p = 0.29) Recurrence: 5/18 (28%) vs. 8/21 (38%), RR = 0.73 (p = 0.73) Recurrence and/or concomitant medication: 10/19 (53%) vs. 10/21 (48%), RR = 1.11 (p = 1.00) Recurrence and/or concomitant medication and/or severe adverse events: 12/21 (57%) vs. 12/22 (52%), RR = 0.91 (p = 1.00) Recurrence and/or subclinical recurrence: 11/20 (55%) vs. 17/24 (71%), RR = 0.78 (0 = 0.35) Survival time was significantly higher under lithium than under carbamazepine (p=0.03)	NSD in survival times by Kaplan-Meier estimates (ITT, p = 0.17 to 0.94)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	Not reported	Not reported	Carbamazepine vs. Lithium Total withdrawals: 11/29 (38%) vs. 7/28 (25%) Withdrawals due to adverse events: Not reported

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Greil, 1999 "bipolar II/NOS" (--) Germany MAP Study (Poor)	Open-label design. It is not clear whether the subgroup analysis was decided a priori or post hoc. Adjustment for multiple testing was not reported. Because of the naturalistic (open-label) study design, generalizability may be possible.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Same as Greil, 1997	Same as Greil, 1997; also bipolar I disorder (DSM-IV, corresponding to bipolar disorder under DSM-III-R)	Same as Greil, 1997

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	None	Same as Greil, 1997	Psychopathology severity and type rating scale (1 = no disturbance, 4 = subclinical recurrence, 5 = recurrence, 6 = extremely severe recurrence) monthly. Criteria for treatment failure: (a) hospitalization; (b) recurrence (psychopathology rating of 5 or 6); (c) recurrence and/or concomitant psychotropic medication for at least 6 mo; (d) recurrence and/or concomitant psychotropic medication and/or side effects prompting discontinuation of treatment; and (e) recurrence and/or subclinical recurrence (psychopathology rating of 4, 5, or 6)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Age, mean, y: 40 Male / Female: 50% / 50% Ethnicity not reported	171 patients met DSM-IV diagnosis of bipolar disorder; 114 had bipolar I disorder	171/114/114/114	22 withdrew / Number lost to follow-up not reported / 114 analyzed in Kaplan-Meier survival analyses; up to 103 completers analyzed for failure rates

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Carbamazepine vs. Lithium *Failure rates, relative risk (RR)* Hospitalization: 21/38 (55%) vs. 20/54 (37%), RR 1.49 (p = 0.09) Recurrence: 23/39 (59%) vs. 21/53 (40%), RR 1.49 (p = 0.09) Recurrence / concomitant medication: 28/42 (67%) vs. 24/54 (44%), RR 1.52 (p = 0.04) [calculated NNt (95% CI): 5 (2.36) Recurrence / concomitant medication / severe adverse events: 34/48 (71%) vs. 25/55 (46%), RR 1.54 (p = 0.01) [calculated NNt (95% CI): 4 (2.14)] Recurrence / subclinical recurrence: 31/44 (71%) vs. 29/56 (48%), RR 1.48 (p = 0.04) Note: There appears to be an error: 29156 does not equal 48%, but equals 52% this produces a nonsignificant RR of 1.46 (p = 0.06)	Symptomatology leading to rehospitalization Depression / mania / other: 37% / 21% / 42% vs. 38% / 31% / 31% (NSD) Kaplan-Meyer survival for clinical or subclinical recurrence at 30 mo, estimated 0.34 vs. 0.55 (p = 0.03)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Not reported	Not reported	Total withdrawals: 17/56 (30%) vs. 5/58 (8%) Withdrawals due to adverse events: Not reported

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Open-label design. It is not clear whether the subgroup analysis was decided a priori or post hoc. Adjustment for multiple testing was not reported.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	Same as Greil, 1997; supplemental evaluation of inter-episodic morbidity and dropout Outpatient setting	Same as Greil, 1997. Patients with bipolar affective disorder (DSM-IV) were analyzed in this report.	Same as Greil, 1997

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	None	Same as Greil, 1997	Morbidity Index (MI) (for assessing recurrences leading to re-hospitalization and inter-episodic symptoms); retrospective symptomatology scale (manic, depressive, mixed, schizoaffective, or other); 4-point severity scale (0 = no affective symptoms; 3 = affective symptoms that necessitate hospitalization); dropouts; KK-Scale for illness concepts; Munich Personality Test for pre-morbid personality every 8 to 12 wk Good responders = average inter-episodic morbidity below the median, no re-hospitalization, no dropout

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	Carbamazepine (N = 85) vs. Lithium (N = 86) Age, mean (SD), y: 39 (13) vs. 41 (13) Male / Female: 42% / 58% vs. 45% / 55% Ethnicity not reported	Number of previous episodes, mean (SD): 3.27 (2.32) vs. 3.07 (2.22) GAS score, mean (SD): 79 (10) vs. 79 (10) Psychiatric comorbidity: 16% vs. 16% Pre-morbid personality scores were similar between treatment groups except for Extraversion, mean (SD): 13.5 (5.7) vs. 11.2 (6.6); p < 0.05	Numbers screened, eligible, and enrolled were not reported / 171 randomized	40/171 (23.4%) withdrew / None lost to follow-up / 171 (ITT) or 80 (Per-Protocol) analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	Carbamazepine vs. Lithium Dropouts: 29/85 (34.1%) vs. 11/86 (12.8%) (p = 0.001) Dropouts mostly related to treatment,n: 26 vs. 10 Re-hospitalization: 28% vs. 31% (p=0.74)	% of time between affective episodes: 42% vs. 36% Inter-episodic symptomatology requiring treatment; 64% vs. 60% Average inter-episodic morbidity correlated with re-hospitalization: r = 0.22 (p = 0.045) vs. r = 0.34 (p = 0.0013) Average inter-episodic morbidity index over time, first vs. last 6 mo Carbamazepine: 0.54 vs. 0.44 (p = 0.11) Lithium: 0.54 vs. 0.30 (p = 0.0051)	Good responders (ITT): 20/85 (23.5%) vs. 34/86 (39.5%) (p = 0.032).

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	Not reported	Not reported	Total withdrawals: 29/85 (34.1%) vs. 11/86 (12.8%) Withdrawals due to adverse events: 8/85 (9.4%) vs. 3/86 (3.5%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Kleindienst, 2002 (--) Germany, Switzerland MAP Study (Poor)	The study took place when carbamazepine was relatively new to mood disorders; therefore, open-label design may have biased against carbamazepine because of unfamiliarity with the drug. The principal goals and contribution of this study were the refined evaluations of drop-outs and of subthreshold symptomatology. However, it is unclear whether these analyses were planned a priori.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Hartong, 2003(90) The Netherlands (Fair)	Multicenter Double-blind, double-dummy RCT 18 outpatient clinics	Bipolar disorder (DSM-III-R criteria) with at least 2 symptomatic episodes during the previous 3 yr; no antidepressants, antipsychotics, or benzodiazepines above allowed dosages; at least 18 yr old; Dutch-speaking. Report excluded 6 schizoaffective patients who had been recruited per protocol. Total of less than 6 months of previous lithium or carbamazepine treatment	Lithium 400 to 800 mg/d, then titrated to blood concentrations between 0.6 and 1.0 mmol/l vs. Carbamazepine 200 to 400 mg/d, then titrated to blood concentrations between 6 and 10 mg/l for 2 yr

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Hartong, 2003(90) The Netherlands (Fair)	Run-in acutely randomized patients on double-blind treatment; entered actual prophylactile phase after recovery from acute episode.	Benzodiazepines at doses equivalent to a maximum of 50 mg/d of oxazepam. For impending relapse, doses equivalent to a maximum of 100 mg/d of oxazepam were allowed for up to 14 days. Medications for somatic diseases (not specified).	Recurrence of an episode of (hypo)mania or major depression (DSM-III-R criteria) (Primary Outcome Measure); Comprehensive Psychiatric Rating Scale (CPRS); Bech Rafaelsen mania Scale (BRMAS), Bech Rafaelsen M,elancholia Scale (BRMES) at baseline then every month.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Hartong, 2003(90) The Netherlands (Fair)	Mean age (SD) 41.9 (13.9) 45.7% male, 54.3% female Ethnicity not reported	Bipolar I 72/94 Bipolar II 22/94 Rapid Cycling 10/94 Non-rapid cycling 84/94	--/--/150/144	46 withdrawn/50 (34.7%) lost to follow-up/94 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Hartong, 2003(90) The Netherlands (Fair)	Lithium vs Carbamazepine Recurrence: 27.3% vs. 42.0% (p-value not reported) Episodes on lithium primarily occurred in first 3 months (hazard 0.3 at 100 d) while risk with carbamazepine was 40%/yr. Dropped out: 36.4% vs. 26.0% Completed 2 yr without episode: 36.4% vs. 32.0% (p-value not reported)	Recurrence, prophylactically randomized patients: 14.3% vs. 46.7%. Recurrence, acutely randomized patients: 42.8% vs. 35.0%. About 40% of these patients experienced an episode within the first 3 mo on lithium. Thereafter, the risk of recurrence with lithium was < 10%/y.	Recurrence in prophylactically randomized patients with (hypo)manic index episode: 0% vs. 61.5% (p < 0.01) Recurrence in bipolar II patients: 0% vs. 50.0% (p < 0.05)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Hartong, 2003(90) The Netherlands (Fair)	Monitored	Lithium vs. Carbamazepine AEs with > 10% treatment difference at 2 wk (N = 88): Blurred vision 26% vs. 11% Difficulty concentrating 45% vs. 33% Feeling thirsty 41% vs. 22% Decreased appetite 21% vs. 9% Hand tremor 31% vs. 4% Muscular weakness 14% vs. 4% Increased appetite 17% vs. 33%	Lithium vs. Carbamazepine: Total withdrawals: 16/44 (36.4%) VS. 13/50 (26.0%) Withdrawals due to adverse events: 5/144 (3.5%) vs. 4/144 (8%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Hartong, 2003(90) The Netherlands (Fair)	Two randomization points: prophylactically randomized (at start of prophylactic treatment phase, the actual study entry) or acutely randomized (during an acute episode of (hypo)mania or depression). Uneven randomization with more patients prophylactically randomized to carbamazepine (n = 30) than lithium (n = 23). Few bipolar II patients were acutely randomized and they were unequally distributed between treatments. Did not incorporate secondary outcome measures a priori. The proportional hazard assumption did not hold; therefore, instead of the intended Kaplan-Meier analysis, post hoc sensitivity analyses were performed.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Lerer, 1987 (--) U.S. (Poor)	Double-blind, double-dummy, parallel-group RCT Outpatient and inpatient setting	Bipolar disorder, manic (DSM-III); age 21 to 65 y; physically healthy without seizure disorder	Carbamazepine starting at 600 mg/d and titrated to serum concentration of 8 to 12 µg/ml vs. Lithium starting at 900 mg/d and titrated to serum concentration of 1.0 mEq/l for 4 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Lerer, 1987 (--) U.S. (Poor)	7- to 14-d washout of psychotropic medications other than chloral hydrate or barbiturates for sedation	Chloral hydrate or barbiturates for sedation	Clinical Global Impression (CGI) scale; Brief Psychiatric Rating Scale (BPRS); Beigel-Murphy Manic State Rating SCale (MSRS) at baseline and weekly thereafter

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Lerer, 1987 (--) U.S. (Poor)	Carbamazepine (N = 14) vs. Lithium (N = 14) (Completer Population) Age, median, y: 44 vs. 37 Male / Female: 57.1% / 42.9% vs. 35.7% / 64.3% Ethnicity not reported	Previous response to lithium: Moderate/Good 6 (42.9%) vs. 9 (64.3%)	Number screened and eligible not reported / 34 enrolled / 34 randomized	6 withdrew / None lost to follow-up / 28 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Lerer, 1987 (--) U.S. (Poor)	Carbamazepine vs. Lithium Change in mean BPRS score, baseline to wk 4 (estimated from figure): -6 vs. -10 Calculated difference between changes in mean scores: 4 (NSD for improvement scores, data not reported) Individual BPRS items with significant treatment differences: --hostility ($p < 0.05$) --hostility-suspiciousness factor ($p < 0.01$).	Change in mean MSRS, baseline to wk 4 (estimated from figure): -50 vs. -101 Calculated difference between changes in mean scores: 51 (NSD for improvement in MSRS scores, data not reported)	Mean CGI change in severity of illness scores, baseline minus wk 4 (estimated from figure): 1.3 vs. 2.6 ($p < 0.05$)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Lerer, 1987 (--) U.S. (Poor)	Monitoring	Carbamazepine (n): reversible increase in liver enzyme test results > 4 to 6 times above normal (1); hepatitis, consistent with drug-induced type (1); severe pruritic maculopapular rash (1) decreased white blood cell count (1). Overall, there was a mean (SD) decreased in WBC count of 35% (from baseline of 8143 (3438.7) ml to 5264 (1801) ml. Lithium (n): tremor and nausea (1); pruritic maculopapular rash (1); drowsiness and slured speech (2)	Unable to determine because of discrepancies in data

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lerer, 1987 (--) U.S. (Poor)	Cannot exclude the possibility of a type II error.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Lusznat, 1988 (--) U.K. (Poor)	Double-blind, double-dummy, parallel-group RCTwith 6-wk acute trial then 12-month follow-up Initially inpatient then outpatient setting affiliated with a Dept. of Psychiatry	Confirmed diagnosis of mania or hypomania; age 17 to 64 y; Bech-Rafaelson mania rating scale score >/= 10	Carbamazepine (starting at 200 mg/d and titrating to serum concentration of 0.6 to 1.2 mg/dl) vs. Lithium (starting at 400 mg/d and titrating to serum concentration of 0.6 to 1.4 mmol/l) for 18 mo

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Lusznat, 1988 (--) U.K. (Poor)	None	Neuroleptics had been given to 52 patients prior to baseline assessment and during acute trial. Hypnotics (usually temazepam), antidepressants, or neuroleptics during follow-up trial.	Bech-Rafaelsen Mania Rating Scale (B-R MRS), side effect rating scale (ranging from 0 to 2, 13 or more symptoms); 16-h Dexamethasone Suppression Test (DST) at baseline, 3-4 d after starting medication, then at 1 wk and weekly until week 6. Global rating of severity of mania, B-R MRS, side effecting rating, Hamilton Rating Scale for Depression (HRSD, 17 items) when global rating of mania was 0, and rescue medications monthly for a year.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Lusznat, 1988 (--) U.K. (Poor)	Not reported	DSM-III diagnosis, n: Schizoaffective (2), bipolar without psychotic features (35) Carbamazepine vs. Lithium History of alcohol abuse, n: 8 vs. 4 B-R MRS score: 15.8 vs. 14.6	128 screened / 54 eligible / 54 enrolled / 54 randomized	27 withdrawn / Lost to follow-up not reported / Number analyzed for B-R MRS scores not reported

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Lusznat, 1988 (--) U.K. (Poor)	Carbamazepine vs. Lithium B-R MRS score, calculated change in mean B-R MRS score from baseline to wk 6, estimated: -12 vs. -13 (NSD) HRSD scores: NSD (data not reported) Daily neuroleptic dose, calculated change in mean daily neuroleptic dose from baseline to wk 6, estimated, mg/d: -700 vs. -800 (NSD)	Length of hospital stay, mean (SD), d: 30 (22) vs. 32 (28) (NSD)	Follow-up trial: B-R MRS score, time point not reported, mean: 1.1 vs. 1.2 (NSD) HRSD scores, mean: 2.9 vs. 3.2 (NSD) Response Predictors to carbamazepine: lower DST at admission ($p < 0.05$) Overall result (definitions not reported) "Poor": 7/27 (25.9%) vs. 12/27 (44.4%) "Satisfactory": 9/27 (33.3%) vs. 5/27 (18.5%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Lusznat, 1988 (--) U.K. (Poor)	Monitored and graded on a side effect rating scale (13 symptoms, rated 0 to 2 according to severity) The mean side effect rating score was the average of total scores for all assessments.	Carbamazepine vs. Lithium Acute trial Side effect rating scale score, mean: 2.8 vs. 2.8 More likely reported side effect: Ataxia on carbamazepine vs. Nausea and tremor on lithium Follow-up trial Side effect rating scale score, mean: 1.2 vs. 1.7 (NSD) Specific side effects not reported	Only partial data on withdrawals were reported by treatment Carbamazepine vs. Lithium Total withdrawals: 11/27 (40.7%) vs. 10/27 (37.1%) Withdrawals due to adverse events: 1/27 (3.7%) vs. 2/27 (7.4%) Adverse events resulting in withdrawals Carbamazepine: skin rash Lithium: Seizure, psoriasis worsened

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lusznat, 1988 (--) U.K. (Poor)	High rate of drop-outs, which appeared to occur at random.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Coxhead, 1992 (--) U.K. (Fair)	Double-blind, double-dummy, placebo-controlled, parallel-group RCT Outpatient	Current lithium prophylaxis; bipolar disorder (DSM-III); no other psychotropic medication.	Carbamazepine (starting at 400 mg/d and titrated to serum concentration of 38 to 51 mmol/l) vs. Lithium (starting at 800 mg/d and titrated to serum concentration of 0.6 to 1.0 mmol/l) for 1 y

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Coxhead, 1992 (--) U.K. (Fair)	Run-in on previous lithium dose. Patients were randomized to treatment if, after 4 wk of lithium at previous doses, their mania rating score remained zero, Hamilton Rating Scale for Depression (HRSD) score stayed below 4 at -4, -2, and 0 wk, and no other psychotropic medication was taken.	Temazepam up to 20 mg at night for sedation	Bech-Rafaelsen Mania Rating SCale (B-R MRS), HRSD, global rating of affective state; rating of duration and severity of mood changes since previous assessment, recorded at baseline, wk 2, wk 4, then every 4 wk for 1 y. Affective morbidity index was calculated using the global ratings of duration and severity of mood changes since previous assessment.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Coxhead, 1992 (--) U.K. (Fair)	Carbamazepie (N = 15) vs. Lithium (N = 16) Age, mean (SD), y: 47 (14) vs. 49 (10) Male / Female: 5 / 10 vs. 5 / 11 Ethnicity not reported	Number of previous admissions, mean (SD): 6.1 (3.7) vs. 7.1 (4.6) Duration of illness, mean (SD), y: 17 (11) vs. 17 (14) Nature of last inpatient episode, mania / depression: 11 / 4 vs. 13 / 3	145 screened / Number eligible not reported / 32 enrolled / 31 randomized	2 withdrew / None lost to follow-up / 31 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Coxhead, 1992 (--) U.K. (Fair)	Carbamazepine (N = 15) vs. Lithium (N = 16) Relapsed (admitted): 6 (5) vs. 8 (5) Completed (remaining relapse-free at 1 y): 7/15 (46.7%) vs. 7/16 (43.8%) Number of patients surviving at 3 mo and 1 y: 8 vs. 10 and 7 vs. 7; NSD	*Maximum mania and depression scores during the year (no statistical analyses)* B-R MRS, n --0 to 3 (no or few symptoms): 10 vs. 9 --4 to 7 (moderate symptoms): 1 vs. 1 --8 or higher (severe symptoms): 4 vs. 6	HRSD, n --0 to 5 (mild symptoms): 12 vs. 12 --6 to 11 (moderate symptoms): 3 vs. 2 --12 or higher (severe symptoms): 1 vs. 1	Affective morbidity index, mean --Relapsing (N = 6 vs. 8): 0.86 vs. 0.41 --Completing (N = 7 vs. 7): 0.12 vs. 0.22 (NSD)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Coxhead, 1992 (--) U.K. (Fair)	Monitored	Most frequent adverse events Carbamazepine: drowsiness, dizziness, giddiness, nausea, indigestion (12/15 patients had at least 1 of these adverse events during the first 4 wk) Lithium: thirst and/or polyuria (9/16 patients, 56.2%, including 3 severe cases); weight gain (mean, 4 kg) (9/16 patients, 56.2%)	Total withdrawals: 1/16 (6.2%) vs. 2/15 (13.3%) Withdrawals due to adverse events: 0/16 (0%) vs. 2/15 (13.3%) 2/15 (13.3%) vs. 0/16 (0%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Coxhead, 1992 (--) U.K. (Fair)	Primary efficacy variable was not reported. Negative results may be due to a type II error (small sample population).

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Small, 1991 (--) U.S. (Poor)	Double-blind, double-dummy, parallel-group RCT with 2-y double-blind follow-up Tertiary Care Facility; initially inpatient then 87% discharged to community	Newly hospitalized with bipolar disorder presenting in manic or mixed phases (diagnosis by Schedule for Affective Disorders and Schizophrenia-Lifetime version); manic episode (DSM-III-R) with or without coexisting symptoms of depression; history of at least one affective episode within the previous 2.5 y; bipolar I disorder (Research Diagnostic Criteria); score of 7 or more on the manic subsection of the Depresion and Mania Scale (SDMS-D&M: score range, 3 to 15) and scores of 60 or less on the Global Assessment Scale (GAS: score range, 1 to 100)	Carbamazepine starting at 200-400 mg/d, titrated until serum concentrations 25-50 micromol/l vs. Lithium starting at 300-600 mg/d, titrated until serum concentration 0.6-1.5 mmol/l for 8 wk. Patients who were improved or in remission continued to receive double-blind medications for up to 2 y.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Small, 1991 (--) U.S. (Poor)	Run-in off therapy following washout of previous medications and baseline measurements; patients who continued to display significant psychopathology (Manic Subsection of the Depression and Mania Scale, SDMS-M, score >/= 7, Global Assessment Scale, GAS, score </= 60) were randomized. 2-wk washout of previous lithium and carbamazepine, 1-wk washout of previous neuroleptics	Chloral hydrate for insomnia Amobarbital for disturbed behavior	SDMS-D&M, GAS, Manic Rating Scale (MRS) of Young et al., 24-item Hamilton Depression Rating Scale (HDRS), Brief Psychiatric Rating Scale (BPRS) expanded to include an additional rating of elevated mood, and Clinical Global Impression Scale (CGIS), recorded at baseline and weekly; Shopsin-Gershon Social Behavior Checklist, daily for 5 d / wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Small, 1991 (--) U.S. (Poor)	Carbamazepine vs. Lithium Age, mean, y: 34.3 vs. 42.6 Male / Female: 41.7% / 58.3% vs. 45.8% / 54.2% Ethnicity: Not reported	Mean age at onset, y: 23.3 vs. 26.0 No. of previous episodes of mania, 1-4 / 5-9 / >= 10: 12/10/2 vs. 11/11/2 No. of previous episodes of depression, 1-4 / 5-9 / >=10: 17/6/1 vs. 14/ 7/3 Ratio, manic:depressed: 1.4:1 vs. 1.2:1 Lithium treatment of index episode before admission to study, adequate / inadequate / none, n: 9/12/3 vs. 8/10/6 Scores on Schedule for Affective Disorders and Schizophrenia-Lifetime version Best level of social relations in past 5 y: 3.0 vs. 3.3 Healthiest overall functioning in past 5 y: 2.9 vs. 2.3 Outcome of last episode: 2.14 vs. 1.92 Comorbid personality disorders, physical and neurologic problems, and/or hisory of significant substance abuse, n: 7 vs. 12	94 screened / 52 eligible / 52 Enrolled / 52 Randomized	32 withdrawn at the end of 8 wk (before entering 2-y double-blind phase) / 24 (46%) lost to follow-up / 28 analyzed at 8 wk Of 16 who entered long-term phase, 15 withdrew within 2 y / Number lost to follow-up not reported

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Small, 1991 (--) U.S. (Poor)	Lithium vs. Carbamazepine % difference in scores MRS: 4% SDMS-M: -1% SDMS-D: -18% HAM-D: 10 BPRS: 2 CGI-1: 1 GAS: 3 BCL: 8 NSD for any scores.	Use of as-needed medications at 8 wk, chloral hydrate / amobarbital, n: 4/17 (23.5%) / 4/17 (23.5%) vs. 3/11 (27.3%) / 1/11 (9.1%)	Statistically significant ($p < 0.05$) predictors of response to therapy Lithium: None Carbamazepine: Scores reflecting less psychopathology at baseline: higher GAS score and lower scores on MRS, BPRS total, CGI-item 1, BPRS Hostile-Suspicious, SDMS-Manic subsection, and BPRS Thinking-Disturbance	Recurrence during long-term phase, n (%): 5/8 (62.5%) vs. 3/8 (37.5%) (statistics not reported)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Small, 1991 (--) U.S. (Poor)	Monitored with the general inquiry part of the Systematic Assessment of the treatment of Emergent Events (SAFTEE)	Adverse events leading to withdrawal 2 reported for Carbamazepine (n): Rash (1) during 8-wk phase, Low granulocyte count (1) during 2-y double-blind follow-up	Carbamazepine vs. Lithium At wk 8 Total withdrawals: 7/24 (29.2%) vs. 13/24 (54.2%) Withdrawals due to adverse events: 0/24 (0%) vs. 1/24 (4.2%) After wk 8 Total withdrawals: 24/24 (100%) by 24 wk vs. 23/24 (95.8%) by 1 y (NSD) Withdrawals due to adverse events: 1/8 (12.5%) vs. 0/8 (0.0%) Withdrawals due to noncompliance during long-term phase: 2/8 (25.0%) vs. 4/8 (50.0%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Small, 1991 (--) U.S. (Poor)	Maintenance of treatment blinding during long-term phase was tested by asking physicians and nurses to guess the assigned treatment; accuracy did not reach statistical significance. High dropout rates during run-in limits external validity of study; high dropout rate during long-term follow-up limited the amount and value of follow-up data.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Denicoff, 1997 (--) U.S. (Poor)	Double-blind, crossover RCT following open-label admission phase (average 149.6 +/- 104.1 d) Outpatient clinics of the National Institute of Mental Health (NIMH), Bethesda, MD	Bipolar disorder (DSM-III-R)	Phase I or II: Carbamazepine titrated up to 1600 mg/d (target serum concentration: 4 to 12 mg/l) Phase I or II: Lithium titrated to clinical response (target serum concentration: 0.5 to 1.2 mmol/l) Phase III: Combination Carbamazepine + Lithium for 1 y per treatment phase (total 3 y of treatment)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Denicoff, 1997 (--) U.S. (Poor)	Washout - previous carbamazepine or lithium was tapered over 1 mo if patient had been randomized to the other treatment	Not reported	NIMH-Life Chart Method and Manual prospective (LCM-p) daily life charting, which included daily mood scale (manic, depressed, or euthymic) and functional incapacity scale (none, mild, moderate, or severe), recorded twice daily; average severity score (calculated by multiplying the number of days at each severity level [2.5 for mild, 5.0 for moderate, and 10.0 for severe] and dividing by the number of days in the treatment phase). Beck Depression Inventory (BDI), Modified Spielberger State-Trait Anxiety Inventory (MSSTAI), Hamilton Rating Scale for Depression (HAM-D), Young Mania Rating Scale (YMRS), and Raskin Severity of Depression and Mania (RSDM) scale, recorded monthly. Clinical Global Impression (CGI) scale, recorded during treatment phase in comparison with clinical response in the year prior to the patient taking a mood stabilizer or in the worst year when patient took ineffective medications. Relapse was defined as patient required hospitalization or became severely incapacitated for at least several days

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Denicoff, 1997 (--) U.S. (Poor)	Age, mean (SD), y: 41.3 (11.4) Male / Female: 25 / 27 Ethnicity not reported	Employment status: 29 (55.8%) were employed full-time; 8 (15.4%) were employed part-time; 3 (5.8%) were housewives; 3 (5.8%) were students; 5 (9.6%) were retired; and 4 (7.7%) were not working. Bipolar II disorder (Research Diagnostic Criteria [RDC]): 19 (36.5%) Bipolar I disorder (RDC): 33 (63.5%) (with stipulation that there must be a full-blown manic episode that led to a hospitalization ro it sequivalent) History of hospitalization: 39 (75.0%) History of rapid cycling (4 or more episodes in any 1-year period prior to entering study): 31/51 (60.8%; 1 patient not assessable) History of psychosis: 27 (51.9%) Previous moderate or marked response to Lithium: 16/47 (34%) Carbamazepine monotherapy: 1/4 (25%) Carbamazepine + Lithium: 1/6 (16.7%)	Numbers screened not reported/eligible not reported/ 52 enrolled / 50 randomized	21/127 patient episodes of withdrawal (excluding early discontinuation due to treatment failure) / 6 patient episodes of dropping out or moved during treatment (lost to follow-up?) / 106 patient episodes analyzed Note: Since patients crossed over to other treatments, they were counted as patient episodes in this review.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Denicoff, 1997 (--) U.S. (Poor)	Carbamazepine vs. Lithium vs. Combination CGI marked or moderate improvement (good treatment response): 31.4% vs. 33.3% vs. 55.2% (NSD) Percentage of time ill (N = 29), mean (SD) Mania: 19.0 (19.5) vs. 9.1 (6.8) vs. 8.4 (10.6) (p < 0.01) Depression: 26.3 (22.8) vs. 30.6 (25.3) vs. 29.1 (27.5) (NSD)	Average severity of illness (N = 29), mean Mania: 0.63 vs. 0.26 vs. 0.25 (p = 0.004; post hoc analyses showed differences between lithium or combination and carbamazepine) Depression: 0.93 vs. 1.15 vs. 1.05 (NSD) Total: 1.57 vs. 1.41 vs. 1.30 (NSD) Number of episodes/year, mean Mania: 4.55 vs. 3.66 vs. 2.90 (p = 0.041; post hoc analyses showed differences between combination and either carbamazepine or lithium) Depression: 2.16 vs. 2.59 vs. 1.74 (NSD) Total: 6.71 vs. 6.25 vs. 4.64 (NSD)	Depression rating scales (score range), mean HAM-D (0 to 64): 7.8 vs. 7.1 vs. 7.1 (NSD) RSDM (depression) (3 to 15): 4.9 vs. 4.7 vs. 5.0 (NSD) BDI (0 to 63): 7.2 vs. 6.9 vs. 7.2 (NSD) Mania rating scales (score range), mean YMRS (0 to 60): 5.2 vs. 3.3 vs. 4.4 (NSD) RSDM (mania) (3 to 15): 4.3 vs. 3.8 vs. 3.9 (NSD)	*Correlates of response* Predictors of a... --Positive response to lithium: younger age at study entry; first treatment by age 20 or earlier; fewer years elapse since onset of first bipolar symptoms; </= 1 lifetime hospitalization for mania --Poor response to carbamazepine: > 10 y elapse between onset of first bipolar symptoms and entry into study and past history of rapid cycling --Positive response to combination: rapid cycling; prior course of illness variable reflecting less severity of illness --Poor response to combination: greater number of hospitalizations for mania; > 1 hospitalization for mania; greater mean number of weeks hospitalized per year

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Denicoff, 1997 (--) U.S. (Poor)	Not reported	Adverse events leading to withdrawal Carbamazepine: rash (9), decreased white blood cell and platelet counts (1) Lithium (n): cystic acne (1), psoriasis (1) Combination: None (because patients were not re-exposed to drug if they were intolerant)	Carbamazepine vs. Lithium vs. Combination, n/N (%) (where N = no. of patients entering treatment phase) Total withdrawals: 11/46 (23.9%) vs. 8/50 (16.0%) vs. 2/31 (6.5%) Withdrawals due to adverse events: 10/46 (21.7%) vs. 2/50 (4.0%) vs. 0/31 (0.0%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Denicoff, 1997 (--) U.S. (Poor)	Randomization order was changed in 1 patient. Research nurses were not necessarily blinded to the third (combination) phase Selective population of patients previously treated with carbamazepine or lithium; about 45% of the patients had had minimal or no response to lithium.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Bowden, 2000 Canada, U.S. (Fair)	Multicenter, long-term, double-blind, placebo-controlled, parallel-group RCT with < / = 3-mo initial open phase followed by 52-wk double-blind randomized maintenance phase Outpatient setting	Open-label phase: age 18 to 75 yr; bipolar disorder (DSM-III-R); index manic episode < / = 3 mo before randomization; at least 1 other manic episode in previous 3 yr Double-blind phase: scores of < / = 11 on Mania Rating Scale (MRS), < / = 13 on Depressive Syndrome Scale (DSS), > 60 on Global Assessment Scale (GAS) on 2 consecutive occasions at least 6 d apart.	Open-label stabilization phase: Investigator's choice of medication (including divalproex, lithium, both, or neither) for up to 90 d Double-blind phase: Divalproex (titrated to serum valproate concentration of 71 to 125 mg/l) vs. Lithium (titrated to serum concentration of 0.8 to 1.2 mEq/l) for 52 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Bowden, 2000 Canada, U.S. (Fair)	Up to 90-day run-in on investigator's choice of medication; patients were randomized if they had, on two consecutive visits at least 6 d apart, a Global Assessment Scale (GAS) score > 60, Mania Rating Scale (MRS) score (derived from the Schedule for Affective Disorders-Change Version [SADS-C]) < /= 11; and a Depressive Syndrome Scale (DSS) score (derived from SADS-C) < 14 Washout of psychotropic medication other than lithium or divalproex before randomization; washout of open-label divalproex and lithium occurred while blinded drugs were titrated up during first two weeks of maintenance phase	Lorazepam up to 6 mg/d for 14 d during first month and no more than 7 d for remainder of study. Haloperidol up to 10 mg/d during second consecutive wk of lorazepam in first month only.	Time to either a manic or depressive episode ("any mood episode") (Primary Outcome Measure); time to a manic episode; time to a depressive episode; scores on MRS, DSS, and GAS during maintenance therapy

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Bowden, 2000 Canada, U.S. (Fair)	Divalproex vs. Lithium vs. Placebo Mean (SD) age, y: 38.9 (12.7) vs. 40.3 (9.8) vs. 38.7 (11.9) 48.8% Male, 51.2% Female 91.3% White, 4.1% Black, 4.6% Other	Divalproex vs. Lithium vs. Placebo MRS, mean (SD): 3.4 (3.7) vs. 3.2 (3.7) vs. 3.4 (3.4) Prior manic episodes 1 to 10: 48.9% 11 to 20: 13.3% > 20: 36.6% Prior depressive episodes 0: 4.9% 1 to 10: 44.7% > 10: 48.8% 61% had at least one previous hospitalization 18% hospitalized for the index episode	4758/--/571/372	199 withdrew / Number lost to follow-up not reported / 369 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Bowden, 2000 Canada, U.S. (Fair)	Divalproex vs. Lithium vs. Placebo Time to 50% relapse of any mood episode (95% CI), d: 275 (167 to not calculable [NC]) vs. 189 (88 to NC) vs. 173 (101 to NC) Time to 25% relapse with mania (95% CI), d: >365 (NC) vs. 293 (71 to NC) vs. 189 (84 to NC)Time to 25% relapse with depression (95% CI), d: 126 (100 to 204) vs. 81 (33 to 234) vs. 101 (55 to 190) (p = 0.08 for divalproex vs. lithium)	Proportion of patients remaining in study (estimated from Kaplan-Meier survival curve at 52 wk): 0.48 vs. 0.42 vs. 0.41 (p = 0.06) Median time to 50% survival without any mood episode based on 4-wk intervals, wk: 40 vs. 24 vs. 28 (no statistical analyses)	Mean changes from baseline in scores (Center Effects model) MRS: 3.1 vs. 3.0 vs. 3.4 (p > 0.05 for all analyses) DSS: 3.9 vs. 5.7 vs. 6.1 (p > 0.05 for all analyses) GAS: -4.7 vs. -7.8 vs. -5.7 (p > 0.05 for all analyses) Mean changes from baseline in scores (Mania Subtype model) MRS: 1.7 vs. 2.6 vs. 2.7 (p > 0.05 for all analyses) DSS: 3.6 vs. 7.0 vs. 4.4 (p < 0.001 Divalproex vs. Lithium; p=0.02 Lithium vs. Placebo) GAS: -4.7 vs. -10.8 vs. -6.2 (p=0.001 Divalproex vs. Lithium; p=0.03 Lithium vs. Placebo)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Bowden, 2000 Canada, U.S. (Fair)	Not reported	Rate of AEs higher on... Divalproex than Lithium: sedation, infection, tinnitus Lithium than Divalproex: polyuria, thirst Divalproex than Placebo: tremor, weight gain Lithium than Placebo: tremor Divalproex vs. Placebo Change in platelet count, 109/l: -53 vs. 3.4 (p < 0.001) Change in white blood cell count, 109/l: -1.1 vs. -0.3 (p < 0.009) Change in hepatic enzymes: NSD	Open-label phase Total withdrawals: 199/571 (34.9%) Withdrawals due to adverse events: 10/199 (5.0%) Divalproex vs. Lithium vs. Placebo Double-blind phase Total withdrawals: 116/187 (62%) vs. 69/91 (76%) vs. 71/94 (75%) (p = 0.03 Divalproex < Lithium) Withdrawals due to intolerance or noncompliance: 41/187 (22%), 32/91 (35%) vs. 11/94 (12%) (p=0.02 Divalproex < Lithium)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Bowden, 2000 Canada, U.S. (Fair)	Fewer patients randomized to lithium than divalproex. Failure to achieve remission within 3 months of manic episode was a major reason for exclusion from randomization (28 (14.1%) of 199 patients not randomized to maintenance phase). Study had inadequate power to detect treatment differences in the primary outcome variable (i.e., 0.3 instead of the planned power of > 0.8). High dropout rate may have biased the results. Further data available in Commentary by Baldessarini, 2000 and systematic review by Macritchie 2004.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Gyulai, 2003 (--) U.S. (Fair)	Same as Bowden, 2000; presents additional analyses to Bowden, 2000 Outpatient setting implied	Same as Bowden, 2000	Same as Bowden, 2000

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Gyulai, 2003 (--) U.S. (Fair)	Same as Bowden, 2000	Lorazepam, haloperidol, sertraline, paroxetine	DSS and MRS for symptom severity (from SADS-C); frequency unclear (weekly x 6 wk, biweekly till wk 12, then monthly?). Breakthrough depression was defined by either need for antidepressant treatment, which should have been initiated if DSS score > / = 25, or early discontinuation for depression, including SADS-C suicide item score >/= 4, attempted suicide, or hospitalization for depression.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Gyulai, 2003 (--) U.S. (Fair)	Age, mean (SD), y: 39.2 (11.8) Male / Female: Data not reported Ethnicity not reported	Same as Bowden, 2000	4758/-/571/372 (number screened from Baldessarini 2000)	256/372 (68.8%) withdrew / Number lost to follow-up not reported / 372 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Gyulai, 2003 (--) U.S. (Fair)	Divalproex (N = 187) vs. Lithium (N = 91) vs. Placebo (N = 94) Early Discontinuation for Breakthrough Depression: 12 (6%) vs. 9 (10%) vs. 15 (16%) (NSD for divalproex vs. lithium and lithium vs. placebo; p = 0.017 for divalproex vs. placebo) --Hospitalization for depression: 3 (1.6%) vs. 2 (2.2%) vs. 6 (6.4%) --Suicide attempt: 2 vs. 2 vs. 2 Early discontinuation for any reason: 116 (62%) vs. 69 (76%) vs. 71 (75%) (p = 0.05) Among SSRI users: 23/41 (56%) divalproex vs. 17/20 (85%) placebo (p = 0.043)	*Predictors of Early Discontinuation for Depression* Negative Predictors: --Divalproex (OR = 0.426 (0.182 to 0.997--interval not defined) vs. placebo; p = 0.049) Positive Predictors: --Higher number of previous depressive episodes (OR = 1.30 [1.055 to 1.598] per category (p = 0.014) --Psychiatric hospitalizations (OR = 1.68 [1.100 to 2.577] per category (p = 0.017)	Time to Depressive Relapse: NSD (data not reported) For the subset of open-label divalproex responders (n = 142), time to depressive relapse was longer with divalproex (n = 71) than lithium (n = 41) (p = 0.03).	*Predictors of Depressive Relapse* Positive Predictors: --Higher lifetime number of manic and depressive episodes (increase in OR = 1.12 [1.04 to 1.21] for every category increase; p = 0.002) --Female gender (OR = 1.98 [1.22 to 3.22]; p = 0.006 vs. males) *Predictors of Worsening Depressive Symptoms* Positive Predictors: --Lifetime number of manic episodes (p = 0.015) --Number of psychiatric hospitalizations (p = 0.015) Negative Predictors: --Baseline DSS score (p = 0.002)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Gyulai, 2003 (--) U.S. (Fair)	Not reported (see Bowden, 2000)	Not reported (see Bowden, 2000)	Total withdrawals was reported as an efficacy outcome measure (Early Discontinuation for Any Reason) Withdrawals due to adverse events: Not reported (see Bowden, 2000)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Gyulai, 2003 (--) U.S. (Fair)	Subgroup of SSRI-treated patients was analyzed *post hoc*. This was the first study to suggest that the life time number of manic episode is associated with continuing depressive morbidity in bipolar disorder. Low placebo relapse rate reduced the effect size, thereby decreasing the probability of detecting differences between active treatment groups and the placebo group.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Tohen, 2002 U.S. (Fair)	Multicenter Double-blind RCT (test of noninferiority) Inpatient for at least one week then outpatient	Age 18 to 75 y; diagnosis of bipolar I disorder (DSM-IV criteria), manic or mixed episode, with or without psychotic features; Young Mania Rating Scale minimum total score of 20	Olanzapine 5 to 20 mg/d vs. Divalproex 500 to 2500 mg/d for 3 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Tohen, 2002 U.S. (Fair)	None	Lorazepam < 2 mg/d and not within 8 h of a symptom rating scale; benztropine < 2 mg/d	Young Mania Rating Scale (YMRS, 11-item) and Hamilton Depression Rating Scale (HDRS, 21-item) daily for one week then weekly Response defined as >/= 50% reduction in YMRS score Remission defined as end point YMRS </= 12

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Tohen, 2002 U.S. (Fair)	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian	Nonpsychotic 54.6% Mixed Episode 43.0% Manic Episode 57.0% Rapid Cycling 57.4%	330/--/--/251	79/--/248

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Tohen, 2002 U.S. (Fair)	Divalproex vs. Olanzapine Total YMRS score, mean change from baseline (Primary Efficacy Variable): -10.4 vs. -13.4 Lower limit of 95.76% one-tailed CI for assessment of noninferiority: 0.96 (exceeds predefined -1.9 margin of therapeutic equivalence) Difference in mean change in YMRS score: 3.0 (p < 0.03)	Responders: 42.3% vs. 54.4% (p = 0.058) Remission: 34.1% vs. 47.2% (p < 0.04) HDRS, mean change from baseline: -3.46 vs. -4.92 (NSD)	Time to response: Faster on olanzepine (data not reported) Time to remission, d (25th percentile): 6 vs. 3 Mean change in YMRS score in subgroup... --without psychosis: -8.7 vs. -14.1 (difference: 5.4; p < 0.001) --with psychosis: -12.8 vs. -12.6 (p = 0.93)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Tohen, 2002 U.S. (Fair)	Monitored	Common (> 10%) treatment-emergent AEs: More common on olanzapine: Dry mouth, increased appetite, somnolence More common on divalproex: Nausea Greater weight gain on olanzapine (2.5 kg) vs. divalproex (0.9 kg)	Total withdrawals: 39/125 (31.2%) vs. 37/126 (35.7%) Withdrawals due to adverse events: 9 (7.1%) vs. 12 (9.6%); p = 0.50

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Tohen, 2002 U.S. (Fair)	3 Divalproex patients excluded from primary efficacy analysis because of no postbaseline assessment.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Tohen, 2003 U.S. (Fair)	Multicenter 47-wk double-blind RCT Extension phase to study by Tohen, 2002 Tested for noninferiority Inpatient for at least one week then outpatient	Same as Tohen, 2002	Olanzapine 5 to 20 mg/d vs. Divalproex 500 to 2500 mg/d for 47 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Tohen, 2003 U.S. (Fair)	None	Same as Tohen, 2002	Young Mania Rating Scale (YMRS, 11-item), Hamilton Depression Rating Scale (HDRS, 21-item), Clinical global Impression scale for bipolar disorder (CGI-BP) severity of illness rating, and Positive and Negative Syndrome Scale (PNSS) daily for one week then weekly from weeks 1 to 5, biweekly from weeks 5 to 11, monthly from weeks 11 to 23, and bimonthly from weeks 23 to 47 Definitions Symptomatic remission of mania: YMRS </= 12. Symptomatic remission of mania and depression: endpoint total YMRS </= 12 and HDRS </= 8. Syndromal remission of mania: no "A" criterion worse than mild in severity and no more than two "B" criteria rated as mild in severity using DSM-IV criteria Syndromal remission of mania and depression was defined as the preceding mania criteria plus the following depression criteria: no DSM-IV A criteria for a major depressive episode that were worse than mild in severity and the presence of no more than three A criteria rated as mild Symptomatic relapse into an affective episode (depression, mania, or mixed): YMRS >/= 15, HDRS >/= 15 in a patient who previously met criteria for symptomatic remission Syndromal relapse into an affective episode - achievement of syndromal remission according to both mania and depression criteria followed by relapse into either mania or depression

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Tohen, 2003 U.S. (Fair)	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian	Mean (SD) YMRS total score: 27.7 (5.9; severe) Mixed bipolar 43.0% Rapid cycling 57.4% Psychotic 45.4% Treatment resistant (did not respond to previous adequate treatment for acute mania with lithium, valproate, or carbamazepine) 21.1%	--/--/251/251	Not reported / 25 / 248

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Tohen, 2003 U.S. (Fair)	Divalproex vs. Olanzapine YMRS total score, mean difference: 2.4 (p = 0.002) Mean change in YMRS total score (baseline to wk 47): -12.5 vs. -15.4 (p = 0.03) Improvement in YMRS was significantly superior from wk 2 to 15 and wk 23; NSD from wk 30 to 47. NSD in HDRS, PNSS, and CGI-BP severity of illness	Median time to symptomatic / syndromal remission of mania,d: 62 / 109 vs. 14 / 28 (p = 0.05 / p = 0.01) Symptomatic mania remission rates: 45.5% vs. 56.8% (p=0.10) Syndromal mania remission rates: 38.2% vs. 50.8% (p=0.06) Time to symptomatic / syndromal remission of both mania and depression (25th percentile),d: 13 / 34 vs. 14 / 7 [*sic*] (p = 0.62 / p = 0.86) p = 0.86 / p = 0.62 Symptomatic remission of both mania and depression: 30.9% vs. 30.9% (p = 1.00) Syndromal remission of both mania and depression: 27.6% vs. 29.8% (p=0.78)	Time to symptomatic recurrence of any affective episode (25th percentile),d: 27 vs. 27 Symptomatic recurrence of any affective episode: 13/23 (56.5%) vs. 14/33 (42.4%) (p = 0.42) Time to syndromal recurrence of any affective episode (median),d: 42 vs. 14 Syndromal recurrence of any affective episode: 13/20 (65.0%) vs. 20/31 (64.5%) (p = 1.00)	Relation of valproate serum concentration to outcome (data not shown here): NSD for any analyses

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Tohen, 2003 U.S. (Fair)	Monitored	*Treatment-emergent AEs* Significantly more common on olanzapine: somnolence, dry mouth , increased appetite, weight gain, akathisia, increased alanine aminotransferase Significantly more common on divalproex: nausea, nervousness, rectal disorder, low albumin, low platelets Olanzapine vs. divalproex Mean weight gain: 2.79 vs. 1.22 kg (p = 0.001) Mean change in cholesterol: 9.7 vs. -2.33 mg/dl (p = 0.007) Mean change in Fridericia-corrected QT interval: 7.97 msec vs. -3.06 (p = 0.002) Potentially clinically significant change in QTc interval (> 430 in men, > 450 in women): 2/102 (2.0%) vs. 2/96 (2.1%) (p = 1.00)	Olanzapine vs. Divalproex Total withdrawals: 106/125 (84.8%) vs. 106/126 (84.1%) (p = 1.00) Withdrawals due to adverse events: 31/125 (24.8%) vs. 25/126 (19.8%) (p = 0.37) Withdrawals due to weight gain: 4/125 (3.2%) vs. 0/126 (0.0%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Tohen, 2003 U.S. (Fair)	High dropout rate limits the power to detect differences in relapse. For most patients, initial olanzapine doses (15 mg/d) may be therapeutic while initial divalproex doses (750 mg/d) may be subtherapeutic. This difference may have favored an earlier response with olanzapine.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Zajecka, 2002 (--) U.S. (Fair)	Multicenter, double-blind, double-dummy, parallel-group RCT Inpatient (< 3 wk) then outpatient (9 wk) setting	Randomization criteria: Age 18 to 65 y; bipolar disorder type I (DSM-IV); hospitalized for an acute manic episode (defined as a score of >/= 25 on the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C) Mania Rating Scale (MRS), with at least 4 scale items rated >/= 3). Improvement criteria (on or before day 21, for discharge from hospital and follow-up as outpatients for remainder of study): SADS-C MRS score reduced >/= 30% from the last day of screening, with no SADS-C item score > 3, and discharge recommended by the investigator.	Divalproex Delayed-release starting at 20 mg/kg/d and titrated to a maximum of 20 mg/kg/d + 1000 mg (range, 750 to 3250 mg) vs. Olanzapine 5 to 25 mg/d for 12 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Zajecka, 2002 (--) U.S. (Fair)	1- to 3-day non-drug run-in 1- to 3-day washout of previous psychoactive medications	Lorazepam, benztropine, chloral hydrate, zolpidem (but not within 8 h prior to efficacy ratings)	MRS at baseline, and days 3, 5, 7, 10, 14, 21, 28, 42, 56, 70, and 84; Brief Psychiatric Rating Scale (BPRS) at baseline and days 3, 5, 7, 14, 21, 28, 42, 56, 70, and 84; Hamilton Rating Scale for Depression (HAM-D) at baseline and days 7, 14, 21, 28, 42, 56, 70, and 84; Clinical Global Impressions-Part I, severity of illness scale (CGI-S) at baseline, and days 3, 7, 14, 21, 28, 42, 56, 70, and 84

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Zajecka, 2002 (--) U.S. (Fair)	Divalproex (N = 63) vs. Olanzapine (N = 57) Age, mean (SD), y: 38.9 (12.1) vs. 38.1 (12.2) Male / Female: 56% / 44% vs. 53% / 47% Ethnicity, n (%) --Asian/Pacific Islander: 2 (3) vs. 1 (2) --White: 50 (79) vs. 40 (70) --Black: 8 (13) vs. 14 (25) --Other: 3 (5) vs. 2 (4)	DSM-IV diagnosis Mixed mania: 31 (49%) vs. 26 (46%) Rapid cycling: 19 (30%) vs. 16 (28%)	Numbers screened, eligible, enrolled not reported / 120 randomized	83 (69.2%) / 16 (13.3%) / 115

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	
Zajecka, 2002 (--) U.S. (Fair)	Divalproex vs. Olanzapine Change from baseline to day 21 (last observation carried forward), mean MRS (with baseline as covariate, Primary Efficacy Variable): -14.9 vs. -16.6 (NSD) BPRS: -8.1 vs. -10.2 (NSD) HAM-D: -6.7 vs. -8.1 (NSD) CGI-S: -0.8 vs. -1.0 (NSD)	NSD in antipsychotic effect (although numbers small and variability of change in BPRS scores was high). Data for 12-wk tx were not reported.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Zajecka, 2002 (--) U.S. (Fair)	Monitored	Divalproex (N = 61) vs. Olanzapine (N = 57) Increase in weight (baseline to final evaluation), mean, kg: 2.5 vs. 4.0 (p = 0.049) Divalproex (N = 63) vs. Olanzapine (N = 57) Adverse Events Significantly more frequent on olanzapine than divalproex: somnolence (29% vs. 47%), weight gain, rhinitis, edema, speech disorder (slurred speech) Significantly more frequent on divalproex: None Deaths and Serious Adverse Events 1 Death on olanzapine attributed to diabetic ketoacidosis that was considered to be possibly/probably related to study drug 5 Divalproex patients: abnormal electrocardiogram results; anticholinergic syndrome; catatonic reaction; psychotic depression; somnolence (possibly/probably related to study drug) 2 Olanzapine patients: depression, diabetic ketoacidosis (possibly/probably related to study drug) Change from baseline to final values, mean	Divalproex vs. Olanzapine Total withdrawals: 45/63 (71%) vs. 38/57 (67%) Withdrawals due to adverse events: 7/63 (11%) vs. 5/57 (9%) p = 0.766

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Zajecka, 2002 (--) U.S. (Fair)	Washout period of 1 to 3 days may be inadequate. Baseline MRS scores were significantly different; effect on results was not explained. This trial used higher doses of divalproex and serum concentrations were also higher than those in the trial by Tohen. The higher doses would not intuitively explain the difference in results between Tohen's positive study and this negative study. Limited by selection bias, as previous study drug failures were excluded.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Multicenter double-blind, parallel-group, placebo-controlled RCT with 2-wk screening phase, 8- to 16-wk open-label phase on lamotrigine treatment, and a 76-wk double-blind phase Clinic setting	18 yr or older; bipolar I disorder; manic or hypomanic (DSM-IV) currently or within 60 d; manic or hypomanic symptoms at enrollment; at least 1 additional manic or hypomanic episode and 1 depressed episode within 3 yr of enrollment; Clinical Global Impression-Severity (CGI-S) score of 3 or less for at least 4 continuous wk during open-label phase	Open-label: Lamotrigine 100 to 200 mg/d for 8 to 16 wk Double-blind: Lamotrigine 100 to 400 mg/d vs. Lithium titrated to serum concentrations 0.8 to 1.1 mEq/l vs. Placebo for up to 76 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Run-in: beginning at wk 8 of open-label lamotrigine, patients who had reached a stable dose of lamotrigine and met criterion for response (CGI-S scale score of 3 or less for at least 4 continuous wk) were eligible for double-blind phase. Patients who developed adverse events were not randomized. Patients who did not meet response criteria by wk 16 were discontinued from study.	Open-label phase: AEDs, psychotropic medications up to 1 to 2 wk before entry into double-blind phase. Double-blind phase: No psychotropics except short-term, intermittent use of chloral hydrate, lorazepam, temazepam, or oxazepam at low doses. Institution of antidepressant, antipsychotic, benzodiazepine, AED, mood stabilizer, and electroconvulsive therapy for a mood episode constituted the primary study end point.	Time to intervention (addition of pharmacotherapy or electroconvulsive therapy) for any mood episode (primary efficacy end point); time to early discontinuation for any reason; time to intervention for manic, hypomanic, or mixed episode; time to intervention for depressive episode; scores on Mania Rating Scale (MRS), Hamilton Rating Scale for Depression (HAM-D, 17-item), Clinical Global Impression-Severity (CGI-S) and -Improvement (CGI-I), and Global Assessment Scale (GAS) weekly for 4 wk, biweekly through wk 8, then every 4 wk through wk 76.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Open-label Lamotrigine; Double-blind Lamotrigine, Lithium, and Placebo Mean (SD) age: 40.7 (11.8); 40.6 (12.6), 41.9 (11.3) vs. 40.9 (11.0) Male: 50%; 45%, 48% vs. 49% Ethnicity not reported	Open-label Lamotrigine; Double-blind Lamotrigine, Lithium, and Placebo Mean (SD) MRS: 22.9 (6.7); 22.3 (6.8), 22.3 (5.6) vs. 22.4 (7.8) History of psychotic episodes: 46%; 38%, 46% vs. 41% Ever hospitalized for mood-related disturbance: 66%; 60%, 67% vs. 61% Ever attempted suicide: 29%; 28%, 41%, 19% (Lithium vs. Placebo, p=0.01)	--/--/349/175	Open-label phase: 165/30/184 (completed) Double-blind phase: 41/5/171

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Lamotrigine vs. Lithium vs. Placebo (p-values shown for lamotrigine vs. lithium, lamotrigine vs. placebo, and lithium vs. placebo, respectively) Median time to any mood episode (95% CI), d: 141 (71 to > 547) vs. 292 (123 to > 547) vs. 85 (37 to 121) (p = 0.46, 0.02, and 0.003) Median survival in study (95% CI), d: 85 (44 to 142) vs. 101 (59 to 202) vs. 58 (34 to 108) (p = 0.72, 0.03, and 0.07) Proportion of patients remaining in study (estimated from Kaplan-Meier survival curve at 76 wk, Figure 1 of article): 0.43 vs. 0.47 vs. 0.15 (p = 0.46, 0.02, and 0.003)	Time to mania and depression episodes: Not evaluable for lamotrigine and lithium; 269 (95% CI: 183 to > 547) for placebo Kaplan-Meier survival estimates to manic episode (from Fig. 2 of article): 0.65 vs. 0.55 vs. 0.40 (p = 0.09, 0.28, 0.006) Kaplan-Meier survival estimates to depressive episode (from Fig. 2 of article): 0.80 vs. 0.70 vs. 0.40 (p=0.36, 0.02, 0.17)	Mean change from baseline scores; calculated differences and p-values shown for lamotrigine vs. lithium, lamotrigine vs. placebo, and lithium vs. placebo MRS: 1.79 vs. -0.04 vs. 2.3; calculated differences: 1.83, -0.51, and -2.34 (p = 0.03, p > 0.05, and p = 0.001) HAM-D: 2.05 vs. 2.68 vs. 3.92; calculated differences: -0.63, -1.87, and -1.24 (p > 0.05, p = 0.03, and p > 0.05) GAS: -3.19 vs. -3.85 vs. -5.63; calculated differences: 0.66, 2.44, and 1.78 (p > 0.05 for all comparisons) CGI-S: 0.37 vs. 0.44 vs. 0.56; calculated differences: -0.07, -0.19, and -0.12 (p > 0.05 for all comparisons)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Monitored	Lamotrigine vs. Lithium vs. Placebo Adverse events occurring in at least 10% of patients and at rates showing treatment differences --Headache: 12/59 (20%) vs. 2/46 (4%) vs. 11/69 (6%) (p = 0.02, lamotrigine vs. lithium) --Diarrhea: 3/59 (5%) vs. 13/46 (28%) vs. 6/69 (9%) (p = 0.002, lamotrigine vs. lithium; p = 0.009, lithium vs. placebo Other common AEs (no treatment differences): Any rash, infection, somnolence, nausea, insomnia, influenza	Lamotrigine vs. Lithium vs. Placebo Total withdrawals: 13 (22.0%) vs. 18 (39.1%) vs. 10 (14.3%) Withdrawals due to adverse events: 3 (5%) vs. 11 (24%) vs. 3 (4%) (p = 0.01 for both lithium vs. lamotrigine and lithium vs. placebo)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Slow rate of recruitment led to closure of lithium arm about midway through study and termination of study before full planned enrollment (100 per group). Possible implications of baseline differences in suicide rates on study results were not reported. Higher enrollment of patients with more severe depression (higher rate of past suicide attempts) in the lithium group may have influenced treatment results for depressive episodes. Double-blind results are confounded by discontinuation of patients who experienced AEs or lack of efficacy to lamotrigine in open-label phase. Survival in study, in which all dropouts were included as events, was used to confirm the primary efficacy analysis, which excluded dropouts other than those due to defined events.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	Multicenter, double-blind, double-dummy, placebo-controlled, parallel-group RCT with open-label run-in phase Outpatient clinic setting	Age at least 18 y; bipolar I disorder; currently experiencing a major depressive episode (DSM-IV) or residual depressive symptoms present from a major depressive episode within 60 d of screening; at least 1 manic or hypomanic episode within 3 y of enrollment; at least 1 additional depressed episode (including a mixed episode) within 3 y of enrollment.	Open-label phase: Lamotrigine titrated to 100 to 200 mg/d as adjunctive or monotherapy for 8 to 16 wk (target dose halved when used adjunctively with valproate) Double-blind phase: Lamotrigine 50 mg/d vs. Lamotrigine 200 mg/d vs. Lamotrigine 400 mg/d vs. Lithium titrated to serum concentrations of 0.8 to 1.1 mEq/l vs. Placebo for 76 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	8- to 16-wk open-label run-in phase on lamotrigine monotherapy or adjunctive therapy (target dose, 100 to 200 mg/d); beginning at wk 8 of the open-label phase, patients who had Clinical Global Impression-Severity of Illness (CGI-S) scores of 3 (mildly ill) or lower maintained for at least 4 continuous wk were randomized. 1- to 2-wk washout of previous psychotropic medications including AEDs; 4-wk washout for fluoxetine	Chloral hydrate, lorazepam, temazepam, oxazepam, midazolam	Time to intervention (addition of pharmacotherapy or electroconvulsive therapy) for any mood episode (primary efficacy end point); time to intervention for a manic or hypomanic episode; time to intervention for a depressive episode; HAM-D, MRS, CGI-S, and Global Assessment Scale (GAS), at baseline (day 1 of double-blind phase) and during double-blind phase (intervals not reported).

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	Open-label lamotrigine (N = 958), Placebo (N = 121), Lithium (N = 120) vs. Lamotrigine (N = 169) Age, mean (SD), y: 42.2 (12.2) vs. 42.1 (13.0) vs. 43.6 (12.3) vs. 44.1 (11.7) Men: 39% vs. 50% vs. 40% vs. 41% Ethnicity not reported	History of psychotic episodes: 31% vs. 30% vs. 29% vs. 29% Ever hospitalized for mood-related distrubances: 66% vs. 64% vs. 63% vs. 57% Ever attempted suicide: 37% vs. 36% vs. 35% vs. 25% Age at first depression, mean (SD), y: 22.7 (11.6) vs. 22.4 (11.9) vs. 23.1 (12.1) vs. 23.5 (11.8) Age at first mania/mixed episode, mean (SD), y: 26.7 (12.5) vs. 25.7 (12.8) vs. 28.4 (14.6) vs. 27.7 (12.2) 4 to 6 mood episodes in past year: 28% vs. 34% vs. 32% vs. 25%	Number screened not reported / 966 eligible for open-label phase, 480 eligible for double-blind phase / Number enrolled not reported / 463 randomized	Open-label phase: 486/966 (50.0%) withdrew; 60/966 (6%) were lost to follow-up from the open-label phase Double-blind phase: 156/463 (33.7%) withdrew / 25/463 (5.4%) lost to follow-up / 457 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results			
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	Lamotrigine 200/400 (N = 165) vs. Lithium (N = 120) vs. Placebo (N = 119); p-values shown for lamotrigine vs. lithium, lamotrigine vs. placebo, and lithium vs. placebo Time to any mood episode (primary efficacy measure), median (95% CI), d: 200 (146 to 399) vs. 170 (105 to not evaluable) vs. 93 (58 to 180); p = 0.915, p = 0.029, and p = 0.029 Overall survival in study, median (95% CI), d: 92 (59 to 144) vs. 86 (63 to 111) vs. 46 (30 to 73); p = 0.516, p = 0.003, and p = 0.022 Proportion of patients remaining in study for time to intervention for any mood episode at 76 wk (estimated from Kaplan-Meier survival curve, Fig. 2A): 0.36 vs. 0.40 vs. 0.25; p = 0.915, 0.029, and 0.029	Calculated differences and p-values shown for lamotrigine vs. lithium, lamotrigine vs. placebo, and lithium vs. placebo Intervention-free for depression at 1 y: 57% vs. 46% vs. 45%; calculated differences: 11%, 12%, and 1% (p = 0.434, p = 0.047, and p = 0.209) Intervention-free for mania at 1 y: 77% vs. 86% vs. 72%; calculated differences: -9%, 5%, and 14% (p = 0.125, p = 0.339, and p = 0.026)	Change from baseline, mean; calculated differences and p-values shown for lamotrigine vs. lithium, lamotrigine vs. placebo, and lithium vs. placebo HAM-D (17-item): 2.5 vs. 2.9 vs. 4.9 (p > 0.05, p < 0.05, p < 0.05) MRS: 0.7 vs. 0.7 vs. 1.1 (p > 0.05 for all comparisons) GAS: -2.8 vs. -4.1 vs. -6.9 (p > 0.05, p < 0.05, p < 0.05)	Change from baseline, mean CGI-Severity of Illness: 0.7 vs. 0.4 vs. 0.3; p < 0.05 lithium or lamotrigine vs. placebo CGI-Improvement: 2.6 vs. 2.5 vs. 2.5 (NSD)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	Not reported	Open-label phase (N = 958), Placebo (N = 121), Lithium (N = 120), vs. Lamotrigine (N = 169) Most common treatment-emergent adverse events showing treatment differences, n (%) Any rash: 104 (11) vs. 3 (2) vs. 5 (4) vs. 12 (7); p < 0.05 lamotrigine vs. placebo Somnolence: 83 (9) vs. 7 (6) vs. 16 (13) vs. 16 (9); p < 0.05 lithium vs. placebo Diarrhea: 81 (8) vs. 10 (8) vs. 19 (16) vs. 12 (7); p < 0.05 lamotrigine vs. lithium Tremor: 46 (5) vs. 6 (5) vs. 20 (17) vs. 9 (5); p < 0.05 lithium vs. placebo and lamotrigine vs. lithium	Double-blind phase Placebo (N = 121) vs. Lithium (N = 121) vs. Lamotrigine (N = 221) Total withdrawals: 43 (36%) vs. 45 (37%) vs. 68 (31%) Withdrawals due to adverse events: 15/169 (9%) vs. 19/120 (16%) vs. 12/121 (10%) (NSD)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Calabrese, 2003 (--) U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	An a priori decision was made to combine the existing 200- and 400-mg/d lamotrigine groups for the primary analysis of efficacy. Survival in study, in which all dropouts were included as events, was used to confirm the primary efficacy analysis, which excluded dropouts other than those due to defined events. Efficacy and safety comparisons between lamotrigine and lithium are limited because patients with intolerance or lack of efficacy to open-label lamotrigine were excluded from the maintenance phase. Even with the enriched enrollment of lamotrigine responders, there was no significant difference between lamotrigine and lithium for the primary efficacy measure (time to any mood episode).

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
McIntyre, 2002 (--) Canada (Poor)	Single-blind, parallel-group RCT Bipolar Clinic setting	Bipolar I/II disorder (DSM-IV) with most recent episode depression. Patients receiving divalproex or lithium must have received the medication for at least 2 wk.	Topiramate 50 to 300 mg/d (mean dose: 176 mg/d) vs. Bupropion sustained release (SR) 100 to 400 mg/d (mean dose: 250 mg/d) (added on to mood stabilizer) for 8 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
McIntyre, 2002 (--) Canada (Poor)	None	Atypical antipsychotics, lithium (mean +/- SD dose: 980 +/- 388.3 mg/d; mean plasma concentration: 1.16 mEq/l; mean duration: 4.4 y), divalproex (1106 +/- 400.36 mg/d; 498.4 mol/l; 6.2 y)	Hamilton Depression Rating Scale (HDRS-17 item); Young Mania Rating Scale (YMRS); Clinical Global Impression for Severity (CGI-S) and Improvement (CGI-I); and AMDP [not defined] side effects rating scale, at baseline and weekly. Montgomery Asberg Depression Rating Scale (MADRS) at baseline and end point. Primary efficacy measure was percentage of patients responding. Response was defined a priori as >/= 50% decrease from baseline in the mean total HDRS-17 score. Remission was defined as an end point HDRS-17 score </= 7.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
McIntyre, 2002 (--) Canada (Poor)	Topiramate (N = 18) vs. Bupropion SR (N = 18) Age, mean, y: 39 vs. 43 Male / Female: 11 / 7 vs. 10 / 8	Age of onset of illness, mean, y: 24 vs. 22 Rapid cyclers: 8 (44%) vs. 7 (39%) Number of lifetime episodes, mean --Manic: 4.3 vs. 3.0 --Hypomanic: 1.8 vs. 2.4 --Depressive: 4.0 vs. 3.0 Duration of current episode, mean, mo: 6.5 vs. 7.5 Concomitant psychiatric medication, n --Atypical antipsychotics: 3 vs. 3 --Lithium: 5 vs. 8 --Divalproex: 13 vs. 10 Previously treated with benzodiazepines: 29% vs. 35% Previously treated with antidepressants: 40% vs. 45%	Numbers screened and eligible not reported / 36 enrolled / 36 randomized	13 / 36 (36.1%) withdrew / None lost to follow-up / 36 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results		
McIntyre, 2002 (--) Canada (Poor)	Responder rate: 56.2% vs. 58.7% (p-value not reported) Calculated difference in responder rate: -2.5% Remission rate: 24.8% vs. 27.5% Calculated difference in remission rate: -2.7% Time to response: 2 to 4 wk for both treatment groups	Mean HDRS-17 scores, calculated change from baseline to 8 wk : 10.5 vs. 10.5 (NSD)	CGI-I scores: NSD (data not reported) CGI-S scores: Not reported Mean YMRS scores, calculated change from baseline to end point: -5 vs. -6 (NSD)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
McIntyre, 2002 (--) Canada (Poor)	Monitored	Topiramate vs. Bupropion SR Adverse event rate: 11/18 (61.1%) vs. 9/18 (50.0%) Topiramate (n = 14) vs. Bupropion SR (n = 13) Most common adverse events reported more frequently on Bupropion Difficulty sleeping: 16.0% vs. 27.8% (p = 0.03) Paresthesias: 17.4% vs. 27.6% (NSD) Tremors: 18.1% vs. 25.1% (NSD) Mean weight loss, kg: 5.8 vs. 1.2 (p = 0.04) No patient exhibited a manic switch	Topiramate vs. Bupropion Total withdrawals: 8/18 (44.4%) vs. 5/18 (27.8%) Withdrawals due to adverse events: 6/18 (33.3%) vs. 4/18 (22.2%)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
McIntyre, 2002 (--) Canada (Poor)	Lacked placebo arm. Small sample size; lacked sufficient power to detect a treatment difference. Concomitant medications confound results. Results should be considered preliminary.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)
Okuma, 1990 (--) Japan (Poor)	Multicenter, double-blind, double-dummy RCT Outpatient and inpatient psychiatric university clinics and hospitals	Endogenous manics (ICD-9); also met criteria for bipolar disorders in the affective disorders of DSM-III; psychopharmacologic treatment-naïve or experienced; age 13 to 65 y	Carbamazepine starting at 400 mg/d and titrated to symptoms and adverse effects Lithium starting at 400 mg/d and titrated to symptoms and adverse effects for 4 wk

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(5) Run-in/Washout period	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment
Okuma, 1990 (--) Japan (Poor)	None	Antipsychotics without sufficient antimanic effect prior to study could be continued at stable doses	5-point severity of illness scale (ranging from Normal to Extremely Severe) at baseline and weekly; 6-point scale for global improvement rate relative to first day of treatment (ranging from Markedly Improved to Alteration to Depressive or Mixed State), recorded weekly; 6-point scale for Final Global Improvement Rate (FGIR) on last day of treatment; 14-item Clinical Psychopharmacology Research Group (CPRG) Rating Scale for Mania, Doctor's Use, before and weekly

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Okuma, 1990 (--) Japan (Poor)	Carbamazepine (N = 50) vs. Lithium (N = 51) Age, mode, y: 20 to 29 y (range, less than 19 to over 70 y; note: this exceeds eligible age limit) Male / Female: 26 / 24 vs. 22 / 29 Ethnicity: not reported	Bipolar, Manic: 49 vs. 48 Bipolar, Mixed: 1 vs. 3 At least moderate severity: 43 (86.0%) vs. 44 (86.3%) Inpatient: 47 (94.0%) vs. 40 (78.4%) Outpatient: 3 (6.0%) vs. 11 (21.6%)	Numbers screened and eligible not reported / 105 enrolled / 105 randomized	24 withdrawn / 3 lost to follow-up / 101 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	
Okuma, 1990 (--) Japan (Poor)	Carbamazepine vs. Lithium Marked or Moderate Global Improvement, final assessment: 62% vs. 59% (NSD) Marked or Moderate Global Improvement, wk 1: 11/50 (22.0%) vs. 5/51 (9.8%)	Total CPRG scores for mania, wk 4: 35.3 vs. 39.2 (NSD) Serum carbamazepine concentration in good (N = 20) vs. poor (N = 13) responders, wk 4: 8.0 vs. 6.3 mcg/ml ($p < 0.05$); NSD in daily doses Serum lithium concentration in good (N = 19) vs. poor (N = 9) responders: 0.41 vs. 0.56 mEq/l ($p < 0.10$); NSD in daily doses

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Okuma, 1990 (--) Japan (Poor)	Monitored	Carbamazepine vs. Lithium Frequency of adverse events: 60% vs. 43% (NSD) Cutaneous symptoms (exanthema): 12% vs. 0% ($p < 0.05$)	Carbamazepine vs. Lithium Total withdrawals: 9/51 (17.6%) vs. 15/54 (27.8%) Withdrawals due to adverse events: 5/51 (9.8%) vs. 0/54 (0.0%) ($p < 0.05$)

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Okuma, 1990 (--) Japan (Poor)	Quality of trial conduct is questionable; 2 lithium patients were given only placebo tablets of carbamazepine by mistake and an erroneous report of blood concentration of lithium led to unblinding of treatment in one case. Concomitant antipsychotics "without sufficient antimanic effects" is unclear. Their use may have confounded the results.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Solomon, 1997(38) (--) U.S. (Poor)	Pilot long-term, double-blind, placebo-controlled RCT Inpatient then outpatient setting	Current episode of mania or major depression; bipolar I disorder (DSM-III-R); > 1 mood episode in previous 3 y; age 18 to 65 y	Divalproex (titrated to serum concentration of 50 to 125 µg/ml) vs. Placebo for up to 12 mo. Both agents in combination with lithium (titrated to serum concentration of 0.8 to 1.0 mmol/l)	Run-in on treatment directed at controlling the acute episode (details not reported); patients were randomized once subjects began to show signs of improvement from the index episode

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Solomon, 1997(38) (--) U.S. (Poor)	Neuroleptics, antidepressants, benzodiazepines	Modified version of the Longitudinal Interval Follow-up Evaluation (LIFE), recorded at baseline and every 2 mo. This included a 6-point Psychiatric Status Rating (PSR) scale (1 = no symptoms, 6 = symptoms that meet full criteria for a DSM-III-R disorder along with psychosis or extreme impairment in functioning). *Partial remission* = improvement, but continued moderate to marked symptoms not meeting full criteria for a mood episode (PSR of 3 or 4). *Relapse* = return of symptoms that met DSM-III-R criteria for a definite mood episode (PSR of 5 or 6) and occurred during a period of partial remission. *Recovery* = at least 8 consecutive weeks of no symptoms or minimal symptoms (PSR of 1 or 2, respectively). *Recurrence* = reappearance of the DSM-III-R disorder at full criteria (PSR of 5 or 6) after recovery from the preceding episode (i.e., new mood episode).	Divalproex (+ Lithium) vs. Placebo (+ Lithium) Age, range, y: 31 to 65 vs. 30 to 41 Male / Female: 4 / 1 vs. 4 / 3 Ethnicity: Not reported	Number of lifetime mood episodes, range: 2 to 51 vs. 3 to 30 (mean data not reported; NSD) Past lithium treatment, n (%): 1/5 (20.0%) vs. 6/7 (85.7%) Major depression at intake, n (%): 4/5 (80.0%) vs. 2/7 (28.6%) (NSD) Mania episode at intake, n (%): 1/5 (20.0%) vs. 5/7 (71.4%) (NSD)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results	(12) Results	(12) Results
Solomon, 1997(38) (--) U.S. (Poor)	Numbers screened and eligible not reported / 12 enrolled / 12 randomized	4 withdrew / None lost to follow-up / 12 analyzed	Divalproex vs. Placebo Partial remission, n: 5/5 (100%) vs. 6/7 (85.7%) (1 divalproex patient recovered prior to randomization; 1 placebo patient recovered abruptly in wk 4 with no intervening period of partial remission) Time to partial remission, range, wk: 0 to 1 vs. 1 to 11 Relapse or recurrence, n (%): 0/5 (0.0%) vs. 5/7 (71.4%) (p = 0.014)		

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Solomon, 1997(38) (--) U.S. (Poor)		Monitored	Most common adverse events on divalproex (+ lithium): gastrointestinal distress, tremor, cognitive impairment, alopecia Adverse events on placebo (+ lithium): not reported

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Solomon, 1997(38) (--) U.S. (Poor)	Total withdrawals: 2/5 (40.0%) vs. 2/7 (28.6%) Withdrawals due to adverse events: 2/5 (40.0%) vs. 0/7 (0.0%)	Results are inconclusive (pilot study). Small sample size, confounding co-medications, nonblinded research psychiatrist.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Calabrese, 1999(94) (--) Australia, France, U.K., U.S. (Fair)	Multicenter, double-blind, double-dummy, placebo-controlled, parallel-group RCT Outpatient setting	Bipolar I disorder (DSM-IV); at least 2 previous mood episodes in past 10 years with at least 1 episode a manic or mixed episode; current major depressive episode of >/= 2 wk but </= 12 months in duration; minimum score of 18 on 17-item Hamilton Rating Scale for Depression (HAM-D)	Lamotrigine titrated to 50 mg/d (at target dose from wk 3 to 7) vs. Lamotrigine titrated to 200 mg/d (at target dose from wk 5 to 7) vs. Placebo for 7 wk	Washout of previous psychoactive drugs within a time equivalent to 5 elimination half-lives prior to randomization

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Calabrese, 1999(94) (--) Australia, France, U.K., U.S. (Fair)	Chloral hydrate, lorazepam, temazepam. oxazepam during first 3 wk of treatment	HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS); Mania Rating Scale (MRS), Clinical Global Impressions scale for Severity (CGI-S) at baseline and weekly for 7 wk, and Clinical Global Impressions scale for Improvement (CGI-I) from day 4 onward. Response was defined as 50% or more reduction on the 17-item HAM-D or MADRS scales or a rating of very much improved or much improved on the CGI-I scale.	Lamotrigine 50 mg/d (N = 66) vs. Lamotrigine 200 mg/d (N = 63), vs. Placebo (N = 66) Age, mean, y: 41 vs. 42, vs. 42 Male / Female: 33% / 67% vs. 44% / 56% vs. 41% / 59% Ethnicity not reported	Age of onset of affective symptoms, mean, y: 22 vs. 21 vs. 21 No. of mood episodes in last 12 mo per patient, mean (SD): 2.2 (0.8) vs. 2.2 (0.9) vs. 2.2 (0.8) Duration of current episode --2 to 8 wk: 39% vs. 37% vs. 29% --> 8 to 24 wk: 44% vs. 41% vs. 42% --> 24 wk: 17% vs. 22% vs. 29% Moderate intensity of depression: 58% vs. 54% vs. 61% CGI-S score (% of patients) --Mildly ill: 3% vs. 10% vs. 2% --Moderately ill: 64% vs. 51% vs. 65% --Markedly ill: 23% vs. 30% vs. 28% --Severely ill: 11% vs. 10% vs. 11% Melancholic features: 39% vs. 40% vs. 50% Prior hospitalization for mood episode: 44% vs. 51% vs. 62% Prior suicide attempts: 32% vs. 32% vs. 36% Lithium use in last 5 mo: 23% vs. 19% vs. 23%

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results	(12) Results	(12) Results
Calabrese, 1999(94) (--) Australia, France, U.K., U.S. (Fair)	Numbers screened, eligible, and enrolled not reported / 195 randomized	60 withdrew / None lost to follow-up / 192 analyzed for efficacy, 194 analyzed for safety	Lamotrigine 50 mg/d (N = 64) vs. Lamotrigine 200 mg/d (N = 63) vs. Placebo (N = 65) (Last observation carried forward [LOCF] analysis) *Change in scores from baseline, mean* 17-item HAM-D (Primary efficacy variable): -9.3 vs. -10.5 vs. -7.8 (p = 0.084) (Analysis for observed change showed a significant treatment difference in change from baseline: -12.6 (N = 43) vs. -13.2 (N = 45) vs. -9.3 (N = 47) (p < 0.05 for both lamotrigine groups vs. placebo) Significant improvement was first noted for lamotrigine 200 mg/d only vs. placebo at week 5 (p < 0.05).	Change in scores from baseline, mean MADRS: -11.2 vs. -13.3 vs. -7.8 (p < 0.05 for lamotrigine 200 vs. placebo) CGI-S: -1.0 vs. -1.2 vs. -0.7 (p < 0.05 for lamotrigine 200 vs. placebo) CGI-I: 3.0 vs. 2.6 vs. 3.3 (p < 0.05 for lamotrigine 200 vs. placebo) MRS: 0.9 vs. 0.3 vs. -0.5 (NSD)	Combined week 3 analysis (lamotrigine </= 50 mg/d for both active groups) (N = 127): significant improvements (p < 0.05) were seen by week 3 in HAM-D Item 1 and MADRS for LOCF analyses. Subgroup analysis: No significant effect of recent lithium use on treatment group differences for any efficacy measure.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Calabrese, 1999(94) (--) Australia, France, U.K., U.S. (Fair)	*Responder rate* 17-item HAM-D: 45% vs. 51% vs. 37% (NSD) MADRS: 48% vs. 54% vs. 29% (p < 0.05 for each lamotrigine group vs. placebo) CGI-I: 41% vs. 51% vs. 26% (p < 0.05 for lamotrigine 200 vs. placebo)	Elicited by investigator	Lamotrigine 50 mg/d (N = 66) vs. Lamotrigine 200 mg/d (N = 66) vs. Placebo (N = 65) Patients reporting any adverse event: 79% vs. 79% vs. 92% Of the most common (>/= 5%) adverse events, only headache showed a significant treatment difference (n, %): 23 (35%) vs. 20 (32%) vs. 11 (17%) (p < 0.05 for each lamotrigine group vs. placebo) Other common adverse events: --Nausea: 11 (17%) vs. 10 (16%) vs. 10 (15%) --Pain: 5 (8%) vs. 7 (11%) vs. 5 (8%) --Rash: 9 (14%) vs. 7 (11%) vs. 7 (11%) --Dizziness: 6 (9%) vs. 6 (10%) vs. 2 (3%) Manic / hypomanic / mixed episodes (as reported by investigator) (n, %): 2 (3%) vs. 5 (8%) vs. 3 (5%) (NSD) Patients reporting any serious adverse event: 4 vs. 2 vs. 3 Illness-related Serious Adverse Events --Probable suicide: 0 vs. 0 vs. 1 --Attempted suicide: 1 vs. 0 vs. 1 --Suicidal ideation: 1 vs. 1 vs. 0 --Worsening depression: 1 vs. 0 vs. 0 --Psychotic episode: 1 vs. 0 vs. 0 (All illness-related serious adverse events in the lamotrigine 50-mg/d group except for the attempted suicide [3 out of 4 events] were considered to be possibly drug related.)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Calabrese, 1999(94) (--) Australia, France, U.K., U.S. (Fair)	Lamotrigine 50 mg/d vs. Lamotrigine 200 mg/d vs. Placebo Total withdrawals: 23 (35%) vs. 18 (29%) vs. 19 (29%) Withdrawals due to adverse events: 12 (18%) vs. 10 (16%) vs. 10 (15%) Adverse events accounting for more than one withdrawal --Rash: 3 vs. 4 vs. 2 --Worsening of psychiatric depression: 3 vs. 0 vs. 1 --Pruritus: 0 vs. 1 vs. 1 --Suicidal ideation: 1 vs. 1 vs. 0 --Suicide attempt: 1 vs. 0 vs. 1 --Mania: 0 vs. 2 vs. 0	Modified ITT analyses were used for efficacy and safety. Dosage escalation was faster than the recommended regimen and may have increased the risk of rash. The fixed-dose titration schedule resulted in unequal treatment durations for the 50-mg group (5 wk) and the 200-mg group (3 wk). The 17-item HAM-D scale (weighted toward somatic symptomatology) may have been less sensitive and reliable for detecting effects on bipolar depression or treatment differences than the MADRS.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Calabrese, 2000 (--) U.S., Canada (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Age 18 y or older; bipolar disorder I or II with rapid cycling (DSM-IV); euthyroid or, if taking thyroid replacement therapy, on stable dose for 3 mo	Open-label preliminary phase: Lamotrigine started at 25 mg/d and slowly titrated to target dose of 200 mg/d (max. 300 mg/d) for 4 to 8 wk Double-blind phase: Lamotrigine 100 to 500 mg/d vs. Placebo for 26 wk Lamotrigine doses were adjusted for concomitant valproate or carbamazepine therapy.	4- to 8-wk run-in on lamotrigine; patients were randomized if they were taking a minimum dose of 100 mg/d of lamotrigine and had a score of </= 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D) and </= 12 on the Mania Rating Scale (MRS) from the Schedule for Affective Disorders and Schizophrenia (SADS)-Change version over a 2-wk period; they were eligible to enter the randomized phase if they successfully completed a taper of all other psychotropic medications while maintaining the minimum criteria for wellness, had no change in lamotrigine dosage during the final week of the preliminary phase, and had no mood episodes requiring additional drug or electroconvulsive therapy after the first 4 wk of the preliminary phase.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Calabrese, 2000 (--) U.S., Canada (Fair)	Open-label phase: Lithium (60, 19%), divalproex (63, 19%), carbamazepine (14, 4%), antidepressants (96, 30%), antipsychotics (24, 7%), and benzodiazepines (88, 27%) Double-blind phase: Lorazepam. Other psychotropics (e.g., lithium, divalproex, antipsychotics, electroconvulsive therapy) could be added only if an increase in lamotrigine dose was not effective or appropriate (i.e., patients reached primary study end point).	Open-label phase: 17-item HAM-D, MRS, Clinical Global Impressions-Severity scale (CGI-S), Global Assessment Scale (GAS), and retrospective life chart at screening (within -14 d), day 1, then weekly till randomization. Double-blind phase: HAM-D, MRS, CGI-S, GAS, and prospective life chart on day 1, then wk 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 26. *Relapse* was operationally defined as the need for additional pharmacotherapy for a mood episode or one that was thought to be emerging.	Open-label Lamotrigine (N = 324); Double-blind Placebo (N = 88) vs. Lamotrigine (N = 92) Age, mean, y: 38.6; 37.4 vs. 38.5 Female, n (%): 190 (59%); 52 (59%) vs. 51 (55%) Ethnicity: Not reported	Age at onset of first episode of depression / mania, mean, y: 17.5 / 20.2; 17.0 / 19.1 vs. 17.3 / 20.7 Bipolar I, n (%): 225 (69%); 60 (68%) vs. 68 (74%) Bipolar II, n (%): 98 (30%); 28 (32%) vs. 24 (26%) No. of mood episodes in last 12 mo, mean: 6.3; 5.9 vs. 6.3 Prior hospitalizations for mood episode, mean: 1.8; 1.3 vs. 1.5 Prior suicide attempt, n (%): 117 (36%); 34 (39%) vs. 25 (27%) Lifetime prevalence of psychosis, n (%): 88 (27%); 21 (24%) vs. 25 (27%) Type of mood episode at screening, % --Depression: 57%; 56% vs. 55% --Mania/Hypomania: 20%; 19% vs. 20% --No episode: 18%; 17% vs. 21% --Mixed: 5%; 9% vs. 4%

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results	(12) Results	(12) Results
Calabrese, 2000 (--) U.S., Canada (Fair)	Numbers screened and eligible not reported / 324 enrolled / 182 randomized	Open-label phase: 142 withdrew / 19 lost to follow-up / 324 analyzed for safety Double-blind phase: 28 withdrew / 10 lost to follow-up / 177 analyzed for efficacy, 180 for safety	Lamotrigine vs. Placebo Time to relapse (Primary Efficacy Measure), median survival time, wk: 18 vs. 12 (p = 0.177) --In bipolar I subgroup (N = 125): 18 vs. 14 (estimated; p = 0.738) --In bipolar II subgroup (N = 52): 17 vs. 7 (p = 0.073) Required additional pharmacotherapy for emerging mood episode, n (%): 45 (50%) vs. 49 (56%)	Time to premature discontinuation for any reason, median survival time, wk: 14 vs. 8 (p = 0.036) --In bipolar I subgroup: 10 vs. 12 (estimated; p = 0.426) --In bipolar II subgroup: 16 vs. 5 (estimated; p = 0.015) Stable without relapse for 6 mo, n (%): 37/90 (41%) vs. 23/87 (26%) (p = 0.03) --In bipolar I subgroup: 39% vs. 31% (NSD) --In bipolar II subgroup: 46% vs. 18% (p = 0.04)	CGI-S, change from baseline: NSD (data not reported) --In bipolar I subgroup: NSD --In bipolar II subgroup: NSD GAS, change from baseline: NSD (data not reported) --In bipolar I subgroup: NSD --In bipolar II subgroup: p </= 0.03 at wk 3, 6, and 12 17-item HAM-D, change from baseline: NSD (data not reported) MRS, change from baseline: NSD (data not reported)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Calabrese, 2000 (--) U.S., Canada (Fair)		Monitored	Double-blind phase--Lamotrigine (N = 92) vs. Placebo (N = 88) Serious adverse events, n: 1 vs. 2 Adverse events considered reasonably related to study treatment: 24 (27%) vs. 28 (30%) (NSD); most common: nausea (4, 4% vs. 4, 5%) and headache (6, 7% vs. 8, 9%) Most Common (>/= 10%) Treatment-emergent Adverse Events: headache (21, 23% vs. 15, 17%), nausea (13, 14% vs. 10, 11%), infection (11, 12% vs. 10, 11%), pain (9, 10% vs. 7, 8%), and accidental injury (10, 11% vs. 4, 5%). Rash occurred in 3 (3%) vs. 2 (2%) patients. Treatment-related rash: 0 (0%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Calabrese, 2000 (--) U.S., Canada (Fair)	Double-blind phase Total withdrawals: 11/93 (12%) vs. 17 (19%) Withdrawals due to adverse events: 1 (1%) vs. 2 (2%)	The analyses for double-blind treatment were based on a selective cohort of patients who were more likely to be lamotrigine responders and less prone to develop rash. The primary efficacy measure, time to relapse, depended on the investigator's discretion of whether additional psychotropic medication was necessary to treat an emerging mood episode.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Mishory, 2003(36) (--) Israel (Poor)	Double-blind, placebo-controlled, crossover RCT Outpatient setting	Bipolar disorder I or schizoaffective disorder (DSM-IV); no unstable physical illness; out of hospital for at least 1 mo; inadequate prophylaxis in the past on lithium, carbamazepine, or valproate; at least 1 episode per year for previous 2 years despite compliance with their mood stabilizer	Phenytoin (starting at 100 mg and titrated by 100 mg/wk; mean dose and serum concentration at 6 mo: 380 +/- 80 mg and 10.7 +/- 4.2 mcg/ml) vs. Placebo for 6 mos then crossover	1-mo phased washout during crossover

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Mishory, 2003(36) (--) Israel (Poor)	Ongoing prophylactic treatment remained unchanged (lithium, carbamazepine, valproate, or neuroleptic)	Brief Psychiatric Rating Scale (BPRS), Young Mania Scale (YMS), Hamilton Depression Scale (HMS), and Global Clinical Impression at baseline and monthly thereafter Primary outcome measure was time to 'event,' an affective relapse. Criteria for an 'event' were need for hospitalization or emergent symptoms of sufficient severity to require addition of a neuroleptic or antidepressant, according to the masked clinical psychiatrist.	Age. mean (SD), y: 45.2 (9.6) Male / Female: 9 / 14 Ethnicity not reported	Age of onset of illness, mean (SD), y: 26.5 (9.0) Number of affective episodes, mean (SD): 13.8 (8.5) Time in remission before entering trial, mo: 4.0 (range: 1 to 13) Last affective episode --Mania: 11 --Depression: 7 --Mixed: 5

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results	(12) Results	(12) Results
Mishory, 2003(36) (--) Israel (Poor)	Number screened, eligible, enrolled not reported / 23 randomized	4 withdrew (and were replaced with new enrolled patients) / None lost to follow-up / 23 analyzed (30 6-mo observation periods)	Phenytoin vs. Placebo Time to clinical relapse (event), median (estimated from figure), mo: > 6 vs. 5 (p = 0.02) Relapsed during first 6 mo: 3/10 (30.0%) vs. 8/13 (61.5%) (p = 0.053) Data for rating scales were not reported.		

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Mishory, 2003(36) (--) Israel (Poor)		Not reported	Phenytoin (n = 14) vs. Placebo (n = 16) Common adverse events during 30 observation periods Slight weakness and sleepiness: 1 (7.1%) vs. 1 (6.2%) Temporary dizziness, resolved without change in treatment: 3 (21.4%) vs. 0 (0.0%) Psoriasis-like symptoms: 1 (7.1%) vs. 0 (0.0%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Mishory, 2003(36) (--) Israel (Poor)	Phenytoin vs. Placebo Total withdrawals: 9/23 (39.1%) vs. 7/23 (30.4%) (if 4 dropouts during the first 3 wk of phenytoin treatment are counted, total for phenytoin would be 13/27, 48.1%) Withdrawals due to adverse event: 1/23 (4.3%) vs. 0/23 (0.0%) (psoriasis-like symptoms due to concomitant lithium treatment)	Small sample size; dropouts excluded from analyses; short study duration; incomplete reporting of data. Results reflected a selective population of compliant patients because any post-randomization dropout was excluded from analyses and replaced with a new patient who was assigned the dropout's randomization number.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Pande, 2000(41) U.S. (Fair)	Multicenter, double-blind, parallel-group RCT Outpatient setting	Age 16 y or older; lifetime diagnosis of bipolar I disorder (DSM-IV) with manic/hypomanic or mixed symptoms; Young Mania Rating Scale (YMRS) >/= 12 despite ongoing treatment with lithium, valproate, or both in combination; lithium serum concentration >/= 0.5 mEq/l or valproate concentration >/= 50 mcg/ml	Gabapentin 600 to 3600 mg/d Placebo 10 wk (Added on to lithium, valproate, or combination)	2-wk, single-blind, placebo run-in during which lithium and/or valproate doses were adjusted based on clinical response and to achieve minimum threshold concentrations; patients were randomized to double-blind treatment if they met entry criteria at the end of the placebo run-in

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Pande, 2000(41) U.S. (Fair)	Lithium and valproate at steady doses unless dosage changes were necessary for patient safety	YMRS, Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), CInical Global Impression of Severity (CGI-S) and Change (CGIC), recorded weekly for 4 wk after randomization, then biweekly for 6 wk. Self-assessed internal state scale (ISS), Life Chart for Recurrent Affective Illness (Life Chart), and SF-36 Quality of Life Questionnaire Responders were defined as "much improved" or "very much improved" on CGIC	Gabapentin (N = 58) vs. Placebo (N = 59) Age, mean (SD), y: 40.7 (.4) vs. 38.2 (10.5) Male / Female, %: 50 / 50 vs. 54 / 46 Ethnicity not reported	Ongoing treatment for bipolar disorder --Lithium only, n: 22 vs. 17 --Valproate only, n: 26 vs. 31 --Both, n: 10 vs. 11

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results	(12) Results	(12) Results
Pande, 2000(41) U.S. (Fair)	Numbers screened and eligible not reported / 117 enrolled / 117 randomized	48 withdrawn / None lost to follow-up / 114 analyzed	Gabapentin vs. Placebo Adjusted means included treatment and center in ANCOVA model and YMRS baseline score as covariate YMRS, adjusted mean: -6.5 vs. -9.9 (difference -3.34; 95% CI: -6.35 to -0.32; p = 0.03) HAM-D, adjusted mean: 0.01 vs. -1.3 (difference -1.32; 95% CI: -4.40 to 1.77; p = 0.40)	Change in score from baseline to last observation carried forward HAM-A, total score: 0.36 vs. -1.05 (p = 0.24) CGI-S: -0.63 vs. -0.98 (p = 0.10) ISS, % of patients --Manic (>/= 70): 9 vs. 8 --Depressed (</= 30): 17 vs. 17 --Normal (31 to 69): 74 vs. 75	CGIC "much improved" or "very much improved" (responders), % : 37 vs. 47 (p = 0.30)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Pande, 2000(41) U.S. (Fair)		Monitoring	Gabapentin vs. Placebo Serious adverse events: 6 vs. 5 (3 of the 6 serious adverse events in the gabapentin group started during the placebo lead-in) Most frequent adverse events, % --Somnolence: 24.1 vs. 11.9 --Dizziness: 19.0 vs. 5.1 --Diarrhea: 15.5 vs. 11.9 --Headache: 10.3 vs. 11.9 --Amnesia: 10.3 vs. 3.4

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Pande, 2000(41) U.S. (Fair)	Gabapentin vs. Placebo Total Withdrawals: 27/58 (46.6%) vs. 21/59 (35.6%) Withdrawals due to adverse events: 7/58 (12.1%) vs. 5/59 (8.5%)	Primary efficacy variables were the YMRS and HAM-D. Placebo was superior to gabapentin in terms of changes in YMRS scores. A post hoc analysis determined that more lithium dosage adjustments were made during the placebo lead-in in the placebo group (n = 12) than in the gabapentin group (n = 4; p < 0.01). When the data from these 16 patients were excluded from analysis, the treatment difference in YMRS change score was no longer significant.

Evidence Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Phenytoin vs. Carbamazepine				
Skelton, 1991(43) U.S. (Poor)	RCT Single-center, Veterans Affairs office practice	Not reported. Patients described as having severe thiamine deficiency or beriberi with painful peripheral neuropathy unrelieved by conventional medications; 9 of 12 patients (75%) had severely affected nerve conduction velocities and 3 (25%) had abnormal electromyogram results.	Phenytoin starting at 100 mg/d vs. Carbamazepine starting at 200 mg/d, doses increased as tolerated, for 6 mo	None

Evidence Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Phenytoin vs. Carbamazepine				
Skelton, 1991(43) U.S. (Poor)	Not reported	Pain scale ranging from 1 (barely noticeable pain at rest) to 10 (incapacitating pain), weekly	Age range, y: 63 to 67 100% White men	Former prisoners of war (WWII)

Evidence Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost follow-up /analyzed	(12) Results	(13) Method of adverse effects assessment?
Phenytoin vs. Carbamazepine				
Skelton, 1991(43) U.S. (Poor)	Number screened not reported / Number eligible not reported / 12 enrolled / 12 randomized	1 withdrawn / None lost to follow-up / 11 analyzed	Phenytoin vs. Carbamazepine Calculated change (%) in mean pain scores, baseline to final: -4.43 (-67.4%) vs. -6.00 (-77.4%) (no statistical analysis) Number of patients achieving complete relief: 2 vs. 1	Not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Leijon, 1989(47) Sweden (Poor)	Double-blind, 3-phase, crossover, placebo-controlled, double-dummy RCT Research program on Central Post-stroke Pain (CPSP)	Unequivocal stroke episode; patient seeks remedy for constant or intermittent pain that started after the stroke; pain not of nociceptive, peripheral neuropathic, or psychogenic origin	Carbamazepine up to 800 mg/d vs. Amitriptyline up to 75 mg/d vs. Placebo for 4 wk	7-d washout before crossover

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Leijon, 1989(47) Sweden (Poor)	Acetaminophen 2000 mg/d (n = 1) and Transcutaneous Electrical Nerve Stimulation (n = 2, one for nociceptive knee pain and the other for CPSP)	10-point verbal scale for pain intensity, daily; 5-point global assessment scale fo pain relief (1 = pain worsened, 5 = pain-free) on day 28 of each treatment period; 10-item Comprehensive Psychopathological Rating Scale (CPRS) for depression before each treatment and on day 28 of each treatment period. Responders on the daily pain rating scale were defined as patients who obtained a pain reduction of at least 20% as compared with the placebo period.	Mean age (range), y: 66 (53 to 74) 80% Male, 20% Female Ethnicity not reported	Location of cerebrovascular lesion, n: brainstem (7), thalamic (5), supratentorial, extrathalamic (2), unidentified (1) Duration of pain, mean (range), mo: 54 (11 to 154) Dominant pain qualities: burning, aching, and throbbing Other types of chronic pain, n: low back pain (3), chronic tension headache (1), sciatica (1)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Leijon, 1989(47) Sweden (Poor)	27/15/15/15	1 discontinued carbamazepine on day 25 because of interaction with warfarin (included in analyses); 1 not randomized to carbamazepine because of allergy / none lost to follow-up / 14, 15, and 15 analyzed for carbamazepine, amitriptyline, and placebo, respectively	Carbamazepine vs. Amitriptyline vs. Placebo Week 4 Daily Pain Rating, mean: 4.2 vs. 4.2 vs. 5.3 ($p < 0.05$ for amitriptyline vs. placebo)	Improved on Global Assessment of Change in Pain: 5/14 (36%) vs. 10/15 (67.8%) vs. 1/15 (6.7%) ($p < 0.05$ for amitriptyline vs. placebo; NSD between amitriptyline and carbamazepine)	Depression Scores at end of each treatment period, mean (range): 3.0 (0 to 7) vs. 2.2 (0 to 8) vs. 2.6 (0 to 6) (NSD) Almost all patients had low baseline depression scores (mean 2.9; range 0 to 6.5) and no patients appeared to be depressed

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Leijon, 1989(47) Sweden (Poor)	Monitored	Most frequent AEs-- On carbamazepine: vertigo, tiredness, gait disturbances On amitriptyline: tiredness and dry mouth	Total withdrawals: 1 (carbamazepine) Withdrawals due to adverse events: None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Leijon, 1989(47) Sweden (Poor)	Pain rating scores at baseline and change from baseline were not reported.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Gomez-Perez, 1996(45) Mexico (Poor)	Double-blind, placebo-controlled, crossover RCT Clinic setting	Severe symmetric, distal diabetic peripheral neuropathy for at least 6 mo; abnormally prolonged motor nerve conduction velocity	Carbamazepine titrated up to 600 mg/d vs. Nortriptyline / Fluphenazine titrated up to 60 mg / 3 mg for total of 32 d (15 d at maximum dose)	2- to 4-wk washout on placebos of both therapies until symptoms returned to baseline level, before crossover

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Gomez-Perez, 1996(45) Mexico (Poor)	Not reported	Vertical visual analogue scale for pain and paresthesia at baseline and every 15 d	Sequence A (Nortriptyline / Fluphenazine first) vs. Sequence B (Carbamazepine first) Mean (SD) age, y: 51.5 (8.4) vs. 43.1 (19.4) (p > 0.05) 50.0% vs. 37.5% Male (p > 0.05) Ethnicity not reported	Sequence A (Nortriptyline / Fluphenazine first) vs. Sequence B (Carbamazepine first) Mean (SD) diabetes mellitus duration, y: 8.9 (7.8) vs. 9.9 (4.4) Mean (SD) neuropathy duration, y: 2.0 (1.9) vs. 2.3 (2.8) (p > 0.05) Mean (SD) HgA1c, %: 10.2 (2.8) vs 9.5 (1.9)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Gomez-Perez, 1996(45) Mexico (Poor)	--/--/16/16	2/0/14	Carbamazepine vs. Nortriptyline / Fluphenazine Mean % change in pain at 30 d: Sequence A: -53.7 vs. -56.1 (NSD) Sequence B: -44.4 vs. -77.0 (NSD)	Carbamazepine vs. Nortriptyline / Fluphenazine Mean % change in paresthesia at 30 d: Sequence A: -68.2 vs. -62.2 (NSD) Sequence B: -48.0 vs. -82.0 (NSD)	

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Gomez-Perez, 1996(45) Mexico (Poor)		Not reported	Nortriptyline / Fluphenazine Adverse events (units not reported): 8 vs. 3 Dryness of the mouth and dizziness reported with nortriptyline / fluphenazine Epigastric pain reported with carbamazepine

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Gomez-Perez, 1996(45) Mexico (Poor)	Carbamazepine vs. Nortriptyline / Fluphenazine Total withdrawals: 1/16 (6.3%) vs. 1/16 (6.3%) Withdrawals due to adverse events: 1/16 (6.3%) vs. 0/16 Limited by small sample size.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Lechin, 1989(42) (--) Venezuela (Poor)	Multicenter, double-blind, crossover RCT followed by open-label study Outpatient setting	None reported per se. Patients were described as having facial pain without relief for at least 2 y; clinical diagnosis of trigeminal neuralgia; normal results on tests that excluded other neurologic diseases; failed baclofen, benzodiazepines, phenytoin	Carbamazepine 300 to 1200 mg/d vs. Pimozide 4 to 12 mg/d for 8 wk each (Total blinded treatment duration, 24 wk) Open-label pimozide (duration not reported)	Placebo washout for 4 wk before starting active treatment and before crossover. Placebo responders (improvement in trigeminal neuralgia score of 20% or more during the initial placebo washout phase) were excluded from the study.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Lechin, 1989(42) (--) Venezuela (Poor)	Analgesic (aspirin)	Trigeminal neuralgia scores (range: 0 to 100) weekly; 7-point numerical rating scale for bursts of pain (0 = No pain; 6 = Pain present, cannot be ignored, prompt medical advice sought); 4-point scale for basal pain and sensitivity of trigger zones (range: 0 to 3; ratings not defined); number of pain relief tablets	Age, mean (range), y: 59.3 (48 to 68) Male / Female, n: 24 / 24 Ethnicity not reported	Not reported (see eligibility criteria)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Lechin, 1989(42) (--) Venezuela (Poor)	Number screened and eligible not reported / 68 enrolled / 59 randomized	9 withdrew during placebo washout before randomization / 3 lost to follow-up / 48 analyzed (11 excluded from analyses)	Carbamazepine vs. Pimozide Reduction in total trigeminal neuralgia score at wk 6, mean: 49.7% vs. 78.4% ($p < 0.001$) Similar results were obtained at wk 7 and 8 ($p < 0.001$ for each analysis). (It is unclear whether percentages are relative or absolute changes.)	Onset of significant improvement, wk: 4 vs. 2 "Improved" (It is unclear whether "improved" was based on 20% or more reduction in the trigeminal neuralgia score.) --Before crossover: 14 (58%) vs. 24 (100%) --After crossover: 13 (54%) vs. 24 (100%)	Dose achieving maximal response, mg/d: 900 vs. 12

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Lechin, 1989(42) (--) Venezuela (Poor)	Monitored	Serious toxic effects of carbamazepine: sluggishness (mental and physical) (18/48, 37.5%); related to blood elements [*sic*]; liver function abnormalities; inappropriate secretion of vasopression in association with a decreased ability to excrete a water load; erythematous exanthem (resolved after trial ended) (1 patient, 2.1%, each) Frequent adverse events during pimozide therapy: physical and mental retardation, hand tremors, memory impairment, involuntary jerking movements during sleep, and slight Parkinson's disease manifestations (attenuated by small doses of biperiden or dosage reduction) (total 40/48, 83.3%). Despite experiencing adverse events on pimozide, all patients refused interruption of pimozide therapy.	Total withdrawals: 9 (before randomization) Withdrawals due to adverse events: None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lechin, 1989(42) (--) Venezuela (Poor)	Exclusion of placebo responders before randomization may have resulted in treatment responses smaller than those that might be seen in clinical practice. Although patients had obtained partial and temporary improvement followed by "total failure" of prior

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Keczkes, 1980(98) (--) U.K. (Poor)	Parallel-group RCT (blinding not reported) Inpatient for 2 wk then outpatient setting	Inclusion criteria unclear; patients described as being over 50 years old with early, severe painful herpes zoster (mean duration of rash before treatment was 5.0 days for carbamazepine- and 5.3 days for prednisolone-treated patients.	Carbamazepine (acting as placebo) 400 mg/d for 4 wk vs. Prednisolone 40 mg/d for 10 d then gradually tapering off over next 3 wk. Treatments were given prophylactically.	None
Lindström, 1987(46) Sweden (Poor)	DB CO RCT Double-blind, crossover RCT	Active, typical idiopathic trigeminal neuralgia; seeral attacks daily over a long period of time	Carbamazepine in maximum tolerated dose vs. Tocainide 20 mg/kg/d	None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Keczkes, 1980(98) (--) U.K. (Poor)	Topical neomycin plus gramicidin ointment; talcum powder; analgesics allowed only in posthperpetic neuralgia phase (not acute phase)	Presence or absence of postherpetic neuralgia recorded every 2 wk Postherpetic neuralgia was defined as pain in the affected area that lasted beyond 2 mo from the onset of pain.	Age, mean (range), y: 66.4 (50 to 81) Male / Female: 14 / 6 in both groups Ethnicity not reported	Duration of rash before study treatment: 5 days (carbamazepine) and 5.3 days (prednisolone)
Lindström, 1987(46) Sweden (Poor)	None	11-point scale for pain frequency and severity daily; patient activity pattern, pain precipitation factors twice weekly by telephone interview	Age range, y: 41 to 78 42% Male, 58% Female Ethnicity not reported	Disease duration: 5 to 19 y

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Keczkes, 1980(98) (--) U.K. (Poor)	Numbers screened and eligible not reported / 40 enrolled / 40 randomized	None withdrew / None lost to follow-up / 40 analyzed	Carbamazepine vs. Prednisolone (no statistical analyses) Developed postherpetic neuralgia (pain lasting > 2 mo): 13/20 (65%) vs. 3/20 (15%)	Duration of postherpetic neuralgia, mo: > 3 to 18 vs. 4 to 6 Duration of postherpetic neuralgia >/= 1 y, n (%): 4 (20%) vs. 0 (0%)	
Lindström, 1987(46) Sweden (Poor)	--/--/12/12	0/0/12	No Medication (N = 8) vs. Carbamazepine (N = 11) vs. Tocainide (N = 11) Range of Mean Pain Scores for the Last 10 Days of Each 2-wk Treatment Period: 4 to 10 vs. 0.6 to 7.9 vs. 0.8 to 8.1 Number of mean pain scores </= 4.0: 1/8 (12.5%) vs. 9/11 (81.8%)		

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Keczkes, 1980(98) (--) U.K. (Poor)	Not reported	Not reported	No withdrawals; No withdrawals due to adverse events
Lindström, 1987(46) Sweden (Poor)	Monitored	No adverse events reported for carbamazepine. Tocainide: nausea, apical paresthesias, skin rash	Total withdrawals: 1 (due to rash on tocainide)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Keczkes, 1980(98) (--) U.K. (Poor)	Blinding was not reported. Spontaneous resolution of postherpetic neuralgia may have confounded treatment response rates. Treatment regimens differed, with a tapering schedule for prednisolone and stable dosing for carbamazepine. Double-dummy was not used
Lindström, 1987(46) Sweden (Poor)	Limited by small sample size and problems with internal validity. Serious hematologic side effects of tocainide infrequently cause death.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Dallocchio, 2000(69) Italy (Poor)	Open-label RCT Outpatient setting implied (not reported)	Age >/= 60 y; type II diabetes with stable glycemic values; clinically relevant lower limb polyneuropathy with significant pain and paresthesias lasting at least 6 mo; absent Achilles reflexes or reduction of vibration sensitivity; pain intensity score of at least 2 on a 5-point categorical scale (0 = no pain; 4 = excruciating pain)	Gabapentin titrated from 400 to 2400 mg/d vs. Amitriptyline titrated from 10 to 90 mg/d over 4 wk then stable dosing for 8 wk (total 12 wk)	1-month washout of previous adjuvant analgesics

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Dallocchio, 2000(69) Italy (Poor)	Benzodiazepines if dose had been stable for at least 1 mo and remained unchanged during the study	Pain score measured on a 5-point categorical scale (0 = no pain; 4 = excruciating pain); paresthesia score (measured on a 5-point categorical scale similar to the pain scale), at baseline and 12 wk	Gabapentin vs. Amitriptyline Age, mean (SD or SE, not specified), y: 71 (7) vs. 71 (6) Male / Female: 38.5% / 61.5% vs. 41.7% / 58.3% Ethnicity not reported	Duration of pain, mean (SD or SE, not specified), mo: 34 (11) vs. 22 (12) (p = 0.026) Duration of diabetes, mean (SD or SE, not specified), y: 12 (4) vs. 9 (7)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Dallocchio, 2000(69) Italy (Poor)	Number screened not reported / Number eligible not reported / 25 enrolled / 25 randomized	None withdrawn / None lost to follow-up / 25 analyzed	Gabapentin vs. Placebo Mean change in pain score (scale, 0 to 4): -1.9 (0.8) vs. -1.3 (0.6) (p = 0.026)	Achieved goal pain intensity score of 1 or less: 10/13 (76.9%) vs. 8/12 (66.7%) (no statistical analysis)	

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Dallocchio, 2000(69) Italy (Poor)	Not reported	Gabapentin vs. Amitriptyline Total patients reporting >/= 1 adverse event: 4/13 (30.8%) vs. 11/12 (91.7%) Most common adverse events: Dizziness: 2/13 (15.4%) vs. 5/12 (41.7%) Somnolence: 1/13 (7.7%) vs. 6/12 (50.0%) Dry mouth: 0/13 (0.0%) vs. 5/12 (41.7%) Constipation: 0/13 (0.0%) vs. 4/12 (33.3%)	None of the patients withdrew

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Dallocchio, 2000(69) Italy (Poor)	Dissimilarity in duration of pain at baseline (a difference of 1 yr), while probably not clinically relevant, suggests that randomization may have been inadequate. Open-label design introduces possibility of bias. On the 5-point pain scale, the mean changes in pain scores were equivalent to reducing pain from moderate-to-severe to mild pain for gabapentin as compared with reducing pain from moderate-to-severe to mild-to-moderate for amitriptyline.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Morello, 1999(44) U.S. (Fair)	Double-blind, double-dummy, crossover RCT, single center (Veterans Affairs San Diego Healthcare System, Ambulatory Care Clinic)	> / = 18 yr old; stable glycemic control; chronic daily pain for more than 3 mo during which both quality and location were consistent with Diabetic Peripheral Neuropathy (DPN) pain as diagnosed by a neurologist; creatinine clearance [> / =] 30 ml/min	Gabapentin 900 to 1800 mg/d vs. Amitriptyline 25 to 75 mg for 6 wk	2-wk washout before applying entry criteria for randomization 1-wk washout before crossover

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Morello, 1999(44) U.S. (Fair)	Acetaminophen up to 1300 mg/d for severe pain or non-DPN pain	Pain Scale Rating System (13-point verbal rating scale ranging from none to extremely intense), Global Rating Scale of pain relief (6-point scale ranging from worse pain to complete relief)	Mean (SD) age, y: 60.4 (10.8) 96% Male; 4% Female 92% White; 8% African American	Mean (SD) duration of diabetes, y: 13.4 (11.3) Mean (SD) initial hemoglobin A1c: 0.071 (0.005) Mean (SD) duration of pain: 5.7 (4.2)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Morello, 1999(44) U.S. (Fair)	--/28/25/25	4/0/19 or 21 (2 Early Crossovers)	Mean difference in pain intensity scores at 6 wk: 0.091 units (95% CI: -0.074 to 0.256; p = 0.26) (Note: 0.35 units was the difference between moderate and mild pain) Gabapentin vs. Amitriptyline Patients with moderate or greater pain relief: 11/21 (52%) vs. 14/21 (67%) (p > 0.1)		

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Morello, 1999(44) U.S. (Fair)	Not reported	More common on amitriptyline than gabapentin: weight gain (6 vs. 0; p = 0.01) No statistically significant difference (top 10 adverse events): sedation, dry mouth, dizziness, postural hypotension, ataxia, constipation, lethargy, edema, headache, pruritus	Gabapentin vs. Amitriptyline Total Withdrawals: 2 vs. 2 Withdrawals due to adverse event: 2 vs. 1 Early Crossover Because of Intolerable Adverse Events: 2 vs. 1

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Morello, 1999(44) U.S. (Fair)	The limited number of patients enrolled introduces the possibility of a type II error. Post hoc analysis revealed that a sample size of 260 patients per paired crossover study would be necessary to provide 80% power to detect a significant treatment difference of one third of the difference between mild and moderate pain.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Lockman, 1973(97) (--) U.S. (Poor)	Double-blind, crossover RCT Outpatient setting implied	Not reported per se; patients described as hemizygote or heterozygote for Fabry's disease with frequent episodes of pain; diagnoses confirmed biochemically; frequent episodes of painful crises or continuous acroparesthesias not relieved by either convention	Phenytoin 300 mg/d (or 4 to 6 mg/kg/d) vs. Aspirin 1800 mg/d vs. Multivitamin (used as placebo) 3 tablets/d for 3 wk per treatment period (total 9 wk)	None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Lockman, 1973(97) (--) U.S. (Poor)	Not reported	Self-assessed pain relief (0 = No relief, 3 = Complete relief), recorded daily	Age, median (range), y: 19 (13 to 32) Male / Female: Not reported Ethnicity not reported	7 hemizygotes, 1 heterozygote for Fabry's disease

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results	(12) Results	(12) Results
Lockman, 1973(97) (--) U.S. (Poor)	Numbers screened and eligible not reported / 8 enrolled / 8 randomized	None withdrawn / None lost to follow-up / 8 analyzed	Phenytoin vs. Aspirin vs. Multivitamin Pain relief score, mean (range): 2.7 (1.0 to 3.0) vs. 0.5 (0 to 2.1) vs. 0.9 (0 to 2.6) ($p < 0.001$ for phenytoin vs. aspirin or multivitamin; NSD for aspirin vs. multivitamin)	Adherence (percentage of doses taken), median (range): 95 (55 to 100) vs. 75 (28 to 95) vs. 81 (71 to 98)	

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse events reported	(15) Total withdrawals; withdrawals due to adverse events
Lockman, 1973(97) (--) U.S. (Poor)	Monitoring	Dizziness, drowsiness, and headache: 1 patient on phenytoin (serum concentration 33 mcg/ml)	No withdrawals

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lockman, 1973(97) (--) U.S. (Poor)	Adherence (percentage of doses taken) seemed to be lower with aspirin than the other two treatments. No washout before crossovers; possible carryover effects.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lockman, 1973(97) (--) U.S. (Poor)	Adherence (percentage of doses taken) seemed to be lower with aspirin than the other two treatments. No washout before crossovers; possible carryover effects.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Campbell, 1966(50) U.K. (Poor)	Multicenter, double-blind, double crossover RCT; treatment sequences: C-P-C-P vs. P-C-P-C (C = Carbazepine; P = Placebo) Outpatient setting implied	Trigeminal neuralgia; patients otherwise admitted to trial without selection	Carbazepine (Tegretol) up to 4 tab/d (strength not reported) vs. Placebo for two alternate 2-wk periods each (total 4 wk per treatment) One of the three centers limited maximum dosage to 3 tab/d.	None
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)	Double-blind, crossover RCT Outpatient setting implied	Not reported per se; patients had "classical" tic douloureux (trigeminal neuralgia).	Carbamazepine 600 mg/d vs. Placebo for 3 days each (total 6 days of treatment) One patient was studied for 16 d (six 2- to 4-d treatment periods)	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Campbell, 1966(50) U.K. (Poor)	Not reported	4-point numeric pain rating scale (0 = nil to 3 = severe) Sum of upgradings or downgradings in pain score as a % of the sum of the possible upgradings or downgradings	Mean age (range), y: 59 (20 to 84) 34% Male Ethnicity not reported	Not reported
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)	Not reported	Self-assessed pain observations recorded daily. Treatment was considered to be effective if there was a significant change in pain patterns.	Not reported	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Campbell, 1966(50) U.K. (Poor)	Number screened not reported / Number eligible not reported / 77 enrolled / 77 randomized	7 withdrawn / 3 lost to follow-up and 1 records were lost / 70 analyzed	Carbazepine (C) vs. Placebo (P) Upgrading rates (sum of upgrading / sum of possible upgradings, %) C-P-C-P treatment sequence: 51/89 (58%) - 2/37 (5%) - 38/59 (64%) - 4/26 (15%) P-C-P-C treatment sequence: 22/86 (26%) - 27/66 (41%) - 7/41 (17%) - 28/54 (52%) Difference in upgrading rate in first treatment period (without carryover effects): 32% ($p < 0.01$)
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)	Numbers screened and eligible not reported / 10 enrolled / 10 randomized	None withdrawn / None lost to follow-up / 10 analyzed	Carbamazepine vs. Placebo Drug effective (pain relief): 10 vs. 0 ($p < 0.002$)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Campbell, 1966(50) U.K. (Poor)			
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)			

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Campbell, 1966(50) U.K. (Poor)	Elicited by investigator	Carbazepine adverse events (placebo AEs not reported) Giddiness, unsteadiness, drowsiness, rash
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)	Not reported	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Campbell, 1966(50) U.K. (Poor)	Total withdrawals: 7 Withdrawal due to adverse event: 1 (rash on carbazepine)	Carryover effects were possible because there was no washout between treatments. Study used a novel system of scoring pain severity (upgrading and downgrading rates).
Dalessio, 1966(63) (--), only RCT described here U.S. (Poor)	None	Open-label pilot study, which preceded the RCT, is not described here. Insufficient information and small sample size make it difficult to generalize results.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Harke, 2001(49) Germany (Poor)	Single center, two-phase parallel-group, double-blind RCT Pain clinic	Neuropathic pain, pain relieved by Spinal Cord Stimulation (SCS) without taking any analgesics and pain recurrence upon switching off SCS; not otherwise reported	Phase I: Carbamazepine 600 mg/d vs. Placebo for 15 d or longer Phase II: Morphine sustained release 90 mg/d vs. Placebo for 10 d or longer	Run-in: Spinal Cord Stimulation (SCS) test periods for median of 13 mo; after patients achieved pain relief on SCS without medication, those who experienced recurrence of pain in an initial SCS switch-off test were included in the trial. Washout: Phase I patients who preferred to remain on carbamazepine did not enter Phase II; those not remaining on carbamazepine were tapered off over 7 d.
Nicol, 1969(51) U.S. (Poor)	Double-blind parallel-group RCT; only failures crossed over Outpatient setting implied	Trigeminal neuralgia	Carbamazepine 100 to 2400 mg/d vs. Placebo for a minimum of 2 to 46 mo; patients could be switched to the other agent if pain relief was unsatisfactory	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Harke, 2001(49) Germany (Poor)	Reactivation of SCS in case of intolerable pain	Numeric Analog Scale (NAS) of pain intensity (ranging from 0 to 10 points) recorded in diary every 2 h	Median age, y: 55 48.8% male, 52.2% female Ethnicity not reported	Median pain duration: 6 y Median pain intensity (NAS range 0 to 10): 9 Median pain increase on NAS of 4.6 after switching off SCS Median duration of SCS switch-off: 145 min Neuropathic diagnoses (n): isolated radiculitis (17), postherpetic thoracic neuralgia (6), phantom limb pain (3), diabetic neuropathy (3), peripheral nerve lesion (7), reflex sympathetic dystrophy (Complex Regional Pain Syndrome I) (7)
Nicol, 1969(51) U.S. (Poor)	Phenytoin	4-point descriptive pain rating scale (Excellent to Unchanged) sent weekly and thereafter evry four to eight weeks dependent upon the patients' clinical progress	47.7% Male, 52.3% Female Age and Ethnicity not reported	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Harke, 2001(49) Germany (Poor)	Phase I: 77/68/43/43 Phase II: '--/38/38/38	Phase I: 5/--/38 Phase II: --/--/35	Phase I Carbamazepine vs. Placebo Mean maximum pain intensity (NAS) Responders (analgesia comparable to SCS): 2.5 vs. no data Partial responders: 5.9 vs. 7.7 (p = 0.04) Nonresponders (reactivated SCS because of severe pain): 7.2 vs. 9.0 (p = 0.06)
Nicol, 1969(51) U.S. (Poor)	Number screened not reported / 64 eligible / 44 enrolled / 44 randomized (Carbamazepine, N = 20; Placebo, N = 24)	None withdrawn / None lost to follow-up / 44 analyzed; however, treatment groups that were analyzed consisted of Carbamazepine (N = 20), Placebo followed by carbamazepine (N = 17), and Placebo only (N = 7)	(I) Carbamazepine vs. (II) Placebo followed by carbamazepine vs. (III) Placebo only At least good clinical response: 8 vs. 12 vs. 6 (no statistical analyses)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Harke, 2001(49) Germany (Poor)	Phase II Morphine vs. Placebo Mean maximum pain intensity (NAS) Responders: 1 vs. no data Partial Responders: 6.7 vs. 6.1 (p = 0.41) Nonresponders: 8.3 vs. 8.3 (p = 0.83)		
Nicol, 1969(51) U.S. (Poor)			

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Harke, 2001(49) Germany (Poor)	Not reported	Carbamazepine: ataxia, dizziness, vomiting, nausea, fatigue, sweating, headache Morphine: dizziness, vomiting, nausea, fatigue, sweating, headache, constipation Frequency not reported by number of patients
Nicol, 1969(51) U.S. (Poor)	Reported spontaneously by patient; laboratory tests monitored	Carbamazepine: Generalized pruritis; erythematous skin eruption; drowsiness; staggering gait; minor stomach upset; tremulousness; impaired recent memory; lightheadedness; blurred vision; asymptomatic decrease in white blood cell count; asymptomatic increase in liver transaminases Placebo: Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Harke, 2001(49) Germany (Poor)	Phase I, Carbamazepine vs. Placebo Total Withdrawals: 5/43 (11.6%) Adverse Event Withdrawals: Not reported Phase II, Morphine vs. Placebo Total Withdrawals: Not reported Adverse Event Withdrawals: 1/19 (5.3%) vs. 2/19 (10.5%)	Method of diagnosing neuropathic pain was not reported. Changes in pain intensity from baseline were not reported by treatment groups.
Nicol, 1969(51) U.S. (Poor)	Carbamazepine Total withdrawals: 2, both due to adverse events (generalized pruritis and generalized erythematous eruption) Placebo: Not reported	Patients were not analyzed in the treatment groups to which they were originally randomized; a third treatment group was added (Placebo followed by carbamazepine) apparently when results were evaluated. Small sample size and unorthodox analyses.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Rockliff, 1966(99) (--) U.S. (Fair)	Double-blind, placebo-controlled, crossover RCT with extended open-label trial Outpatient setting implied	Active, typical trigeminal neuralgia	Carbamazepine (investigational drug G-23883) 600 mg/d vs. Placebo for 3 d each in crossover fashion Open-label carbamazepine for up to 1 y	None (no washout before crossover)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Rockliff, 1966(99) (--) U.S. (Fair)	Controlled Trial: Not reported Extended Open Trial: Phenytoin, mephenesin carbamate)	Patients indicated treatment preference when asked which treatment was more effective in reducing pain	Group 1, Controlled Trial + Extended Open Trial Age, median (range), y: 68 (37 to 81) Male / Female: 1 / 8 Ethnicity not reported Group 2, Additional Patients in Extended Open Trial Age, median (range), y: 66 (52 to 76) Male / Female: 7 / 4 Ethnicity not reported	Group 1 Previous surgical treatment: 4/9 (44.4%) Previous AED treatment: 7/9 77.8%) Group 2 Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Rockliff, 1966(99) (--) U.S. (Fair)	Group 1, Controlled Trial + Extended Open Trial Numbers screened and eligible not reported / 9 enrolled / 9 randomized Group 2, Additional Patients in Extended Open Trial Numbers screened and eligible not reported / 11 enrolled / Number randomized not applicable	Of total 20 patients: 9 withdrew / 1 lost to follow-up / 9 analyzed in controlled trial; 11 in extended open trials	Controlled Trials (Group 1) Preferred carbamazepine: 8/9 (88.9%) ($p < 0.05$ using a "closed" sequential design method) Both equally effective: 1/9 (11.1%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Rockliff, 1966(99) (--) U.S. (Fair)	<u>Extended Open Trial (Group 1)</u> Major (two thirds of pain relieved or almost pain-free) to complete relief following controlled trial: 7/9 (77.8%) Required addition of phenytoin: 1/9 11.1% Remission, off medication: 3/9 (33.3%) Maintained partial relief (frequency and severity of pain markedly reduced): 2/9 (22.2%)	<u>Extended Open Trial (Group 2)</u> Partial, Moderate, Marked, or Complete Relief Initially: 11/11 (100%) Relapse of Pain (after 2 d to 4 mo): 5/11 (45.4%) --Relapse, controlled after addition of phenytoin +/- other treatments: 3/11 (27.3%) --Relapsed, elected surgery: 2/11 (18.2%) Partial relief initially, controlled after addition of phenytoin: 1/11 (9.1%) Remission, off medication: 2/11 (18.2%) Maintained on carbamazepine: 3/11 (27.3%)	<u>Combined results from both groups</u> Treatment satisfactory on carbamazepine alone or combined with phenytoin (and mephenesin carbamate in one case): 16/20 (80%) Remained in remission, off medication: 5/20 (25%) Required continuous or intermittent medication: 11/20 (55%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Rockliff, 1966(99) (--) U.S. (Fair)	Monitoring	Controlled Trial: Treatment comparisons not reported Extended Open Trial on carbamazepine Any adverse event, n: 14/20 (70.0%) Most common adverse events: drowsiness, dizziness, headache, and nausea

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Rockliff, 1966(99) (--) U.S. (Fair)	Controlled Trial: No withdrawals Extended Open Trial Total withdrawals: 6/20 (30.0%) Withdrawals due to adverse events: 1/20 (5.0%)	This study used an unconventional statistical method, called a "closed" sequential design, to limit the duration of the trial. The probability of a preference for carbamazepine was based on the assumptions that the response rates would be 80% for carbamazepine and 40% for placebo. A design was then chosen such that if the preference path crossed an outside boundary, then the null hypothesis would be rejected with p = 0.05.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Rull, 1969(60) (--) Mexico (Poor)	Double-blind, placebo-controlled, double crossover RCT Outpatient setting implied	Not reported per se; patients described as having well established sensory manifestations of somatic neuropathy; differential diagnosis carefully established; symptoms longer than 1 mo; mostly moderate or severe symptoms.	Carbamazepine 600 mg/d "in most instances" vs. Placebo for 2 wk each treatment period (total 6 wk per treatment sequence, A-B-A and B-A-B, where A = Carbamazepine and B = Placebo)	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Rull, 1969(60) (--) Mexico (Poor)	Not reported	Subjective changes in intensity, distribution, and duration of symptoms in comparison with baseline, graded by a blinded author from 0 (no change) to 5↓ (disappearance) or 5↑ (maximal increase); frequency of assessments not reported. Overall results for each patient at end of each 2-wk period were obtained by algebraic summation of all positive and negative changes.	Age, mean (range), y: 54.2 (21 to 81) Male / Female: 9 / 21 Ethnicity not reported	Duration of diabetes, mean (range), y: 10.9 (3 to 24) Degree of control (n) --Good: 11 --Fair: 5 --Poor: 14 Treatment (n) --Diet alone: 2 --Insulin: 10 --Oral hypoglycemic: 18

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Rull, 1969(60) (--) Mexico (Poor)	Numbers screened and eligible not reported / 30 enrolled / 30 randomized (14 to A-B-A and 16 to B-A-B treatment sequence, where A = carbamazepine and B = placebo)	3 withdrawn / 1 lost to follow-up (reason for not attending visit was not reported) / 27 analyzed (with 3 marked as results not recorded)	Carbamazepine (44 patient-periods) vs. Placebo (46 patient-periods) (Results shown here were tallied and calculated from reported data that was presented by treatment period. No statistical analyses were reported.) Change in symptoms (No. of patient-periods. %) --Disappearance (5↓): 2 (4.5%) vs. 2 (4.3%) --Improvement (3↓ to 4↓): 23 (52.3%) vs. 4 (8.7%) --Improvement (1↓ to 2↓): 15 (34.1%) vs. 20 (43.5%) --No change: 2 (4.5%) vs. 4 (8.7%) --Increase (1↑ to 5↑): 0 (0.0%) vs. 15 (32.6%) --Not recorded: 2 (4.5%) vs. 1 (2.2%) (Note: A patient-period represents the patient exposure; i.e., number of patients multiplied by the number of treatment periods for each drug.)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Rull, 1969(60) (--) Mexico (Poor)			

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Rull, 1969(60) (--) Mexico (Poor)	Monitoring	No treatment comparisons. Adverse events reported during carbamazepine periods or in the first few days of placebo following carbamazepine treatment were the following (n, %): --Somnolence: 16/30 (53.3%) --Dizziness: 12/30 (40.0%) --Gait changes 4/30 (13.3%) --Urticaria: 2/30 (6.6%) --Nausea: 2/30 (6.6%) --Vomiting: 1/30 (3.3%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Rull, 1969(60) (--) Mexico (Poor)	Carbamazepine vs. Placebo Total withdrawals: 2/30 (6.6%) vs. 1/30 (3.3%) Withdrawals due to adverse events: 2/30 (6.6%) vs. 0/30 (0.0%)	Lack of washout between treatment periods resulted in carryover effects, which may have reduced any treatment differences. Double-blinding may have been breached because adverse events tended to occur only during carbamazepine therapy.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Backonja, 1998(72) U.S. (Fair)	Multicenter double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Pain attributed to diabetic neuropathy for 1 to 5 y; diagnosis of diabetes mellitus (type 1 or 2); pain rating score of at least 40 mm on 100-mm Visual Analogue Scale (VAS); and average pain score of at least 4 on an 11-point Likert scale, at least 4 observations recorded in daily pain diary, and a hemoglobin A1c </= 0.11 during the 1-wk screening period	Gabapentin titrated from 900 to 3600 mg/d vs. Placebo, reaching maximal tolerated dose in 4 wk and continuing for another 4 wk (total 8 wk)	1-wk run-in screening phase; patients meeting eligiblity criteria and who had an average pain score of at least 4 on an 11-point Likert scale, at least 4 observations recorded in daily pain diaries during the screening week, and a hemoglobin A1c level of 0.11 or less (normal: 0.048 to 0.067) were randomized. 30-d washout of previous analgesics and centrally-acting medications

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Backonja, 1998(72) U.S. (Fair)	Acetaminophen up to 3 g/d; aspirin up to 325 mg/d for prophylaxis of myocardial infarction or transient ischemic attacks; stable doses of serotonin reuptake inhibitors	11-point Likert scale for pain intensity (0 = no pain; 10 = worst possible pain), recording daily; Short Form McGill Pain Questionnaire (SF-MPQ), consisting of weekly pain rating (0 = no pain, 3 = severe pain), 100-mm VAS for pain during the previous week (no pain to worst possible pain), and a 6-point Present Pain Intensity (PPI) Scale (0 = no pain, 5 = excruciating pain); 11-point sleep interference scale (0 = did not interfere, 10 = unable to sleep due to pain), recorded upon awakening; 7-point Patient Global Impression of Change (PGIC) scale (much improved to much worse); 7-point Clinical Global Impression of Change (CGIC) scale; Profile of Mood States (POMS); Short Form-36 (SF-36) quality of life questionnaire. Frequency only reported for those assessments as noted.	Gabapentin (N = 84) vs. Placebo (N = 81) Age, mean (SD), y: 53.0 (10.5) vs. 53.0 (10.2) Male / Female: 58.3% / 41.7% vs. 61.7% / 38.3% Ethnicity, % White: 79.8% vs. 82.7% Black: 6.0% vs. 7.4% Other: 14.3% vs. 9.9%	Gabapentin vs. Placebo Duration of neuropathic pain: Not reported Duration of diabetes, mean (SD), y: 12.0 (9.6) vs. 11.2 (8.7)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Backonja, 1998(72) U.S. (Fair)	232 screened / 165 eligible // 165 enrolled / 165 randomized	30 withdrew / None lost to follow-up / 162 analyzed for efficacy, 165 for safety (3 patients excluded from efficacy analyses apparently because they either did not receive study medication or were missing data, and therefore, did not meet the definition of the ITT population)	Gabapentin (N = 82) vs. Placebo (N = 80) Likert Pain score (Primary efficacy measure) Difference in mean scores at end point (95% CI): -1.2 (-1.9 to -0.6) (p < 0.001) Calculated change (%) in mean scores from baseline to end point: -2.5 (39.1%) vs. -1.4 (21.5%) Gabapentin vs. Placebo At least moderate improvement, n/N (%) CGIC: 39/81 (48.1%) vs. 16/75 (21.3%) (p = 0.001) [Calculated NNT (95% CI): 4 (2.8)] PGIC: 59/79 (74.7%) vs. 25/76 (32.9%) (p = 0.001) [Calculated NNT (95% CI): 2 (2.4)]

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Backonja, 1998(72) U.S. (Fair)	Sleep interference score, difference (95% CI): -1.47 (-2.2 to -0.8) (p < 0.001) Total SF-MPQ, difference (95% CI): -5.9 (-8.8 to -3.1) (p < 0.001) SF-MPQ VAS, difference (95% CI): -16.9 (-25.3 to -8.4) (p < 0.001) Calculated change (%) in mean scores from baseline: 30.8 (45.5%) vs. 17.4 (24.4%)]	SF-MPQ PPI, difference (95% CI): -0.6 (-0.9 to -0.3) (p < 0.001) SF-36 QoL, [calculated change in means from baseline]; difference at end point (95% CI) Bodily pain: [14.6 vs. 9.9]; 7.8 (1.8 to 13.8) (p = 0.01) Mental health: [3.7 vs. 3.9]; 5.4 (0.5 to 10.3) (p = 0.03) Vitality: [12.0 vs. 2.9]; 9.7 (3.9 to 15.5) (p = 0.001) Note: Increase in score reflects improvement.	POMS, [calculated change in means from baseline]; differences at end point (95% CI) Anger/hostility: [-2.1 vs. -2.4]; -2.2 (-4.1 to -0.3) (p = 0.02) Vigor/activity: [0.7 vs. 0]; 1.96 (0.5 to 3.5) (0 = 0.01) Fatigue/inertia: [-3.5 vs. -1.1]; -1.96 (-3.4 to -0.5) (p = 0.01) Total mood: [-10.2 vs. 8.1]; -9.14 (-17.3 to -1.0) (p = 0.03) Note: Increase in vigor/activity score reflects improvement.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Backonja, 1998(72) U.S. (Fair)	Monitoring	Gabapentin (N = 84) vs. Placebo (N = 81) Most frequently reported adverse events with treatment difference, n (%) Dizziness: 20 (23.8%) vs. 4 (4.9%) (p < 0.001) Somnolence: 19 (22.6%) vs. 5 (6.2%) (p = 0.004)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Backonja, 1998(72) U.S. (Fair)	Gabapentin vs. Placebo Total Withdrawals: 14/84 (16.7%) vs. 16/81 (19.8%) Withdrawals due to adverse events: 7/84 (8.3%) vs. 5/81 (6.2%)	The diagnosis of diabetic neuropathy was based on clinical examination. Electrophysiologic studies could have excluded other causes for neuropathy. The calculated change in mean pain intensity scores from baseline (-2.5, -39%) with gabapentin meet criteria for clinically relevant changes in chronic pain by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Bone, 2002(66) U.K., Ireland (Fair)	Double-blind, placebo-controlled, crossover RCT Disablement Services Clinic setting	18 to 75 y old; established phantom limb pain for minimum of 6 mo after a previous surgical amputation; pain score of at least 40 mm on a 100-mm visual analog scale (VAS)	Gabapentin titrated from 300 mg/d to 2400 mg/d or maximum tolerated dose vs. Placebo, for two 6-wk periods Gabapentin dose, median (range): 2400 mg (1800 to 2400)	1-wk run-in screening phase; patients meeting eligibility criteria and had an average VAS pain score of 40 mm during episodes of phantom limb pain were randomized. 1-wk washout before crossover 1-wk washout of previous muscle relaxants, other AEDs, and topical analgesics

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Bone, 2002(66) U.K., Ireland (Fair)	Stable, low doses of tricyclic antidepressants; combination codeine (30 mg) plus acetaminophen (500 mg) as rescue medication (up to 360 and 6000 mg/d, respectively). Amitryptiline (25 mg/d) was taken by 2 patients during the study.	100-mm VAS pain intensity, recorded daily; categorical pain intensity (0 = none, 3 = severe pain), recorded daily; 11-point sleep interference scale for past 24 hours (0 = did not interfere, 10 = unable to sleep due to this pain); mood using a 14-item Hospital Anxiety and Depression (HAD) scale (higher scores reflect greater degrees of anxiety and depression); Barthel index for activities of daily living (10 activities rated on a 3- or 4-point scale with higher score reflecting a greater level of assistance required); amount of prescribed rescue medication. Frequency of assessments not reported except as noted.	Age, mean (range), y: 56.2 (24 to 68) Male / Female: 79% / 21% 13/19 (68.4%) Caucasian, 4/19 (21.1%) Asian	Duration since amputation, mean (range), mo: 18 (6 to 51)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Bone, 2002(66) U.K., Ireland (Fair)	Number screened not reported / 33 eligible / 19 enrolled / 19 randomized	5 withdrew / None lost to follow-up	Gabapentin vs. Placebo VAS Pain Intensity score, mm Pain Intensity Difference (PID) at wk 6 compared with baseline (Primary efficacy measure): 3.2 vs. 1.6 (p = 0.03) Calculated relative change in pain score from baseline: 52.5% vs. 23.9% Categorical pain, mean Baseline: 1.5 vs. 1.8 (NSD) End of therapy, wk 6: 1.45 vs. 1.6 (NSD)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Bone, 2002(66) U.K., Ireland (Fair)	Rescue medication, no. of tablets, mean: 177 vs. 187 (NSD) Sleep interference, median (interquartile range, IQR) Baseline: 4 (2 to 5) vs. 4 (2 to 5) End of therapy: 3 (1 to 5) vs. 4 (1 to 5) (NSD) HAD depression scale, median (IQR) Baseline: 14 (5 to 25) vs. 15 (25 to 25) End of therapy: 12 (4 to 22) vs. 14 (5 to 25) (NSD)	Barthel Index, median (IQR) Baseline: 90 (70 to 105) vs. 85 (65 to 100) End of therapy: 85 (70 to 105) vs. 87 (65 to 105) (NSD)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Bone, 2002(66) U.K., Ireland (Fair)	Not reported	Gabapentin vs. Placebo Most frequently reported adverse events, n (%) [% calculated based on N = 19] Somnolence: 7 (36.8%) vs. 2 (10.5%) Dizziness: 2 (10.5%) vs. 1 (5.3%) Headache: 2 (10.5%) vs. 1 (5.3%) Nausea: 1 (5.3%) vs. 1 (5.3%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Bone, 2002(66) U.K., Ireland (Fair)	Gabapentin vs. Placebo Total withdrawals: 2/19 (10.5%) vs. 3/19 (15.8%) Withdrawals due to adverse events: None	The mean categorical pain intensity scores indicated that the patients started and ended with mild to moderate pain. The pain may not have been of sufficient severity to demonstrate a significant improvement on treatment using a 4-point categorical pain scale. The magnitude of change in VAS pain intensity scores (3.2 from a baseline of 6.1 on a 100-mm scale) with gabapentin was sufficient to show a statistically significant treatment difference, but seems small from a clinical standpoint and was not accompanied by improvements in sleep, mood, or function. The small study population limited the power of the study to detect differences in efficacy measures other than the VAS pain score.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Gorson, 1999(68) U.S. (Fair)	Double-blind, placebo-controlled crossover RCT Outpatient setting implied	Painful diabetic neuropathy; diabetes for at least 6 mo; stable dose of insulin or oral hypoglycemic agent; distal symmetric sensorimotor neuropathy (impaired pin prick, temperature, or vibration sensation in both feet and absent or reduced ankle reflexes); daily neuropathic pain in the acral extremities of at least moderate severity for over 3 mo that interfered with daily activity or sleep	Gabapentin 300 to 900 mg/d vs. Placebo for 6 wk	3-wk washout of chronic analgesic medications before study entry 3-wk washout before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Gorson, 1999(68) U.S. (Fair)	Nonsteroidal antiinflammatory drugs or narcotics at stable doses	10-cm Visual Analogue Scale (VAS) (0 = no pain, 10 = worst pain ever) at beginning and end of treatment period; Present Pain Intensity (PPI) (0 to 10 scale) and McGill Pain Questionnaire (MPQ) recorded at initial and final visits of each treatment period; 4-point Patient Global Assessment of pain relief (none to excellent) at end of treatment, as compared with the level of pain preceding each treatment period	Age, mean (SD), y: 62 (10.9) range 43-82 years 31/40 (77.5%) Male / 9/40 (22.5%) Female Ethnicity not reported	Duration of neuropathic pain, mean (SD), y, range: 4 (3.5), 4 mo to 15 y Previous use of narcotics or other chronic analgesics for pain: 25/40 (62.5%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Gorson, 1999(68) U.S. (Fair)	Number screened not reported / Number eligible not reported / 40 enrolled / 40 randomized	None withdrawn / None lost to follow-up / 40 analyzed	Gabapentin vs. Placebo (Number randomized, 1st period: 19 vs. 21) Mean reduction (difference) MPQ: 8.9 vs. 2.2 (6.7) (p = 0.03) VAS: 1.8 vs. 1.4 (0.4) (p = 0.42) PPI: 1.2 vs. 0.3 (0.9) (p = 0.2)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Gorson, 1999(68) U.S. (Fair)	Patient Global Assessment, moderate or excellent pain relief, n: 17 vs. 9 (p=0.11) In gabapentin-treated patients, MPQ and VAS scores did not return to baseline after crossover, suggesting that the washout period was inadequate.		

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Gorson, 1999(68) U.S. (Fair)	Not reported	Most common adverse events on gabapentin (n): drowsiness (6), fatigue (4), and imbalance (3). Adverse events not reported for placebo

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gorson, 1999(68) U.S. (Fair)	None	The study had 80% power to detect a 20% reduction in pain scores. Primary efficacy measure was not specified. Carryover of gabapentin effects into the placebo phase may have resulted in underestimation of the treatment benefit.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient clinic and general practice setting	At least 18 y old; pain present for more than 3 mo after healing of acute herpes zoster skin rash; average pain score of >/= 4 on an 11-point Likert scale during the 1-week baseline period	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo, using a 4-day forced titration schedule and reaching the target dose in 2 to 3 wk, then continuing stable doses for a total treatment duration of 7 wk	1-wk run-in baseline period: patients who had average pain scores of 4 or more on an 11-point Likert scale during the 1-week baseline period were randomized. 14-d washout of previous benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, nonsteroidal antiinflammatory drugs (if prescribed for postherpetic neuralgia), and AEDs. 30-d washout for strong opioids

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Stable doses of antidepressants, mild opioids, aspirin (up to 300 mg/d) for cardiovascular prophylaxis, and nonsteroidal antiinflammatory drugs	11-point Likert scale (0 = no pain, 10 = worst possible pain) of pain intensity over the previous 24 h, recorded daily upon waking, and 11-point Likert scale for sleep interference (0 = pain does not interfere with sleep, 10 = pain completely interferes with sleep), both assessed at screening, wk 0, 1, 2, and 7; Short Form McGill Pain Questionnaire (SF-MPQ) and Short Form-36 (SF-36) Health Survey for quality of life, assessed at wk 0 and 7; 7-point Clinician and Patient Global Impression of Change (CGIC and PGIC) scales (ranging from very much improved to very much worse), assessed at wk 7 Response defined as >/= 50% reduction in mean pain score from baseline	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo Age, median, y: 74.8 vs. 76.3 vs. 74.9 Male / Female: 40% / 60% vs. 43% / 57% vs. 41% vs. 59% Ethnicity not reported	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo (N = 111) Years since diagnosis, median (range): 1.9 (0.1 to 19.4) vs. 2.5 (0.3 to 30.7) vs. 2.2 (0.1 to 28.4) Previous number of drugs tried, median: 3 vs. 3 vs. 3 Drug categories tried, n (%) AEDs: 69 (60%) vs. 72 (67%) vs. 62 (56%) Amitriptyline: 83 (72%) vs. 83 (77%) vs. 79 (71%) Mild analgesics: 107 (93%) vs. 100 (93%) vs. 102 (92%) Overall, 16% of patients were newly diagnosed (< 6 mo) and the median duration of postherpetic neuralgia was about 4 years.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	411 / 359/ 334/ 334	62 withdrew / None lost to follow-up / 334 analyzed	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo (N = 111) Change (%) in average daily pain score (Primary efficacy measure), mean [back-calculated from % change]: -2.2 (-34.5%) vs. -2.2 (-34.4%) vs. -1.0 (-15.7%) ($p < 0.01$ vs. placebo for both gabapentin groups)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Response rate, % of patients: 32% vs. 34% vs. 14% (p = 0.001 for both gabapentin groups vs. placebo) Additional data from Rice, 2002, Response to Comments (Rice, 2002): Response rate for 30% reduction in pain, n (%): 61/115 (53%) vs. 59/108 (55%) vs. 32/111 (29%). NNT for 30% / 50% reduction: 4.13 / 5.63 for 1800 mg; 3.88 / 5.04 for 2400 mg Sleep interference (0 to 10, Likert scale), difference at final week (95% CI) Gabapentin 1800 mg/d vs. placebo: 0.9 (0.4 to 1.4; p < 0.01) Gabapentin 2400 mg/d vs. placebo: 1.1 (0.7 to 1.6; p < 0.01)	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo SF-MPQ, difference in improvements in scores between gabapentin and placebo were statistically significant for the following: Sensory score (0 to 33), mean: 13.9 vs. 15.0 vs. 13.2 (p < 0.05 for both doses) Total score (0 to 45), mean: 17.8 vs. 19.6 vs. 17.1 (p < 0.05 for both doses) Visual analogue scale (0 to 100 mm), mean: 67 vs. 70 vs. 68 (p < 0.05 for 2400 mg only) No significant treatment differences were found for affective scores.	PGIC much or very much improved, n/N (%): 44/107 (41%) vs. 42/98 (43%) vs. 24/105 (23%) (p </= 0.005 for both analyses) CGIC much or very much improved, n/N (%): 48/108 (44%) vs. 45/103 (44%) vs. 20/107 (19%) (p </= 0.002 for both analyses) SF-36 Quality of Life domains showing statistically (p < 0.05) greater improvements in mean score on gabapentin than placebo: vitality (both doses), bodily pain (1800 mg only), and mental health (1800 mg only).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Elicited by investigator	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo All adverse events, n (%): 81 (70.4%) vs. 81 (75.0%) vs. 55 (49.5%) Possibly / probably treatment-related, n (%): 65 (56.5%) vs. 65 (60.2%) vs. 31 (27.9%) Serious, nonfatal adverse events, n (types): 3 (fever, infection, retinal vein thrombosis and hemoptysis) vs. 1 (congestive heart failure) vs. 1 (depression) -- all considered to be not related to study drug Common adverse events (> 5% of patients), n (%) Dizziness: 36 (31%) vs. 36 (33%) vs. 11 (9.9%) Somnolence: 20 (17.4%) vs. 22 (20.4%) vs. 7 (6.3%) Peripheral edema: 6 (5.2%) vs. 12 (11.1%) vs. 0 (0%) Asthenia: 7 (6.1%) vs. 6 (5.6%) vs. 4 (3.6%) Dry mouth: 7 (6.1%) vs. 5 (4.6%) vs. 1 (0.9%) Diarrhea: 7 (6.1%) vs. 5 (4.6%) vs. 1 (0.9%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Rice, 2001(74) U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo Total Withdrawn: 22/115 (19.1%) vs. 23/108 (21.3%) vs. 17/111 (15.3%) Withdrawals due to adverse events: 15/115 (13.0%) vs. 19/108 (17.6%) vs. 7/111 (6.3%) Most withdrawals (76%) due to adverse events on gabapentin occurred during the first 3 wk. Most common adverse events resulting in withdrawal: dizziness (7% of each dose group) and drowsiness (5% to 6%)	The absolute and relative reductions in Likert pain intensity scores met criteria for clinically relevant changes by Farrar (Farrar, 2001). There were also significant differences between gabapentin and placebo in terms of improvements in sleep, vitality, mental health, and bodily pain, but not mood, physical functioning, or social functioning. The 2400-mg dose did not appear to confer additional benefits over the 1800-mg dose. The distribution of patients with newly diagnosed (< 6 mo) postherpetic neuralgia (which is more likely to spontaneously resolve than a longer-standing (> 12 mo) condition) among the three treatment groups was not reported. The impact of this possible confounding factor on the treatment effects is uncertain.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Rowbotham, 1998(73) U.S. (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	At least 18 y old; pain present for > 3 mo after healing of a herpes zoster skin rash; pain intensity score at least 40 mm on 100-mm Visual Analog Scale (VAS) on the Short Form McGill Pain Questionnaire (SF-MPQ) at screening and randomization; average daily diary pain score at least 4 (on 0 to 10 scale) and at least 4 completed daily diaries during baseline week; discontinuance of muscle relaxants, AEDs, mexiletine, topical analgesics, and antiviral agents at least 2 wk before screening	Gabapentin 300 to 3600 mg/d using a forced titration schedule vs. Placebo; titration for 4 wk, stable dosing for 4 wk	Run-in off study medications for 1-wk baseline; patients who continued to meet the eligibility criteria and who had completed at least 4 diaries were randomized Washout of prior medications for 2 wk before screening

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Rowbotham, 1998(73) U.S. (Fair)	Tricyclic antidepressants and narcotics if doses stable before and during study	11-point Likert scale, SF-MPQ with 100-mm VAS at baseline and wk 2, 4, and 8; Short Form-36 (SF-36) Quality of Life Questionnaire and Profile of Mood States (POMS) at baseline and wk 8; Subject's and Investigator's Global Impression of Change Questionnaires at wk 8.	Gabapentin (N = 109) vs. Placebo (N = 116) Median age (range), y: 73 (40 to 90) vs. 74 (39 to 89) Male / Female: 56.9% / 43.1% vs. 48.3% / 51.7% Ethnicity, White / Others: 87.2% / 12.8% vs. 94.0% / 6.0% (p = 0.08)	Median time since last zoster eruption, mo: 27.4 vs. 29.8 Prior postherpetic neuralgia medications, 0 / 1 / 2 to 3: 79.8% / 15.6% / 4.6% vs. 78.5% / 15.5% / 6.0% Concomitant medications, None / Tricyclic antidepressants / Opioid / Combination opioid and tricyclic antidepressants: 65.1% / 11.9% / 17.4% / 5.5% vs. 62.9% / 9.5% / 23.3% / 4.3%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Rowbotham, 1998(73) U.S. (Fair)	292 screened / number eligible not reported / number enrolled not reported / 229 randomized	45 withdrawn / 5 other reasons for withdrawal (including lost to follow-up) / 225 analyzed for primary efficacy variable, 229 for safety	Gabapentin vs. Placebo Average daily pain (0 to 10; Primary Efficacy Measure), mean change from baseline to wk 8: -2.1 vs. -0.5 ($p < 0.001$) Physician's Clinical Global Impression of Change, Moderately or Much Improved at wk 8: 39.5% vs. 12.9%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Rowbotham, 1998(73) U.S. (Fair)	Mean change from baseline to week 8 Sleep rating score: -1.9 vs. -0.5 (p < 0.001) SF-MPQ for total pain: -5.8 vs. -1.8 (p < 0.001)	SF-36 physical functioning, role-physical, bodily pain, vitality, and mental health measures showed gabapentin to be superior to placebo (p </= 0.01) Improvements in POMS depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment, and total mood disturbance showed gabapentin to be superior to placebo (p </= 0.01)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Rowbotham, 1998(73) U.S. (Fair)	Monitored	Most frequently reported AEs Numerically higher rate on gabapentin than placebo: somnolence (27.4% vs. 5.2%), dizziness (23.9% vs. 5.2%), ataxia (7.1% vs. 0.0%), peripheral edema (9.7% vs. 3.4%), and infection (8.0% vs. 2.6%) Numerically higher rate on placebo than gabapentin: pain (10.3% vs. 4.4%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Rowbotham, 1998(73) U.S. (Fair)	Gabapentin vs. Placebo Total Withdrawals: 24/113 (21.2%) vs. 21/116 (18.1%) Adverse Event Withdrawals: 21/113 (18.6%) vs. 14/116 (12.1%)	For early terminations, wk 8 assessments were done at the last study visit. ITT population included randomized subjects who took at least 1 dose of study medication and provided at least 1 follow-up efficacy assessment. ITT and efficacy evaluable (per-protocol) analysis results were similar. Change in average daily pain of -2.1 on gabapentin meets the validated definition of clinically relevant improvement (reduction of 2 on 11-point numerical rating scale) in chronic pain by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	Multicenter double-blind, placebo-controlled, parallel-group RCT Outpatient pain clinics	Age at least 18 y; definite diagnosis of neuropathic pain, made and confirmed by a chronic pain specialist, and based on clinical history, examination, and investigations; at least two of the following: allodynia, burning pain, shooting pain, or hyperalgesia; at least 4 daily pain diaries and average pain score >/= 4 during baseline period The International Association for the Study of Pain (IASP) Classification of Chronic Pain was used for definitions of diagnostic criteria.	Gabapentin vs. Placebo titrated from 900 to 2400 mg/d over 5 wk, and continued for an additional 3 wk (total 8 wk)	1-wk run-in baseline period; patients who completed at least 4 daily pain diaries during the 7 days before randomization and yielded an average score >/= 4 out of 11 were randomized. 3-mo washout of guanethidine or sympathetic blocks; 30-d washout of strong opioids, acupuncture, and homeopathic remedies; 14-d washout of benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, nonsteroidal antiinflammatory drugs used for neuropathic pain, and AEDs.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	Antidepressants if stable for 30 d prior to entering study; aspirin (up to 300 mg/d) for cardiovascular prophylaxis; nonsteroidal antiinflammatory drugs for non-neuropathic pain conditions; mild opioids (e.g., codeine preparations); acetaminophen (up to 4000 mg/d); combination codeine (up to 240 mg/d) plus acetaminophen (up to 4000 mg/d) as rescue medication. 45/305 patients (15%) reported taking no additional medication for neuropathic pain. 6/305 patients (2%) reported taking prohibited medications (carbamazepine, morphine, and sodium valproate); doses were stable for 2 patients but drug was started or stopped in 4 patients during the baseline or treatment evaluation periods and may have affected the estimates of efficacy.	11-point Likert scale for pain intensity (0 to 10), recorded each morning; Visual Analogue Scale (VAS, 0 to 10) for allodynia and hyperalgesia; diary assessment of allodynia, burning pain, shooting pain, and hyperalgesia (pain scale not specified); Short Form-McGill Pain Questionnaire (SF-MPQ); Clinician Global Impression of Change (CGIC); Patient Global Impression of Change (PGIC); Short Form-36 (SF-36) Health Survey for quality of life. Assessments were made very 2 wk. SF-MPQ, CGIC, PGIC, and SF-36 were recorded at wk 7.	Gabapentin (N = 153) vs. Placebo (N = 152) Age, median (range), y: 57.7 (25.9 to 88.4) vs. 56.1 (20.3 to 86.2) Male / Female: 41.2% / 58.8% vs. 51.3% / 48.7% Ethnicity not reported	Duration of disease, median (range), y: 5.2 (0 to 30.8) vs. 4.4 (0 to 27.7) Pain < 3 mo, n (%): 18 (12%) vs. 19 (12%) Pain > 5 y, n (%): 47 (31%) vs. 44 (29%) Previous drugs tried, median (range): 1 (0 to 10) vs. 2 (0 to > 10); 1 vs. 3 patients were "not known" Drug categories tried, n (%) AEDs: 53 (35%) vs. 44 (29%) Amitriptyline: 101 (66%) vs. 95 (65%) Mild analgesics: 136 (89%) vs. 142 (93%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	351 screened / 327 eligible / 307 enrolled / 305 randomized	73 withdrew / None lost to follow-up / 305 analyzed (excluded 2 randomized patients who withdrew before receiving study drug)	Gabapentin vs. Placebo Average daily pain diary score, change from baseline (Primary efficacy measure): 1.5 (21%) vs. 1.0 (14%) (p = 0.048) Mean pain scores showed significant treatment differences for wk 1, 3, 4, 5, and 6 (p < 0.05) but there was no significant difference for wk 7 and 8. Tests for interaction of the treatment effect with baseline pain score and cluster (study centers) were not significant. Response rate (> 50% reduction in mean pain score from baseline): 21% vs. 14% (p = 0.16)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	Change in individual pain symptoms from baseline to wk 8 (last observation carried forward), mean (estimated from figure) Allodynia: -1.4 vs. -1.1 (NSD) Shooting pain: -1.8 vs. -1.5 (NSD) Burning pain: -1.6 vs. -1.2 (NSD) Hyperalgesia: -1.7 vs. -1.1 (NSD) Treatment differences were noted at wk 1 and 3 for burning pain ($p < 0.05$) and wk 3, 4, 5, and 6 for hyperalgesia ($p < 0.05$). No interactions of treatment with baseline or center. Response rates for individual symptoms (no statistics) Allodynia: 23% vs. 15% Shooting pain: 32% vs. 24% Burning pain: 23% vs. 15% Hyperalgesia: 26% vs. 17%	SF-MPQ Greater improvement was seen on gabapentin than placebo for sensory score and total score (no data reported; $p < 0.05$) PGIC, much or very much improved: 48/141 (34%) vs. 22/138 (16%) ($p = 0.03$) CGIC, much or very much improved: 53/142 (38%) vs. 25/142 (18%) ($p = 0.01$)	SF-36 Health-related quality of life Mean change from baseline showed significantly ($p < 0.05$) greater improvement on gabapentin than placebo for the following domains (estimated from figure): Bodily pain 10 vs. 5 Social functioning 10 vs. 3 Role-emotional 11 vs. -4 Interaction test showed no differences in treatment effect according to type of pain ($p = 0.29$).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	Elicited by investigator	Gabapentin (N = 153) vs. Placebo (N = 152), n (%) All adverse events: 117 (76.5%) Possibly/probably treatment related: 88 (57.5%) vs. 56 (36.8%) Deaths: 0 (0%) vs. 2 (1.3%) Serious, nonfatal adverse events: 4 (2.6%) vs. 2 (1.3%) Common adverse events (> 5% of patients) occurring at a rate 5% greater (absolute difference) in either treatment group Dizziness: 37 (24.2%) vs. 12 (7.9%) Somnolence: 22 (14.4%) vs. 8 (5.3%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Serpell, 2002(70) U.K. and Republic of Ireland (Fair)	Gabapentin vs. Placebo Total Withdrawals: 32/153 (20.9%) vs. 41/152 (27.0%) Withdrawals due to adverse events: 24/153 (15.7%) vs. 25/152 (16.4%)	The absolute and relative reductions in Likert pain intensity score of 1.5 points and 21% in the gabapentin group do not meet even the conservative criteria for clinically relevant changes (>/= 2.0 points and >/= 30%) in chronic pain as defined by Farrar, 2001. However, gabapentin was better than placebo in the proportion of patients reporting "much" or "very much improved" on the PGIC as well as certain domains of the quality of life instruments. The responder rate (> 50% decrease in pain) showed gabapentin to be no better than placebo. A lower threshold of 30% decrease in pain was not evaluated.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Simpson, 2001(65) U.S. (Poor)	Two-part double-blind, placebo-controlled, parallel-group RCT plus uncontrolled trial phase Setting not reported	Part 1: Pain attributed to diabetic neuropathy for 3 mo to 1.5 y; diagnosis of diabetes mellitus from 6 mo to 17 y; pain score of at least 40 mm on 100-mm visual analog scale (VAS) of the Short Form McGill Pain Questionnaire (SF-MPQ); average score of 4 on 11-point Likert scale in daily pain diaries over the next week Part 2: PGIC and CGIC of minimal improvement, no change, or worse on gabapentin therapy in Part 1 Part 3: Failed to improved on maximally tolerated doses of gabapentin	Part 1: Gabapentin titrated from 300 to 3600 mg/d vs. Placebo for 4 wk, then fixed doses for 8 wk Part 2: Gabapentin at maximal tolerated doses as taken in Part 1 plus venlafaxine extended release 37.5 to 150 mg/d, titrated vs. gabapentin plus placebo for 3 wk, then fixed doses for 5 wk Part 3: Gabapentin titrated to maximal tolerated dose, then venlafaxine (37.5 to 150 mg/d) titrated for 3 wk, then fixed maximal doses for 5 wk	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Simpson, 2001(65) U.S. (Poor)	None	11-point Likert scale for pain severity (0=no pain, 10=worst possible pain) recorded daily; 11-point Likert scale for sleep interference (0=did not interfere, 10=unable to sleep) recorded daily; 7-point Patient Global Impression of Change (PGIC) at wk 8; 7-point Clinical Global Impression of Change (CGIC) at wk 8; Profile of Mood States (POMS) and Short Form-36 Quality of Life (SF-36 QOL) Questionnaire at baseline and wk 8; SF-MPQ at baseline and wk 2, 4, and 8	Patients included in Parts 1 and 2 Gabapentin vs. Placebo Mean age, y: 48 vs. 52 Male / Female, %: 60 / 40 vs. 60 / 40 Ethnicity not reported Demographics of the additional patients included in Part 3 were not reported	Mean duration of diabetes, y: 8 vs. 9 Type 1 diabetes, %: 20 vs. 17 Type II diabetes, %: 80 vs. 83

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Simpson, 2001(65) U.S. (Poor)	Part 1: --/--/--/60 Part 2: --/12/--/11 Part 3: 42 were considered	Part 1: 6 / 0 / Number analyzed not reported for efficacy; 54 for safety Part 2: 4/0/Number analyzed not reported for efficacy, 11 for safety Part 3: 4/0/Number analyzed not reported for efficacy or safety	Part 1 Gabapentin vs. Placebo Change in mean pain score, baseline to final: -2.4 vs. -0.5 (p< 0.01) Much / Moderately improved on PGIC and CGIC: 15 (55.5%) vs. 7 (25.9%) Change in mean sleep interference scores, SF-McGill total pain scores, SF-McGill Present Pain Intensity, SF-VAS, POMS, and SF-36 QOL showed significant improvement in the gabapentin group.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Simpson, 2001(65) U.S. (Poor)	Part 2 Gabapentin + venlafaxine vs. gabapentin + placebo Change in mean pain score, baseline to final: -2.0 vs. -0.5 ($p < 0.001$) Much / Moderately improved on PGIC and CGIC: 3 (75%) vs. 1 (33.3%) Change in sleep interference scores, SF-McGill total pain scores, SF-McGill PPI, SF-McGill VAS, POMS and SF-36 QOL showed significant improvement in the gabapentin + venlafaxine group.	Part 3 Gabapentin + venlafaxine Change in mean pain score, baseline to final: -2.1	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Simpson, 2001(65) U.S. (Poor)	Monitored	Gabapentin (N = 27) vs. Placebo (N = 27) Dizziness: 6 (22.2%) vs. 1 (3.7%) Somnolence: 6 (22.2%) vs. 1 (3.7%) Headache 3 (12.3%) vs. 1 (3.7%) Diarrhea: 3 (12.3%) vs. 1 (3.7%) Confusion: 2 (7.4%) vs. 0 (0%) Nausea: 2 (7.4%) vs. 1 (3.7%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Simpson, 2001(65) U.S. (Poor)	Part 1: 3 total withdrawals from each group; 2 withdrawals due to adverse event from each group Part 2: 2 total withdrawals from each group; 1 withdrawal due to adverse event on gabapentin plus venlafaxine Part 3: 4 total withdrawals; 3 withdrawals due to adverse event	Small sample size.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Tai, 2002(48) U.S. (Poor)	Double-blind, placebo-controlled, crossover RCT Outpatients and inpatients (proportions not reported)	Traumatic spinal cord injury (SCI); inpatients and outpatients; age 18 to 85 y; neuropathic pain confirmed by an SCI physician; traumatic injury for greater than 30 d; Neuropathic Pain Scale (0 to 10) > 4 (representing moderate to severe pain)	Gabapentin titrated from 300 mg/d to 1800 mg/d vs. Placebo for 4 wk per treatment period. Placebo was also given during the 2-wk washout between active treatments. For outpatients, the increased number of tablets was given to the subjects for the week. For inpatients, dosage adjustments were ordered in the medical record.	2-wk washout before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Tai, 2002(48) U.S. (Poor)	Ongoing AED, antidepressant, and other analgesic medications. As-needed analgesics (i.e., nonsteroidal antiinflammatory drugs, tricyclic antidepressants, and narcotics).	11-point Neuropathic Pain Scale at baseline for both treatment groups and at wk 4 of both treatment periods	Age range, y: 27 to 48 6 Male / 1 Female Ethnicity not reported	Etiology of injury: 5 motor vehicle crash; 1 fall; 1 diving Duration of injury, range: 1 mo to 20 y (</= 3.5 mo in 5 patients) Short Form Beck Depression Inventory score, median (range): 11 (8 to 16)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Tai, 2002(48) U.S. (Poor)	Number screened and eligible not reported / 14 enrolled / 14 randomized	7 withdrew / 2 lost to follow-up / 7 analyzed	Of 10 items assessed on the Neuropathic Pain Scale, only 1 ("unpleasant feeling") showed a statistically significant treatment difference (p = 0.028). Data presented for individual patients; no descriptive statistical data were reported. Gabapentin vs. Placebo Average Pain Intensity at wk 4, range (estimated from figure): 0 to 7 vs. 2 to 10 (NSD; no descriptive statistical data were reported)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Tai, 2002(48) U.S. (Poor)	3 patients required additional analgesic medications (oxycodone controlled release, ibuprofen, and amitriptyline, and combination oxycodone plus acetaminophen)		

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Tai, 2002(48) U.S. (Poor)	Monitoring	1 patient had urinary retention

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Tai, 2002(48) U.S. (Poor)	Total withdrawals: 7 Withdrawals due to adverse events: 1 (urinary retention, treatment group not reported)	Study had a high (7/14, 50%) dropout rate, mostly due to lack of compliance with the long duration (10 wk) of the study (4 patients). Two patients had medical complications unrelated to the study (spinal hardware infection and recurrent hip dislocation) and were transferred to another facility and lost to follow-up. One patient withdrew because of an adverse event (urinary retention). The assigned treatment at the time of the dropout was not reported.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Finnerup, 2002(53) Denmark (Poor)	Double-blind, placebo-controlled, crossover RCT Outpatients of a rehabilitation center for spinal cord injury	Neuropathic pain after traumatic spinal cord injury (SCI) at or below level of spinal lesion; age 18 to 70 yr; pain intensity >/= 3 on a 0-to-10-point numeric rating scale	Lamotrigine titrated from 25 to 400 mg/d vs. Placebo, reaching maximal dose at wk 8 and continuing to wk 9	2-wk washout before crossover 1-wk washout of previous medications with potential analgesic effects
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	Double-blind, placebo-controlled, parallel-group RCT Pain Clinic setting	Intractable neuropathic pain (at least 3 of the cardinal symptoms of neuropathic pain shooting/lancinating, burning, numbness, alodynia, paresthesia/dysesthesia); failed codeine-based analgesics or nonsteroidal antiinflammatory drugs	Lamotrigine dispersible tablets titrated from 25 to 200 mg/d vs. Placebo, reaching maximum at wk 7 and continuing to wk 8	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Finnerup, 2002(53) Denmark (Poor)	Spasmolytics (baclofen, tizanidine), sedatives (zolpidem or zopiclon), simple analgesics (nonsteroidal antiinflammatory drugs, aspirin) were allowed at stable doses during trial; acetaminophen up to 3 g/d for escape medication	11-point Numeric Rating Scale (NRS) (0 = No pain, 10 = Worst imaginable pain), daily; 6-point descriptive pain scale for pain relief (complete to worse); pain impact on sleep; escape medication use; Danish version of the McGill Pain Questionnaire (MPQ); acute version of the Short Form-36 (SF-36) quality of life questionnaire; 11-point spasticity intensity scale; combined score of muscle tone using the Ashworth scale and clinical grading of tendon reflexes; quantitative skin testing (QST) (frequency of these outcome measurements was not reported)	Age, mean (range), y: 49 (27 to 63) 81.8% Male, 18.2% Female Ethnicity not reported	Duration of pain, median (range), y: 7 (1 to 31) Pain intensity (NRS 0 to 10), median (range): 5 (3 to 8) Allodynia, n: 9 Pain descriptor, n Shooting: 12 Tingling: 11 Taut: 11 Pricking: 10
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	Analgesics (not otherwise specified)	11-point linear visual analogue scale (VAS) for average daily pain, other neuropathic symptoms, quality of life, mobility, sleep, and mood, daily. Analgesic consumption, daily.	Lamotrigine vs. Placebo Age, mean, y: 47.1 vs. 44.7 Male / Female, %: 55.6 / 44.4 vs. 39.5 / 60.5 (p > 0.05) Ethnicity not reported	Duration of pain, mean, mo: 87 vs. 61 (p > 0.05)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Finnerup, 2002(53) Denmark (Poor)	436 screened / 100 eligible / 30 enrolled / 30 randomized	8 withdrawn / none lost to follow-up / 22 analyzed	Lamotrigine vs. Placebo Change in pain score, median All patients: 1 vs. 0 Incomplete SCI lesions (n = 12), estimated from figure: -2 vs. 0 (p = 0.02) Complete SCI lesions (n = 10), estimated from figure: -0.5 vs. -0.5 Difference in pain reduction Incomplete SCI lesions, median (25% CI): 25% (8% to 42%) NNT for 50% pain relief (25% CI): 12 (2 to ∞) NNT for 33% pain relief (25% CI): 3 (1.41 to ∞)
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	Number screened not reported / Number eligible not reported / 100 enrolled / 100 randomized	18 withdrew / 8 failed to attend for end of study review; 26 not analyzed / 74 analyzed	Lamotrigine vs. Placebo Mean change in scores (0 to 10 VAS) from baseline to wk 8 on treatments --Overall pain: -0.01 vs. 0.03 --Mood: -0.08 vs. -0.22 --Sleeping: -0.27 vs. -0.15 --Quality of life: -0.38 vs. -0.15 (p > 0.05 for all analyses)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Finnerup, 2002(53) Denmark (Poor)	Difference in pain reduction Incomplete SCI lesions, median (25% CI): 25% (8% to 42%) NNT for 50% pain relief (25% CI): 12 (2 to ∞) NNT for 33% pain relief (25% CI): 3 (1.41 to ∞)	Categorical pain relief, period preference, sleep interference, acetaminophen use, MPQ, SF-36, and spasticity: NSD Plasma concentration of lamotrigine between responders and nonresponders for whole group or subgroup with incomplete injury: NSD	Predictors of positive outcome: All 7 patients (100%) with evoked pain (brush allodynia or wind-up-like pain) were responders (reduction in pain >/= 2) vs. 1 of 14 patients (7.1%) without evoked pain was a responder (p < 0.001).
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	50% reduction in overall pain, n: 0 vs. not reported Change in analgesic use, baseline to wk 8, no. of tablets: 0.35 vs. 0.29	Withdrew due to lack of pain relief, n/N: 4/36 (11.1%) vs. 2/38 (5.3%)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Finnerup, 2002(53) Denmark (Poor)	Elicited by investigator	Lamotrigine (N = 27) vs. Placebo (N = 28), n (%) CNS: 12 (44.4%) vs. 9 (32.1%) Skin: 4 (14.8%) vs. 4 (14.3%) Gastrointestinal: 4 (14.8%) vs. 3 (10.7%) Other: 5 (18.5%) vs. 6 (21.4%)
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	Not reported	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Finnerup, 2002(53) Denmark (Poor)	Lamotrigine vs. Placebo Total withdrawals: 4/15 (26.7%) vs. 4/15 (26.7%) Withdrawals due to adverse events: 1/15 (6.7%) vs. 2/15 (13.3%)	Only patients whose final dose was at least 200 mg/d for at least 2 wk were to be considered completers and included in analyses. Apparently no patients were excluded because of this criterion.
McCleane, 1999 "lamotrigine"(54) U.K. (Fair)	Lamotrigine vs. Placebo Total withdrawals: >/= 10/36 (27.8%) vs. >/= 8/38 (21.1%) (8 patients who failed to attend for end of study review were not reported by treatment group) Withdrawals due to adverse events: 6/36 (16.7%) vs. 6/38 (15.8%)	Relatively low maximal dose of lamotrigine (200 mg/d) may account for lack of efficacy. Type of neuropathic pain not specified in report. Baseline values only given for overall group, not by treatment group. Inclusion criterion may be questioned ("intractable" not defined).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Simpson, 2000(67) U.S. (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	HIV infected subjects with distal sensory polyneuropathy (DSP) established by a study neurologist (primary symptoms of burning or dysesthetic pain in both feet for at least 2 wk; rated on the Gracely Pain scale as at least "mild" all of the time or "moderate" for a total of at least 2 hours a day; and either absent or diminished ankle reflexes or distal diminution of either vibration sensation or pain and temperature sensation). No neurotoxic antiretroviral therapy for at least 8 wk or history of stable dose of these agents for at least 8 wk.	Lamotrigine titrated up to 300 mg/d vs. Placebo, reaching maximal dose at wk 7 and continuing to wk 14	8-wk washout of neurotoxic antiretroviral therapy (stavudine [d4T], didanosine [ddI], zalcitabine [ddC])

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Simpson, 2000(67) U.S. (Fair)	Analgesics (not otherwise specified)	Gracely Pain Scale (log 10 scale) for average and peak neuropathic pain, daily; patient-rated global pain relief; change in worst pain; use of concomitant analgesics	Data reported only for evaluable subjects. Lamotrigine vs. Placebo Mean (SD) age, y: 44.6 (8.4) vs. 44.4 (10.6) (p = 0.96) Male/ Female: 88.9% / 11.1%, 80.0% / 20% (p = 0.56)	Lamotrigine vs. Placebo Baseline CD4 count, cells/mm3, mean (SD), n: 377 (179), 4 vs. 153 (89), 9

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Simpson, 2000(67) U.S. (Fair)	Number screened not reported / Number eligible not reported / 42 enrolled /42 randomized	13/42 (31.0%) withdrew before wk 6 (before maximal dose) and 1 withdrew after wk 6 Discrepancy in loss to follow-up between text (5/20, 25.0% Lamotrigine vs. 1/22, 4.5% Placebo; total 6/42, 14.3%) and Figure 1 (2/20, 10.0% vs. 1/22, 4.5%; total 3/42, 7.1%) 29/42 (69.0%) analyzed (9 lamotrigine, 20 placebo)	Lamotrigine vs. Placebo, ITT Population (N = 42) Mean adjusted change in Gracely pain scores (Primary Efficacy Measure): -0.242 vs. -0.183 Calculated difference: -0.059 (p = 0.65)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Simpson, 2000(67) U.S. (Fair)	Increased / Decreased Use of Concomitant Analgesics at wk 14: 1 / 0 vs. 2 / 0 (p = 0.99) No treatment differences in global pain score and worst pain score (data not reported).	Subgroup Analysis by Neurotoxin Exposure (ddI, ddC, or d4T) Lamotrigine vs. Placebo Mean change in average pain (difference) --Neurotoxin-yes: -0.54 vs. -0.41 (-0.13) (p = 0.51) --Neurotoxin-no: -0.66 vs. -0.05 (-0.61) (p = 0.03)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Simpson, 2000(67) U.S. (Fair)	Not reported	Lamotrigine (n): rash (5), gastrointestinal infection (1), fatigue, pneumonia, diarrhea (number not reported). Placebo: no adverse events reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Simpson, 2000(67) U.S. (Fair)	Lamotrigine vs. Placebo Total withdrawals: 11/20 (55.0%) vs. 2/22 (9.1%) (no statistics) Withdrawals due to adverse events: 6/20 (30.0%) vs. 0/22 (0.0%) (no statistics) Withdrawals due to adverse events on lamotrigine, n: rash (5), gastrointestinal infection (1)	Higher apparent rates of loss to follow-up and withdrawals were seen in the lamotrigine group compared with the placebo group. Selection bias as well as the small sample size may have produced dissimilar treatment groups and affected the study results. Baseline differences in CD4+ counts between lamotrigine and placebo groups were unexplained. ITT analysis was performed using last value carried forward (LVCF) and a longitudinal analysis with no LVCF. The latter showed pain reduction in both groups (data not given here); however, selection bias may have occurred because of the greater number of lamotrigine dropouts. An extension of this study in a larger population was done by Simpson, 2003.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting	Age 18 to 65 y; weight at least 40 kg; HIV-associated sensory neuropathy (either distal sensory polyneuropathy [DSP] or antiretroviral toxic neuropathy [ATN]); Karnofsky Performance Scale of at least 60; experiencing pain despite previous symptomatic treatment for neuropathy; no prior exposure to dideoxynucleoside analogue (ddX) ART, discontinued ddX ART at least 8 wk prior, or treated with stable dose of ddX ART for at least 8 wk; pain score of at least moderate for both average and worst pain intensity on Gracely Pain Scale during at least 4 of 7 days of baseline period. Criteria for HIV-associated sensory neuropathy: symptoms of neuropathic pain in both distal lower extremities for at least 6 wk and either diminished ankle reflexes compared with the knees or diminished distal vibration, pain, or temperature sensation in the legs, as established by a neurologist.	Lamotrigine titrated from 25 mg every other day to 400 mg/d (if no concomitant enzyme inducing drugs) or 25 to 600 mg/d (if taken with concomitant enzyme inducing drugs) over 7 wk vs. Placebo then maintenance phase for 4 wk (total 11 wk on treatment)	1-wk run-in baseline phase: eligible patients reporting a pain score of at least moderate for both average and worst pain intensity on the Gracely Pain Scale during at least 4 of 7 days were randomized 8-wk washout of ddX therapy if applicable and 4-wk washout of valproate before starting study

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Stable doses of neurotoxic ddX ART; adjustable doses of other ART; analgesics (if taken for at least 4 wk prior); adjustable doses of as-needed opioid and non-opioid analgesics; stable doses of tricyclic antidepressants, class I antiarrhythmics, or AEDs; stable doses of herbal remedies and alternative therapies (e.g., massage, acupuncture; if taken for at least 4 wk prior); analgesics for new, acute non-neuropathic pain conditions for up to 10 d only	Gracely Pain Scale for average and worst pain, daily; 100-mm Visual Analogue Scale (VAS) for average pain intensity over the previous week ("no pain" to "worst possible pain") and Short Form McGill Pain Assessment Questionnaire (SF-MPQ) (15 pain descriptors ranging from none to severe) for average pain over the previous week taken at end of baseline phase and beginning and end of maintenance phase; Clinician Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC) (7-point scales ranging from marked deterioration to marked improvement) recorded at end of maintenance phase	Neurotoxic ART Stratum Lamotrigine (N = 62) vs. Placebo (N = 30) Age, mean (range), y: 44 (32 to 65) vs. 42 (29 to 67) Male: 89% vs. 93% Race: White 63% vs. 60% Black 32% vs. 30% Other 5% vs. 10% No Neurotoxic ART Stratum Lamotrigine (N = 88) vs. Placebo (N = 47) Age, mean (range), y: 45 (26 to 63) vs. 46 (33 to 64) Male: 93% vs. 81% Race: White 58% vs. 60% Black 34% vs. 36% Other 8% vs. 4%	Neurotoxic ART Stratum Lamotrigine vs. Placebo CD4+ Count, median: 278 vs. 250 Karnofsky scale score, mean (SD): 85 (9) vs. 84 (10) HIV-1 RNA, mean log10, copies/ml: 3.16 vs. 2.99 No Neurotoxic ART Stratum Lamotrigine vs. Placebo CD4+ Count, median: 271 vs. 372 Karnofsky scale score, mean (SD): 83 (10) vs. 84 (9) HIV-1 RNA, mean log10, copies/ml: 3.16 vs. 3.23

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Numbers screened and eligible not reported / 227 enrolled /227 randomized	55 withdrew / 55 lost to follow-up / 172 analyzed	<u>Neurotoxic ART Stratum</u> Lamotrigine (N = 45) vs. Placebo (N = 23) Gracely Pain Scale score, average daily pain (Primary efficacy measure, based on completers) Mean change, baseline to wk 11 (calculated difference): -0.27 vs. -0.10 (-0.17) (NSD) VAS score Mean change (calculated difference): -27.1 vs. -9.0 (-18.1) (p = 0.003) VAS-30 Responder rate (at least 30% decrease in VAS): 57% vs. 23% (p = 0.02) SF-MPQ Mean change (calculated difference): -6.9 vs. -1.6 (-5.3) (p = 0.02)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	<u>Neurotoxic ART Stratum (cont'd)</u> CGIC Moderate improvement: 18% vs. 4% Marked improvement: 30% vs. 9% (p = 0.008) At least moderate improvement (calculated): 48% vs. 13% PGIC Moderate improvement: 24% vs. 26% Marked improvement: 29% vs. 4% (p = 0.02) At least moderate improvement (calculated): 53% vs. 30% Use of Any Analgesic, n (%): 29 (47%) vs. 16 (53%) Most common analgesics: Ibuprofen, Acetaminophen	<u>No Neurotoxic ART Stratum</u> Lamotrigine (N = 71) vs. Placebo (N = 33) Gracely Pain Scale score, average daily pain (Primary efficacy measure, based on completers) Mean change, baseline to wk 11 (calculated difference): -0.30 vs. -0.27 (-0.03) (NSD) VAS score Mean change (calculated difference): -23.3 vs. -21.3 (-2.0) (NSD) VAS-30 Responder rate: 52% vs. 45% SF-MPQ Mean change (calculated difference): -6.8 vs. -8.7 (1.9) (NSD)	<u>No Neurotoxic ART Stratum (cont'd)</u> CGIC Moderate improvement: 24% vs. 18% Marked improvement: 31% vs. 24% At least moderate improvement (calculated): 55% vs. 42% PGIC Moderate improvement: 23% vs. 15% Marked improvement: 37% vs. 30% At least moderate improvement (calculated): 60% vs. 45% Use of Any Analgesic, n (%): 43 (49%) vs. 21 (45%) Most common analgesics: Ibuprofen, Acetaminophen

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Elicited by investigator	Lamotrigine (N = 150) vs. Placebo (N = 77) Most common adverse events, n (%) Rash: 21 (14%) vs. 9 (12%) Nausea: 17 (11%) vs. 8 (10%) Headache: 16 (11%) vs. 8 (10%) Adverse events considered to be drug-related by investigator and reported by at least 5% of patients in either treatment group, n (%) Nausea: 11 (7%) vs. 3 (4%) Rash: 7 (5%) vs. 4 (5%) No cases of serious rash (i.e., associated with hospitalization or discontinuation of study drug)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Simpson, 2003(75) Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Lamotrigine vs. Placebo Total Study Population Total withdrawals: 34/150 (22.7%) vs. 21/77 (27.3%) Withdrawals due to adverse events: 10/150 (6.7%) vs. 7/77 (9.1%) Neurotoxic ART Stratum Total withdrawals: 17/62 (27.4%) vs. 7/30 (23.3%) Withdrawals due to adverse events: 5/62 (8.1%) vs. 2/30 (6.7%) No Neurotoxic ART Stratum Total withdrawals: 17/88 (19.3%) vs. 14/47 (29.8%) Withdrawals due to adverse events: 5/88 (5.7%) vs. 5/47 (10.6%)	The primary efficacy results showing a beneficial effect of lamotrigine in patients taking neurotoxic ART but not in those with no neurotoxic ART are opposite of the results found in the author's previous study (Simpson, 2000). The authors attribute the discrepancy to the small sample size and high dropout rate in the earlier study. The baseline differences in CD4+ counts between treatment groups were unexplained in both studies. A surprising finding was the difference in magnitude of change in Gracely pain scores between placebo groups in the two strata (-0.10 vs. -0.27 in the Neurotoxic ART vs. No Neurotoxic ART). The magnitude of the placebo effect (-0.27) in the No Neurotoxic ART stratum was similar to the effect achieved by lamotrigine in either stratum (-0.27 and -0.30). It is possible that a difference in an unidentified confounding factor between treatment populations is affecting the study results.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Vestergaard, 2001(56) Denmark (Fair)	Two-center double-blind, placebo-controlled, crossover RCT Outpatient neurology clinics	Previous stroke episode; pain for more than 3 mo; age older than 18 y; pain following a stroke for which nociceptive, peripheral neuropathic, and psychogenic origin were considered highly unlikely.	Lamotrigine vs. Placebo slowly titrated from 25 to 200 mg/d (or placebo equivalent), reaching maximum at wk 7 and continuing to wk 8	2-wk washout before crossover Previous antidepressants, antipsychotics, AEDs, or analgesics were to be previously tapered off. 2-wk washout of monoamine oxidase inhibitors

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Vestergaard, 2001(56) Denmark (Fair)	Acetylsalicylic acid 300 mg/d (as antithrombotic) and acetaminophen 500 mg as needed for escape medication	Ongoing Pain: 11-point (0 to 10) Likert scale for average pain recorded daily; escape medication use daily; global pain score for physical pain (0 = no pain to 5 = very strong pain) and degree to which pain affected daily activities (1 = not at all to 5 = very much) recorded at end of each treatment period; area of spontaneous pain and dysesthesia or allodynia; acetaminophen intake Evoked pain: 11-point (0 to 10) scale at baseline and end of each treatment period; digitized circumference and calculated area of painful region	Age, median (range), y: 59 (37 to 77) 60% Male / 40% Female Ethnicity not reported	Duration of central post-stroke pain (CPSP), median (range), y: 2.0 (0.3 to 12) Nontrial drugs at study start, median (range): 4 (1 to 8) Barthel Index (0 to 100; higher scores reflect greater independence in functional ability), median (range): 100 (50 to 100) Thalamic / Suprathalamic / Brainstem lesion(s), n (%): 12 (40) / 20 (67) / 9 (33) More than one lesion on magnetic resonance imaging (MRI) or computerized tomography (CT), n (%): 20 (67)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Vestergaard, 2001(56) Denmark (Fair)	Number screened not reported / 31 eligible / 31 enrolled / 30 randomized	Period 1: 3 withdrew, 1 discontinued drug but continued in period 2 / None lost to follow-up / 27 entered period 2 Period 2: 7 withdrawn / None lost to follow-up / 27 analyzed	<u>Ongoing Pain</u> Lamotrigine vs. Placebo Likert Pain Intensity score Baseline--All patients (N = 30), median (range): 6 (4 to 10) End of wk 8 (Primary efficacy measure, N = 27), median: 5 vs. 7 (p = 0.01) NSD in pain scores for the other doses (25 to 100 mg)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Vestergaard, 2001(56) Denmark (Fair)	Lamotrigine Responders (defined as patients who achieved a clinically significant pain reduction in the last week; i.e., >/= 2 points lower than placebo values on 0 to 10 scale,), n/N (%): 12/27 (44.4%) Global pain score Physical Pain, median: 3 (moderate) vs. 4 (strong) (p = 0.02) Pain Affecting Daily Activities, median: 3 (some) vs. 4 (a lot) (p = 0.11) (Reduction of one step on the global nonlinear pain scale was considered to be a clinically significant effect.) Use of Acetaminophen 500 mg as Escape Medication, median: 0 tablets (NSD between the four lamotrigine dosing periods)	<u>Evoked Pain</u> Lamotrigine vs. Placebo Likert Pain Intensity score (0 to 10) (Primary Efficacy Measure), median (range) Acetone Drop: 1 (0 to 10) vs. 2 (0 to 10) (p = 0.01) No significant treatment difference for von Frey hairs and electrical toothbrush Area of Pain / Pain Extension: no significant treatment differences for spontaneous pain or allodynia/dysesthesia	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Vestergaard, 2001(56) Denmark (Fair)	Elicited by investigator	Lamotrigine vs. Placebo vs. Washout, n (%) (N = 30) Total: 17 (56.7%) vs. 18 (60.0%) vs. 10 (33.3%) (NSD between lamotrigine and placebo) CNS: 8 (26.7%) vs. 13 (43.3%) vs. 3 (10.0%) Skin*: 5 (16.7%) vs. 3 (10.0%) vs. 2 (6.7%) Gastrointestinal: 7 (23.3%) vs. 2 (6.7%) vs. 1 (3.3%) Respiratory: 4 (13.3%) vs. 5 (16.7%) vs. 6 (20.0%) Other: 12 (40.0%) vs. 11 (36.7%) vs. 1 (3.3%) *Rash: 2 (6.7%) vs. 2 (6.7%) vs. Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Vestergaard, 2001(56) Denmark (Fair)	Lamotrigine vs. Placebo Total withdrawals: 4/30 (13.3%) vs. 6/30 (20.0%) Withdrawals due to adverse events: 3/30 (10.0%) vs. 0/30 (0.0%) (mild rash, severe headache, and severe pain)	No period or carryover effect was detected. Treatment comparisons in terms of Likert pain scores did not take into account changes from baseline. The calculated absolute and relative reductions in pain from baseline to wk 8 on a 0 to 10 Likert scale were 1 point and 16.7%, which are not considered to be clinically relevant for chronic pain according to Farrar, 2001. However, Farrar's study validating clinical relevant changes on numerical rating scales did not include patients with CPSP. The authors of the present study considered the 30% reduction in pain scores achieved with lamotrigine relative to placebo (5 vs. 7) to be clinically relevant for CPSP, which is typically difficult to treat.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Zakrzewska, 1997(55) U.K. (Poor)	Multicenter, double-blind, placebo-controlled, crossover RCT Outpatient setting implied (not reported)	Refractory trigeminal neuralgia (diagnosed according to the following criteria: paroxysmal pain; trigeminal nerve distribution; shooting, stabbing, or electric shock-like in character; pain potentially provoked by innocuous stimuli); paroxysms of pain in trigeminal nerve distirbution for at least 3 consecutive days immediately prior to entering study; therapy with carbamazepine and/or phenytoin for at least 28 d and daily doses of these agents were unchanged for 5 days	Lamotrigine (dispersible tablet) titrated from 50 mg/d to 400 mg/d, reaching maximal dose on day 4 and continuing to day 14 vs. Placebo	3-day washout on unblinded placebo before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Zakrzewska, 1997(55) U.K. (Poor)	Carbamazepine (n = 13) or phenytoin (n = 4) was continued during study and used as escape medication for uncontrollable pain	Daily pain diary including (1) number of bursts of pain (6-point scale ranging from none to > 20); (2) severity of pain (4-point scale ranging from no pain to severe); and (3) pain relief (5-point scale ranging from complete to none), recorded at bedtime. Global evaluation relative to pre-trial condition (5-point scale ranging from much better to much worse) and daily activities, recorded at end of each treatment.	Lamotrigine/Placebo vs. Placebo/Lamotrigine sequence Age, mean, y: 66 vs. 55 66.7% Male / 33.3% Female vs. 50% Male / 50% Female Ethnicity not reported	Time since onset of first trigeminal neuralgia, median, y: 10 vs. 6 Time since onset of current episode, median, mo: 4 vs. 3 Carbamazepine therapy, n: 5 vs. 8 Phenytoin therapy, n: 2 vs. 2

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Zakrzewska, 1997(55) U.K. (Poor)	Number screened not reported / Number eligible not reported / 14 enrolled / 14 randomized	1 withdrawn (day 14 of placebo) / None reported lost to follow-up / 13 analyzed	Lamotrigine vs. Placebo Composite Efficacy Index (CEI): 11/13 (85%; 95% CI: 61% to 97%) favored lamotrigine vs. 2/13 (15%) favored placebo (p = 0.011) CEI determined in 2 patients by use of escape medication; for 8 patients by total pain score; and for 3 patients by global evaluation.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Zakrzewska, 1997(55) U.K. (Poor)	Lamotrigine/Placebo vs. Placebo/Lamotrigine sequence Daily Total Pain Scores (Burst + Severity + Relief scores, estimated from figure) Period 1, Day 14: 5.5 vs. 7.3 Period 2, Day 31: 7.5 vs. 6.9	Daily activity measure, Day 15 and Day 32 Increases in ability to wash face, comb hair, and brush teeth were apparently reported on lamotrigine. Apparently no treatment differences in chewing, shaving, and talking.	Lamotrigine vs. Placebo Global Evaluations Better or Much Better / Same / Worse or Much Worse: 10 / 3 / 0 vs. 8 / 2 / 4 (p = 0.025 using a randomization test with 100,000 simulations)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Zakrzewska, 1997(55) U.K. (Poor)	Not reported	Lamotrigine vs. Placebo Total: 25 adverse events reported by 7/13 patients (53.8%) vs. 13 adverse events reported by 7/14 patients (50%) Adverse events numerically more frequent on lamotrigine than placebo, n (%): Dizziness 5 (38.5%) vs. 1 (7.1%) Constipation 3 (23.0%) vs. 2 (14.3%) Nausea and Somnolence 3 (23.0%) vs. 1 (7.1%) for each Diplopia and Vomiting 2 (15.4%) vs. 0 (0.0%) for each Abnormal accommodation, Amblyopia, and Ataxia 1 (7.7%) vs. 0 (0.0%) for each

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Zakrzewska, 1997(55) U.K. (Poor)	Lamotrigine vs. Placebo Total withdrawals: 0/13 (0.0%) vs. 1/14 (7.1%)	The primary outcome measure was the Composite Efficacy Index (CEI), which involved assigning greater efficacy for one treatment period over the other based on one of three possible pre-defined hierarchical parameters: (1) Use of escape medication; (2) Total Pain Score (if no escape medication was used); and (3) Global evaluation (if total pain score was the same in each treatment period). The use of this method makes it difficult to compare the results of this study with those of other studies. Daily Total Pain Scores were presented descriptively because of a treatment-by-period interaction that could not be tested statistically because of the small sample size. Results confounded by co-AED therapy.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Chadda, 1978(59) (--) India (Poor)	Double-blind, crossover RCT Outpatient and inpatient setting	Diabetic patients who had peripheral neuritis characteristic of and consistent with diabetic chronic sensorimotor neuropathy (specifically, bilateral peripheral nerve involvement with impaired sensation and deep reflexes). significant pain and/or paresthesia.	Phenytoin 300 mg/d vs. Placebo for 2 wk	1-wk washout before crossover
McCleane, 1999(101) U.K. (Fair)	Double-blind, placebo-controlled, crossover RCT Outpatient Pain Clinic	Neuropathic pain	Phenytoin 15 mg/kg intravenously in 1000 ml 0.9% saline vs. 0.9% Saline (placebo) 1000 ml each given over 2 h	1-wk washout before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Chadda, 1978(59) (--) India (Poor)	Not reported	Intensity and extent of pain and paresthesia in comparison with pre-treatment symptoms, using a 6-point scale (0 = No improvement; 5 = Complete disappearance of symptoms); frequency of assessments was not reported. Definition of relief (response): moderate improvement of symptoms (i.e., more than score of 2)	Age, mean (range), y: 49.9 (20 to 70) Male / Female: 23 / 17 Ethnicity not reported	Duration of diabetes mellitus, mean (range), y: 7.6 (0.25 to 12) Control of diabetes --"Good": 25 --"Poor": 15 Group A (Phenytoin - Placebo) vs. Group B (Placebo - Phenytoin) --Pain: 20/20 (100%) vs. 20/20 (100%) --Paresthesias: 16/20 O80.0%) vs. 18/20 (90.0%)
McCleane, 1999(101) U.K. (Fair)	Not reported	11-point linear visual analogue scale (VAS) for total pain, shooting pain, burning pain, numbness, paresthesia, and sensitivity, recorded every 15 min during infusion and daily for 7 d after infusion	Age, mean (range), y: 40 (25 to 60) Male / Female: 9 / 11 Ethnicity not reported	Duration of neuropathic pain, mean (range), mo: 70 (13 to 132) Diagnosis (n) --Lumbar radiculopathy (6) --Sacral neuritis (3) --Brachial neuritis (2) --Digital neuroma (2) --Diabetic neuropathy (3) --Cervical radiculopathy (4)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Chadda, 1978(59) (--) India (Poor)	--/--/40/40	2 withdrawn / 2 lost to follow-up (reasons for withdrawal were not reported) / 40 analyzed	Phenytoin vs. Placebo Group A Pain Improved (at least moderate improvement or score > 2): 14/20 (70.0%) vs. 5/20 (25.0%) (p < 0.02) Paresthesia improved: 12/16 (75.0%) vs. 5/16 (31.2%) (p < 0.05)
McCleane, 1999(101) U.K. (Fair)	Numbers screened and eligible not reported / 20 enrolled / 20 randomized	None withdrawn / None lost to follow-up / 20 analyzed	Phenytoin vs. Placebo Calculated change in mean overall pain score, baseline to 2 h: -1.37 vs. 0 (no statistical analysis)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Chadda, 1978(59) (--) India (Poor)	Group B Pain Improved: 14/18 (77.8%) vs. 5/18 (27.8%) (p < 0.01) Paresthesia Improved: 11/16 (68.8%) vs. 3/16 (18.8%) (p < 0.02)	Group A Complete Pain Relief (score of 5): 4/20 (20.0%) vs. 0/20 (0.0%) Complete Paresthesia Relief (score of 5): 5/20 (25.0%) vs. 0/20 (0.0%)	Group B Complete Pain Relief: 5/18 (27.8%) vs. 1/18 (5.6%) Complete Paresthesia Relief: 4/16 (25.0%) vs. 0/16 (0.0%) No improvements were seen in sensory deficit, motor strength, or deep reflexes on either treatment.
McCleane, 1999(101) U.K. (Fair)	Calculated change in mean overall pain score, baseline to 1 d / 7 d: -1.34 / -0.55 vs. 0.36 / 0.56 (no statistical analysis)	Patients indicating a reduction in pain scores: 14/20 (70.0%) vs. 0 (0%) Patients rating treatment to be of significant benefit: 8/20 (40.0%) vs. Not reported	No predictive factors for response to phenytoin were apparent.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Chadda, 1978(59) (--) India (Poor)	Not reported	Phenytoin vs. Placebo Group A (Phenytoin - Placebo) Giddiness: 2/20 (10.0%) vs. 0/20 (0.0%) Group B (Placebo - Phenytoin) Giddiness: 2/18 (11.1%) vs. 0/18 (0.0%)
McCleane, 1999(101) U.K. (Fair)	Reported spontaneously by patient	Adverse events on phenytoin, n --Lightheadedness: 20 --Nausea for > 24 h: 4 --Skin rash: 2 No reported adverse events on placebo

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Chadda, 1978(59) (--) India (Poor)	Total withdrawals: 2/20 (10.0%), after 2 wk in group B (during washout/neither treatment?) Withdrawals due to adverse events: None	Pain assessments were relative to baseline levels, suggesting that they may have been confounded by patient's recall. Glucose control was poor in 15 (37.5%) of 40 patients; potential differences in glucose control between treatment groups may have affected responses to study drugs. The authors noted that the majority of patients responded within 4 d. Also, there was no correlation between duration of diabetes and relief of symptoms after phenytoin.
McCleane, 1999(101) U.K. (Fair)	None	Effects of baseline differences in overall pain scores on results were not explained. Magnitude of decrease in pain scores on phenytoin do not meet Farrar's criteria for clinically relevant changes (Farrar, 2001); however, 40% of patients considered phenytoin beneficial. Heterogeneous sample population in terms of neuropathic pain types. Patients were not clearly having pain exacerbations; therefore, results may apply to acute treatment, but not necessarily to pain in flare.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Saudek, 1977(62) (--) U.S. (Poor)	Double-blind, placebo-controlled, multiple crossover RCT Outpatient setting implied	Diabetes; pain, numbness, or paresthesias in symmetrical distribution on distal extremities; absent ankle jerk reflexes; diminished vibratory sensation.	Phenytoin 600 mg loading dose on day 1 of each week then 300 mg/d, titrating to serum concentration, for 3 wk, alternating with Placebo. Dummy dosage changes were made during placebo treatment. Total duration of each treatment, 23 wk	None (likely carryover effects with crossover design)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Saudek, 1977(62) (--) U.S. (Poor)	Not reported	Self-assessed linear analogue scale (range: "None" to "Severe"; score measured as distance in mm from "None" to patient's mark) for pain, numbness, and pins and needles symptoms, recorded daily. Blood glucose.	Age, mean (range), y: 55 (30 to 75) Male / Female: 5 / 7 Ethnicity not reported	All patients had insulin-dependent diabetes for a mean of 15 y (range 1 to 39) Retinopathy: 6 Arteriosclerotic heart disease: 4 Hypertension: 1 Nephropathy: 1

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Saudek, 1977(62) (--) U.S. (Poor)	Numbers screened, eligible, and enrolled not reported / Number randomized is unclear (12?); may be number completed	2 withdrawn / Number lost to follow-up not reported / 12 analyzed	Phenytoin (serum concentration > 5 mg/l) vs. Placebo Symptom level, mean, mm (no. of individual symptom evaluations) --All symptoms: 14.4 vs. 16.2 (246 vs. 299) --Last 3 days: 15.5 vs. 15.9 (137 vs. 135) --Pain only: 7.2 vs. 8.0 (83 vs. 102) NSD for all comparisons

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Saudek, 1977(62) (--) U.S. (Poor)	Phenytoin (serum concentration < 5 mg/l) vs. Placebo Symptom level, mean, mm (no. of individual symptom evaluations) --All symptoms: 22.8 vs. 23.5 (144 vs. 174) --Last 3 days: 20.5 vs. 24.1 (54 vs. 81) --Pain only: 19.1 vs. 20.0 (48 vs. 58)		

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Saudek, 1977(62) (--) U.S. (Poor)	Method not reported for symptoms Blood glucose after fasting and 30, 60, 90, and 120 min after a standard meal (100 gm carbohydrate) was monitored	Phenytoin vs. Placebo Adverse events (no. of occurrences): 16 vs. 4 --Ataxia: 5 vs. 3 --Blurry vision: 3 vs. 0 --Dizziness: 2 vs. 0 --Rash: 3 vs. 0 --Other: 3 vs. 1

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Saudek, 1977(62) (--) U.S. (Poor)	Phenytoin vs. Placebo Total withdrawals: 2/12 (16.7%) vs. 0 (0%) Withdrawals due to adverse events: 2!2 (16.7%) vs. 0 (0%)	Treatment regimens during multiple crossovers were unclear. Washout before crossovers was not reported; therefore, response on placebo may have reflected carryover effects of phenytoin. Method of assessing symptoms is questionable; it may not have used a scale line of standardized length. Numbers randomized and analyzed were not reported. Adverse event results expressed in terms of number of occurrences; therefore, frequency of adverse events (calculated using a known denominator of exposed patients) is unknown. Randomization code was unmasked due to toxicity in a substantial proportion of patients (2/12, 16.7%) during phenytoin treatment.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Gilron, 2001(100) (--) U.S. (Poor)	Double-blind, two-period, crossover RCT ("main study") followed by a double-blind, triple crossover RCT ("confirmatory study") Outpatient setting implied	Not reported per se; patients described as having idiopathic trigeminal neuralgia (which included recurrent trigeminal neuralgia following invasive peripheral nerve or intracranial procedures) and entered the trial after maintaining a stable dose of other pain medications for 2 wk. Patients with a pain score favoring topiramate over plaebo by at least one unit on the 0-to-10 overall pain measure could enter the confirmatory study.	Main Study: Topiramate titrated from 25 to 800 mg/d vs. Placebo for 12 wk Confirmatory Study: Topiramate at maximally tolerated dose from main study (range 75 to 600 mg/d) vs. Placebo for 4 wk per treatment in three 8-wk segments (crossovers)	Main Study: 2-wk washout before crossover and end of study Confirmatory Study: Washout not reported
Drewes, 1994(52) Denmark (Poor)	Double-blind, crossover RCT Hospitalized (n = 3) or outpatients (n = 17) at the spinal cord injury center	Older than 18 y, nonprogressive spinal cord injury, central pain (pain distal to level of injury in area with loss of normal feeling) for > 1 mo, failed to respond to conventional treatments	Valproate 600 to 2400 mg/d titrated to serum concentration and clinical response vs. Placebo for 3 wk each	Washout for 2 wk before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Gilron, 2001(100) (--) U.S. (Poor)	Carbamazepine, baclofen, clonazepam, tricyclic antidepressants, gabapentin	11-point Numeric Rating Scale (NRS) (0 = No pain, 10 = Most pain imaginable for 1 day); 0 to 20 numeric scoring grid with 13 verbal pain intensity descriptors (for intensity of worst pain paroxysms in previous 24 h); frequency and duration of paroxysms; all recorded daily. The means from the last 2 wk of each treatment period were used in analyses.	Age, range, y: 40 to 66 Male / Female: 1 / 2 Ethnicity not reported	Duration of pain, range, y: 5 to 32
Drewes, 1994(52) Denmark (Poor)	Analgesics (not otherwise specified)	Verbal rating scale (1 to 5) of present pain intensity (PPI) by telephone assessment, weekly; Danish version of McGill Pain Questionnaire (MPQ) before and after each treatment series (3 wk apart). MPQ consisted of a Pain Rating Index (PRI), subscales for sensory, affective, evaluate, and miscellaneous dimensions of pain); Number of Words Chosen (NWC); PPI; and pain localization (affected area as percentage of total body area).	Median age (range), y: 32.5 (18 to 75) 75% Male, 25% Female Ethnicity not reported	16 (80%) paraplegic, 4 (20%) tetraplegic 19 (95%) traumatic injury; 1 (5%) spinal stenosis

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Gilron, 2001(100) (--) U.S. (Poor)	Numbers screened and eligible not reported / 3 enrolled / 3 randomized. 3 entered confirmatory study	Main Study: None withdrew / None lost to follow-up / 3 analyzed Confirmatory Study: 1 non-completer apparently withdrawn / 1 lost to follow-up (reason for non-completion was not reported) / 2 appeared to be analyzed	Topiramate vs. Placebo Range of treatment differences for the 3 patients, Topiramate - Placebo (% difference) Main Study --Overall Daily Pain: -1.2 to -2.1 (-31.8% to -64.3%) (p = 0.04) --Paroxysm Frequency (no./d): -3.2 to -59.6 (-10.2% to -93.3%) (NSD) --Paroxysm Intensity: -0.4 to -5.8 (-2.5% to -31.6%) (NSD) --Paroxysm duration (sec): -54.8 to 8.5 (-76.6% to 290.2) (NSD)
Drewes, 1994(52) Denmark (Poor)	Number screened not reported / 20 eligible / 20 enrolled / 20 randomized	1 withdrawn from MPQ analysis / None lost to follow-up / 19 analyzed	Valproate vs. Placebo Patients improved (definition and denominator not reported): 6 vs. 4 (not statistically different) PPI (mean change from baseline to 3 wk): 0.2 vs. -0.1 (not statistically different)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Gilron, 2001(100) (--) U.S. (Poor)	Confirmatory Study and Main Study Plus Confirmatory Study: NSD between treatments in any pain measures when data was analyzed by individual patient or together through all completed treatment periods (data not shown here). Responses sometimes varied between treatment periods; for instance, a reduction in pain scores could occur in one period and an increase in the next period.		
Drewes, 1994(52) Denmark (Poor)	MPQ subscores Not statistically different		

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Gilron, 2001(100) (--) U.S. (Poor)	Monitoring	Adverse events of at least moderate severity during topiramate but not placebo (Main Study) (n): --Irritability and diarrhea (2) --Fatigue/sedation, hyperactivity, nausea, abdominal cramps, lightheadedness, and cognitive impairment (1 each)
Drewes, 1994(52) Denmark (Poor)	Method used in telephone assessments not reported; laboratory tests monitored	Valproate: Gastroenteritis (authors retrospectively believed this was not a side effect); dizziness Placebo: none of the patients had adverse events

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gilron, 2001(100) (--) U.S. (Poor)	1 apparent withdrawal during Confirmatory Study (reason not reported) Withdrawals due to adverse events were not reported	Baseline pain scores were not reported; therefore, change from baseline could not be assessed. Complete data were available for analysis from only 2 of the 3 patients from crossover treatment periods #2 and #3. Multiple crossovers and repeated measures over time may have increased the power of the study; however, the sample size is still extremely small (N = 3). Failure to confirm the positive results in the main study may be due to chance variation or development of tolerance to topiramate.
Drewes, 1994(52) Denmark (Poor)	Total withdrawals: 2 Withdrawal due to adverse event: 1 on valproate	Authors reported that there was no statistical evidence of carry-over effect or regression towards the mean.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Kochar, 2002(58) India (Poor)	Double-blind, placebo-controlled, parallel-group RCT Diabetes clinic setting	Not reported; patients described as having type 2 diabetes mellitus with painful neuropathy	Sodium valproate 600 to 1200 mg/d vs. Placebo for 4 wk	None
Kochar, 2004(57) India (Fair)	Double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Diabetes for at least 6 mo; stable dosage of insulin or oral hypoglycemic agent; HgA1c < 11; daily neuropathic pain of at least moderate severity for > 3 mo that interfered with daily activity or sleep; pain intensity of > 4 on a visual analogue scale (VAS)	Sodium valproate 500 to 1000 mg/d vs. Placebo for 3 mo	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Kochar, 2002(58) India (Poor)	Analgesics (not otherwise specified) -- no changes were allowed	Short Form McGill Pain Questionnaire (SF-MPQ) at baseline, day 7, and end of 1 mo.	Valproate (N = 28) vs. Placebo (N = 24) Age, y (statistical units not reported): 58.5 (7.6) vs. 53.9 (8.3) Male / Female: 57.1% / 42.9% vs. 54.2% / 45.8% Ethnicity not reported	Duration of type 2 diabetes, y, statistical units not reported: 9.2 (6.2) vs. 8.1 (6.2)
Kochar, 2004(57) India (Fair)	None reported	Short Form McGill Pain Questionnaire (SF-MPQ), VAS and present pain intensity (PPI) at baseline, 1 mo, then 3 mo. Motor and sensory nerve conduction studies (MNCV and SNCV) at baseline and 3 mo.	Sodium valproate (N = 21) vs. Placebo (N = 18) Age, units not reported: 54.4 (8.8) vs. 56.2 (8.8) Male / Female: 57.1% / 42.9% vs. 50% / 50% Ethnicity not reported	Duration of type 2 diabetes, statistical units not reported, y: 8.8 (4.2) vs. 8.8 (3.8) HbA1c, %: 8.8 (1.3) vs. 8.6 (1.1) Duration of diabetic neuropathy: not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Kochar, 2002(58) India (Poor)	60 screened / Number eligible, enrolled, and randomized not reported / 57 treated	8 withdrawn / Number lost to follow-up not reported / 52 analyzed	Valproate (N = 28) vs. Placebo (N = 24) SF-MPQ, mean: Baseline: 5.0 vs. 4.9 1 mo: 3.4 vs. 4.6 (p = 0.028) Calculated change (%) in mean score from baseline to 1 mo: 1.6 (31.8%) vs. 0.3 (6.1%) Calculated difference between changes in mean scores: 1.3
Kochar, 2004(57) India (Fair)	48 Screened / 43 eligible / 43 enrolled / 43 randomized	4 withdrawn / None lost to follow-up / 39 analyzed	Valproate (N = 21) vs. Placebo (N = 18) Difference at 3 mo SF-MPQ: -8.1 (p < 0.001) VAS: -3.0 (p < 0.001) PPI: -1.28 (p < 0.001)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Kochar, 2002(58) India (Poor)	Patients with at least moderate pain relief: 24/28 (85.7%) vs. 5/24 (20.8%)	Electrophysiologic studies showed significant ($p < 0.05$) deterioration in isolated ulnar (placebo only) and sural (both treatment groups) sensory conduction studies. Significant ($p < 0.05$) improvement was seen in isolated tibial motor conduction on valproate.	
Kochar, 2004(57) India (Fair)	Change from baseline to 3 mo: SF-MPQ: -9.81 vs. 0.12 VAS: -3 vs. 0.29 PPI: -1.38 vs. 0.04 NCV data: no improvement from baseline to 3 mo		

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Kochar, 2002(58) India (Poor)	Elicited by investigator	Valproate: 1/28 (3.6%) with increased liver function tests (bilirubin 3.5 mg%, AST 80 ku/ml, ALT 90 ku/ml; normal ranges not reported) Placebo: none
Kochar, 2004(57) India (Fair)	Elicited by investigator	On valproate, n: Nausea (2) Drowsiness (1) Increased liver function tests (bilirubin, AST, ALT) (1, at 1 mo) On placebo: none

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Kochar, 2002(58) India (Poor)	Valproate vs. Placebo Total Withdrawals: 2/30 (6.7%) vs. 4/30 13.3%) and 2 unaccounted for Withdrawals due to adverse events: 1/30 (3.3%) vs. 0 (0%)	Primary efficacy variable was not defined. Adjustment for multiple statistical tests was not done.
Kochar, 2004(57) India (Fair)	Valproate vs. Placebo Total Withdrawals: 1/22 (4.5%) vs. 3/21 (14.3%) Withdrawals due to adverse events: 1/22 (4.5%) vs. 0/21 (0%)	Small sample size limits generalizability of results.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Eisenberg, 2001(61) (--) Israel (Poor)	Single-center, double-blind, placebo-controlled, parallel-group RCT Outpatient setting (physician's office)	Diabetes mellitus type 1 or 2; no change in antidiabetic medications within 3 wk; evidence of peripheral neuropathy as indicated by at least 2 of the following 3 measures: (a) medical history, (b) neurologic examinations, or (c) abnormal nerve conduction test results; pain attributed to diabetic neuropathy for > 6 mo; 11-point numerical pain scale (NPS) score of at least 4	Lamotrigine 25 mg/d x 2 wk, 50 mg/d x 2 wk, then increased weekly by 100 mg/d up to 400 mg/d vs. Placebo for 8 wk	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)
Eisenberg, 2001(61) (--) Israel (Poor)	Acetaminophen, dipyrone, nonsteroidal antiinflammatory drugs	11-point NPS (0 = no pain; 10 = worst imaginable pain) for present pain intensity, recorded twice daily; rescue analgesic use recorded daily; McGill Pain Questionnaire (MPQ), Beck Depression Inventory (BDI), and Pain Disability Index (PDI) recorded before and after treatment phase; global assessment of both efficacy and tolerability (on 0 to 10 scale) recorded at end of treatment phase (score of 8 to 10 = high, 4 to 7 = moderate, 0 to 3 = low)	Lamotrigine (N = 27) vs. Placebo (N = 26) Age, mean, y: 52.7 vs. 57.8 Male/ Female: 17 / 10 vs. 16 / 10 Ethnicity not reported	Diabetes type 1 / type 2: 3 / 24 vs. 2 / 24 Duration of diabetes, mean, y: 13.9 vs. 9.6 (p = 0.04) Previous treatment for neuropathic pain --Antidepressants: 8 vs. 10 --Antiepileptic drugs: 7 vs. 8 --Capsaicin cream: 4 vs. 2 --Other: 2 vs. 3

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed	(12) Results
Eisenberg, 2001(61) (--) Israel (Poor)	160 screened / Numbers eligible and enrolled not reported / 59 randomized	13 withdrawn / None lost to follow-up / 53 analyzed	Lamotrigine (N = 27) vs. Placebo (N = 26) Change in weekly mean pain intensity from baseline to wk 8 (calculated): -2.2 vs. -1.2 (calculated difference: -1.0; p < 0.001) Relative (%) change in weekly mean pain intensity (calculated): 34.4% vs. 18.5% Maximal pain reduction from baseline: 37% vs. 20% Achieved 50% reduction in pain during the last 3 wk of treatment: 12/25 (48.0%) vs. 5/22 (22.7%) (p = 0.05)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Eisenberg, 2001(61) (--) Israel (Poor)	Intake of > 7 tablets/wk of an analgesic --Lamotrigine, baseline / last 4 wk of treatment / calculated change, n: 7 / 2 / 5 --Placebo, baseline / end of treatment / calculated change, n: 3 / 3 / 0	Calculated change from baseline --MPQ, words: 0.5 vs. -0.4 (NSD) --BDI, total score: 0.4 vs. -1.2 (NSD) --PDI, total score: -0.2 vs. -0.1 (NSD)	Global assessment of efficacy, n (%) --High: 7/22 (32%) vs. 2/21 (10%) --Moderate: 9/22 (41%) vs. 7/21 (33%) --Low: 6/22 (27%) vs. 12/21 (57%) p = 0.07 Global assessment of tolerability, n (%) --Highly tolerable: 18/22 (81%) vs. 18/21 (86%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported
Eisenberg, 2001(61) (--) Israel (Poor)	Monitoring	Lamotrigine (N = 29) vs. Placebo (N = 30) Reported adverse event, n (calculated %): 17/29 (58.6%) vs. 21/30 (70.0%) Specific adverse events, n --Rash: 2 vs. 0 --Nausea: 4 vs. 4 --Epigastric pain: 3 vs. 1 --Headache: 2 vs. 2 --Drowsiness: 1 vs. 4 --Dizziness: 3 vs. 4 --Other: 2 vs. 6

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Eisenberg, 2001(61) (--) Israel (Poor)	Lamotrigine vs. Placebo Total Withdrawals, n (calculated %): 5/29 (17.2%) vs. 8/30 (26.7%) Withdrawals due to adverse events: 2/29 (6.9%) vs. 2/30 (6.7%)	Method of concealing allocation of treatment appeared to be inadequate (one patient was able to open the emergency blinding code).

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Goodwin, 2003(2) (Fair)	2 large integrated health plans in California and Washington	Retrospective cohort; mean follow-up of 2.9 y per individual (total 60,060 person-years for cohort)	Plan members aged >/= 14 y; record of outpatient treatment for bipolar I or II disorder (DSM-IV); enrolled in Kaiser Permanente (KP) or Group Health Cooperative (GHC) at any time from Jan. 1, 1994 to Dec. 31, 2001; at least 1 prescription for lithium, divalproex, o carbamazepine filled at a KP or GHC pharmacy	Schizophrenia; schizoaffective disorder recorded before first diagnosis of bipolar disorder; dementia or cognitive disorders occurring before first diagnosis of bipolar disorder. Patients with schizoaffective disorder occurring after the first diagnosis of bipolar disorder were included but censored on the date of the first schizoaffective diagnosis.
Malmgren, 2001(77) (Poor)	Not reported	Cohort with 62-month follow up of treated group only (range, 31 to 124 mo)	Completed presurgical neuroophthalmologic workup between 1988 and 1998	Field map depressions and contractions attributable to surgery

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed
Goodwin, 2003(2) (Fair)	Treatment exposure (% of all person-years of follow-up, based on computerized pharmacy records): Lithium (27%) Divalproex (18%) Carbamazepine (4%) Combination (4%) None of above (47%)	Number screened not reported / 20,638 eligible / Number "enrolled" not applicable	Numbers withdrawn and lost to follow-up not reported / 20,638 analyzed
Malmgren, 2001(77) (Poor)	Vigabatrin (n = 99) No vigabatrin at time of visual field test (n = 56)	Numbers screened and eligible not reported / 155 enrolled	Numbers withdrawn and lost to follow-up not reported / 155 analyzed On follow-up, 4 of 16 not evaluable; 12 analyzed

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Goodwin, 2003(2) (Fair)	KP (n = 16,248) vs. GHC (n = 4390) Age, mean (SD), y: 38.7 (14.6) vs. 37.9 (14.7) Female, n (%): 10,429 (64) vs. 2945 (67) Ethnicity not reported	KP vs. GHC First mood stabilizer, n (%) --Lithium: 7121 (44) vs. 2050 (47) --Divalproex: 7595 (47) vs. 1676 (38) --Carbamazepine: 909 (6) vs. 474 (11) --Combination: 623 (4) vs. 190 (4) Ever exposed to --Lithium: 8935 (55) vs. 2609 (59) --Divalproex: 10,171 (63) vs. 2476 (56) --Carbamazepine: 2265 (14) vs. 1020 (23) --Antidepressants: 12,222 (75) vs. 3337 (76) --Typical antipsychotics: 3420 (21) vs. 1061 (24) --Atypical antipsychotics: 5218 (32) vs. 1110 (25)
Malmgren, 2001(77) (Poor)	Age, mean (range), y: 34.8 (17.5 to 58) Gender not reported Ethnicity not reported	Duration of epilepsy, mean (range), y: 18.3 (1 to 43) Number of other AEDs, median (range): 4 (1 to 11)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	How adverse events assessed	Adverse events reported
Goodwin, 2003(2) (Fair)	Suicide mortality: mortality files from state departments of health using ICD-9 codes Suicide attempts: computerized records of all emergency department (ED) visits or inpatient discharges using ICD-9 codes; also specific suicide terms on ED encounter forms for KP only	Numbers (event rates per 1000 person-years during periods of exposure, both sites (p-values for treatment vs. lithium) Suicide attempts resulting in hospitalization --Lithium: 67 (4.2) --Divalproex: 112 (10.5) (p < 0.001) --Carbamazepine: 39 (15.5) (p < 0.001) --Combination: 30 (12.4) (p < 0.001) --None: 135 (4.8) (p = 0.44) Suicide deaths --Lithium: 9 (0.7) --Divalproex: 14 (1.7) (p = 0.04) --Carbamazepine: 2 (1.0) (p = 0.86) --Combination: 3 (1.5) (p = 0.40) --None: 25 (1.2) (p = 0.20)
Malmgren, 2001(77) (Poor)	Depressions and contractions on Goldmann perimetry full-field maps, evaluated by blinded investigator	Vigabatrin vs. No vigabatrin Visual field defects (VFDs) present (1st exam): 19/99 (19%) vs. 6/56 (11%) (no statistics) Complained of visual symptoms: 5/19 (26.3%) vs. 2/6 (33.3%) None of the patients with visual field abnormalities complained of tunnel vision.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported
Goodwin, 2003(2) (Fair)	Divalproex vs. Lithium Risk of Suicide Attempts and Deaths, Hazard Ratio (95% CI) --Suicide attempts ascertained in ED: 1.8 (1.4 to 2.2) (p < 0.001) --Suicide attempts resulting in hospitalization: 1.7 (1.2 to 2.3) (p = 0.002) --Suicide deaths: 2.7 (1.1 to 6.3) (p = 0.03)	Carbamazepine vs. Lithium Risk of Suicide Attempts and Deaths, Hazard Ratio (95% CI) --Suicide attempts ascertained in ED: 1.4 (1.0 to 2.0) (p = 0.09) --Suicide attempts resulting in hospitalization: 2.9 (1.9 to 4.4) (p < 0.001) --Suicide deaths: 1.5 (0.3 to 7.0) (p = 0.6)
Malmgren, 2001(77) (Poor)	Frequency of VFDs by cumulative vigabatrin dose (n = 84) Total vigabatrin dose: No. of patients (%): < 1 kg: 2/51 (4%) 1 to 2 kg: 2/12 (17%) 2 to 3 kg: 3/7 (43%) 3 to 5 kg: 6/8 (75%) > 5 kg: 4/6 (67%) (p < 0.0001) Duration of vigabatrin treatment, mean (range), mo With VFDs (n = 19): 52 (4 to 152) Without VFDs (n = 80): 14.6 (1 to 90) (p < 0.0001)	Follow-up of VFDs in vigabatrin-treated patients VFD unchanged vs. VFD worsened, n: --Stopped vigabatrin before first perimetry: 5 vs. 2 --Taking vigabatrin at second perimetry: 2 vs. 3 No patients improved.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Withdrawals due to adverse events	Comments
Goodwin, 2003(2) (Fair)	Not reported	Adjustments for some confounders were done but not for prior suicide attempts or disease severity. Accuracy and sensitivity of diagnosis and outcome ascertainment methods are uncertain. Actual treatment exposure (adherence) is uncertain. Estimates of drug exposures were based on assumptions. These limitations should apply equally to the main treatment groups and not produce systematic bias; however, potential differences in case mix cannot be adjusted for. No sensitivity analyses for residual confounding were performed.
Malmgren, 2001(77) (Poor)	Not reported	Follow-up was not performed on the untreated group. Concomitant AED therapy confounds association between vigabatrin and VFDs. Authors note that phenytoin, valproate, lamotrigine, progabide, and diazepam have also been associated with VFDs.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Rzany, 1999(80) (--) (Fair)	Inpatient hospital setting; rash developed in outpatient setting Participating countries: France, Germany, Italy, Portugal	Multinational, multicenter matched case-control study with comparison of AEDs Study period: Started February 1989 (in Italy) to March 1992 (in Germany); ended January 1993 (in France) to July 1995 (other countries)	Developed skin reaction when not hospital inpatients; reactions validated and classified as Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) by an expert committee. Controls were patients admitted to the same hospital for an acute illness	Not reported
Tohen, 1995(78) (--) (Poor)	Inpatient psychiatric hospital	Retrospective cohort; May 1989 to May 1993	Baseline white blood cell count (WBC) of > 4,000/mm3, hematocrit > 30%, and platelet count > 100,000/mm3 before starting an index agent.	Blood dyscrasia associated with a probably causal medical illness or other agents

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed
Rzany, 1999(80) (--) (Fair)	Phenobarbital Phenytoin Carbamazepine Valproate Lamotrigine	Numbers screened and eligible not reported / 352 cases and 1579 controls enrolled	Numbers withdrawn and lost to follow-up not reported / 352 cases and 1579 controls analyzed
Tohen, 1995(78) (--) (Poor)	Carbamazepine Valproate Imipramine Desipramine	Not reported. 11,720 admitted, 1251 received valproate, 977 received carbamazepine; 65 both agents; 317 both agents at different times	Numbers withdrawn and lost to follow-up not reported / 29 analyzed

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Rzany, 1999(80) (--) (Fair)	Characteristics of 73 patients on AEDs Age, n (%) --0 to 24 y: 16 (22%) --25 to 49 y: 29 (39%) --50 y or older: 28 (39%) Female: 41 (56%) Characteristics of all cases vs. controls Ethnicity, n --France: 117 vs. 498 --Germany: 116 vs. 659 --Italy: 90 vs. 369 --Portugal: 29 vs. 53	AED Cases (N = 73/352. 20.7%) vs. Controls (N = 28/1579, 1.8%) Previous adverse drug reaction to AEDs: 6 (8%) vs. 1 (4%) --Previous adverse drug reaction to phenobarbital: 2/6 (33.3%) cases --Previous adverse drug reaction to other AED not taken at time
Tohen, 1995(78) (--) (Poor)	Reported for patients with leukopenia (n = 25) Age, range, y: 13 to 63 Male / Female: 6 / 19 Ethnicity not reported	Major affective disorder: 20/25 (80.0%)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	How adverse events assessed	Adverse events reported
Rzany, 1999(80) (--) (Fair)	Expert committee; diagnostic criteria not reported	All cases (N = 352) Stevens-Johnson Syndrome (SJS): 136 cases Toxic Epidermal Necrolysis (TEN): 216 cases Definite diagnosis: 266/352 (76%) Probable diagnosis: 86/352 (24%) AED Cases (N = 73) --SJS: 30 (41%) --TEN: 43 (59%) Deaths among AED cases: 8/73 (11%)
Tohen, 1995(78) (--) (Poor)	Blood dyscrasias defined as WBC 3000 to 4000/mm3 (moderate leukopenia) or < 3000/mm3 (severe leukopenia); platelet count < 100,000/mm3; hematocrit < 30%. Cases identified from laboratory records. Blood cell counts were required at least weekly for patient	Carbamazepine vs. Valproate All Leukopenia: 21/977 (2.1%) vs. 5/1251 (0.4%) Odds ratio [OR] 5.4 (95% CI: 2.0 to 2.3); p = 0.0001) Moderate leukopenia: OR 6.9 (1.9 to 29.9; p = 0.0003) Severe leukopenia: NSD Combination carbamazepine + valproate vs. carbamazepine All leukopenia: 1/65 (1.5%) (NSD) Thrombocytopenia: 1 vs. 0 Anemia: 0 vs. 0

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported
Rzany, 1999(80) (--) (Fair)	Univariate analysis of individual AEDs identified short-term use for all drugs and long-term use of phenobarbital and valproate as risk factors for SJS / TEN. Multivariate risk estimates for use longer than 8 wk were not significant. Univariate / Multivariate relative risk of SJS / TEN for </= 8 wk of use (95% CI) --Phenobarbital: 57 (16 to 360) / 59 (12 to 302) --Phenytoin: 91 (26 to ∞) / Not calculated (NC) --Carbamazepine: 120 (34 to ∞) / NC --Valproate: 24 (5.9 to ∞) / NC --Lamotrigine: 25 (5.6 to ∞) / NC	Univariate / Multivariate relative risk of SJS / TEN for > 8 wk of use (95% CI) --Phenobarbital: 6.2 (2.4 to 17.0) / 2.1 (0.5 to 9.3) --Phenytoin: 1.2 (0 to 5.4) / NC --Carbamazepine: 0.4 (0.02 to 2.1) / NC --Valproate: 7.0 (2.4 to 21.0) / 2.0 (0.3 to 15.0) --Lamotrigine: NC Confounders for association of long-term use of phenobarbital: region, short-term use of other AEDs, recent radiotherapy, intake of glucocorticoids, sulphonamides, anti-infective drugs, all other suspected drugs, and all other drugs. Confounders for the association with valproate: mostly short-term us of other AEDs
Tohen, 1995(78) (--) (Poor)	Carbamazepine vs. Tricyclic antidepressants All leukopenia: 21/977 (2.1%) vs. 3/1,031 (0.3%); Risk ratio 7.4 (95% CI: 2.2 to 24.7; p = 0.0001) Valproate vs. Tricyclic antidepressants All leukopenia: 0.4% vs. 0.3% (NSD) Latency of onset of leukopenia on carbamazepine, mean / median (range), d: 29 / 16 (3 to 47) Recovery time to WBC >/= 4000/mm3, mean (range), d: 6.5 (2 to 14)	

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Withdrawals due to adverse events	Comments
Rzany, 1999(80) (--) (Fair)	Not reported	Lamotrigine was not available in every country for the entire study period. It became available in Germany in 1993, and in Italy and Portugal in 1994. It was not available in France at the time of the study. Methods used to identify and diagnose cases were not clear.
Tohen, 1995(78) (--) (Poor)	Not reported	Ascertainment of outcome may be biased with respect to risk factor. Laboratory monitoring was required to be at least weekly for AEDs but a similar requirement did not exist for the antidepressants. No statistical analysis of potential confounders. Drug exposure assumed from pharmacy records.

Quality Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Yes	Yes	Yes	No	Yes	Yes	Yes
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Yes	Yes	Yes	No	Yes	Yes	Yes
Vasudev, 2000(29) (--) India	Yes	Method not reported	Yes	Yes	Yes	No	No

Quality Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Yes-attrition, crossovers. No-adherence, contamination.	No	No	Yes	Fair
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Yes-attrition, crossovers. No-adherence, contamination.	No	No	Yes	Fair
Vasudev, 2000(29) (--) India	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	No	Poor

Quality Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	--/38/38/38	Not reported	Washout (taper old/titrate new drug)	No	Yes	Ted and Vada Stanley Foundation
Obrocea, 2002(19) U.S. Extension of Frye, 2000	--/--/45/(?) 45	Not reported	Washout (taper old/titrate new drug)	No	Yes	Theodore and Vada Stanley Foundation
Vasudev, 2000(29) (--) India	--/--/30/30	Seizure disorder, cerebrovascular disease, neurologic disorder, overt hematologic, cardiac, hepatic, renal, or thyroid disorder; mental retardation; any drug taken for present mania episode; drug/alcohol dependence or abuse within past 12 mo; need for electroconvulsive therapy or neuroleptic at any time during study	Washout (medication-free for at least a period of 6 months)	Unable to determine	Yes	1) Novartis India Ltd and Novartix Pharma, Basel, Switzerland for CBZ. 2) Torrent Pharmaceutical Ltd.

Quality Table 1. Head-to-Head Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Possible. Applicable to hopitalized patients with refractory bipolar disorder with rapid cycling. The dosage titration was probably faster than what would be used in an outpatient setting. Small sample size limits generalizability.
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Results applicable to hospitalized patients with refractory bipolar disorder with rapid cycling. The dosage titration was probably faster than what would be used in an outpatient setting. Small sample size limits generalizability.
Vasudev, 2000(29) (--) India	As subjects were inpatients with acute mania, the dosage titration was probably done faster than what would be used in an outpatient setting. Small sample size limits generalizability..

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Hartong, 2003(90) The Netherlands	Yes	Yes	Yes, but data not presented by treatment group.	Yes	Yes
Tohen, 2002(87) U.S.	Yes	Method not reported	Yes	Yes	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Hartong, 2003(90) The Netherlands	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination	Yes	No
Tohen, 2002(87) U.S.	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination	No	Yes (modified)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Hartong, 2003(90) The Netherlands	Yes	Fair	--/--/144/144	Deviant laboratory values; nonpsychiatric medications that could interfere	Run-in for acutely randomized patients on double-blind treatment; entered actual prophylactice phase after recovery from acute episode
Tohen, 2002(87) U.S.	Unable to determine	Fair	330/--/--/251	Serious and unstable medical illness; DSM-IV substance dependence; intolerance to study drugs; treatment with lithium, AED, or an antipsychotic medication within 24 h of randomization	None

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Hartong, 2003(90) The Netherlands	No	Yes	Supported partly by Ciba-Geigy (later Novartis Pharma) and the Dutch Fund for Mental Health	Results are applicable to prevention of bipolar II (DSM-IV) recurrence in patients not previously treated prophylactically.
Tohen, 2002(87) U.S.	No	No (olanzapine is not established antimanic therapy)	Sponsored by Lilly Research Laboratories	Patients were hospitalized for at least the first week; therefore, results may not be generalizable to a solely outpatient population. Sham reporting of valproate concentrations may have limited the ability of investigators to fine-tune doses to maximize response and may not reflect clinical practice.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country
Hartong, 2003(90) The Netherlands
Tohen, 2002(87) U.S.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Tohen, 2003(21) U.S.	Yes	Method not reported	Yes	Yes	Yes
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Method not reported	Method not reported	No	Yes	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Tohen, 2003(21) U.S.	Not reported	Yes	Yes-attrition, adherence No-crossover, contamination	Yes	No
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	No	Yes (modified)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Tohen, 2003(21) U.S.	Unable to determine	Fair	--/--/--/251	Same as for Tohen, 2002 with addition of treatment with clozapine within 4 wk of randomization and serious suicidal risk	None
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Yes	Fair	--/--/349/175	> 6 DSM-IV manic, hypomanic, mixed, or depressive episodes in previous year; DSM-IV diagnosis of or treated within prior year for panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; epilepsy; cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; actively suicidal; score >/= 3 on item 3 of 31-item Hamilton Rating Scale for Depression	Run-in

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Tohen, 2003(21) U.S.	No	No (olanzapine is not established antimanic therapy)	Sponsored by Lilly Research Laboratories	Patients were hospitalized for at least the first week; therefore, results may not be generalizable to a solely outpatient population. Sham reporting of valproate concentrations may have limited the ability of investigators to fine-tune doses to maximize response and may not reflect clinical practice.
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	No	Yes	Grant from Glaxo-SmithKline	Results may be applicable to less severely ill bipolar cases.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Tohen, 2003(21) U.S.	
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Effects of baseline differences between treatment groups on results were not explained.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Bowden, 2000(22) Canada, U.S.	Method not reported	Method not reported	Yes	Yes	Not reported
Small, 1991(30) (--) U.S.	Method not reported	Method not reported	No--Carbamazepine was significantly youner (p = 0.02); nalysis of covariance for the effects of age did not change the significance of any of the rating scale data	Yes	Yes
Lusznat, 1988 (--) U.K.	Method not reported	Method not reported	No	Yes	Yes, but method not described

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Bowden, 2000(22) Canada, U.S.	Not reported	Not reported	Yes-attrition, adherence No-crossover, contamination	Yes	Yes (modified)
Small, 1991(30) (--) U.S.	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	Yes	No
Lusznat, 1988 (--) U.K.	Yes	Yes	Yes-attrition, adherence. No-crossover contamination	Yes	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Bowden, 2000(22) Canada, U.S.	Yes	Fair	4758/--/571/372 (Number screened from Baldessarini, 2000)	Intolerance to divalproex or lithium; alcohol abuse in past 6 mo; current substance dependence or positive urine toxicology test; concomitant confounding drug treatment; central nervous system, neuromuscular, or uncontrolled systemic disorders; serious suicidal risk; ongoing individual psychotherapy; failure to adhere to open-phase protocol; pregnancy	Run-in, washout
Small, 1991(30) (--) U.S.	Yes	Poor	94/52/52/52	Axis I DSM-III-R diagnoses, significant medical problems, affective episodes associated with physical illness, current substance abuse, or any contraindiation to either lithium or carbamazepine	Yes-run-in and washout
Lusznat, 1988 (--) U.K.	Yes	Poor	128/54/54/54	Not reported	None

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Bowden, 2000(22) Canada, U.S.	No	Yes	Sponsored by Abbott Laboratories	Results may be applicable to mainly uncomplicated and less severely ill patients; trial sample may represent a minority of patients with bipolar disorder.
Small, 1991(30) (--) U.S.	No	Yes (lithium)	Grant from the National Institute of Mental Health	Limited by high dropout rate and small sample size entering follow-up. Results mainly applicable to a difficult-to-treat cohort of patients.
Lusznat, 1988 (--) U.K.	Unable to determine	Yes	Partially supported by grant from Ciba-Geigy	Limited by small sample size. Results may not be applicable to a solely outpatient population.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Bowden, 2000(22) Canada, U.S.	Unable to determine LTFU (30/187 (16%) Divalproex vs. 9/91 (10%) Lithium vs. 24/94 (25%) Placebo discontinued for "Other" reasons, which included lost to follow-up, intercurrent illness, administrative reasons, or other reasons; p = 0.01 for Lithium vs. Placebo) (see Bowden, 2000)
Small, 1991(30) (--) U.S.	External validity is compromised by a high dropout rate (partly due to noncompliance by patients in manic episodes). The study methods are mainly applicable to a difficult-to-treat cohort of patients referred to a tertiary care facility who were initially hospitalized (87% were ultimately discharged); long-term results are difficult to generalize because of small number of patients (n = 16) entering 2-yr double-blind follow-up stage.
Lusznat, 1988 (--) U.K.	

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Greil, 1997(24) (--) Germany	Yes	Yes	No (An apparently higher proportion of carbamazepine patients had no prior suicide attempts and 2 episodes of illness.)	Yes	No
Greil, 1999(89)(--"bipolar I") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes	No
Greil, 1999(89)(--"bipolar II/NOS") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes (in Greil, 1997)	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Greil, 1997(24) (--) Germany	No	No	Yes-attrition, adherence No-crossover, contamination	Yes	Yes
Greil, 1999(89)(--"bipolar I") Germany	No	No	Yes-attrition, adherence, contamination No-crossover,	Yes	Yes
Greil, 1999(89)(--"bipolar II/NOS") Germany	No	No	Yes-attrition, adherence No-crossover, contamination	Yes	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Greil, 1997(24) (--) Germany	No	Poor	Not reported/375/175/144	Not reported	None
Greil, 1999(89)(--"bipolar I") Germany	No	Poor	Not reported/Not reported/Not reported/114	Prophylactic treatment immediately before onset of the index episodes; alcohol or drug abuse	None
Greil, 1999(89)(--"bipolar II/NOS") Germany	No	Poor	Not reported/Not reported/Not reported/57 (This population is a subset of the population described in Greil, 1997	Not reported	None

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Greil, 1997(24) (--) Germany	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state whether AEDs could be used as acute treatment for prior episodes)	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)	Not applicable to rapid cyclers.
Greil, 1999(89)(--"bipolar I") Germany	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state whether AEDs could be used as acute treatment for prior episodes)	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)	Applicable to patients with bipolar I disorder (DSM-IV).
Greil, 1999(89)(--"bipolar II/NOS") Germany	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state whether AEDs could be used as acute treatment for prior episodes)	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)	Applicable to patients with bipolar II disorder or bipolar disorder NOS (DSM-IV).

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Greil, 1997(24) (--) Germany	Results may be applicable to patients who are initially hospitalized, stabilized, in remission, and in need of maintenance treatment (excludes rapid cyclers). No major differences were observed between study patients and non-study patients and between completers and non-completers.
Greil, 1999(89)(--"bipolar I") Germany	Applicable to a selective population of patients with bipolar I disorder (DSM-IV) who have been hospitalized at least once and require prophylaxis.
Greil, 1999(89)(--"bipolar II/NOS") Germany	Applicable to selective population of patients with bipolar II disorder or bipolar disorder NOS (DSM-IV) who have been hospitalized at least once and require prophylaxis.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Lerer, 1987(25) (--) U.S.	Method not reported	No (blinded physician reported directly to unblinded psychiatrist)	No (An apparently higher proportion of lithium patients had a moderate or good previous response to lithium.)	Yes	Yes
Coxhead, 1992(26) (--) U.K.	Method not reported	Method not reported	Yes	Yes	Yes, but method not described
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes	Method not reported	No (apparently higher proportion of men in placebo group; NSD)	Yes	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Lerer, 1987(25) (--) U.S.	Yes	Yes	Yes-attrition No-crossover, adherence, contamination	Yes	No
Coxhead, 1992(26) (--) U.K.	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination	Yes	Yes
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	No	Yes (modified)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Lerer, 1987(25) (--) U.S.	Yes	Poor	Not reported/Not reported/34/34	Not reported	Washout
Coxhead, 1992(26) (--) U.K.	No	Fair	145/Not reported/32/31	Not reported	Run-in
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes	Fair	--/--/966 enrolled/463 randomized	> 6 DSM-IV manic, hypomanic, mixed, or depressive episodes in the year prior to enrollment; DSM-IV diagnosis of, or had received treatment within the year pior to enrollment for, panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; history of or current epilepsy; clinically significant cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; actively suicidal or Hamilton Rating Scale for Depression (HAM-D) score >/= 3 on item 3 (suicidality)	Run-in Washout of prior psychotropic medications

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Lerer, 1987(25) (--) U.S.	Not reported	Yes	Carbamazepine and placebo supplied by Ciba-Geigy, U.S.A.	Diagnostic classification has changed since DSM-III. Results may apply to a mixture of bipolar types under DSM-IV.
Coxhead, 1992(26) (--) U.K.	Yes	Yes	Ciba-Geigy provided support and financial assistance	Limited by small sample size.
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	No	Yes	Supported by GlaxoSmithKline	Probably generalizable bipolar I disorder with depressive episode.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Lerer, 1987(25) (--) U.S.	Applicable to bipolar disorder; however, the diagnostic classification has changed since DSM-III. Therefore, these data would apply to a mixture of bipolar types under DSM-IV.
Coxhead, 1992(26) (--) U.K.	
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Results generalizable to patients with bipolar I disorder who recently experienced a depressive episode and who were able to be stabilized on lamotrigine mono- or add-on therapy.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Kleindienst, 2002(31) (--) Germany, Switzerland	Yes	No (open-label)	No (higher extraversion score in carbamazepine group; extraversion was found to be unrelated to both inter-episodic morbidity and risk for drop-out)	Yes	No
Greil, 1998(32) (--) Germany, Switzerland	Yes	No (open-label)	Yes (although data not reported in this article)	Yes	No
Denicoff, 1997(27) (--) U.S.	Method not reported	No	Not reported	Yes	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Kleindienst, 2002(31) (--) Germany, Switzerland	No	No	Yes-attrition, adherence No-crossovers, contamination	Yes	Yes
Greil, 1998(32) (--) Germany, Switzerland	No	No	Yes-attrition No-crossover, adherence, contamination	Yes	Yes
Denicoff, 1997(27) (--) U.S.	No	Yes	Yes-attrition, crossovers, adherence No-contamination	Yes	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Kleindienst, 2002(31) (--) Germany, Switzerland	No	Poor	--/--/--/171	Not reported	None
Greil, 1998(32) (--) Germany, Switzerland	No	Poor	--/--/--/171	Affective and schizoaffective psychoses; bipolar disorder according to DSM-IV criteria; preventive treatment immediately before the onset of the index episode; alcohol or drug abuse; rapid cyclers	None
Denicoff, 1997(27) (--) U.S.	Yes	Poor	--/--/52/52	Other severe medical illness; another current Axis I disorder, usch as substance abuse	Washout

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Kleindienst, 2002(31) (--) Germany, Switzerland	Not reported	Yes	Grant from BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)	May apply to hospitalized patients, possibly more severe cases. Limited by threats to internal validity (open-label design).
Greil, 1998(32) (--) Germany, Switzerland	Not reported	Yes	Grant from BMFT, Ministry of Research and Technology of the Federal Republic of Germany (abbreviations not defined)	May apply to hospitalized patients, possibly more severe cases. Limited by threats to internal validity (open-label design). Some caution is warranted in generalizing the results because the study involved subgroup analyses.
Denicoff, 1997(27) (--) U.S.	No	Yes	Research assistant support from Ciba-Geigy; support of the Ted and Vada Stanley Foundation	Nonselective study population; threats to internal validity weaken generalizability of results.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Kleindienst, 2002(31) (--) Germany, Switzerland	Open-label design introduces possibility of bias. No major differences between study patients and non-study patients was found; therefore, results may be generalizable to hospitalized bipolar patients who need prophylactic treatment. However, the study was conducted in psychiatric university hospitals in Germany and may have included more severe cases.
Greil, 1998(32) (--) Germany, Switzerland	Open-label design introduces possibility of bias. The study was conducted in psychiatric university hospitals in Germany and may have included more severe cases. Some caution is warranted in generalizing the results because the study involved subgroup analyses ("classical" vs. "nonclassical") (Note: The patient sample is the same one used in the study by Kleindienst (2000), which evaluated bipolar I and bipolar II/NOS subgroups.)
Denicoff, 1997(27) (--) U.S.	

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Zajecka, 2002(28) (--) U.S.	Method not reported	Method not reported	No	Yes	No
Gyulai, 2003(33) (--) U.S.	Method not reported	Method not reported	Yes	Yes	Not reported
McIntyre, 2002(37) (--) Canada	Method not reported	Method not reported	Yes	Yes	Yes, but method not described

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Zajecka, 2002(28) (--) U.S.	No	Yes	Yes-attrition, adherence No-crossovers, contamination	Yes	Yes (modified)
Gyulai, 2003(33) (--) U.S.	Not reported	Not reported	Yes-attrition No-crossover, adherence, contamination	Yes	Yes (modified)
McIntyre, 2002(37) (--) Canada	Unable to determine if careprovider was the assessor	No	Yes-attrition No-crossovers, adherence, contamination	No	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Zajecka, 2002(28) (--) U.S.	Yes	Fair	--/--/--/120	Axis I or II disorder that would interfere with compliance; unstable medical condition or interfereing medication; drug or alcohol withdrawal symptoms; platelet count < 100,000 mm^3; mood disorder secondary to a medical condition; previous divalproex or olanzapine failures (investigator's opinion)	Run-in Washout of prior psychotropic medications
Gyulai, 2003(33) (--) U.S.	Yes	Fair	4758/--/571/372 (Number screened from Baldessarini, 2000)	History of substance dependence; substance abuse within 6 mo; severe medical conditions (see Bowden, 2000 for other exclusion criteria not mentioned in this report)	Run-in (open-label phase)
McIntyre, 2002(37) (--) Canada	No	Poor	--/--/36/36	Prior bupropion SR or topiramate exposure; substance dependence diagnosed within past 30 d; electroconvulsive therapy within prior 4 wk; suicide risk; nephrolithiasis; seizures; active neurological or medical problems; psychotic symptoms.	None

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Zajecka, 2002(28) (--) U.S.	No	No (olanzapine is not established antimanic therapy)	Supported by Abbott Laboratories	Limited by possible selection bias, as previous study drug failures were excluded.
Gyulai, 2003(33) (--) U.S.	No	Yes	Sponsored by Abbott Laboratories	Results may be applicable to mainly uncomplicated and less severely ill patients; trial sample may represent a minority of patients with bipolar disorder.
McIntyre, 2002(37) (--) Canada	No	Yes	Not reported	Limited by small sample size. Results may be applicable to patients with mild-to-moderate bipolar depression who have an inadequate response to mood stabilizers.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	
Zajecka, 2002(28) (--) U.S.	
Gyulai, 2003(33) (--) U.S.	
McIntyre, 2002(37) (--) Canada	Results may be applicable to patients with mild-to-moderate bipolar depression who have an inadequate response to mood stabilizers and have low suicide risk. Small sample size may limit generalizability of results.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity				
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**
Okuma, 1990(34) (--) Japan	No and method not reported; 2 patients received only placebo tablets of carbamazepine by mistake	No (blind was erroneously broken in 1 case)	No (Fewer patients aged and age of onset 20 to 29 y and more outpatients in lithium group; statistical analyses showed no significant deviation in the improvement rate in both treatment groups.)	Yes	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Okuma, 1990(34) (--) Japan	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)	Yes	Yes-attrition, adherence, contamination No-crossovers	No	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

			External Validity		
Author, year Country	**(11) Post-randomization exclusions?**	**(12) Quality rating**	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Okuma, 1990(34) (--) Japan	Yes	Poor	--/--/105/105	Carbamazepine or lithium treatment immediately prior to trial; renal, cardiovascular, liver, or hematologic disease	None

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Okuma, 1990(34) (--) Japan	Not reported	Yes	Not reported	May be a selective population of Asian patients; questionable quality of trial conduct.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country
Okuma, 1990(34) (--) Japan

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Solomon, 1997(38) (--) U.S.	Method not reported	Method not reported	No	Yes	Yes	No

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Solomon, 1997(38) (--) U.S.	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Poor

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Solomon, 1997(38) (--) U.S.	--/--/12/12	Treatment of acute (index) episode with valproate or carbamazepine; medical contraindication including significant renal, liver, or cardiovascular disease; encephalopathy, mental retardation, or terminal illness; focal neurologic deficits; seizure disorder or paroxysmal activity on electroencephalogram within past 2 y; structural brain damage from trauma, cerebrovascular disease, or demyelinating disease	Run-in	No (but yes for divalproex)	Yes	Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression; Grant from Abbott Laboratories

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Solomon, 1997(38) (--) U.S.	Limited by pilot study results and small sample size.	Pilot study results prevent definitive conclusions. Small sample size limits generalizability of results.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Calabrese, 2000(35) (--) U.S., Canada	Method not reported	Method not reported	No (an apparently higher proportion of patients had a prior suicide attempt in the lamotrigine group than the placebo group)	Yes	Yes, but masking not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Calabrese, 2000(35) (--) U.S., Canada	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Calabrese, 2000(35) (--) U.S., Canada	--/--/324/182	DSM-IV Axis II diagnosis suggestive of likely noncompliance or nonresponsiveness to pharmacotherapy; actively suicidal or score > / = 3 on item 3 of the 17-item Hamilton Rating Scale for Depression (HAM-D); panic disorder, obsessive-compulsive disorder, social phobia, or eating disorder within previous year; previous lamotrigine therapy if treatment duration was >/= 6 wk and was within 6 mo of study; allergic or idiosyncratic reaction to treatment, including rash; previous lamotrigine therapy in clinical study	Run-in	No	No (placebo)	Grant from Glaxo Wellcome, Inc.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Calabrese, 2000(35) (--) U.S., Canada	Results may apply to patients with rapid cycling disorder (DSM-IV).	Results may be applicable to a selective population of patients with rapid cycling disorder (DSM-IV) who tolerated < 6 wk of lamotrigine or are lamotrigine-naïve.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Mishory, 2003 (--) Israel	Method not reported	Method not reported	Not reported	Yes	Yes	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Mishory, 2003 (--) Israel	Yes	Yes-attrition, crossovers No-adherence, contamination	No	No	Yes	Poor

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Mishory, 2003 (--) Israel	--/--/--/23	Rapid cycling	Washout	No	No (placebo)	NARSAD Young Investigator Award and a grant from the Dreyfus Health Foundation

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Mishory, 2003 (--) Israel	Limited by small sample size. Results may reflect a selective population of compliant patients.	Small sample size limits generalizability of results. Results may reflect a selective population of compliant patients since any post-randomization dropout was excluded from analyses and replaced with a new patient who was assigned the dropout's randomization number.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Calabrese, 1999(94) (--) Australia, France, U.K., U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Calabrese, 1999(94) (--) Australia, France, U.K., U.S.	Yes	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	Yes	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Calabrese, 1999(94) (--) Australia, France, U.K., U.S.	--/--/--/195	Rapid-cycling bipolar disorder; abnormal thyroid function tests; panic disorder; obsessive-compulsive disorder; social phobia; bulimina nervosa in previous 12 mo; history of substance dependence (previous year) or abuse (previous month); positive toxicologic screen; chronic cardiac, renal, or hepatic condition; unstable medical condition; epilepsy; active suicidal ideation	Washout	No	No (placebo monotherapy)	Grant from Glaxo Wellcome Research and Development

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Calabrese, 1999(94) (--) Australia, France, U.K., U.S.	May be generalizable to patients with uncomplicated bipolar I depression.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Pande, 2000(41) (--) U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Pande, 2000(41) (--) U.S.	Not reported	Yes-attrition No-crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Pande, 2000(41) (--) U.S.	--/--/117/117	Uncontrolled medical illnesses; DSM-IV Axis I disorders; medications other than lithium and/or valproate that could alter assessments of efficacy	Run-in	No	No (placebo add-on)	Parke-Davis Pharmaceutical Research

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Pande, 2000(41) (--) U.S.	May be generalizable to patients with bipolar I disorder not responding to lithium, valproate, or combination of both

Quality Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

	Internal Validity										
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**	**(8) Reporting of attrition, crossovers, adherence, and contamination?**	**(9) Loss to follow-up: differential/ high?**	**(10) Intention-to-treat (ITT) analysis?**	**(11) Post-randomization exclusions?**
Skelton, 1991(43) U.S.	Method not reported	Method not reported	Not reported	No	Not reported	Not reported	Not reported	No	No	No	Yes

Quality Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

Author, year Country	(12) Quality Rating	Small Trial (N < 40 / gp)
Skelton, 1991(43) U.S.	Poor	y

Quality Table 4. Head-to-Head Controlled Trials: Neuropathic Pain

	External Validity							
Author, year Country	**(1) Number screened/eligible/ enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**	
Skelton, 1991(43) U.S.	--/--/12/12	Not reported	None	Unable to determine	No (both study treatments were AEDs)	Not reported	Limited by small sample size, selective population, and threats to internal validity.	Small trial size, selective population (veterans with neuropathy due to thiamine deficiency), and threats to internal validity limit the generalizability of results.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Morello, 1999(44) U.S.	Method not reported	Method not reported	Yes (crossover trial)	Yes	Yes	Yes
Gomez-Perez(45) Mexico	Method not reported	Method not reported	No	Yes	Not reported	Yes
Lindstrom, 1987(46) Sweden	Method not reported	Method not reported	Not reported	Yes	Not reported	Not reported

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality Rating
Morello, 1999(44) U.S.	Yes	Yes-attrition, crossovers, adherence No-contamination	No	No	No	Fair
Gomez-Perez(45) Mexico	Yes	Yes-attrition, crossovers, adherence No-contamination	No	No	Yes	Poor
Lindstrom, 1987(46) Sweden	Not reported	Yes- attrition, crossover. No- adherence contamination.	Not reported	No	No	Poor

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	External Validity		
Author, Year Country	**(1) Number screened/eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**
Morello, 1999(44) U.S.	--/28/25/25	Non-diabetic peripheral neuropathy (DPN) pain more severe than DPN pain; severe depression by diagnosis or Beck Inventory; receiving treatment for seizures; symptomatic postural hypotension; symptomatic coronary artery or peripheral vascular disease; creatinine clearance < 30 ml/min; prior treatment with gabapentin or amitriptyline only if doses exceeded the study's maximum dosage of either drug.	Washout
Gomez-Perez(45) Mexico	--/--/16/16	Mild diabetic peripheral neuropathy; normal nerve conduction velocity, cardiac disease, liver disease, renal failure, hematologic abnormalities, glaucoma, myasthenia gravis, monoamine oxidase inhibitor therapy within 15 d	Washout
Lindstrom, 1987(46) Sweden	--/--/12/12	Cardiovascular disease, liver and/or renal insufficiency	None

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Morello, 1999(44) U.S.	No	Yes	Not reported	Limit on maximal dose of gabapentin may not reflect usual clinical practice. Small sample size limits generalizability of results.
Gomez-Perez(45) Mexico	Previous therapy not reported	No (control was nortriptyline-fluphenazine combination, first reported to be effective by the authors in 1985)	Ciba-Geigy Mexicana provided active drugs and placebos	Limited by small sample size.
Lindstrom, 1987(46) Sweden	No	No (tocainide)	Folksam Research Foundation and the Vivian L. Smith Foundation for Restorative Neurology	Limited by small sample size and problems with internal validity.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Leijon, 1989(47) Sweden	No. One patient had a known allergy to carbamazepine and was therefore randomized only to amitriptyline and placebo. In this case, allocation of treatment was not random.	Yes (pharmacy carried out randomization and distribution of drugs)	Yes	Yes	Yes	Yes
Dallocchio, 2000(69) Italy	Method not reported	No (open-label)	No (Duration of pain was significantly longer in the gabapentin group than the amitriptyline group: mean (SD), 34 (11) vs. 22 (12) mo).	Yes	No	No
Lechin, 1989(42) (--) Venezuela	Method not reported	Method not reported	Yes (according to authors; data not reported)	Yes	Yes	Yes

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality Rating
Leijon, 1989(47) Sweden	Yes	Yes-attrition, crossovers No-adherence, contamination	No	No	Yes	Poor
Dallocchio, 2000(69) Italy	No	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Poor
Lechin, 1989(42) (--) Venezuela	Yes	Yes-attrition, adherence No, contamination	No	No	Yes	Poor

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria	(3) Run-in/Washout
Leijon, 1989(47) Sweden	27/15/15/15	Contraindication to amitriptyline and carbamazepine; patients who could not be evaluated in a satisfactory way	Washout
Dallocchio, 2000(69) Italy	--/--/25/25	Renal, hepatic, or cardiovascular insufficiency; diabetic neuropathy not meeting entry criteria; neuropathy of different etiology; current or previous diagnosis of psychiatric disorder	Washout
Lechin, 1989(42) (--) Venezuela	--/--/68/59	Severe physical illness, psychotic episodes, drug or alcohol addiction, epilepsy, mental retardation	Run-in, washout

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Leijon, 1989(47) Sweden	Yes	Yes (amitriptyline)	Grants from the County Council of Östergötland and the Swedish Association of the Neurologically Disabled	Limited by small sample size and problems with internal validity.
Dallocchio, 2000(69) Italy	No	Yes (amitriptyline)	Not reported	Limited by small sample size and threat to internal validity (open-label design).
Lechin, 1989(42) (--) Venezuela	No	No (pimozide)	Grant from the Foundation of the Institute of Experimental Medicine	Results pertain to patients with severe, refractory trigeminal neuralgia.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Keczkes, 1980(98) (--)	Method not reported	Method not reported	Not reported	Yes	No	No
Lockman, 1973(97) (--) U.S.	Method not reported	Method not reported	Yes	No	Not reported	Yes

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality Rating
Keczkes, 1980(98) (--)	No	No for all	No	Yes	No	Poor
Lockman, 1973(97) (--) U.S.	Yes	Yes-attrition, adherence, crossover No- contamination	No	Yes	No	Poor

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria	(3) Run-in/Washout
Keczkes, 1980(98) (--)	--/--/40/40	Bacterial infection (other than those secondary to herpes zoster), tuberculosis, diabetes mellitus, peptic ulcer, hypertension, cardiovascular disease, lymphomas, leukemia	None
Lockman, 1973(97) (--) U.S.	--/--/8/8	Not reported	None

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Keczkes, 1980(98) (--)	Yes (prior AED therapy was not reported)	No (prednisolone)	Not reported	Limited by small sample size.
Lockman, 1973(97) (--) U.S.	Yes (pain not relieved by either conventional or narcotic analgesics)	No (aspirin or multivitamin)	Supported in part by research grants from the National Institutes of Health, American Heart Association, National Foundation-March of Dimes, and U.S. Public Health Service	Limited to rare patients with Fabry's disease and very small sample size.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Backonja, 1998 U.S.	Yes	Method not reported	Yes	Yes	Yes	Yes	Yes
Bone, 2002 U.K., Ireland.	Yes	Method not reported	Yes	Yes	Not reported	Yes	Yes
Tai, 2002 U.S.	Yes	Method not reported	Yes	Yes	Yes (for adverse events)	Yes	Yes
Serpell, 2002 U.K. and Republic of Ireland	Yes	Yes	No, lower ratio of men to women in gabapentin group (63:90) than placebo group (78:74)	Yes	Not reported	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Backonja, 1998 U.S.	Yes – attrition No - crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair
Bone, 2002 U.K., Ireland.	Yes – attrition, adherence, crossovers No - contamination	No	Yes	No	Fair
Tai, 2002 U.S.	Yes – attrition, adherence, crossovers No - contamination	No	No	Yes	Poor
Serpell, 2002 U.K. and Republic of Ireland	Yes – attrition, adherence No – crossovers, contamination	No	Yes (modified)	Yes	Fair

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Backonja, 1998 U.S.	232/--/165/165	Presence of other severe pain that could confound assessments; investigational drug within 30 days of screening; amputations other than toes; creatinine clearance less than 60 ml/min	run in and washout	No
Bone, 2002 U.K., Ireland.	33/19/19/19	Coexisting epilepsy; allergy to gabapentin; significant hepatic or renal insufficiency; severe hematologic disease; history of illicit drug or alcohol abuse; serious psychiatric condition; other severe pain that could confound assessments	Non-treatment run-in. Washout.	No
Tai, 2002 U.S.	--/--/14/14	Severe cognitive impairment; pregnancy; seizure disorder; major depression or Beck Depression Inventory score > 16; hypersensitivity to gabapentin; renal insufficiency (creatinine clearance < 60 ml/min)	Washout	No
Serpell, 2002 U.K. and Republic of Ireland	351/351/307/307	Failure to respond to previous treatment with gabapentin >/= 900 mg/d or failure to respond to gabapentin at any dose level due to side effects; creatinine clearance </= 60 ml/min or renal impairment; clinically significant hepatic, respiratory, hematologic illnesses, or unstable cardiovascular disease; significant neurologic or psychiatric disorders unrelated to causes of neuropathic pain; other severe pain that might impair assessments; other serious or unstable condition; illicit drug or alcohol abuse within the past year	Washout (prior to screening). Non-treatment run-in.	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Backonja, 1998 U.S.	No (placebo control)	Sponsored and authored by Parke-Davis	Large sample size and 71% of screened patients were randomized, suggesting results are probably generalizable to most patients with painful diabetic neuropathy.
Bone, 2002 U.K., Ireland.	No (placebo control)	Pfizer Pharmaceuticals supplied study drugs	Small sample size limits generalizability of results
Tai, 2002 U.S.	No (placebo control)	Year 2000 New Investigator Award; clinical SCI grant from the Eastern Paralyzed Veterans Association	Very small sample size limits generalizability of results
Serpell, 2002 U.K. and Republic of Ireland	No (placebo control)	Sponsored by Parke-Davis	About 88% of screened pain clinic patients were randomized and eligibility criteria did not limit selection of patients according to type of neuropathic pain, suggesting results are likely to be generalizable to most patients in a specialized pain treatment setting. Excluding patients who were nonresponsive or intolerant of gabapentin introduced a possibility of selection bias. According to the authors, in a response to comments on the article (McCleane, 2003), only a very few of the 24 excluded patients had a history of nonresponsiveness or intolerance to gabapentin.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Rowbotham, 1998 U.S.	Method not reported	Yes	Yes	Yes	Not reported	Yes	Yes
Rice, 2001 U.K., Republic of Ireland	Yes	Method not reported	Yes	Yes	Not reported	Yes	Yes
Harke, 2001 Germany	Yes	Method not reported	Not reported (data not presented by treatment groups)	No	Not reported	Yes, but method not reported	Yes, but method not reported
Campbell, 1966 U.K.	Yes	Method not reported	No (6% of the group that received carbamazepine first had been injected for pain vs. 29% of the group that received placebo first)	Yes (However, patients with trigeminal neuralgia were admitted to the trial without selection.)	Yes	Yes	Yes
Nicol, 1969 U.S.	Method not reported	Method not reported	Not reported (data not presented by treatment groups)	No	Not reported	Not reported	Not reported
Drewes, 1994 Denmark	Method not reported	Method not reported	Yes	Yes	Yes	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Rowbotham, 1998 U.S.	Yes-attrition, adherence. No-crossover, contamination	No	Yes (modified)	Yes	Fair
Rice, 2001 U.K., Republic of Ireland	Yes-attrition, adherence. No-crossover, contamination	No	Yes (modified)	No	Fair
Harke, 2001 Germany	Yes-attrition No-crossovers, adherence, contamination	No	No	No	Poor
Campbell, 1966 U.K.	Yes-attrition, crossovers, adherence, contamination	No	No	Yes	Poor
Nicol, 1969 U.S.	Yes-crossovers No-attrition, adherence, contamination	No	No	No	Poor
Drewes, 1994 Denmark	Yes-attirtion, crossovers, adherence No-contamination	No	No	No	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	*External Validity* (1) Number screened/eligible/enrolled/randomized	(2) Exclusion criteria	(3) Run-in/Washout	(4) Class naïve patients only?
Rowbotham, 1998 U.S.	292/--/--/229	Prior treatment with gabapentin; hypersensitivity to drug or ingredients; neurolytic or neurosurgical therapy for postherpetic neuralgia; immunocompromised; significant hepatic or renal insufficiency; significant hematologic disease; other type of severe pain; experimental drug or study within 2 months of screening; history of illicit drug or alcohol abuse within past year; any serious or unstable medical or psychological condition	Run-in, washout of prior medications	No
Rice, 2001 U.K., Republic of Ireland	411/359/--/334	Failure to respond to previous treatment with gabapentin >/= 1200 mg/d; failure to respond to gabapentin at any dose level due to side effects; contraindications to gabapentin	Run-in, washout of prior medications	No
Harke, 2001 Germany	77/68/43/43	Strong psychological and affective components in Minnesota Multiphasic Personality Inventory and interview by psychiatrists; arrhythmia, angina, allergy, cardiopulmonary insufficiency, analgesic use	Run-in	No
Campbell, 1966 U.K.	--/--/77/77	Difficulty attending regularly due to age, infirmity, geography; pain due to disseminated sclerosis	None	No
Nicol, 1969 U.S.	--/--/64/44	Facial pain diagnosis other than trigeminal neuralgia	None	No
Drewes, 1994 Denmark	--/--/20/20	Severe obesity, liver disease, anticoagulant therapy, phenobarbital, primidone, intolerance to valproate	Washout	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Rowbotham, 1998 U.S.	No (placebo control)	Sponsored and authored by Parke-Davis	Results mainly applicable to uncomplicated patients not previously treated with gabapentin for postherpetic neuralgia.
Rice, 2001 U.K., Republic of Ireland	No (placebo control)	Fully funded by Pfizer Ltd.	Results applicable to patients who did not previously fail gabapentin >/= 1200 mg/d or were not previously treated with the drug. There may have been selection bias for previous responders to higher doses of gabapentin.
Harke, 2001 Germany	No (placebo with Spinal Cord Stimulation upon recurrence of pain)	Not reported	Results pertain to patients who already achieved pain relief with Spinal Cord Stimulation; small sample size limits generalizability of results.
Campbell, 1966 U.K.	No (placebo control)	Geigy Pharmaceutical Company Limited supplied carbamazepine	Nonselective patient population with trigeminal neuralgia; however, small sample size limits generalizability of results.
Nicol, 1969 U.S.	No (placebo control)	Geigy Pharmaceuticals supplied carbamazepine and placebo	Small sample size and unorthodox analyses of treatment effects limit the interpretation and generalizability of results
Drewes, 1994 Denmark	No (placebo control)	Sponsored by Rhône-Poulenc Rorer A/S	Small sample size limits generalizability of results

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Simpson, 2000 U.S.	Yes	Yes	No (CD4+ count was higher in the evaluated lamotrigine group vs. placebo group; 377 vs. 153 cells/mm3; p = 0.01) The effects of these differences on the trial results were not explained.	Yes	Not reported	Yes	Yes
Finnerup, 2002 Denmark	Yes	Yes	Yes	Yes	Not reported	Yes	Yes
McCleane, 1999 U.K.	Yes	Method not reported	No (mean duration of pain was 87 mo in the lamotrigine group vs. 61 mo in the placebo group; not statistically significant)	Yes	Not reported	Yes	Yes
Zakrzewska, 1997 U.K.	Method not reported	Method not reported	Not reported but age clinically different	Yes	Not reported	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Simpson, 2000 U.S.	Yes-adherence, crossover No-attrition, contamination	Yes	Yes	Yes	Fair
Finnerup, 2002 Denmark	Yes-attrition, crossovers, adherence No-contamination	Yes	No	Yes	Poor
McCleane, 1999 U.K.	Yes-attrition, crossover No-adherence, contamination	Yes (26%)	No	Yes	Fair
Zakrzewska, 1997 U.K.	Yes-attrition, crossover, contamination No-adherence	No	No	Yes	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Simpson, 2000 U.S.	--/--/42/42	Alternative causes of neuropathy; drugs that could be contributing to neuropathy (other than antiretroviral agents); acute, active opportunistic infections except oral thrush, orogenital or rectal herpes, and *Mycobacterium avium* - intracellular bacteremia within 2 wk; major, active psychiatric disorders; chemotherapeutic agents; systemic corticosteroids or immune modulators; addition of dideoxynucleosides to existing antiretroviral regimen; valproic acid therapy.	Washout	No
Finnerup, 2002 Denmark	436/100/30/30	Concomitant cerebral damage; dementia, serious hepatic or renal disease; other significant illness	Washout	No
McCleane, 1999 U.K.	--/--/--/100	AED therapy	None	Yes
Zakrzewska, 1997 U.K.	--/--/14/14	Surgery for trigeminal neuralgia (including nerve injections but excluding local anesthetic injections) within 1 yr	Washout	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Simpson, 2000 U.S.	No (placebo control)	Research grant support and study drug provided by Glaxo Wellcome, Inc.	Results should be considered preliminary (see larger study by Simpson, 2003). Small sample size and high dropout rate (mainly due to lamotrigine-induced rash) compromise external validity.
Finnerup, 2002 Denmark	No (placebo control)	Grants from several foundations and legacies. Glaxo Wellcome A/S Denmark provided lamotrigine and placebo. Pharma + Medico International Aps provided hCG tests.	Small sample size limits generalizability of results
McCleane, 1999 U.K.	No (placebo control)	Not reported	May apply to broad range of neuropathic pain types, as a particular type was not specified.
Zakrzewska, 1997 U.K.	No (placebo added on to existing carbamazepine or phenytoin)	Glaxo-Wellcome R and D	Results may apply to lamotrigine add-on therapy for refractory trigeminal neuralgia; however, problems with internal validity and complex statistical analyses complicate the estimations of the treatment effect, and the small sample size limits the generalizability of results.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Simpson, 2003 U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes	Yes
Vestergaard, 2001 Denmark	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gorson, 1999 U.S.	Method not reported; also unclear if baseline measurements were taken before randomization	Method not reported	Not reported	Yes	Yes	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Simpson, 2003 U.S.	Yes-attrition, adherence No-crossovers, contamination	Yes (24%)	No	No	Fair
Vestergaard, 2001 Denmark	Yes-attrition, crossovers, adherence No-contamination	No	No	Yes	Fair
Gorson, 1999 U.S.	Yes-contamination No-attrition, crossovers, adherence	No	Yes	No	Fair

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	*External Validity* (1) Number screened/eligible/enrolled/randomized	(2) Exclusion criteria	(3) Run-in/Washout	(4) Class naïve patients only?
Simpson, 2003 U.S.	--/--/227/227	Valproate therapy within 4 wk; any previous or current use of lamotrigine; other neurologic disorders that could confound the diagnosis of peripheral neuropathy (e.g., myelopathy)	Run-in and Washout	No
Vestergaard, 2001 Denmark	--/31/31/30	Dementia; other severe cognitive impairment; diabetic neuropathy; malignancy; recent myocardial infarction; severe heart insufficiency; liver or renal failure; history of alcohol or drug abuse	Washout of prior medications and before crossover	No
Gorson, 1999 U.S.	--/--/40/40	Diabetes and chronic renal insufficiency, painful diabetic plexopathy, or lumbosacral polyradiculopathy, peripheral vascular disease, another painful condition, or other cause for neuropathy	Washout--may have been inadequate, since improvement in pain scores on gabapentin seemed to carryover into the placebo treatment period	Unable to determine

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Simpson, 2003 U.S.	No. Placebo control, added on to existing stable doses of analgesics, tricyclic antidepressants, class I antiarrhythmics, or AEDs, herbal remedies, alternative therapies (e.g., massage, acupuncture); or adjustable doses of as-needed opioids; or analgesics for new acute conditions (up to 10 d).	GlaxoSmithKline and individual grants	According to protocol, patients who developed serious rash or hypersensitivity were to be discontinued from the trial and would have been excluded from efficacy analyses. No cases of serious rash (associated with hospitalization and discontinuation of study drug) were reported in the study and the frequency of discontinuation due to adverse events was similar between LTG and placebo. The primary efficacy analysis was based on patients who completed the trial per protocol. Therefore, the generalizability of results may be limited.
Vestergaard, 2001 Denmark	No (placebo control)	Grants from the Danish Medical Research Council and the Danish Pain Research Center. Glaxo Wellcome A/S Denmark provided lamotrigine and placebo tablets and covered transport expenses	Small sample size limits generalizability of results
Gorson, 1999 U.S.	No (placebo control added on to any existing stable doses of nonsteroidal antiinflammatory drugs or narcotics)	Warner Lambert (Parke-Davis Pharmaceuticals)	Small sample size. Results may not be applicable to a substantial proportion of patients with diabetes who have coexistent peripheral vascular disease or renal insufficiency.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Kochar, 2004(57) India	Method not reported	Yes	Yes; however, duration of diabetic neuropathy not reported	Yes	Yes	Yes	Yes
Kochar, 2002 India	Method not reported	Method not reported; administration of study drugs by an apparently unblinded researcher might have compromised blinding.	No (under Results, a greater proportion of valproate patients had pain scores >/= 5 at baseline) Duration of diabetic neuropathy and concomitant analgesics not reported	No	Yes	Yes	Not reported
Saudek, 1977 (--) U.S.	Method not reported	Method not reported	Yes	Yes	Yes	Yes	Yes
Dalessio, 1966 (--), only RCT described here U.S.	Method not reported	Yes	Not reported	No	Not reported	Not reported	Not reported (however, patients were able to identify active agent based on pain relief)

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Kochar, 2004(57) India	Yes-attrition No-crossovers, adherence, contamination	No	No	Yes	Fair
Kochar, 2002 India	Yes-attrition No-crossovers, adherence, contamination	Yes	No	Yes	Poor
Saudek, 1977 (--) U.S.	Yes-adherence, crossover No-attrition, contamination	Not reported	Unable to determine	Yes	Poor
Dalessio, 1966 (--), only RCT described here U.S.	No for all	No	Unable to determine	Unable to determine	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Kochar, 2004(57) India	48 screened / 43 eligible / 43 enrolled / 43 randomized	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, steroid therapy	None	Not reported
Kochar, 2002 India	60 screened / Number eligible not reported / Number enrolled not reported / 57 randomized	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, steroid therapy. Patients who did not tolerate study drug were dropped from the study.	None	Not reported
Saudek, 1977 (--) U.S.	--/--/--/12?	Other diabetic neuropathies (radiculopathy, mononeuropathy, amyotrphy, or autonomic neuropathy); alcoholism; uremia; carcinoma; other possible etiologies of neuropathy	None	Not reported
Dalessio, 1966 (--), only RCT described here U.S.	--/--/10/10	Not reported	None	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Kochar, 2004(57) India	No (placebo)	Not reported	Small sample size limits generalizability of results
Kochar, 2002 India	No (placebo)	Not reported	Results may reflect selection bias, as only patients who tolerated medication were continued in the study. Small sample size limits generalizability of results.
Saudek, 1977 (--) U.S.	No (placebo)	Supported in part by the Cornell General Clinical Research Center Division of Research Resources, National Institutes of Health, and by the New York Diabetes Association	Threats to internal validity and small sample size limit generalizability of results.
Dalessio, 1966 (--), only RCT described here U.S.	No (placebo)	Not reported	Small sample size and short duration of therapy (3 days) limit generalizability of results to long-term treatment of patients.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
McCleane, 1999 U.K.	Yes	Method not reported	No	Yes	Not reported	Not reported	Not reported (however, there was potential for burning at infusion site with phenytoin and not with the saline placebo)
Gilron, 2001 (--) U.S.	Method not reported	Method not reported	Yes	No	Not reported	Yes	Yes
Rockliff, 1966 (--) U.S.	Method not reported	Method not reported	Not reported	Yes	Not reported	Yes	Yes
Chadda, 1978 (--) India	Method not reported	Method not reported	Not reported	Yes	Yes	Yes, method not reported	Yes
Rull, 1969 (--) Mexico	Method not reported	Method not reported	Not reported	No	Yes	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
McCleane, 1999 U.K.	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Fair
Gilron, 2001 (--) U.S.	Yes-attrition, crossovers No-adherence, contamination	No for main study Yes for confirmatory study	Yes?	Unable to determine	Poor
Rockliff, 1966 (--) U.S.	Yes-attrition, crossovers No-adherence, contamination	No	Yes	No	Fair
Chadda, 1978 (--) India	Yes-attrition No-crossovers, adherence, contamination	No	No	No	Poor
Rull, 1969 (--) Mexico	Yes-attrition, crossover No- adherence, contamination	No	No	Yes	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	*External Validity* (1) Number screened/eligible/enrolled/randomized	(2) Exclusion criteria	(3) Run-in/Washout	(4) Class naïve patients only?
McCleane, 1999 U.K.	--/--/20/20	Oral AEDs, membrane stabilizers	Washout	No
Gilron, 2001 (--) U.S.	--/--/3/3	Multiple sclerosis, continuous pain, dense sensory loss related to an invasive procedure (I.e., anesthesia dolorosa)	Washout	No
Rockliff, 1966 (--) U.S.	--/--/9/9	Atypical facial pain, posthperpetic neuralgia	None	Not reported
Chadda, 1978 (--) India	--/--/40/40	Other causes of neuropathy	Yes, washout.	Not reported
Rull, 1969 (--) Mexico	--/--/30/30	Not reported	None	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
McCleane, 1999 U.K.	No (placebo)	Not reported	Limited to acute treatment of neuropathic pain using parenteral phenytoin. Small sample size limits generalizability of results.
Gilron, 2001 (--) U.S.	No (placebo)	Supported by Intramural Project Grant from the National Institute of Dental and Craniofacial Research and by Ortho-McNeil Pharmaceuticals	Multiple crossovers increased power of study, but extremely small sample size limits generalizability of results.
Rockliff, 1966 (--) U.S.	No (placebo)	Study performed by Geigy Pharmaceuticals	Small sample size limits generalizability of results.
Chadda, 1978 (--) India	No (placebo)	M/S. Parke-Davis (India) Ltd. Kindly supplied the drug for the trial.	Small sample size limits generalizability of results.
Rull, 1969 (--) Mexico	No (placebo)	JR Geigy Laboratories furnished the drug and placebo used in the study	Patients represented a heterogeneous group of different types of peripheral diabetic neuropathy. Absence of eligiblity criteria and small sample size make it difficult to generalize results.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Simpson, 2001 U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Yes	Yes
Eisenberg, 2001 (--) Israel	Yes	No	No	Yes	Not reported	Yes	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Simpson, 2001 U.S.	Yes-attrition No-crossovers, adherence, contamination	No	Unable to determine	No	Poor
Eisenberg, 2001 (--) Israel	Yes-attrition, adherence No-crossovers, contamination	No	No	Yes	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Simpson, 2001 U.S.		Part 1: --/--/60/60 Part 2: --/12/11/11 Part 3: --/42/42/Not applicable	Severe pain other than diabetic neuropathy pain; amputations other than toes; renal failure (creatinine clearance < 60 ml/min); treatment in last 30 d with tricyclic antidepressants, mexiletine, carbamazepine, phenytoin, valproate, dextromethorphan, opioids, capsaicin, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, benzodiazepines, or over-the-counter centrally acting agents	30-d washout of previous medications
Eisenberg, 2001 (--) Israel	160/--/--/59	Age < 18 or > 75 y; renal or liver dysfunction; epilepsy; other painful conditions; received antiepileptics, antidepressants, or membrane-stabilizing agents for reasons other than pain relief, or use of opioids	None	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding	(7) Relevance?
Simpson, 2001 U.S.	No	No (placebo)	Not reported
Eisenberg, 2001 (--) Israel	No	Supported by Glaxo-Wellcome	May apply to patients not treated with other systemic agents for neuropathic pain; limited by small sample size

Quality Table 7. Quality Assessment: Observational Studies

Author, year	(1) Non-biased selection?	(2) Low overall loss to follow-up?	(3) Adverse events pre-specified and defined?	(4) Ascertainment techniques adequately described?	(5) Non-biased and adequate ascertainment methods?	(6) Statistical analysis of potential confounders?	(7) Adequate duration of follow-up?	(8) Overall adverse event assessment quality
Goodwin, 2003(2)	Yes	Not clear	Yes	Yes	No	Yes	Yes	Fair
Malmgren, 2001(77)	No	Not clear	Yes	Yes	Yes	Yes	Yes	Poor
Rzany, 1999(80)	Yes	Not clear	Yes	No	Unable to determine	Yes	Yes	Fair
Tohen, 1995(78)	Yes	Not clear	Yes	Yes	No	No	Yes	Poor