

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

Final Report

May 2006



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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 (FDA) for the treatment of bipolar I disorder with acute mania or mixed episodes (carbamazepine); maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy (lamotrigine); treatment of manic episodes associated with bipolar disorder (divalproex); prophylaxis of migraines (divalproex); management of neuropathic pain associated with diabetic peripheral neuropathy (pregabalin); management of postherpetic neuralgia (gabapentin and pregabalin); and treatment of pain associated with trigeminal neuralgia (carbamazepine). Depending on the results of ongoing trials evaluating their usefulness in the management of fibromyalgia (gabapentin, pregabalin), FDA approval may also be sought for this indication as well. There has been a dramatic increase in the use of AEDs in both bipolar disorder (particularly with valproate) and neuropathic pain (particularly with gabapentin), and growing interest in determining whether AEDs are efficacious for fibromyalgia.

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. 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.

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}

Fibromyalgia syndrome, a sometimes disabling condition characterized by chronic widespread musculoskeletal pain, has an estimated worldwide prevalence of 0.5% to 5.0% with women affected four times more often than men.⁷ It is one of the most common conditions treated by rheumatologists. The diagnosis of fibromyalgia is based on clinical history and examination; no diagnostic laboratory or radiologic test exists. The American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia require a history of spontaneous pain along the spine and all four quadrants of the body for more than 3 months and pain on digital palpation at 11 of 18 tender point sites. Other comorbid symptoms are common in patients with fibromyalgia, although they are not part of the ACR diagnostic criteria. These symptoms include chronic fatigue syndrome, sleep dysfunction, headaches, mood disorders, irritable bowel syndrome, and neurocognitive disturbances. Under experimental conditions, allodynia and hyperalgesia have been demonstrated in patients with fibromyalgia. These observations of abnormal pain perception support the theory that the etiology of fibromyalgia involves increased central pain sensitization with altered levels or activity of neurotransmitters and neuromodulators, such as substance P. The underlying cause of fibromyalgia remains unknown.

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, as well as the Canadian Consensus Document on Fibromyalgia Syndrome, recommend AEDs (Table 1).

Table 1. Clinical practice guideline recommendations on antiepileptic drugs

Practice Guideline	Indication	Recommendations				
		CBZ	GBP	LTG	OXC	VPA
<i>Bipolar disorder</i>						
APA ⁸	Acute Mania/Mixed	✓	—	—	✓	✓
	Acute Bipolar Depression	—	—	✓	—	—
	Acute Rapid Cycling	—	—	✓	—	✓
	Maintenance	✓	—	✓	✓	✓
BAP ²	Acute Mania/Mixed	✓	—	—	—	✓
	Acute Bipolar Depression	—	—	✓	—	✓
	Rapid Cycling	—	—	✓	—	✓
	Maintenance	✓	—	✓	✓	✓
ANZ ⁹	Acute Mania/Mixed	✓	No	—	—	✓
	Acute Bipolar Depression	✓	No	✓	—	✓
	Maintenance, Rapid Cycling	✓	No	✓	—	✓
	Maintenance	—	No	✓	—	✓
<i>Neuropathic pain</i>						
Expert Panel ³	Neuropathic Pain	✓	✓	✓	—	—
IRF for RSD / CRPS ¹⁰	RSD / CRPS	✓	✓	—	—	—
SIGN ¹¹	Painful diabetic neuropathy	—	✓	—	—	—
WSMA ^{12, 12, 12, 12}	Neuropathic pain, certain types	—	✓	—	—	—
AAPMR ¹³	Chronic nonmalignant pain	AEDs in general				
AMDA ¹⁴	Chronic pain in LTC	AEDs in general				
APA–MSS on HIV / AIDS ¹⁵	HIV-related neuropathies	AEDs used; not supported by published evidence				
<i>Fibromyalgia syndrome</i>						
HCECP ¹⁶	Pain w/ neuropathic features	✓				
Organization Abbreviations:						
ANZ, Australian and New Zealand						
APA, American Psychiatric Association						
BAP, British Association of Psychopharmacology						
HCECP, Health Canada Expert Consensus Panel						
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						

Responses to conventional therapies in bipolar disorder, neuropathic pain, and fibromyalgia have 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 In fibromyalgia syndrome, pharmacotherapy often requires the use of different agents to treat the various symptoms associated with the disorder.

Since newer AEDs have become available, there has been increasing interest to evaluate their efficacies and safety in bipolar disorder, neuropathic pain, and fibromyalgia 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 in bipolar disorder and neuropathic pain. 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. In fibromyalgia, there is a need to determine whether there is adequate evidence to justify the use of any AEDs. 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, neuropathic pain, and fibromyalgia.

This is the first annual update of the original report (dated November 2004), which addressed AEDs for bipolar disorder and neuropathic pain. The AEDs covered in the original report were carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, tiagabine, topiramate, valproate/valproic acid/divalproex, and zonisamide. Added to this first report update were fibromyalgia (as a primary diagnosis of interest) and two AEDs, pregabalin (which was FDA-approved after completion of the original report) and ethosuximide (an older phenytoin-like AED that is seeing a resurgence in use at some centers).

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, neuropathic pain, and fibromyalgia. 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 the review for this report update:

1. For adult outpatients with bipolar disorder or 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, neuropathic pain, and fibromyalgia?
 - 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 (1966–2005), and Embase (1974–2005). 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, fibromyalgia, 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 A for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 9.0).

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 was 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
- c. Fibromyalgia or fibromyalgia syndrome as diagnosed by ACR criteria.

This report update used specific search terms for fibromyalgia. This approach differed from that used for the original report (dated November 2004) in which 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, ethotoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, 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
CARS-M	Clinician Administered Rating Scale for Mania
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
HRSA	Hamilton Rating Scale for Anxiety
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) and an alternate abbreviation for the Bech-Rafaelsen Mania Rating Scale (BRMS).

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 and Fibromyalgia: 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, for neuropathic pain 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 Numerical Rating Scale, also called Likert 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.¹⁷ The change of at least 2 points in this report update was based on the population

mean change, which may not reflect actual changes for any individual. None of the studies reported the percentage of patients who achieved a change from baseline of at least 2 points on the numerical rating scale. 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.¹⁸ 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 (including overdoses); 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) retrospective or prospective observational 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 and QFM in the original report dated November 2004; and MM and PS for the update) 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 and 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 randomized patients.

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 Force¹⁹ and the U.K. National Health Service Centre for Reviews and Dissemination.²⁰ 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 D 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. We conducted meta-analysis by homogenous subgroup only when 3 or more studies were available to pool. Since there were fewer than 3 studies per subgroup, the studies are only discussed qualitatively in terms of effectiveness. In terms of safety, we did pool studies quantitatively as discussed below. There were no trials for fibromyalgia that met inclusion criteria and therefore none were added to the pooled analysis for this report update.

Meta-Analysis of Adverse Event Data

We aggregated the more commonly documented (or expected) adverse events using patient-level data. 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. It should be noted that 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.

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.²¹

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.

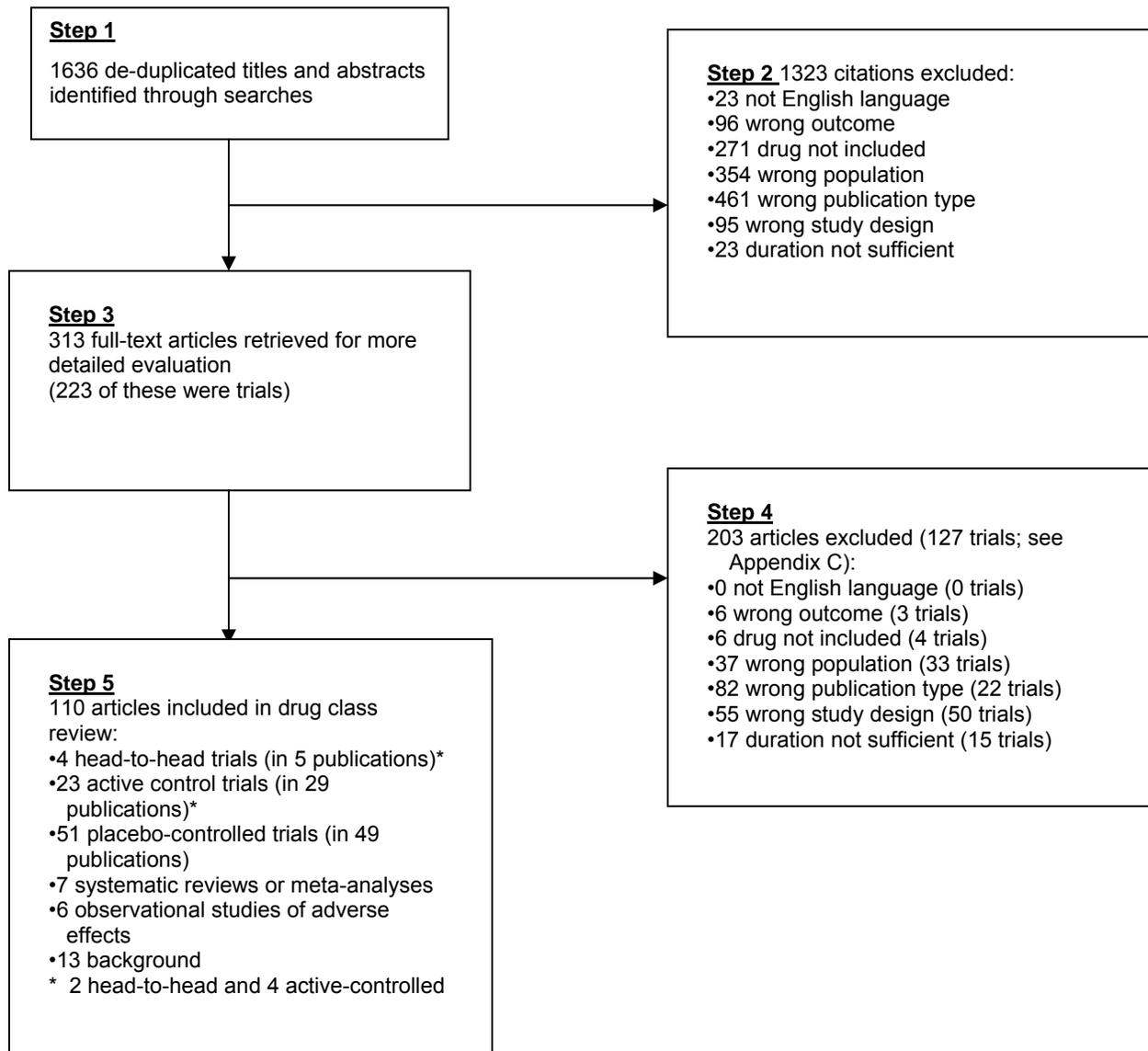
Peer and Public Review

The original and updated reports underwent a review process that involved solicited peer review from clinical experts and the opportunity for public review on the Drug Effectiveness Review Project Web site (<http://www.ohsu.edu/drugeffectiveness/index.htm>)..

RESULTS

Overview

Searches identified 1636 de-duplicated citations: 631 from the Cochrane Library, 769 from Medline/PubMed, 192 from Embase, 30 from reference lists, and 14 from 6 pharmaceutical company dossiers submitted by Abbott Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Novartis Pharmaceuticals Corporation, Ortho-McNeil Pharmaceutical, Inc., and Shire U.S. We included 26 reports in this update in addition to the 85 reports covered in the original report, and excluded 1 observational study from the original report (wrong drug) for a total of 110 included reports: 82 papers on 77 RCTs, 10 systematic reviews, 6 long-term (> 1 year) observational safety studies, and 13 background articles. Of the 30 articles identified from reference lists, 3 were included, and one of the articles from company dossiers was included. A total of 1525 articles were excluded for the reasons listed in Figure 1. Appendix C lists the excluded trials.

Figure 1. Results of literature search

Of the 78 included RCTs (4 head-to-head, 23 active control, and 51 placebo-controlled; total 83 publications), 26 (33 publications) dealt with bipolar disorder and 52 (50 publications) pertained to neuropathic pain. For the 7 systematic reviews, the numbers were 4 for bipolar disorder and 3 for pain. No papers on fibromyalgia therapies met inclusion criteria.

The internal validity of the 26 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.^{22, 23} Many trials did not report methods to mask the designated outcome assessor or did not use an outcome assessor other than the care provider and patient. 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) loss to follow-up rates.²⁴⁻³¹ Nine trials did not use intent-to-treat analysis.^{23, 24, 26, 30, 32-34, 37, 41}

External validity of the trials or their subgroup analyses was often limited by selective patient populations^{22, 23, 25, 31, 33, 35-42} or small sample size (number randomized was less than 40 per treatment group).^{22, 23, 26, 29, 33, 36, 37, 43-45} 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^{25, 32, 40, 42, 46, 47} or placebo responders were excluded.⁴⁸ Only 2 trials reported both the numbers of patients screened and eligible;^{26, 37} the remainder did not report one or both of these figures.

All of the 52 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 the designated 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 24 trials⁴⁸⁻⁷¹ and could not be determined in 4 trials.⁷²⁻⁷⁵ Applicability of the trial results to adult outpatients with neuropathic pain was limited because most trials were small;^{49, 51, 54-57, 59-63, 65-68, 75-80} two trials had selective populations;^{59, 65} and 6 large trials⁸¹⁻⁸⁶ introduced the possibility of selection bias by excluding patients who had inadequate responses or intolerance to previous treatment with gabapentin. One trial provided inclusion but not exclusion criteria.⁵³ Most trials did not report the number of patients who were screened or eligible.^{50, 76, 77, 82-85, 87-90, 135} and a pooled analysis of 3 trials did not report the number of randomized patients.⁸⁸ In addition to these published trials, we found a summary of an unpublished placebo-controlled trial in a systematic review.⁹⁴ We excluded this trial because it was not published in full and its internal and external validity could not be fully assessed.

We found 2 good-quality observational studies on adverse events.^{95, 96} Another 3 observational studies on adverse events were rated fair in internal validity because nonbiased selection was unclear,⁹⁷ loss to follow-up was not clear,^{98, 99} ascertainment techniques were not adequately described,^{97, 99} or ascertainment methods were inadequate^{97, 98} or could not be determined.⁹⁹ The quality of the remaining 2 observational studies was considered to be poor because selection was biased,¹⁰⁰ loss to follow-up was not clear,^{100, 101} ascertainment techniques were not adequate,¹⁰¹ or statistical analysis of potential confounders was not performed.¹⁰¹

Key Question 1.

For adult outpatients with bipolar disorder or neuropathic pain do AEDs differ in effectiveness?

1a. Bipolar Disorder**Systematic reviews**

There were 4 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) ¹⁰² (Good)	Acute Mania 5 (397)	Psychotic symptoms, BPRS	= Lithium	= Lithium	
		Global symptoms, CGI	= Lithium	—	
		Responder rate	= Lithium	= Lithium	
Bridle (2004) ¹⁰³ (Good)	Acute Mania 3 trials in adults (315)	Mania symptoms, SADS-C MRS or YMRS	—	> Placebo = Lithium = Haloperidol ≤ Olanzapine	
		Acute Mania or Mixed with psychotic symptoms 1 haloperidol trial in adults (42) 2 olanzapine trials in adults (377)	Depression, HAM-D	—	= Olanzapine
			Responder rate, SADS-C MRS or YMRS	—	> Placebo = Lithium = Haloperidol
	Psychiatric symptoms, BPRS, ADRS, or SAPS		—	> Placebo = Olanzapine = Lithium = Haloperidol	
	Macritchie (2004) ¹⁰⁴ (Good)	Maintenance 1 (372)	Functional capacity / Global effects, GAS	—	≥ Placebo = Lithium
			Global symptoms, CGI-I	—	= Olanzapine
			Lower use of lorazepam	—	> Placebo = Lithium
			Length of hospital stay	—	= Haloperidol
			Recurrence rate, any mood episode	—	= Lithium > Placebo
			Recurrence rate, manic episodes	—	= Placebo
Recurrence rate, depressive episodes			—	= Lithium > Placebo	
Time to recurrence	—	= Lithium = Placebo			
Tondo (2003) ¹⁰⁵ (Good)	Maintenance, rapid cycling 16 (1856) total; see text for N of meta-analyses	Functional capacity, GAS	—	= Lithium = Placebo	
		Recurrence rate	= Lithium	—	
		Non-improvement rate	= Lithium	—	

ADRS, Affective Disorder Rating Scale subscales for mania, elation/grandiosity, psychosis; AED, Antiepileptic drug; BPRS, Brief Psychiatric Rating Scale; CGI (CGI-I), Clinical Global Impression (of Improvement) rating scale; GAS, Global Assessment Scale (a measure of global functioning); HAM-D, Hamilton Depression Rating Scale; SADS-C MRS, Schedule for Affective Disorders and Schizophrenia–Change Version Mania Rating Scale; SAPS, Scale for Assessment of Positive Symptoms subscales for hallucination, delusion, bizarre thinking, thought disorder; YMRS, Young Mania Rating Scale; =, no statistically significant difference between AED and comparator; > or <, AED was statistically superior or inferior, respectively, to comparator

In acute mania, two systematic reviews showed that both carbamazepine and valproate were not statistically different from lithium in terms of responder rate and improvement in symptoms.^{102, 103}

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).¹⁰⁴ 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.¹⁰⁵ 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 evidence to support a 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 6 head-to-head trials (7 publications)^{22, 23, 36, 106-109} for possible inclusion and none of the reports met eligibility criteria for trials in outpatient populations. Two trials (for which original data were published in three reports)^{22, 23, 36} 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)^{22, 23} 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 two trials were not double-blind and did not report allocation concealment or method of randomization; they were rated poor in quality.^{36, 106} The generalizability of the results of these three trials to a bipolar outpatient community population may be limited. The four publications on these three 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.²³ 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 and placebo 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.²² 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 second 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 .³⁶ 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%).

The third head-to-head trial was a poor-quality, open-label randomized trial evaluating the effectiveness and tolerability of topiramate and divalproex, each given concurrently with risperidone, in the treatment of 74 Korean inpatients diagnosed with bipolar I disorder with current mania (DSM-IV).¹⁰⁶ The study showed no statistically significant differences between topiramate and divalproex in YMRS and CGI scores, proportions of patients with at least a 50% decrease in YMRS and CGI-S scores, and remission rates.

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. In patients with bipolar disorder with recent mania, valproate may be superior to carbamazepine, and divalproex is not significantly different from topiramate when used in combination with risperidone; however, the evidence is poor for each of these comparisons.

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),^{24, 24, 25, 25, 26, 26, 27, 27, 28, 28, 29, 29, 30, 30, 31, 31, 32, 34, 34, 37, 37, 38, 38, 39, 39, 40, 40, 41, 41, 44, 44, 47, 47, 110, 110, 111, 111, 112, 112-114} and 7 fair-quality trials (9 publications)^{24,25,29,31,32, 34,40,47,110} are discussed here. 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,^{24, 110} a selective sample population was studied, (e.g., rapid cyclers, milder forms of bipolar disorder, AED responders),^{25,31, 32, 40} or the sample size was small.^{26, 29} Of the 14 included trials, 8 were multicenter,^{25,27,31,32,34,41,47,110} 12 double-blind,^{25, 26, 28-32, 34, 37, 41, 47, 110} 1 open-label,^{27, 27, 38, 39, 112-114} 1 crossover,³⁰ 8 double-dummy,^{26, 28, 29, 31, 34, 37, 41, 47} and 3 included a placebo control in addition to the active control.^{25, 32, 47} 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),^{29, 34} divalproex (1 trial in 2 publications),^{25, 40, 40} or lamotrigine (2 trials),^{32, 47} was compared with lithium or both lithium and placebo, and 2 trials (in 3 publications) compared divalproex with olanzapine.^{24, 24, 31, 31, 110}

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),^{24, 31, 110} and divalproex and lamotrigine were each compared with lithium in 1 trial²⁵ and 2 trials,^{32, 47} 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
<i>Acute Therapy</i>						
Tohen (2002) ¹¹⁰	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) ³¹	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
<i>Maintenance Therapy</i>						
Tohen (2003); ²⁴ extension of Tohen (2002) ¹¹⁰	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) ²⁵	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) ³²	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
				CGI-S	0.7 vs. 0.4 vs. 0.3	LTG = LI LTG > PBO LI > PBO
Calabrese (2003) ⁴⁷	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 (2 publications) 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.^{24, 110} Another, smaller trial showed that divalproex was not statistically different from olanzapine on any symptom scale in the acute treatment of mania.³¹ 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).²⁵ 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.¹¹⁵

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.³² 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).⁴⁷

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.

Response: Responder Rate

Only one fair-quality trial reported responder rate;¹¹⁰ 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,^{25, 29, 32, 47} and one (reported in two publications) in which divalproex was compared with olanzapine (Table 5).^{24, 110}

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) ²⁹	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) ³⁴	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) ²⁵	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) ³²	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) ⁴⁷	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) ¹¹⁰	Divalproex vs. Olanzapine	3	BPI-M/Mx 251	Symptomatic remission (end point (YMRS total score ≤ 12))	34 vs. 47	DVP < OLN
Tohen (2003), ²⁴ double-blind, randomized trial extension of Tohen (2002) ¹¹⁰	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.^{24, 25, 32, 47, 110} 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 acute¹¹⁰ and maintenance therapy.²⁴ Divalproex and lamotrigine have been compared with lithium on the basis of duration of remission in 1 trial²⁵ and 2 trials, respectively.^{32, 47, 47} 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.²⁵ 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.^{32, 47}

Based on the results discussed above, an indirect comparison of efficacy relative to lithium (titrated to similar serum concentrations in all three trials) does not support that divalproex or lamotrigine are different 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.^{32, 47} A third trial assessed additional use of sertraline or paroxetine after the start of maintenance therapy with divalproex, lithium or placebo.⁴⁰ 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,^{25,29,34,40} and one trial compared divalproex with olanzapine²⁴ 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) ²⁹	Carbamazepine vs. Lithium	52	BP (DSM-III) 31	Relapse (not defined)	40 vs. 50	CBZ = LI [†]
Hartong (2003) ³⁴	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) ²⁵	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); ⁴⁰ additional analyses from Bowden (2000) ²⁵	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) ³²	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) ²⁴	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,^{24, 25, 29, 32, 40} 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 trial²⁹ and $p = 0.136$ in the second trial)³⁴ or lamotrigine ($p = 0.459$).³² The second trial that compared carbamazepine and lithium showed a different pattern of recurrence between the two agents.³⁴ 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.²⁵ Additional analyses from this trial, published separately, did not report statistical analyses,⁴⁰ 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, does not support that the three AEDs are different 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) ²⁵	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Center Effects model: -4.7 vs. -7.8 vs. -5.7 Mania Subtype model: -4.7 vs. -10.8 vs. -6.2	DVP = LI = PBO DVP > LI DVP = PBO LI < PBO
Bowden (2003) ³²	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	-3.19 vs. -3.85 vs. -5.63	LTG = LI = PBO
Calabrese (2003) ⁴⁷	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.²⁵ 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.^{32, 47}

Therefore, indirect comparisons of divalproex (using a Center Effects model) and lamotrigine, based on treatment differences relative to lithium, do not support that either 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.⁴⁰ 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.²⁹ 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).⁴⁰ 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, do not support that carbamazepine and divalproex are different in rates of hospitalization for mood episodes during maintenance therapy.

Placebo-controlled trials

We reviewed 40 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 13 placebo-controlled trials (1 also with AED control,²³ 3 with active controls (4 publications),^{25, 26, 32, 40, 47} and 9 with only placebo control)^{33, 35, 42, 43, 45, 46, 116-118} were included in this report. Of these, 10 trials (3 with active control^{25, 32, 47} and 7 with only placebo control)^{35, 42, 43, 46, 47, 116-118} 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. All 13 included trials were double-blind, 8 were multicenter,^{25, 32, 42, 46, 47, 116-118} 2 used a double dummy,^{46, 47} and 1 was a crossover design.³³ 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 10 fair-quality placebo-controlled trials that reported changes in symptom scores: 2 involving carbamazepine (extended-release capsules),^{116, 117} 3 involving divalproex / valproate,^{25, 35, 43} 1 assessing gabapentin (as add-on therapy to lithium and/or valproate),⁴⁶ and 4 assessing lamotrigine.^{32, 42, 47, 118} Results are displayed in Table 8.

For reducing mania symptoms, only carbamazepine (in 2 trials)^{116, 117}—for either acute or maintenance therapy—was reported to be superior over placebo out of the four AEDs studied. 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.

In 2 acute therapy trials in patients with manic or mixed episodes, carbamazepine improved depressive symptoms as measured by HAM-D total scores;^{116, 117} however, the treatment difference was statistically significant in only one of the trials.¹¹⁷ Short-term (10-week) add-on gabapentin treatment of patients with bipolar I mania, hypomania, or mixed symptoms did not show statistically significant benefits compared with placebo on the HAM-D scale.⁴⁶ In patients with bipolar depression, acute divalproex therapy was effective in decreasing depressive symptoms (1 trial),⁴³ whereas 1 trial evaluating acute lamotrigine therapy (7-week) showed no statistically significant difference on the HAM-D scale. However, lamotrigine 200 mg improved depressive symptoms as measured on the MADRS, whereas a dose of 50 mg was not statistically different from placebo.¹¹⁸

As acute therapy in patients with acute mania or mixed episodes, carbamazepine was effective in improving CGI-S scores. In patients with bipolar I depression, lamotrigine (200 mg daily) was better than placebo in terms of CGI scores, whereas divalproex was no better than placebo. Indirect comparisons suggest that lamotrigine may be better than divalproex / valproate in global improvement in patients with bipolar I depression.

MRS results during maintenance therapy with lamotrigine were consistent with those of acute therapy, in that 2 maintenance therapy trials (one in patients with recent bipolar I depression⁴⁷ and the other in patients with bipolar I mania/hypomania)³² also reported no statistically significant difference between lamotrigine and placebo in terms of effects on manic symptoms.

For antidepressive effects of maintenance AED therapy, indirect comparisons based on placebo-controlled trial results suggest there is a differential treatment effect. Long-term (52-week) divalproex treatment of patients with recent mania²⁵ did not result in statistically significant benefits compared with placebo on the DSS scale. 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/hypomania³² or bipolar I depression.⁴⁷ Another maintenance therapy trial (26-week), however, showed no statistically significant difference on the HAM-D in patient populations with rapid cycling.⁴²

For maintenance therapy, no indirect comparisons between divalproex and lamotrigine could be made for improvement in CGI-S or CGI-I because these outcome measures were only evaluated with lamotrigine.

Thus, acute therapy with carbamazepine improved manic symptoms and decreased depressive symptoms in patients with bipolar I mania or mixed episodes. Lamotrigine maintenance therapy improved depressive, but not mania/hypomania, symptoms. Gabapentin acute therapy had no effect on either symptom complex. Acute divalproex therapy improved depressive but not manic symptoms in patients with bipolar depression. Divalproex maintenance therapy, which was tested in mania only, had no significant therapeutic effect in improving symptoms.

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
<i>Acute Therapy</i>						
Weisler (2004) ¹¹⁶	Carbamazepine extended-release capsules (CBZ ERC) vs. Placebo	4	BPI-M/Mx 204	YMRS	-9 vs. -5	CBZ > PBO
				HAM-D	-5.35 vs. -1.58	CBZ = PBO
				CGI-S	4.07 vs. 3.66	CBZ > PBO
Weisler (2005) ¹¹⁷	CBZ-ERC vs. Placebo	3	BPI-M/Mx 239	YMRS	-15.1 vs. -7.1	CBZ > PBO
				HAM-D	-2.7 vs. -1.0	CBZ > PBO
				CGI-S	1.5 vs. 0.6	CBZ > PBO
Pande (2000) ⁴⁶	Gabapentin vs. Placebo (Add-on)	10	BPI-M/HM/Mx 117	YMRS	-6.5 vs. -9.9	GBP < PBO
				HAM-D	0.01 vs. -1.3	GBP = PBO
Davis (2005) ⁴³	Divalproex vs. Placebo	8	BPI-D 25	CARS-M	Data not shown	DVP = PBO
				HRSD (17-item)	-11.5 vs. -6.8	DVP > PBO
				HRSA	-7 vs. -1.4	DVP > PBO
				CGI	Data not shown	DVP = PBO
Calabrese (1999) ¹¹⁸	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
<i>Maintenance therapy</i>						
Bowden (2000) ²⁵	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
Salloum (2005) ³⁵	Divalproex vs. Placebo (add-on to lithium)	24	BPI-M/Mx/D 59	BRMS	-9.64 vs. -9.20 (calculated)	Not reported for change in scores
				HRSD-25	-4.0 vs. -6.8 (calculated)	Not reported for change in scores
Bowden (2003) ³²	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

Continued

Trial	Interventions	Duration (wk)	Diagnosis N	Symptom Scale	Change in Scores from Baseline, mean	Interpretation of Results
<i>Maintenance therapy</i>						
Calabrese (2003) ⁴⁷	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) ⁴²	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; CARS-M, Clinician Administered Rating Scale for Mania; 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

Four placebo-controlled trials assessed responder rates with carbamazepine,^{116, 117} gabapentin,⁴⁶ or lamotrigine.¹¹⁸ Carbamazepine was superior to placebo (2 trials),^{116, 117} whereas neither gabapentin nor lamotrigine 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 (at least 50% decrease in YMRS score^{116, 117} versus "much improved" or "very much improved" on Clinical Global Impression of Change [CGIC]⁴⁶ versus CGI-I).¹¹⁸

Remission

Two trials compared divalproex with either lithium and placebo²⁵ or placebo only³⁵ and three trials compared lamotrigine with lithium and placebo^{32, 47} or placebo only⁴² 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) ²⁵	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Proportion of patients remaining in study*	48 vs. 42 vs. 41	DVP = LI = PBO
Salloum (2005) ³⁵	Divalproex vs. Placebo	24	Alcohol dependence, BPI-M/Mx/D 59	BRMS score ≤ 7 HRSD-25 score ≤ 7	78 vs. 80 63 vs. 48	DVP = PBO [‡] DVP = PBO [‡]
Bowden (2003) ³²	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) ⁴⁷	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) ⁴²	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.

‡ Post hoc analysis; calculated $p = 0.86$ for BRMS score and $p = 0.42$ for HRSD-25 score (statistical analyses not reported in publication)

Diagnosis and Rating Scales: BPI, Bipolar I disorder; -D, With recent depressive episode; -HM, With recent hypomania; -M, With recent mania; RC, Rapid cycling. BRMS, Bech-Rafaelsen Mania Scale; HRSD-25, Hamilton Rating Scale for Depression

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.²⁵ The other trial comparing divalproex with placebo alone also failed to show a significant difference in responder rates for either manic or depressive symptoms possibly because of insufficient statistical power (the study population was small, $N = 59$) or follow-up was relatively short (24 weeks).³⁵ In contrast, all trials comparing lamotrigine with placebo showed a superiority of lamotrigine over placebo in patients with bipolar I mania/hypomania,³² depression,⁴⁷ or rapid cycling.⁴² It is difficult to make indirect comparisons between the AEDs because of the inconclusive results shown in the two divalproex trials²⁵ and differences in study populations (e.g., the use of patients with alcohol dependence and concurrent bipolar I disorder in one of the divalproex trials³⁵ versus bipolar disorder in the other trials). 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

Two trials noted significantly greater decreases in YMRS total scores with carbamazepine than with placebo beginning after either 1 week¹¹⁷ or 2 weeks¹¹⁶ of starting therapy. In another trial, divalproex was shown to produce faster rates of improvement in both Hamilton rating scale scores for depression and for anxiety over time using random regression analyses.⁴³ Although another trial defined response to treatment, the time to and duration of response with lamotrigine as compared with placebo were not evaluated.¹¹⁸ Indirect comparisons of carbamazepine and divalproex were not possible because different methods of and symptoms for measuring speed of response were used.

Time to remission was evaluated by one of the fair-quality placebo-controlled trials.³⁵ In this trial, the times to remission for mania ($BRMS \leq 7$) and depression ($HRSD-25 \leq 7$) were 2 to 3 weeks and 8 to 9 weeks, respectively. The authors of the paper stated that the time to remission for manic symptoms favored divalproex over placebo ($p = 0.07$); however, times to remission for either mania or depression were not reported by treatment.

Four placebo-controlled trials, including one involving divalproex²⁵ and three involving lamotrigine,^{32, 42, 47} 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) ²⁵	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) ³²	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) ⁴⁷	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) ⁴²	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.²⁵ 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.^{32, 42, 47}

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

Use of other medications for acute episodes

In 2 fair-quality trials, there were no significant differences between carbamazepine extended-release capsules and placebo in the proportion of patients requiring lorazepam, and a similar proportion of patients from each treatment group took allowed co-medication.^{116, 117} 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.⁴⁰ Another fair-quality trial showed that a significantly ($p = 0.03$) smaller proportion of divalproex- than placebo-treated alcohol-dependent patients with bipolar I disorder received trazodone as a hypnotic whereas a similar proportion of patients in the treatment groups received either antidepressants or antipsychotics.³⁵ Three trials (four publications) 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.^{32, 42, 47, 118} No indirect comparisons of the AEDs could be made because the type of rescue medication, reason for additional therapy, and basis for determining the patient's need for such therapy differed between the trials.

Relapse and Recurrence

One fair-quality placebo-controlled trial (2 publications) compared divalproex with placebo and lithium,^{25, 40} and another trial compared lamotrigine with placebo and lithium³² 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.²⁵ 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, do not support that the two AEDs are different 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,⁴² 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)

Five trials assessed improvement in GAS scores;^{25, 32, 35, 42, 47} however, one of these trials⁴² 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.²⁵ Again, these results were inconclusive because the trial lacked sufficient power to detect a moderate sized difference. Another trial showed that similar improvements in global assessment of functioning occurred with divalproex and placebo in patients with alcohol dependence and bipolar I disorder.³⁵

Results of trials comparing lamotrigine with placebo or lithium and placebo were mixed. One trial in 372 patients with recent mania/hypomania³² and another trial in 182 patients with rapid cycling⁴² 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; $p < 0.05$).⁴⁷

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. Nonetheless, only one of the four trials reporting data showed the AED (divalproex) therapy resulted in a positive change from baseline (i.e., improvement, but similar in magnitude to that seen with placebo) in functional capacity,³⁵ whereas negative changes (i.e., worsening) were seen in the other trials.

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) ²⁵	Divalproex vs. Lithium vs. Placebo	52	BPI-M 372	Center Effects model: -4.7 vs. -7.8 vs. -5.7 Mania Subtype model: -4.7 vs. -10.8 vs. -6.2	DVP = LI = PBO DVP > LI DVP = PBO LI < PBO
Salloum (2005) ³⁵	Divalproex vs. Placebo	24	Alcohol dependence, BPI-M/Mx/D 59	18.9 vs. 18.6 (calculated)	No statistical analysis for difference
Bowden (2003) ³²	Lamotrigine vs. Lithium vs. Placebo	76	BPI-M/HM 175	-3.19 vs. -3.85 vs. -5.63	LTG = LI = PBO
Calabrese (2003) ⁴⁷	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) ⁴²	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 placebo⁴⁰ and three trials comparing lamotrigine with placebo^{42, 47, 118} reported suicide attempts or suicide deaths. There were no remarkable differences between either of the AEDs and placebo for both suicide outcomes. One trial evaluating the efficacy of carbamazepine therapy reported suicidality resulting in rehospitalization.¹¹⁶ 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 placebo⁴⁰ and the remaining four trials compared lamotrigine with lithium and placebo^{32, 47, 118} or placebo alone.⁴² 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.⁴⁰ 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. Another trial showed that psychiatric hospitalization was required in 3 of 29 patients (10.3%) on divalproex versus 5 of 30 patients (16.7%) on placebo; post hoc analysis showed no significant difference (calculated $p = 0.924$).³⁵ Two trials comparing lamotrigine with placebo reported no hospitalizations due to adverse events, where mood-related events were counted as adverse events,¹¹⁸ or hospitalizations due to mood-related events or adverse events.⁴² Based on indirect comparisons, there is no evidence to support that divalproex and lamotrigine are different in rates of hospitalization.

Summary

There were 4 good-quality systematic reviews, one fair-quality head-to-head trial, 7 fair-quality active control trials, and 10 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 do not support that carbamazepine and valproate are different in improving psychotic symptoms (BPRS) and responder rate in patients with acute mania. In rapid cycling patients, there was no evidence to support a 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. There is no evidence to support that divalproex and lamotrigine are different 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. 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.

In 10 fair-quality placebo-controlled trials, acute therapy with carbamazepine was shown to be effective in reducing manic symptoms (2 trials) while divalproex / valproate (1 trial) and lamotrigine (1 trial) were not statistically better than placebo, and add-on gabapentin (1 trial) was inferior to placebo. There was no evidence to support that divalproex and lamotrigine are different 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. For reducing depressive symptoms, indirect comparisons suggest that acute therapy with carbamazepine or divalproex may be better than lamotrigine and add-on gabapentin. In acute therapy, carbamazepine and lamotrigine may each be better than divalproex / valproate in global improvement. On the basis of antimanic treatment effects during maintenance therapy relative to placebo, divalproex (2 trials) and lamotrigine (3 trials) were similar. Lamotrigine maintenance therapy improved depressive symptom scores while long-term divalproex did not. Based on treatment differences relative to placebo, divalproex (1 trial) and lamotrigine (1 trial) are similar in reducing recurrence of mood episodes in patients with recent mania or hypomania. Divalproex (2 trials) and lamotrigine (2 trials) are similar in rates of hospitalization. No indirect comparisons of the AEDs could be made for responder rate, remission rates, speed and duration of response, time to remission, duration of remission, use of additional therapies, 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.²⁵ 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^{119,121} and one fair-quality¹²⁰ systematic review provided evidence on the effectiveness or safety of the AEDs in neuropathic pain.¹²¹ One of the good-quality systematic reviews allowed indirect comparisons of AEDs and is discussed below; there was no substantive update to the systematic review since our original report. The other good-quality systematic review evaluated gabapentin only and the fair-quality systematic review assessed two trials that evaluated gabapentin^{91,92} and one trial that evaluated pregabalin⁸³ in the treatment of patients with postherpetic neuralgia. The NNT for gabapentin was 2.8 (95% CI: 1.7 to 3.0) for moderate to much improved on the global impression of change scale (1 trial). Using at least 50% pain reduction on an 11-point numerical rating scale as the measure for response, the NNT was 5.3 (3.6 to 10.2) for gabapentin (1 trial) and 3.3 (2.3 to 5.9) for pregabalin (1 trial). The good-quality systematic review of gabapentin and the fair-quality systematic review of gabapentin and pregabalin are not discussed in further detail here. All 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.¹²¹ 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).¹²¹ 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
<i>Trigeminal neuralgia</i>					
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
<i>Diabetic neuropathy</i>					
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
<i>Postherpetic neuralgia</i>					
Gabapentin	1	Up to 3600	8	RR 3.57	2.09–6.11
<i>Central spinal cord injury pain</i>					
Valproate	1	1200–2400	3	RR 1.50	0.50–4.52
<i>Central stroke pain</i>					
Carbamazepine	1	800	4	OR 7.78	0.78–77.93

Source: Wiffen, 2004¹²¹

[†] Across trials

Three trials included in the systematic review compared phenytoin or a combination of carbamazepine and clomipramine with active controls.¹²¹ 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.⁴⁹ 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 14 randomized active control trials for eligibility and included 9 in this report. Of these 9 trials, 7 were double-blind,^{48, 50, 54-57, 57} 7 were crossover,^{48, 50, 54-57, 122} 1 was multicenter,⁴⁸ 1 was open-label,⁸⁰ and 3 included double dummies.^{50, 54, 57}

There were two fair-quality trials. One was a fair-quality, double-blind, double-dummy, crossover trial.⁵⁴ 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).

The other fair-quality trial was a double-blind, double-dummy, four-period crossover randomized trial that compared gabapentin, morphine, combination gabapentin plus morphine, and placebo in 57 patients with painful diabetic neuropathy or postherpetic neuralgia.⁵⁰ There were no statistically significant differences between treatments in mean pain intensity and between gabapentin and morphine for other efficacy measures (total SF-MPQ score, BPI score, SF-36, BDI score, MMSE score, and percentage of patients who achieved at least moderate pain relief).

Since the active comparators were different and 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

For this report update, we reviewed 16 additional placebo-controlled neuropathic pain trials (14 publications), of which 14 trials (12 publications) were included and 2 trials (2 publications) were excluded. One of the added publications was a pooled analysis of three placebo-controlled trials with identical eligibility criteria and similar study designs.⁸⁸) In all, we have reviewed 55 randomized placebo-controlled trials (53 publications) and 42 trials (40 publications) met criteria for inclusion in this report; the remaining 13 trials (13 publications) were excluded. Of the 42 included trials, 40 were double-blind,^{51-53, 58-73, 75-79, 81-83, 85, 87-89, 91-93, 123-125, 135} 18 were crossover,^{51, 52, 58, 60, 62, 63, 65, 66, 69, 70, 72, 73, 77, 79, 123-126} and 17 were multicenter.^{60, 65, 76, 78, 81-83, 85, 87-93, 135} One trial used an unconventional statistical method, called a "closed" sequential design, to limit the duration of the trial.¹²³ There are 27 fair-quality trials (25 publications) 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 42 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 review⁹⁴ that included 4 other trials^{81, 87, 91, 92} 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.¹²⁷ 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.¹²⁸ Both trials did not meet inclusion criteria because patients with neuropathic pain were excluded from the trials.

Response: Symptom Rating Scales

Among the 27 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 or numerical rating scale (11 trials)^{51, 66, 81-85, 87, 89, 91, 92, 135} and, as a secondary efficacy variable, a VAS, either part of the SF-MPQ (10 trials)^{67, 79, 81, 83-85, 87, 91, 92, 135} and/or as a separate scale (4 trials).^{52, 64, 79, 82, 125, 126} Ten of 13 trials that evaluated the SF-MPQ VAS also used the Likert / numerical rating scale.^{53, 81-84, 87, 91, 92, 135} These trials showed consistent relative treatment effectiveness with the SF-MPQ VAS and the Likert / numerical rating scale; therefore, only the Likert / numerical rating scale scores were presented for these 10 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.⁷⁹ The changes in scores on either the VAS or 11-point Likert / numerical rating pain scales are shown for the 22 trials reporting these variables for the total patient cohort in Table 13. It should be noted that some trials, particularly the recently published trials added to the report update, assessed efficacy based on the difference in pain scores at study end point rather than differences in changes in scores from baseline to end point.

Table 13. Mean change in VAS or 11-point Likert or numerical rating scale 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
<i>Diabetic neuropathy</i>						
Backonja (1998) ⁸⁷	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) ⁷⁹	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 total SF-MPQ; see text)
Lesser (2004) ⁸⁴	Pregabalin 75, 300, or 600 mg/d vs. Placebo 5 wk	338	11-point NRS, mean daily pain	-1.79, -2.40, -2.60 vs. -1.54 (calculated)	-0.15, -1.26, -1.45	PGB75 = PBO PGB300 > PBO PGB600 > PBO
Rosenstock (2004) ⁸²	Pregabalin 300 mg/d vs. Placebo 8 wk	146	11-point NRS, mean daily pain scores	-2.5 vs. -0.8 (calculated)	-1.7 (calculated)	No statistical analysis for change; PGB300 > PBO for mean scores at end point
Thienel (2004); ⁸⁸ pooled analysis of 3 trials	Topiramate 100, 200, or 400 mg/d vs. Placebo 18 to 22 wk	1259	100-mm VAS, pain at end point	-24.0, -17.5, -16.6 vs. -14.6 (calculated)	-9.4, -2.9, -2.0 (calculated)	TPM100 = PBO TPM200 = PBO TPM400 = PBO
Raskin (2004) ⁹⁰	Topiramate 400 mg/d vs. Placebo 12 wk	323	100-mm VAS, pain at end point	-21.8 vs. -15.1 (calculated)	-6.7 (calculated)	No statistical analysis for change; TPM > PBO for mean scores at end point
Kochar (2004) ⁶⁷	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
<i>Postherpetic neuralgia</i>						
Rowbotham (1998) ⁹¹	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) ⁹²	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
Sabatowski (2004) ¹³⁵	Pregabalin 150 vs. 300 mg/d vs. Placebo 8 wk	238	11-point NRS, mean daily pain	-1.76 vs. -2.24 vs. -0.27 (calculated)	-1.20 vs. -1.57	PGB > PBO
Dworkin (2003) ⁸³	Pregabalin 300 or 600 mg/d (depending on creatinine clearance) vs. Placebo 8 wk	173	11-point NRS, mean daily pain	-2.7 vs. -1.11 (calculated)	-1.59 (calculated)	No statistical analysis for change; PGB > PBO for mean scores at end point
Kochar (2005) ⁵³	Divalproex 1000 mg/d vs. Placebo 8 wk	48	11-point Likert, pain score parameter not reported	-3.34 vs. -0.80 (calculated)	-2.54 (calculated)	No statistical analysis for change; DVP > PBO based on reported difference of -1.7 between end point scores
<i>Mixed neuropathic syndromes</i>						
Serpell (2002) ⁸¹	Gabapentin 900	307	11-point	-1.5 vs. -1.0	-0.5	GBP > PBO

Trial	Interventions* Duration	N	Pain Scale	Change in Scores from Baseline, mean	Difference (AED – Placebo)	Interpretation of Results
	to 2400 vs. Placebo 8 wk		Likert, average daily pain			
McCleane (1999) ⁶⁴	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) ¹²⁵	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
Otto (2004) ⁵¹	Valproate 1500 mg/d vs. Placebo 4 wk	37	11-point NRS, median daily pain	–1 vs. 0 (calculated)	–1 (calculated)	No statistical analysis for change; VPA = PBO for median scores at end point
<i>Phantom limb pain</i>						
Bone (2002) ¹²⁶	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
<i>Central post-stroke pain</i>						
Vestergaard (2001) ⁶⁶	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
<i>Spinal cord injury pain</i>						
Levendoğlu (2004) ⁷⁷	Gabapentin 900 to 3600 mg/d vs. Placebo 8 wk	20	100-mm VAS, pain at 8 wk	–54 vs. –9 (calculated)	–45 (calculated)	No statistical analysis for change; GBP > PBO for mean scores at 8 wk
<i>HIV-related painful sensory neuropathy</i>						
Hahn (2004) ⁷⁶	Gabapentin 400 to 2400 mg/d vs. Placebo 4 wk	26	10-cm VAS, median weekly pain	–2.25 vs. –1.40 (calculated)	–0.85 (calculated)	GBP > PBO for relative % change in score
<i>Neuropathic Cancer Pain</i>						
Caraceni (2004) ⁸⁹	Gabapentin 600 to 1800 mg/d vs. Placebo (add-on therapy) 10 d	121	11-point NRS, mean follow- up global pain score	–2.4 vs. –2.3 (calculated difference, mean for follow-up period minus baseline)	–0.1 (calculated)	No statistical analysis for change; GBP > PBO for mean follow- up global pain score
<i>Complex Regional Pain Syndrome Type I</i>						
Van de Vusse (2004) ⁵²	Gabapentin 600 to 1800 mg/d vs. Placebo 21 d	58	VAS, 24-h pain score	1 st tx period: –14 vs. 2 2 nd tx period: 0 vs. –3	1 st tx period: –16 2 nd tx period: 3 (calculated)	1 st tx period: GBP > PBO 2 nd tx period: GBP = PBO Both periods combined: NSD

GBP, Gabapentin; NA, Not applicable; NRS, Numerical Rating Scale; 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.

For painful diabetic neuropathy, indirect comparisons do not support that gabapentin (900 to 3600 mg daily, flexible dosing; 1 trial), pregabalin (300 or 600 mg daily only, 2 trials), topiramate (400 mg daily only, 1 trial), and valproate (1 trial), each of which were shown to be effective in one or more trials, are different in analgesic effects. However, results were inconsistent for topiramate (3 other trials in a pooled analysis showed no treatment effect), and there was evidence that topiramate 100 and 200 mg daily are ineffective. The lack of statistical difference between topiramate and placebo in each of the three trials included in the pooled analysis may have been due to methodologic limitations common to all three trials.⁸⁸ Valproate was shown to be superior to placebo in the treatment of painful diabetic neuropathy based on the difference at the 3-month end point using the total SF-MPQ (-8.10), VAS (-3.0), and VAS for present pain intensity (-1.28) ($p < 0.001$ for each test).⁶⁷ Differences between treatment groups based on the changes in scores from baseline were not provided.

For postherpetic neuralgia, the treatment effects relative to placebo of gabapentin (300 to 3600 mg daily), pregabalin (150 to 600 mg daily), and divalproex (1000 mg daily) are similar.

In mixed neuropathic syndromes, only gabapentin was shown to be significantly better than placebo but the decreases in pain scores were not clinically important. Lamotrigine and valproate were not better than placebo. 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).¹²⁵ Differences between trials in the case mixes of neuropathic pain disorders make indirect comparisons difficult.

Ten of the 27 fair-quality trials compared gabapentin with placebo in a variety of neuropathic pain disorders, including diabetic neuropathy, postherpetic neuralgia, mixed neuropathic pain syndromes, phantom limb pain, spinal cord injury pain, HIV-related painful sensory neuropathy, neuropathic cancer pain, and complex regional pain syndrome. 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, and in complex regional pain syndrome, where the overall results for the primary efficacy measure (VAS pain score) showed no treatment benefit but total and feet sensory deficit scores improved on moderate doses of gabapentin (titrated from 600 to 1800 mg/day). 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).⁹²

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.⁷⁹ 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; $p = 0.03$). The authors' suggestion that the 3-week washout period may have been inadequate is questionable on a pharmacokinetic basis, since gabapentin has a short half-life (5 to 7 hours) and should have been completely eliminated after 25 to 35 hours.

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 ; $p < 0.001$).⁸⁷ 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.

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.⁶⁶

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 or numerical rating 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 ($p = 0.65$).⁷⁸ 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.⁹³ 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*.) In comparison to the two trials showing lamotrigine to be ineffective using Gracely pain scale scores, one small trial showed that gabapentin was effective in reducing HIV-related sensory neuropathic pain in terms of the *relative* percentage change in VAS pain scores; however, the treatment difference in terms of reduction in pain scores was minimal (-0.85 , calculated).⁷⁶

Another 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 ($p < 0.05$).¹²³ (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 $p = 0.05$.)

An 11-point Likert or numerical rating scale was used in 5 placebo-controlled trials evaluating gabapentin,^{81, 87, 89, 91, 92} 4 trials with pregabalin,⁸²⁻⁸⁵ 1 trial with lamotrigine,⁶⁶ and 2 trials with valproate⁵¹/divalproex,⁵³ 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.¹⁷ 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 5 fair-quality gabapentin trials,^{87, 91, 92} all 4 pregabalin trials at doses of 300 mg daily or more,⁸²⁻⁸⁵ the single lamotrigine trial,⁶⁶ and the divalproex trial⁵³ for doses showing significant treatment effects.⁹² 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.⁸¹ 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. For one trial evaluating gabapentin for neuropathic cancer pain, the clinical relevance of the observed change was not evaluable since the “change” in scores was calculated using the difference between baseline and the mean follow-up global pain score, rather than the mean score at end point. None of the trials reported the percentage of patients who achieved a reduction in pain scores of at least 2 points. Reporting of responder rates in this manner would be preferred over assessing the achievement of clinically relevant changes based on the population mean changes.

Indirect comparisons of the AEDs were limited by 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 pregabalin are both generally better than placebo while lamotrigine, topiramate, and valproate showed contradictory 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 and pregabalin is better documented than with other AEDs. Therefore, limited indirect comparisons do not support that gabapentin (8 of 9 trials) and pregabalin (4 trials) are different in reducing neuropathic pain; however, lamotrigine (3 trials), topiramate (4 trials in 2 reports) and valproate/divalproex (2 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 $\geq 33\%$, $\geq 50\%$, or both $\geq 30\%$ and $\geq 50\%$ reduction in pain scores from baseline in 1 trial,⁸⁹ 5 trials,^{53, 81, 82, 85, 92, 135} and 3 trials,^{83, 84, 90} respectively, and as at least moderate improvement on Clinician’s Global Impression of Change (CGIC) or PGIC in 1 trial⁸⁷ or on a 6-item verbal rating scale in 1 trial.⁵¹ 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 two other trials, 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; and another trial that defined an “effect” as a patient scoring “much improvement” on a 7-point global perceived effect rating scale. In total, responder rates were available in 17 of the 27 fair-quality trials (Table 14).

Using $\geq 50\%$ reduction in pain on an 11-point NRS as the criterion for response, pregabalin (150, 300, and 600 mg, 4 trials)⁸²⁻⁸⁵ and divalproex (1 trial)⁵³ have been shown to be superior to placebo, whereas gabapentin (1800 and 2400 mg) was either superior to (1 trial)⁹² or not significantly different from placebo (1 trial).⁸¹ Topiramate (400 mg, 1 trial) was also shown to be superior to placebo⁹⁰ but responder rates were not reported in pooled analysis of the 3 trials that did not show topiramate to be effective.⁸⁸

Seven trials compared gabapentin with placebo. Based on different responder rates, 2 trials showed that gabapentin was superior to placebo.^{87, 92} Gabapentin was numerically better than placebo in one trial (no statistical analyses).^{91, 125} One trial was unclear about the definition of effect. It showed no significant difference between gabapentin and placebo using “much improvement” on the global perceived effect on pain scale, the reported definition of effect; however, it went on to state that gabapentin was significantly better than placebo using “some improvement” or “much improvement.”⁵² Finally, 3 trials showed no significant difference between gabapentin and placebo in terms of the responder rates as defined by the authors.^{79, 81, 89}

One of two trials that compared lamotrigine with placebo involved patients with symptom-based diagnoses of neuropathic pain.⁶⁴ 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.⁶⁶ 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,¹⁷ 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 evaluated as an outcome measure and shown to be significantly higher on pregabalin than placebo in 4 fair-quality trials.⁸²⁻⁸⁵ The responder rate for 30% reduction in pain was reported for gabapentin in one fair-quality trial⁹² in the authors’ reply to comments.⁸⁶ 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. One trial showed no significant difference between gabapentin and placebo when 33% reduction in pain was used to define response.⁸⁹

Overall, responder rates were available for gabapentin in 7 fair-quality trials and for pregabalin in 4 trials, while 2 trials provided these results for lamotrigine, 1 trial for topiramate, 1 trial for divalproex, and 1 trial for single-dose, intravenous phenytoin. Responder rates were not reported in the pooled analysis of the 3 trials which did not show topiramate to be effective. It is difficult to make indirect comparisons between the AEDs in terms of responder rates since the definitions

of response, types of neuropathic pain, interpretation of results, and the sample sizes (i.e., statistical power to show a significant treatment difference using a categorical variable) varied between the trials for the different agents, except in patients with postherpetic neuralgia and populations with mixed types of neuropathic pain. In postherpetic neuralgia, gabapentin (1 trial)⁹² pregabalin (2 trials)^{83, 85} and divalproex (1 trial)⁵³ have similar responder rates ($\geq 50\%$ reduction in pain) relative to placebo. 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
<i>Diabetic neuropathy</i> Backonja (1998) ⁸⁷	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) ⁷⁹	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
Lesser, 2004 ⁸⁴	Pregabalin 75 vs. 300 vs. 600 mg/d vs. Placebo 5 wk	338	≥ 50% reduction in mean pain score from baseline	25% vs. 41% vs. 48% vs. 18%	PGB75 = PBO PGB300 > PBO PGB600 > PBO
			≥ 30% reduction in mean pain score from baseline	37% vs. 62% vs. 65% vs. 33%	PGB75 = PBO PGB300 > PBO PGB600 > PBO
Rosenstock (2004) ⁸²	Pregabalin 300 mg/d vs. Placebo 8 wk	146	≥ 50% reduction in mean pain score from baseline	40% vs. 14.5%	PGB300 > PBO
Raskin (2004) ⁹⁰	Topiramate 400 mg/d vs. Placebo 12 wk	323	≥ 50% reduction in mean pain score from baseline	35.6% vs. 21.1%	TPM400 > PBO
			≥ 30% reduction in mean pain score from baseline	49.5% vs. 33.9%	TPM400 > PBO
<i>Postherpetic neuralgia</i>					
Rowbotham (1998) ⁹¹	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) ^{86, 92}	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
cont'd					
Sabatowski (2004) ¹³⁵	Pregabalin 150 vs. 300 mg/d vs. Placebo	238	≥ 50% reduction in mean pain	26% vs. 28% vs. 10%	PGB150 > PBO PGB300 > PBO

Trial	Interventions Duration (Dose in mg/d)	N	Definition of Response	Responder Rate	Interpretation of Results
	8 wk		score from baseline		
			≥ 30% reduction in mean pain score from baseline	37% vs. 50% vs. 19% (post hoc)	PGB150 and PGB300 provided clinically meaningful pain relief
Dworkin (2003) ⁸³	Pregabalin 300 or 600 mg/d (depending on creatinine clearance) vs. Placebo 8 wk	173	≥ 50% reduction in mean pain score from baseline	50% vs. 20%	PGB300/600 > PBO
			≥30% reduction in mean pain score from baseline	63% vs. 25%	PGB300/600 > PBO
Kochar (2005) ⁵³	Divalproex 1000 mg/d vs. Placebo 8 wk	48	≥ 50% reduction in VAS pain score from baseline	59.1% vs. 11.1% (p = 0.005, calculated post hoc)	DVP > PBO
<i>Mixed neuropathic pain syndromes</i>					
Serpell (2002) ⁶¹	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) ¹²⁵	Phenytoin 15 mg/kg i.v. vs. 0.9% Saline (placebo) over 2 h 1 dose	20	A reduction in pain scores Rated treatment to be of significant benefit	14/20 (70.0%) vs. 0 (0%) (no statistical analysis) 8/20 (40.0%) vs. Not reported	Data inconclusive based on analysis Unable to determine
McCleane (1999) ⁶⁴	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
<i>Central post-stroke pain</i>					
Vestergaard (2001) ⁸⁶	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 [†]
<i>Neuropathic cancer pain</i>					
Caraceni (2004) ⁸⁹	Gabapentin 600 to 1800 mg/d vs. Placebo (add-on therapy) 10 d	121	≥ 33% reduction in mean pain score from baseline to day 10	62% vs. 64%	GBP = PBO
<i>Complex Regional Pain Syndrome Type I</i>					

Trial	Interventions Duration (Dose in mg/d)	N	Definition of Response	Responder Rate	Interpretation of Results
Van de Vusse (2004) ⁵²	Gabapentin 600 to 1800 mg/d vs. Placebo 21 d	58	Much improvement on GPE	17% vs. 4% (overall)	GBP = PBO
			Some improvement or much improvement on GPE	43% vs. 17% (overall)	GBP > PBO

CGIC, Clinician's Global Impression of Change; GBP, Gabapentin; GPE, 7-point Global Perceived Effect on pain scale; 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 12 placebo-controlled trials that reported data showing statistical analyses for response over time, 6 evaluated gabapentin,^{77, 81, 87, 91, 92, 126} 4 evaluated pregabalin,⁸³⁻⁸⁵ 1 evaluated lamotrigine,⁶⁶ 1 evaluated topiramate,⁹⁰ and 1 evaluated intravenous phenytoin.¹²⁵

For gabapentin, the time to the earliest significant treatment effect was 1 to 2 weeks in diabetic neuropathy, postherpetic neuralgia, spinal cord injury, 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 ($N = 19$).¹²⁶ The significant treatment effect was maintained for the remainder of the 6-to-8-week trials in all cases except for 1 trial⁸¹ 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.

The earliest significant treatment effect of pregabalin was observed at 2 days in the treatment of postherpetic neuralgia (1 trial).⁸³ In the other trials, which did not analyze daily pain scores in the first week, the earliest significant analgesic effect was seen 1 week after starting therapy in patients with diabetic neuropathy (2 trials)^{82, 84} or postherpetic neuralgia (1 trial).¹³⁵ The treatment effect was sustained for the duration of the 5- to 8-week trials.

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.⁶⁶ 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.

Topiramate was shown to have to produce a significant treatment effect at 8 weeks (i.e., end of the titration period) in patients with painful diabetic neuropathy, and a significant treatment effect was also observed at the final patient assessment at 12 weeks.

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.¹²⁵

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. Pregabalin

was shown to have an onset of 2 days in postherpetic neuralgia; analyses of daily pain scores within the first week were not reported for the other AEDs. For trials that reported scores measured weekly or monthly, indirect comparisons do not support that, even at lower doses of a titration schedule, gabapentin (based on 6 trials) and pregabalin (3 trials) have different onsets of effect (1 to 2 weeks and 1 week, respectively). In placebo controlled trials, gabapentin and pregabalin had earlier onsets than lamotrigine (7 to 8 weeks, based on 1 trial) and topiramate (8 weeks, 1 trial).

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

Use of Rescue Medications

Six 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.¹²⁶ In a trial involving patients with HIV-related neuropathy, gabapentin was not significantly different from placebo in the number of patients who required concomitant nonsteroidal antiinflammatory drugs.⁷⁶ A trial comparing gabapentin and placebo in patients with neuropathic cancer pain showed a numerically lower percentage of gabapentin-treated patients required doses of either rescue analgesics (47.1% vs. 64.7%; $p = 0.0999$) or as-needed opioids (21.6% vs. 35.8%; $p = 0.0559$), but the difference did not reach the level of statistical significance.⁸⁹

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.⁷⁸ The second trial showed no significant differences between lamotrigine and placebo in the mean change from baseline in the number of analgesic tablets used.⁶⁴ 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).⁶⁶

One trial showed no significant difference between valproate and placebo in the number of acetaminophen tablets taken by patients with polyneuropathy.⁵¹

Indirect comparisons from the 2 gabapentin trials, 3 lamotrigine trials, and 1 valproate trial, based on the lack of treatment differences relative to placebo, suggest that none of these three AEDs 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 14 fair-quality placebo-controlled trials (in 12 publications): 6 trials evaluated gabapentin in the treatment of diabetic neuropathy (1 trial),⁸⁷ postherpetic neuralgia (2 trials),^{91, 92} mixed neuropathic pain syndromes (1 trial),⁸¹ HIV-related neuropathy (1 trial),⁷⁶ and phantom limb pain (1 trial)¹²⁶; 2 trials compared lamotrigine with placebo, one in patients with symptom-based diagnoses of neuropathic pain⁶⁴ and the other in patients with central post-stroke pain⁶⁶; 4 trials evaluated pregabalin in painful diabetic neuropathy (2 trials)^{82, 84} and postherpetic

neuralgia (2 trials)^{83, 85}; and 4 trials (in 2 publications) evaluated topiramate in painful diabetic neuropathy.^{88, 90}

Gabapentin was shown to have a significant benefit over placebo in sleep interference scores (3 trials)^{87, 91, 92} or sleep quality score (1 trial),⁷⁷ in disability due to pain score (1 trial),⁷⁷ and in 1 to 5 domains (range among 4 trials) of the Short-form-36 (SF-36) health-related quality of life questionnaire.^{81, 87, 91, 92} 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). Another trial showed that gabapentin treatment was associated with a numerical improvement in the sleep interference score in comparison with placebo; however, no statistical analysis was performed.⁷⁶ At maximal doses (3600 mg daily), the difference between gabapentin and placebo in end point sleep interference score was 1.47 (95% CI: 0.8 to 2.2; 1 trial).⁸⁷

In a 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.¹²⁶ 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,⁶⁴ or the mean degree to which pain affected daily activities.⁶⁶

Relative to placebo, pregabalin (300 or 600 mg) significantly ($p < 0.05$) decreased the sleep interference score (4 trials)^{82-84, 85} or sleep problem index (i.e., improved sleep quality; 1 trial),⁸³ and significantly ($p < 0.05$) improved SF-36 subscores (4 trials) for social functioning,⁸⁴ mental health,⁸⁵ bodily pain,⁸²⁻⁸⁵ vitality,^{84, 85} and general health perception.⁸³ At maximal doses (600 mg daily), the difference between pregabalin and placebo in end point sleep interference score was 1.58 (95% CI: 0.97 to 2.19) in one trial⁸³ and 1.6 (95% CI not reported) in another trial.⁸⁴

Topiramate was effective in improving the sleep disruption score and the SF-36 mental component summary but not the physical component summary in 1 trial.⁹⁰ However, in the pooled analysis of the 3 trials that did not show topiramate to have analgesic efficacy in painful diabetic neuropathy, 1 trial (NP-003) showed that topiramate was inferior to placebo and 2 trials showed no treatment effect in reducing sleep interference scores.⁸⁸ SF-36 results were not reported.

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. Like gabapentin, pregabalin reduces sleep interference, improves sleep quality, and improves some domains of quality of life, particularly bodily pain and vitality. Results with topiramate were inconsistent. Indirect comparisons of gabapentin, lamotrigine, and pregabalin, based on treatment effects relative to placebo in 4 of 6 trials involving gabapentin, 4 trials involving pregabalin, and 2 trials involving lamotrigine, do not support that gabapentin and pregabalin are different, and each may be better than lamotrigine in improving functional capacity in patients with neuropathic pain. While one trial evaluated the extent to which pain

interfered with daily activities⁶⁶ and another trial assessed disability due to pain,⁷⁷ there is little 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.¹²¹ 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 and all 4 of the fair-quality trials evaluating pregabalin in neuropathic pain showed evidence of some beneficial effects across different types of neuropathic pain in terms of improvement in symptom rating scores, responder rates, speed of response, duration of response, sleep interference, and certain domains of quality of life questionnaires. In terms of these outcomes and regardless of neuropathic pain type, gabapentin (10 trials) and pregabalin (4 trials) are generally similar in analgesic efficacy. For functional capacity, indirect comparisons relative to placebo support that both gabapentin (5 trials) and pregabalin (4 trials) are better than lamotrigine (2 trials). In placebo-controlled trials, gabapentin (6 trials) and pregabalin (4 trials) have earlier onsets of significant treatment effects than lamotrigine (1 trial) and topiramate (1 trial). Gabapentin, lamotrigine, and valproate were not different in terms of use of rescue medications, based on a lack of benefit with each of these AEDs relative to placebo. Inconsistent results with lamotrigine (3 trials), topiramate (4 trials in 2 publications), and valproate (2 trials) and the small number of placebo-controlled trials evaluating other AEDs (1 trial each for carbamazepine and phenytoin), limit the indirect comparisons with these agents. Benefit from AED therapy has not been sufficiently shown for functional capacity in terms of physical abilities. None of the trials evaluated long-term (≥ 1 year) duration of response or relapse rates. Indirect comparisons were limited by differences in neuropathic pain disorders, outcome measures, and durations of therapy between the trials, along with a predominance of gabapentin trials.

Limited indirect comparisons by neuropathic pain type, based on treatment differences relative to placebo, do not support that gabapentin (2 trials), pregabalin (2 trials), topiramate (1 trial), and valproate (1 trial) are different in reducing pain related to diabetic neuropathy, although topiramate showed inconsistent results (3 other trials included in a pooled analysis showed no treatment benefit, possibly because of methodologic deficiencies). In postherpetic neuralgia, gabapentin (2 trials), pregabalin (2 trials), and divalproex (1 trial) were similar. In populations with mixed neuropathic pain types, it was difficult to make indirect comparisons between gabapentin (1 trial), lamotrigine (1 trial), valproate (1 trial), and intravenous phenytoin (1 trial). All of the indirect comparisons described above 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 and pregabalin than there is with other AEDs, particularly in patient populations with diabetic neuropathy and postherpetic neuralgia. 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.⁹²

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

We included adverse event data for the AEDs from 4 systematic reviews, 42 controlled clinical trials evaluating their use in bipolar disorder (17 trials) and neuropathic pain (27 trials), 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 reviews

We found 2 good-quality systematic reviews. One provided comparative data on the adverse events of carbamazepine and valproate relative to lithium. The other systematic review compared valproate with lithium, olanzapine, haloperidol, and placebo in terms of discontinuations due to adverse events and specific adverse events; however, indirect comparisons were not possible because no other AED was evaluated, and therefore this systematic review is not discussed in further detail.¹⁰³ These systematic reviews are 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.¹⁰² 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.²³ 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.²³ 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).²³ 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.¹²⁹ The other trial was excluded because it was available only as a conference abstract.¹³⁰

All 7 of the fair-quality active-control efficacy trials (9 publications) reported adverse events. These compared carbamazepine,^{29, 34} divalproex,^{25, 40} or lamotrigine^{32, 47} with lithium or lithium

and placebo, or divalproex with olanzapine.^{24, 31, 110} 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.^{24, 25, 29, 31, 32, 47, 110}

In comparison with lithium, carbamazepine was associated with a higher frequency (difference in rates of at least 10%) of increased appetite.³⁴ 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,²⁵ infection,²⁵ and tinnitus.²⁵ Relative to lithium, lamotrigine was more frequently associated with headache.³²

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,³¹ lithium,^{32, 47} or olanzapine,^{24, 31, 110} 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)^{29, 34} or lamotrigine (2 trials)^{32, 47} versus lithium or lithium and placebo, and another 2 trials compared divalproex with olanzapine (as acute and maintenance therapy in 1 trial^{24, 110} and acute therapy in 1 trial.)³¹ 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.²⁵

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.²⁹ 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).³⁴ 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 ($p = 0.01$).³² The other trial showed no significant difference between lamotrigine and lithium (or placebo) in patients with a recent depressive episode.⁴⁷ 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,^{29, 34} weight loss with decreased sodium levels,³⁴ and severe general malaise with increased gamma-glutamyltransferase level³⁴ with carbamazepine; and mania,³² somnolence,³² nausea,⁴⁷ tremor,⁴⁷ and non-serious rash⁴⁷ 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 trial²⁹ and 4.0% (2/50) in another trial³⁴ with carbamazepine, and 4% (7/169) with lamotrigine;⁴⁷ 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.⁴⁷

Serious adverse events

One fair-quality trial reported the rate of serious adverse events. Therefore, indirect comparisons of AEDs in terms of serious adverse events were not possible.

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).⁴⁷ Relative to lithium, divalproex was associated with a higher frequency of sedation,²⁵ whereas there was no significant difference in the frequency of somnolence between lamotrigine and lithium.^{47, 110} 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.^{32, 47} Divalproex was associated with a decrease in platelet count, but the change was not significantly different from that seen on lithium.²⁵ 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.²⁵ Similar results were shown in another trial in patients with bipolar I disorder with recent mania/hypomania, where weight gain of $\geq 7\%$ over baseline occurred at comparable rates on lamotrigine (11%, 19/169) relative to lithium (10%, 12/120).³² In patients with bipolar I disorder with recent depression, the proportions of patients experiencing weight gain of $\geq 7\%$ 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; $p < 0.01$).⁴⁷

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.³⁴ 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 9 fair-quality placebo-controlled trials, including 3 trials^{35, 116, 117} added since the original report. Of the 9 trials, 3 had both active and placebo controls^{25, 32, 47} and 6 used a placebo control only.^{35, 46, 116-118} The population of one trial consisted of patients with both alcohol dependence and bipolar disorder,³⁵ and differed from the bipolar populations enrolled in the other trials. It is unclear whether and to what extent alcohol dependence influences the development of adverse events during valproate therapy (e.g., because of cross-tolerance or additive hepatotoxic effects). The differences in study populations between this trial and the others may further confound indirect comparisons of the AEDs. The placebo-controlled trials in bipolar disorder are summarized in Evidence Table 3 and Quality Table 3.

Overall adverse events

Two trials showed that the overall adverse event rates for carbamazepine were higher than that for placebo (88.1% versus 72.8%, $p = 0.0078$ in one trial,¹¹⁶ and 91.8% vs. 56.4%; $p < 0.0001$, in the other¹¹⁷). Divalproex and placebo were not significantly different in terms of adverse event frequency in patients with alcohol dependence and bipolar disorder.³⁵ The overall adverse event rate for lamotrigine 50 and 200 mg was 79% for both strengths and numerically higher for placebo (92%).¹¹⁸ Limited indirect comparisons suggest that overall adverse event rates may be higher with carbamazepine than divalproex and lamotrigine, based on comparisons of each AED with placebo.

Of the treatment-emergent adverse events reported significantly more frequently on carbamazepine than placebo in 2 trials, dizziness, nausea, somnolence, and vomiting were common to both trials.^{116, 117} Relative to placebo, adverse events that occurred more frequently on divalproex were tremor, weight gain, and alopecia.²⁵ Rash⁴⁷ and headache¹¹⁸ occurred more commonly on lamotrigine than placebo. There were no adverse events experienced more frequently on placebo than AED in the fair-quality trials.

In comparison with placebo, carbamazepine was associated with significantly greater increases in alkaline phosphatase¹¹⁶ and cholesterol,^{116, 117} as well as significantly ($p < 0.0001$) greater decreases in white blood cell count (mean change, $10^3/\mu\text{l}$: -1.15 vs. -0.05 in one trial¹¹⁶ and -1.0 vs. -0.2 in another trial).¹¹⁷ In patients with bipolar disorder and alcohol dependence, significantly higher gamma-glutamyl transpeptidase levels were noted on placebo than divalproex, whereas no significant treatment differences were shown in liver transaminase levels (alanine aminotransferase and aspartate aminotransferase).³⁵ Four trials reported that there were no remarkable changes in laboratory test values in either lamotrigine or placebo group.^{32, 42, 47, 118} Another two trials did not report abnormalities in laboratory values.^{25, 46} Indirect comparisons of the AEDs, relative to placebo, suggest that carbamazepine, divalproex, and lamotrigine may differ in the extent of changes in laboratory tests and the type of tests affected (liver enzymes, cholesterol, and leukocytes).

Withdrawals due to adverse events

Two trials showed a higher rate of withdrawals due to adverse events with carbamazepine (12.9% and 9.0%, for first¹¹⁶ and second trial,¹¹⁷ respectively) relative to placebo (5.8% and

5.1%); however, the differences in both trials were not significant ($p = 0.0959$ and $p > 0.05$).¹¹⁶ Two trials did not report a significant difference between divalproex and placebo in terms of withdrawals due to adverse events.^{25, 35} Another 3 trials showed no significant differences between lamotrigine and placebo for the same outcome.^{32, 42, 47} 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.¹¹⁸ Indirect comparisons, based on comparisons between AEDs and placebo, do not support that carbamazepine, divalproex, and lamotrigine are different in tolerability.⁴⁶

Serious adverse events

The frequencies of serious adverse events on carbamazepine and placebo were similar in two trials (4.0% vs. 3.9% of patients in one trial,¹¹⁶ and 3.3% vs. 5.1% in the second trial).¹¹⁷ No serious adverse events were reported for either divalproex or placebo in another trial.³⁵ Serious adverse events occurred in 6 (10.3%) of 58 gabapentin-treated patients and 5 (8.5%) of 59 placebo-treated patients.⁴⁶ 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.¹¹⁸ In another trial, 1 (1.1%) of 92 lamotrigine-treated patients and 2 (2.3%) of 88 placebo-treated patients experienced serious adverse events. Based on limited comparisons between AEDs and placebo, there is no evidence to support that carbamazepine, divalproex, gabapentin, and lamotrigine are different in terms of serious adverse event rates.

Among two trials, the serious adverse events reported with carbamazepine were worsening or exacerbation of bipolar or depressive symptoms,^{116, 117} personality disorder,¹¹⁷ and fever with rash.¹¹⁷ Serious adverse events experienced on gabapentin were manic reaction, manic depressive reaction, psychosis, and cervical carcinoma.⁴⁶ 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.⁴²

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

A higher rate of dizziness was reported during acute therapy with carbamazepine than with placebo in 2 trials (48.5% vs. 12.6% in one trial¹¹⁶ and 39.3% vs. 12.0% in the second trial¹¹⁷; no statistical analyses). Dizziness was reported in 19% of patients on acute add-on therapy with gabapentin,⁴⁶ 8% to 10% on either acute or maintenance therapy with lamotrigine,^{42, 47, 118} and 3% to 14% on placebo. There was no statistically significant difference between lamotrigine and placebo in two trials^{47, 118} and no statistical analyses were performed in another two trials, one comparing the same agents⁴² and the other trial comparing gabapentin and placebo.⁴⁶ Dizziness was not reported as a common adverse event with valproate (1 trial).³⁵ Limited indirect comparisons suggest that dizziness may occur more commonly on carbamazepine than gabapentin, lamotrigine, or valproate.

Somnolence occurred in 32.7% of carbamazepine-treated patients versus 15.5% of placebo patients ($p < 0.05$) in one trial¹¹⁶ and 30.3% versus 10.3% ($p = 0.0001$) in a second trial.¹¹⁷ Somnolence was also reported in 24.1% of gabapentin-treated patients⁴⁶ and 5% to 9% of

lamotrigine-treated patients.^{32, 47, 118} There was no significant difference between either AED and placebo (6% to 12%) for this adverse event.¹¹⁸ Sedation was reported in 42% of patients treated with divalproex and 35% of placebo patients.²⁵ Fatigue occurred in a numerically smaller proportion of valproate-treated patients than placebo patients (30.4% vs. 47.6%).³⁵ Based on effects relative to placebo, indirect comparisons suggest that carbamazepine may be more likely than gabapentin, lamotrigine, and divalproex/valproate to be associated with somnolence, sedation, or fatigue.^{25, 32, 47}

There was no significant difference between carbamazepine (8.9%) and placebo (5.8%) in the frequency of rash (1 trial).¹¹⁶ 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.^{32, 42, 47, 118} 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),⁴⁷ but other trials either showed no significant difference between lamotrigine and placebo as acute¹¹⁸ or maintenance therapy³² or no statistical analyses were performed.⁴² Indirect comparisons of AEDs, relative to placebo, suggest that carbamazepine and lamotrigine may be more likely to cause rash than divalproex and gabapentin.

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%; $p = 0.004$) in 1 trial.²⁵ In another trial involving patients with alcohol dependence and bipolar disorder, there was no statistically significant difference between valproate and placebo in the frequency of weight gain reported as an adverse event (14.3% vs. 23.8%).³⁵ Weight gain was not reported among common adverse events in 2 placebo-controlled trials that evaluated acute carbamazepine therapy^{116, 117} and another trial that assessed acute add-on gabapentin therapy.⁴⁶ Weight gain of $\geq 7\%$ 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.^{32, 47} 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.^{42, 47, 118} There was either no significant difference between lamotrigine and placebo for this outcome^{47, 118} or statistical analyses were not done.⁴² Indirect comparisons were limited by differences in measuring or reporting effects on weight and mixed results with divalproex in diagnostically different study populations. When one considers weight gain reported as an adverse event during acute therapy of patients with bipolar disorder without concurrent alcohol dependence, indirect comparisons relative to placebo suggest that divalproex may be more likely to be associated with weight gain than carbamazepine and gabapentin.

Meta-analysis of specific adverse events: bipolar disorder

The patient-level adverse event analysis included 14 trials and evaluated 8 types of specific adverse events (diarrhea, dizziness, headache, nausea, rash, somnolence, tremor, and weight gain). The results of our meta-analysis of specific adverse events at a patient level are shown in Tables 15, 16, and 17.

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

Adverse Events	Carbamazepine			Valproate		Pooled OR	95% CI
	# of studies	# of patients with event	Sample size	# of patients with event	Sample size		
Dizziness ³⁶	1	9	15	1	15	15.50	(1.53 to 826.43)
Rash ³⁶	1	1	15	0	15	Inf	(0.03 to 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) and carbamazepine (2 trials), but not 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

Adverse Events	Drug	Lithium Intervention Groups					Pooled OR	95% CI
		# of studies	# of patients with event	Sample size	# of patients with event	Sample size		
Depression	Carbamazepine ²⁶	1	1	27	1	27	1.00	(0.01 to 81.48)
Depression	Divalproex/Valproate	0	NR	NR	NR	NR	NC	NC
Depression	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Diarrhea	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Diarrhea	Divalproex ²⁵	1	42	94	65	187	0.66	(0.39 to 1.13)
Diarrhea	Lamotrigine ^{32, 47}	2	32	166	15	228	0.30	(0.14 to 0.59)
Headache	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Lamotrigine ^{32, 47}	2	25	166	42	228	1.27	(0.71 to 2.28)
Nausea	Carbamazepine ²⁸	1	1	14	0	14	0.00	(0.0 to 39.00)
Nausea	Divalproex ²⁵	1	41	94	79	187	0.95	(0.56 to 1.61)
Nausea	Lamotrigine ^{32, 47}	2	33	166	32	228	0.65	(0.37 to 1.16)
Rash	Carbamazepine ^{26, 34, 114}	3	0	97	7	135	Inf	(0.93 to Inf)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Somnolence	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Lamotrigine ^{32, 47}	2	22	166	21	228	0.66	(0.33 to 1.32)
Tremor	Carbamazepine ^{28, 114}	2	7	40	0	72	0.00	(0.0 to 0.30)
Tremor	Divalproex ²⁵	1	38	94	77	187	1.03	(0.61 to 1.77)
Tremor	Lamotrigine ⁴⁷	1	20	120	9	169	0.28	(0.11 to 0.68)
Weight gain	Carbamazepine ²⁹	1	5	16	0	15	0.00	(0.0 to 1.01)
Weight gain	Divalproex ²⁵	1	12	94	39	187	1.80	(0.86 to 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 (carbamazepine, 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 carbamazepine (1 trial) or gabapentin (1 trial), was more likely than placebo to be associated with headache. Carbamazepine (2 trials), and not divalproex (1 trial) or lamotrigine (2 trials), was more likely than placebo to be associated with nausea. Lamotrigine (2 trials), and not carbamazepine (1 trial), was associated with a significantly higher odds of rash relative to placebo. Carbamazepine (2 trials), and not gabapentin (1 trial) or lamotrigine (3 trials), was more likely than placebo to be associated with somnolence. Divalproex (1 trial), and not lamotrigine (1 trial), was associated with significantly higher odds of tremor as compared with placebo. Only divalproex was reported to cause weight gain as an adverse event.

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

Adverse Events	Drug	No. of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			No. of patients with event	Sample size	No. of patients with event	Sample size		
Diarrhea	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Diarrhea	Divalproex ²⁵	1	28	94	65	187	1.25	(0.71 to 2.24)
Diarrhea	Gabapentin ¹³¹	1	7	59	9	58	1.36	(0.41 to 4.66)
Diarrhea	Lamotrigine ^{32, 47, 118}	3	26	255	21	357	0.53	(0.28 to 1.02)
Headache	Carbamazepine ¹¹⁶	1	25	103	23	101	0.92	(0.46 to 1.85)
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Gabapentin ⁴⁶	1	7	59	6	58	0.86	(0.22 to 3.21)
Headache	Lamotrigine ^{32, 42, 47, 118}	4	62	343	220	773	1.59	(1.14 to 2.25)
Nausea	Carbamazepine ^{116, 117}	2	15	220	58	223	5.16	(2.73 to 10.30)
Nausea	Divalproex ²⁵	1	29	94	79	187	1.64	(0.94 to 2.89)
Nausea	Gabapentin	0	NR	NR	NR	NR	NC	NC
Nausea	Lamotrigine ^{32, 118}	2	21	190	32	228	1.23	(0.66 to 2.35)
Rash	Carbamazepine ¹¹⁷	1	3	117	6	122	1.96	(0.41 to 12.40)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Gabapentin	0	NR	NR	NR	NR	NC	NC
Rash	Lamotrigine ^{42, 118}	2	9	153	63	545	2.23	(1.06 to 5.28)
Somnolence	Carbamazepine ^{116, 117}	2	19	220	43	223	2.77	(1.48 to 5.36)
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Gabapentin ⁴⁶	1	7	59	14	58	2.35	(0.80 to 7.51)
Somnolence	Lamotrigine ^{32, 118, 132}	3	21	255	27	357	0.93	(0.49 to 1.79)
Tremor	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Tremor	Divalproex ²⁵	1	12	94	77	187	4.76	(2.38 to 10.26)
Tremor	Gabapentin	0	NR	NR	NR	NR	NC	NC
Tremor	Lamotrigine ⁴⁷	1	6	121	9	169	1.08	(0.33 to 3.79)
Weight gain	Carbamazepine	0	NR	NR	NR	NR	NC	NC
Weight gain	Divalproex ²⁵	1	7	94	39	187	3.26	(1.36 to 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.

One of the limitations of the evaluation of specific adverse events and the pooled analyses of adverse events was the inconsistency among trials in the cut-off used to define common adverse events (e.g., occurring in at least 5%, 8%, or 10% of patients). This variation in reporting of common adverse events may influence indirect comparisons between AEDs.

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.⁹⁸ 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;¹³³ 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, dizziness, nausea, somnolence, and vomiting; 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 do not support that the rates of withdrawals due to adverse events are different for carbamazepine (1 trial), divalproex (2 trials) and lamotrigine (3 trials).

Indirect comparisons of the AEDs relative to placebo do not support that carbamazepine, divalproex, gabapentin, and lamotrigine are different in the frequency of 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). These 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 dizziness, somnolence, rash, thrombocytopenia, and weight gain. The indirect comparisons suggest that dizziness is more common on carbamazepine than gabapentin, lamotrigine, or valproate. Somnolence is more common on divalproex than lamotrigine in indirect comparisons based on lithium-controlled trials, and more common on carbamazepine than gabapentin, lamotrigine, and divalproex / valproate in indirect comparisons based on placebo-controlled trials. Rash was more likely to occur with carbamazepine and lamotrigine than divalproex and gabapentin in indirect comparisons based on results of placebo-controlled trials. Thrombocytopenia was reported with divalproex, whereas it was not reported with the other AEDs. In patients diagnosed with bipolar disorder and who did not have a primary co-diagnosis of alcohol dependence, indirect comparisons of AEDs relative to placebo suggest that divalproex may be more likely to be associated with weight gain than carbamazepine and gabapentin. 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,^{119, 121} 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.¹²¹ 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, as well as a fair-quality systematic review¹²⁰ of placebo-controlled trials involving gabapentin^{91, 92} or pregabalin,⁸³ are 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.⁴⁹

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.⁵⁴ 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%). 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 26 of the 27 fair-quality placebo-controlled trials (24 of 26 publications, including 10 of the 11 publications added to this report update). Of the 26 trials, 11 evaluated gabapentin therapy of 1.5 to 21 weeks duration,^{52, 76, 77, 79, 81, 87, 89, 91, 92, 94, 126} 4 evaluated lamotrigine given for 8 to 14 weeks,^{64, 66, 78, 93} 1 evaluated carbamazepine given for 3 days,¹²³ 1 evaluated a single dose of intravenously administered phenytoin,¹²⁵ 4 trials evaluated pregabalin given for 5 to 8 weeks,⁸²⁻⁸⁵ 4 trials (2 publications) evaluated 12- to 22-week courses of topiramate,^{88, 90} 1 evaluated an 8-week course of divalproex,⁵³ and 1 evaluated a 3-month course of valproate.⁶⁷ For one of the trials that evaluated lamotrigine, the only safety data reported were withdrawals due to adverse events.⁶⁴ These trials are summarized in Evidence Table 6 and Quality Table 6.

We also found a manufacturer-sponsored pooled analysis of adverse events from 3 placebo-controlled trials of gabapentin in patients with postherpetic neuralgia.¹³⁴ We excluded this publication because it did not meet criteria for fair- or good-quality systematic reviews and did not report results from the individual trials.

The dosing regimens of the AEDs varied among the fair-quality placebo-controlled trials. Of the 10 gabapentin trials, 7 titrated doses according to clinical response and tolerability,^{52, 52, 76, 79, 87, 89, 126} 1 compared two fixed doses following forced titration,^{87, 9277, 91} and 1 used a forced titration schedule,⁷⁷ 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 10 trials was 300 to 3600 mg/day. Pregabalin target doses were

75, 150, 300, or 600 mg/day among 4 trials.⁸²⁻⁸⁵ When randomized to lower doses, patients were started at the full target dose (75 mg/day,⁸⁴ 150 mg/day,¹³⁵ or 300 mg/day^{82, 84, 135}) and when randomized to the highest dose, patients were titrated to their target dose (starting from either 150 or 300 mg/day and increasing to 600 mg/day^{83, 84}). Topiramate was titrated from 25 mg/day to target doses of 100, 200, or 400 mg/day among 4 trials (2 publications).^{88, 90} 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;^{64, 66, 78} or 400 or 600 mg depending on the absence or presence, respectively, of enzyme-inducing drugs.⁹³ 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 in one trial,⁶⁷ increased to 1500 mg/day over 5 days in another trial,⁵¹ and 1000 mg/d as divalproex in a trial that did not report the dosage regimen or titration schedule.⁵³

Overall adverse events

The overall rate of adverse events was reported in 10 trials, including 6 with gabapentin,^{52, 77, 79, 81, 89, 92} 1 with pregabalin,⁸³ 1 with lamotrigine,⁶⁶ 1 with divalproex,⁵³ and 1 with parenteral phenytoin.¹²⁵ The trial involving divalproex did not report the overall adverse event rate for placebo and could not be used in indirect comparisons.⁵³ For gabapentin, the overall rates of adverse events were 63.2% at doses of 300 to 900 mg/day,⁷⁹ 43.7% to 95% at 600 to 1800 mg/day,^{52, 89} 70.4% at 1800 mg/day,⁹² 75.0% at 2400 mg/day,⁹² 76.5% at 900 to 2400 mg/day,⁸¹ and 65% at 900 to 3600 mg/day.⁷⁷ The corresponding rates for placebo were 19.0%, 24.3% to 58%, 49.5%, 49.5%, 67.8%, and 25%, respectively. Therefore, the proportions of patients reporting adverse events were higher on gabapentin. Only two trials performed statistical analyses; both showed a significantly higher rate of adverse events with gabapentin (63.2% and 65%) than placebo (19.0% and 25%; $p < 0.001$ and $p < 0.05$, respectively).^{77, 79}

Pregabalin 300 mg/d (creatinine clearance > 30 and $< / = 60$ ml/min) or 600 mg/d (creatinine clearance > 60 ml/min) was associated with an overall adverse event rate of 87% as compared with 63% for placebo (no p-value reported).⁸³

The overall rate of adverse events with lamotrigine was 57% and 60% with placebo (no statistically significant difference).⁶⁶

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 3 trials, the first involving patients with diabetic neuropathy, the second in patients with HIV-related neuropathy, and the third in patients with complex regional pain syndrome type I. These showed that, compared with placebo, gabapentin was associated with a significantly higher rate of somnolence (3 trials)^{52, 76, 87} dizziness (2 trials),^{52, 87} and lethargy (1 trial).⁵² Two trials did not detect a statistically significant difference between the two treatments.^{77, 126} The remaining trials either did not report adverse event rates by treatment^{78, 79, 123} or did not perform statistical analyses of the adverse event data for gabapentin,^{81, 89, 91, 92}

lamotrigine,⁶⁶ pregabalin,⁸²⁻⁸⁵ phenytoin,¹²⁵ topiramate,⁹⁰ or valproate.⁶⁷ All 7 of the trials involving gabapentin reported that somnolence, dizziness, or lethargy were reported at numerically or statistically higher rates on the active drug relative to placebo. Pain was the only adverse event reported at a higher frequency on placebo than gabapentin (no statistics).⁹¹

One trial reported that no abnormalities were detected on liver function tests, urinalyses, or complete blood counts.¹²³ Increased lipase (n = 2) and blood glucose (n = 2) were reported among 15 gabapentin-treated patients.⁷⁶ In 1 of 2 painful diabetic neuropathy trials, hyperglycemia was reported as an adverse event in 3.9% of pregabalin-treated patients and none of the placebo-treated patients.⁸² However, HgA1c concentrations were unchanged from baseline in both the pregabalin and placebo groups. Hypoglycemia / hypoglycemic reaction was reported in 3% of topiramate versus 2% of placebo patients, and clinically important decreases ($\geq 0.5\%$) in HgA1c were seen in 55% to 62% of topiramate patients as compared with 29% of placebo patients (p-value not reported) in the pooled analysis of three trials.⁸⁸ The high frequency and extent of effect on HgA1c seem to be unique to topiramate. The remaining trials did not report laboratory adverse events.

Limited indirect comparisons, based on effects of the orally administered AEDs relative to placebo, suggest that gabapentin and pregabalin may be associated with higher overall adverse event rates than lamotrigine; however, statistical analyses for differences between AED and placebo were performed only for gabapentin. Indirect comparisons of the AEDs in terms of the types of common adverse events were hindered by a lack of statistical analyses between most of the AEDs and placebo. In terms of laboratory adverse events reported by patients treated for painful diabetic neuropathy, pregabalin may result in hyperglycemia, although this was an inconsistent finding between 2 trials, occurred in a small percentage of patients (3.9%), and was not associated with changes in HgA1c. In comparison, topiramate has been associated with hypoglycemia and clinically important decreases in HgA1c. It is difficult to make definite conclusions based on these indirect comparisons because adverse event data were available from only one trial for all of the drugs except for gabapentin.

Withdrawals due to adverse events

Five of the 27 placebo-controlled trials reported no withdrawals due to adverse events during double-blind treatment. The AED in these trials were carbamazepine (1 trial),¹²³ gabapentin (3 trials),^{77, 79, 126} or phenytoin (1 trial).¹²⁵ Each of these trials used a crossover design and randomized a relatively small number of patients (range, N = 9 to 40), and 2 trials used relatively low doses of gabapentin (300 to 900 mg/day⁷⁹ and 300 to 2400 mg/day¹²⁶).

Among 7 trials, the rate of withdrawals due to adverse events ranged from 5.2% to 18.6% with gabapentin therapy and 0% to 16.4% with placebo.^{52, 76, 81, 87, 89, 91, 92, 94} 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.⁹²

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%)^{64, 93} and two other trials showing higher rates on lamotrigine (range: 10% to 30%) versus placebo (0% in both trials) (no statistical analyses).^{66, 78} The adverse events that led to withdrawal of lamotrigine in more than one trial were rash (10 cases among 4 trials)^{64, 66, 78, 93} and nausea (4 cases among 2 trials).^{64, 93}

For pregabalin, withdrawals due to adverse events were generally dose related, occurring in 2.6% to 31.5% of patients treated with daily doses of 75 to 600 mg, as compared with 2.9% to 9.9% of placebo-treated patients (4 trials).⁸²⁻⁸⁵ Rates of withdrawals due to adverse events on pregabalin at lower doses (75 and 150 mg/day) were generally similar to those of placebo, whereas numerically higher withdrawal rates were associated with higher doses of pregabalin (300 and 600 mg/day) than those seen with placebo. Two trials reported the adverse events leading to withdrawal; they were somnolence (2 trials)^{82, 83} and dizziness (1 trial).⁸²

Withdrawals due to adverse events occurred in 24% of patients with topiramate versus 8% with placebo.^{88, 90} The most common treatment-limiting adverse events ($\geq 3\%$ of patients) were nausea, fatigue, dizziness, concentration / attention difficulty, somnolence, and appetite decrease. Another notable treatment-limiting adverse event was development of kidney stones (0.3% vs. 0.2% with topiramate and placebo, respectively).

Valproate was similar to placebo in rates of withdrawals due to adverse events in 2 trials (4.5% and 10.5% vs. 0.0% and 5.6%).^{51, 67} Increased liver function tests (bilirubin and liver transaminases), skin rash, flu-like symptoms, headache, and nausea were the reasons for discontinuation of valproate. In another trial, divalproex was associated with a numerically lower rate of withdrawals due to adverse events than placebo (4.2% versus 16.7%, respectively; no statistical analysis).

Indirect comparisons of gabapentin (7 trials), lamotrigine (4 trials), pregabalin (4 trials), topiramate (4 trials in 2 publications), and valproate/divalproex (3 trials) based on the rates of withdrawals due to adverse events in comparisons with placebo, suggest that gabapentin and valproate/divalproex may be better tolerated than lamotrigine, pregabalin (at higher doses), and topiramate. However, the lamotrigine results were inconsistent and the relative comparison of divalproex and placebo is inconclusive because no statistical analysis was done. The data also suggest that dizziness and somnolence were among the more commonly reported adverse events leading to withdrawal of gabapentin and pregabalin. Central nervous system (e.g., dizziness and somnolence) and gastrointestinal symptoms (e.g., nausea, appetite decrease) were among the more common adverse events leading to withdrawal of topiramate. In comparison, the adverse event more likely to limit tolerability of lamotrigine was rash.^{64, 66, 78, 93} It is important to note that rates of withdrawals due to adverse events can be influenced by study design, population age and co-morbidities, and concurrent medications. Rates tend to be higher in trials that use fixed or higher doses, particularly when the drug shows a dose-response effect for efficacy and tolerability.

Serious adverse events

Serious adverse events were reported in 8 of the 27 placebo-controlled trials (6 of 24 publications) in neuropathic pain. The rate of serious adverse events with gabapentin was low, ranging from 0% to 2.6% among 4 trials.^{76, 89, 92} The corresponding rates with placebo were 0% and 1.3% in 2 trials^{78, 81} and not reported in the other 2 trials.^{89, 92} In one trial, pregabalin was associated with serious adverse events in 3.2% of patients, a rate similar to that seen with

placebo (3.7%).⁸⁵ The frequency of serious adverse events was also similar between topiramate and placebo (7% vs. 8%) in the pooled analysis of three RCTs.⁸⁸ Indirect comparisons of the AEDs do not support that gabapentin, pregabalin, and topiramate are different in terms of their risks of serious adverse events, based on similar rates relative to those observed on placebo.

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: 8.8% to 60%) than placebo (0.0% to 45.5%) in 8 trials;^{52, 76, 81, 87, 89, 91, 92, 126} however, a statistically significant difference was reported in two of these trials^{52, 87} and no significant difference was found in another trial.⁷⁶ Statistical analyses were 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.⁷⁹ Pregabalin was associated with dizziness in 7.8% to 39.0% of patients, with rates showing a dose-related effect, while 5.2% to 15% of placebo patients experienced dizziness among 4 trials.⁸²⁻⁸⁵ A trial comparing carbamazepine with placebo also reported dizziness as a common adverse event, but reported only the rate for placebo (22.2%).¹²³ 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.¹²⁵ Dizziness was not reported as a common adverse event with topiramate (4 trials, 2 publications).^{88, 90} Indirect comparisons of the AEDs suggest that dizziness is more common with gabapentin and pregabalin than topiramate. 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 agents) hinder further AED comparisons.

Somnolence, lethargy, or sedation was another common adverse event reported more frequently on gabapentin (range: 10.5% to 80%) than placebo (0.0% to 18.2%) among 9 trials.^{52, 76, 77, 87, 89, 91, 92, 126} A statistically significant treatment difference ($p \leq 0.006$)^{52, 76} and no significant difference were shown in different trials.⁷⁷ 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.⁷⁹ Pregabalin was associated with somnolence in 3.9% to 26.8% of patients in a dose-dependent manner, as compared with 2.9% to 8.0% of placebo patients.⁸²⁻⁸⁵ Somnolence occurred in 10% of topiramate patients versus 4% of placebo patients,^{88, 90} and fatigue occurred in 16% and 11% of patients, respectively.⁸⁸ Sedation occurred at similar rates with valproate (4.5%) and placebo (0.0%) in one trial.⁶⁷ Somnolence was not reported as a common adverse event with carbamazepine, lamotrigine, and phenytoin. Indirect comparisons suggest that somnolence or similar adverse events (i.e., drowsiness, sedation, and fatigue) are more common during gabapentin, pregabalin (particularly at higher doses), and topiramate therapy than with carbamazepine, lamotrigine, phenytoin, and valproate.

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.⁷⁸ In the second trial, the frequency of rash was the same on lamotrigine and placebo (2/30, 6.7% for each treatment period).⁶⁶ 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.⁹³ There was a single case of maculopapular rash reported as a gabapentin-related adverse event (none on placebo) in 1 trial.⁸⁹ 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.¹²⁵ Rash was not reported as a common adverse event with pregabalin (4 trials),⁸²⁻⁸⁵ or with topiramate (4 trials, 2 publications).^{88, 90} Indirect comparisons of the AEDs are complicated by inconsistent rates of rash with lamotrigine relative to placebo, and low numbers of cases of rash with gabapentin and phenytoin.

A small trial reported 1 case of hepatotoxicity among 22 valproate-treated patients (4.5%); this adverse event led to discontinuation of therapy.⁶⁷

One trial reported no cases of weight gain on valproate.⁶⁷ Topiramate therapy, relative to placebo, was associated with a numerically higher frequency of weight loss as an adverse event (7% vs. 1%; pooled analysis of 3 trials)⁸⁸ and loss of appetite / appetite decrease (10% vs. 1% to 3%; 4 trials, 2 publications).^{88, 90} Clinically significant weight loss (> / = 5% of baseline body weight) occurred in 19% to 38% of topiramate patients as compared with 7% of placebo patients (pooled analysis of 3 trials).⁸⁸

One trial reported no cases of thrombocytopenia on valproate.⁶⁷

Meta-analysis of specific adverse events: neuropathic pain

The patient-level analysis of adverse events reported in neuropathic pain trials included 23 trials and evaluated 9 adverse events (diarrhea, dizziness, edema, headache, nausea, rash, somnolence, tremor, and weight gain). Table 18 summarizes the findings of the patient-level analysis.

Table 18 presents the results of our pooled analyses of the placebo-controlled trials. Gabapentin (7 trials) and pregabalin (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 three agents. Gabapentin and pregabalin were more likely than placebo to be associated with edema (2 and 4 trials for each drug, respectively) and somnolence (8 and 4 trials for each drug, respectively). The 95% confidence intervals overlapped, therefore we cannot conclude that the odds of each adverse event are different for the two agents.

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

Adverse Events	Drug	No. of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			No. of patients with event	Sample size	No. of patients with event	Sample size		
Diarrhea	Divalproex	0	NR	NR	NR	NR	NC	NC
Diarrhea	Gabapentin ^{75, 77, 81, 87, 89, 92}	6	15	422	33	577	1.87	(0.96 to 3.80)
Diarrhea	Lamotrigine ⁹³	1	7	77	16	150	1.19	(0.44 to 3.60)
Diarrhea	Pregabalin ^{82-84, 135}	4	13	251	17	405	0.86	(0.43 to 1.75)
Dizziness	Divalproex	0	NR	NR	NR	NR	NC	NC
Dizziness	Gabapentin ^{75, 76, 76, 81, 87, 89, 92}	7	35	474	171	636	4.80	(3.20 to 7.36)
Dizziness	Lamotrigine ⁷¹	1	4	22	3	24	0.65	(0.08 to 4.40)
Dizziness	Pregabalin ^{82-84, 135}	4	23	251	112	405	3.09	2.04 to 4.79)
Edema	Divalproex	0	NR	NR	NR	NR	NC	NC
Edema	Gabapentin ^{77, 92}	2	0	121	15	233	+Inf	(2.28 to +Inf)
Edema	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Edema	Pregabalin ^{82-84, 135}	4	5	251	45	405	8.42	(3.31 to 27.48)
Headache	Divalproex	0	NR	NR	NR	NR	NC	NC
Headache	Gabapentin ^{52, 75-77, 81, 87, 89}	7	31	373	36	423	1.13	(0.66 to 1.94)
Headache	Lamotrigine ^{71, 93}	2	10	99	18	174	1.01	(0.42 to 2.57)
Headache	Pregabalin ^{82-84, 135}	4	24	251	32	405	1.06	(0.63 to 1.82)
Nausea	Divalproex	0	NR	NR	NR	NR	NC	NC
Nausea	Gabapentin ^{75-77, 81, 87, 89, 92}	7	27	373	44	423	1.54	(0.90 to 2.66)
Nausea	Lamotrigine ^{71, 93}	2	12	99	21	174	1.05	(0.46 to 2.47)
Nausea	Pregabalin ⁸²	1	6	70	6	76	0.91	(0.23 to 3.61)
Rash	Divalproex	0	NR	NR	NR	NR	NC	NC
Rash	Gabapentin ⁸⁹	1	0	41	1	80	+Inf	(0.01 to +Inf)
Rash	Lamotrigine ^{71, 78, 93}	3	9	121	28	194	2.00	(0.87 to 5.05)
Rash	Pregabalin	0	NR	NR	NR	NR	NC	NC
Somnolence	Divalproex	0	NR	NR	NR	NR	NC	NC
Somnolence	Gabapentin ^{52, 75-77, 81, 87, 89, 92}	8	21	371	89	487	4.50	(2.85 to 7.34)
Somnolence	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Somnolence	Pregabalin ^{82-84, 135}	4	12	251	81	405	4.44	(2.60 to 7.97)

Adverse Events	Drug	No. of studies	Placebo		Intervention Groups		Pooled OR	95% CI
			No. of patients with event	Sample size	No. of patients with event	Sample size		
Tremor	Divalproex	0	NR	NR	NR	NR	NC	NC
Tremor	Gabapentin ⁸⁹	1	0	41	1	80	+Inf	(0.01 to +Inf)
Tremor	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Tremor	Pregabalin	0	NR	NR	NR	NR	NC	NC
Weight gain	Divalproex	0	NR	NR	NR	NR	NC	NC
Weight gain	Gabapentin	0	NR	NR	NR	NR	NC	NC
Weight gain	Lamotrigine	0	NR	NR	NR	NR	NC	NC
Weight gain	Pregabalin ⁸²	1	1	70	3	76	2.82	(0.22 to 150.99)

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 26 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 should be considered tentative, as they were limited by differences among the trials in study design, population size, population characteristics, dosage regimens, and the small number of trials reporting the safety outcomes of interest. The limited indirect comparisons suggest that gabapentin (6 trials) and pregabalin (1 trial) may have higher overall adverse event rates than lamotrigine (1 trial). Gabapentin and pregabalin (at lower doses) do not have different tolerability, and gabapentin and valproate/divalproex may be better tolerated than lamotrigine, pregabalin (at higher doses), and topiramate. Rates of withdrawals due to adverse events associated with pregabalin showed a dose-related effect. However, the lamotrigine results were inconsistent and the comparison between divalproex and placebo was inconclusive. The nature of adverse events leading to withdrawal seems to differ among gabapentin, pregabalin, topiramate, and lamotrigine. Dizziness and somnolence seemed to be more consistently reported as reasons for intolerance to gabapentin, pregabalin, and topiramate, and gastrointestinal symptoms were more frequently reported adverse events that resulted in withdrawal with topiramate; whereas rash was a consistent reason for discontinuation of lamotrigine. Gabapentin, pregabalin, and topiramate had similar risks of serious adverse events when each was compared to placebo. These findings should be interpreted with caution due to the small number of reported cases. Overdoses were not reported; therefore, we could not compare the AEDs in terms of toxic potential in poisonings. Indirect comparisons of the AEDs by specific adverse events suggest that gabapentin and pregabalin (at higher doses) are more likely to cause dizziness (8 and 4 trials, respectively) and somnolence (9 and 4 trials, respectively); lamotrigine may be associated with a higher rate of rash (1 of 3 trials); and topiramate may cause loss of appetite (4 trials, 2 publications) and clinically important weight loss (pooled analysis of 3 trials). No indirect comparisons could be made for hepatotoxicity and thrombocytopenia. Our pooled analysis of specific adverse events suggested that gabapentin and pregabalin are 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. Gabapentin and pregabalin also seem to be similar in the likelihoods of being associated with edema and somnolence.

2c. Other diagnoses

Observational studies

A total of 61 observational studies that reported adverse events of AEDs were screened for eligibility and 7 met entry criteria.^{98-101, 119, 136, 137} One of the 7 included studies was discussed in regard to suicide risk under section 2a. *Bipolar disorder, Observational studies.*⁹⁸ Of the

remaining 6 studies, 2 were good-quality case-control studies,^{95,96} 2 were fair-quality, case-control studies comparing either five AEDs⁹⁹ or two AEDs,⁹⁷ and 2 were poor-quality cohort studies,^{100, 100,101} These studies are summarized in Evidence Table 7 and Quality Table7, and the good- and fair-quality studies are discussed here.

Specific adverse events or withdrawals due to specific adverse events: Bone fractures

One of the good-quality case-control studies included 124,655 inpatients or outpatients who had sustained a fracture during the year 2000 as identified in the National Hospital Discharge Register of Denmark and 373,962 randomly selected gender-and age-matched controls from the Civil Registration System records of vital status. Adjusted odds ratios (ORs, 95% CI) for any fracture in patients who used AEDs were significantly increased (lower limit of 95% CI for OR > 1.0) for carbamazepine (1.18; 1.10 to 1.26), oxcarbazepine (1.14; 1.03 to 1.26), and valproate (1.15; 1.05 to 1.26). The ORs were nonsignificant (95% CIs included 1.0) for lamotrigine (1.04; 0.91 to 1.19), phenytoin (1.20; 1.00 to 1.43); tiagabine (0.75; 0.40 to 1.41); and topiramate (1.39; 0.99 to 1.96). Fracture risk analyzed by various skeletal sites was significant for carbamazepine at the hip (1.33; 1.13 to 1.58); lamotrigine at the spine (2.47; 1.13 to 5.39); and oxcarbazepine at the hip (1.48; 1.11 to 1.97). Risk was not significant by skeletal site for phenytoin, tiagabine, topiramate, and valproate. There was a significant dose-response relationship for carbamazepine, oxcarbazepine, and valproate, and no significant dose-response for lamotrigine, phenytoin, tiagabine, and topiramate. The results suggest that the risk for any or site-specific fracture may be greater for carbamazepine, lamotrigine, oxcarbazepine, and valproate than for phenytoin, tiagabine, and topiramate; however, one cannot definitely conclude there are AED differences because the confidence intervals overlapped. No data was available for gabapentin and levetiracetam.

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

Two fair-quality case-control studies provided comparative assessments of risk for Stevens-Johnson syndrome and toxic epidermal necrolysis.^{99, 136}

The first fair-quality, case-control study, which provided comparative data for five AEDs, was conducted in hospitals in France, Germany, Italy, and Portugal.⁹⁹ 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 (\leq 8-week) use of phenobarbital, phenytoin, and carbamazepine. The numbers for lamotrigine were too small for meaningful analysis.

The second fair-quality case-control study identified 35 case subjects with Stevens-Johnson syndrome or toxic epidermal necrolysis based on hospital discharge ICD-9-CM codes, and 105 randomly selected matched controls. The crude relative risk (95% CI) was 33.0 (4.3 to 255.6) for carbamazepine and 9.6 (2.0 to 46.6) for phenytoin. Multivariate risks were 301.8 (13.6 to 6700.2) and 290.8 (9.2 to 9239.3), respectively. The results suggest that carbamazepine and phenytoin are similar in their risks of Stevens-Johnson syndrome or toxic epidermal necrolysis; however confidence intervals were wide because of the small number of cases. Ascertainment of cases may have been incomplete because of misdiagnoses or missing records.

Specific adverse events or withdrawals due to specific adverse events: Aplastic anemia and agranulocytosis

A good-quality population-based case-control study of AED-related agranulocytosis and aplastic anemia was conducted in Barcelona, Spain as part of a 22-year systematic, multicenter (17 hospital hematology units), collaborative surveillance study (International Agranulocytosis and Aplastic Anemia Study, IAAAS).⁹⁶ A total of 177 case subjects who were admitted to hospital from the community and 586 matched controls were included. In the conditional primary analysis, 5 cases and 1 control were exposed to carbamazepine, and 2 cases and 1 control were exposed to phenytoin. The odds of drug exposure within the week before the index day of agranulocytosis were significant for carbamazepine (OR 10.96; 95% CI: 1.17 to 102.64). The OR was not calculated for phenytoin because of the small number of exposures. In the unconditional analysis, 10 cases and 2 controls were exposed to carbamazepine, and 5 cases and 6 controls were exposed to phenytoin. The ORs were 115.24 (23.13 to 574.28) for carbamazepine and 11.62 (3.11 to 43.48) for phenytoin. The population-attributable risk and incidence of agranulocytosis for exposure to carbamazepine within the week before the index day were 2.57% (95% CI: 0.03 to 5.04) and 0.09 (95% CI: < 0.01 to 0.17) per 1 million per year, respectively. These results suggest that the risk of agranulocytosis is greater with carbamazepine than phenytoin; however, confidence intervals were wide.

Summary

Specific adverse event data were available from 4 fair-quality case-control study in patients treated with AEDs for unreported diagnoses. Based on the findings of 1 good-quality case-control study, the odds of bone fractures may be greater for carbamazepine, lamotrigine, oxcarbazepine, and valproate relative to phenytoin, tiagabine, and topiramate; however, we cannot definitely conclude there are AED differences. Two fair-quality case-control studies showed that the rate of Stevens-Johnson syndrome / toxic epidermal necrolysis may be increased for phenytoin and carbamazepine, but we cannot conclude with certainty that there are differences in risk between AEDs. Carbamazepine may be associated with a higher odds of agranulocytosis than phenytoin; however, again we cannot state with certainty that there is a difference between agents. Taken together, the results of these studies consistently implicate carbamazepine as a risk factor for the development of several major adverse events; namely, bone fractures, Stevens-Johnson syndrome / toxic epidermal necrolysis, and agranulocytosis.

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 subgroup analyses that would allow comparisons of AEDs in the 4 good-quality systematic reviews concerning bipolar disorder.¹⁰²⁻¹⁰⁵

Head-to-head trials

There were no head-to-head trials with subgroup analyses in an outpatient population. We therefore evaluated the 3 head-to-head trials (4 publications) conducted in inpatient populations.^{22, 23, 36, 106} One of these trials presented post hoc analyses of subgroup response predictors.²² 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.²² 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.^{40,110} 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.³⁴ All of these trials are summarized in Evidence Table 2 and Quality Table 2.¹¹⁰

Patient characteristics

One trial showed no demographic factors to be predictors of a differential response between divalproex and lithium.⁴⁰

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.⁴⁰

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; $p < 0.001$).¹¹⁰ There was no treatment difference in the subgroup with psychotic features.

Placebo-controlled trials

Subgroup analyses were performed in 3 of the 10 fair-quality placebo-controlled trials. The trials^{42, 116, 117} are summarized in Evidence Table 3 and Quality Table 3.

Patient characteristics

One trial showed that carbamazepine was superior to placebo in the change in YMRS total score from baseline to end point in manic patients (-6.44 ; $p = 0.0092$) but not in mixed patients because of a larger placebo effect (-10.31 ; $p > 0.05$).¹¹⁶ Another trial evaluating carbamazepine showed no differential effect by bipolar subtype for YMRS total scores; however, depressive symptoms, as measured by HAM-D scores, did show a treatment differential in the manic subgroup but not in the mixed episode subgroup.¹¹⁷ These findings suggest that patients with manic episodes may experience greater benefit from carbamazepine, as compared with patients experiencing mixed episodes; however, the findings were inconsistent in the type of symptoms that improved.

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.⁴² 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 three placebo-controlled trials provided evidence from subanalyses on the factors that predict a differential treatment response in patients with bipolar disorder. Because the subgroup types, outcomes, and comparators differed, 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 26 fair-quality placebo-controlled trials (3 of 23 publications) 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).⁸¹

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.⁷⁸ 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.⁹³ 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

A number of trials were published since preparation of the original report (dated November 2004), including a poor-quality head-to-head trial that compared topiramate and divalproex in the acute treatment of mania. Among the fair-quality trials included in this report update were 2 relatively large trials that evaluated the efficacy of carbamazepine in bipolar disorder, 4 trials that evaluated pregabalin⁸²⁻⁸⁵ and 4 trials (2 publications) that assessed topiramate^{88,90} in neuropathic pain, as well as 6 other fair-quality placebo-controlled trials^{51-53, 76, 77, 89} that evaluated other AEDs in the treatment of neuropathic pain. To the best of our knowledge, the first trial investigating an AED (gabapentin) for neuropathic cancer pain was published since the original report. At the time that we performed the literature search, we did not find published randomized trials evaluating AEDs in the treatment of fibromyalgia.

Despite the addition of the new trials, there continues to be a lack of good-quality head-to-head trials and a lack of good-quality trials overall. Our comparisons of AEDs were therefore mostly based on indirect comparisons of AEDs relative to common comparators (e.g., lithium and placebo). The indirect comparisons were limited because of differences in outcome measures, study populations, and other study methods. The interpretation of trial results was often problematic because this report used the difference between treatments in the change in pain

scores to determine treatment effects, whereas many trials analyzed end point pain scores or other measurements (such as relative percentage change) to detect treatment differences. 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, phenytoin, pregabalin, and topiramate for either bipolar disorder or neuropathic pain. No randomized trials were found for levetiracetam, oxcarbazepine, tiagabine, and zonisamide. The only information we found for oxcarbazepine and tiagabine was from a good-quality observational study evaluating risk of bone fractures with various AEDs.¹³⁷

The usefulness of topiramate in painful diabetic neuropathy deserves further study to confirm its effectiveness and explore its potentially beneficial safety profile (e.g., weight loss and improvement in HgA1c). In the three trials which did not show an analgesic benefit with topiramate,⁸⁸ inclusion of patients with mild to moderate pain among patients with more severe degrees of pain may have reduced the possibility of demonstrating a meaningful clinical response. On the other hand, this same methodologic limitation (i.e., treating patients with mild to moderate neuropathic pain in a case mix of patients with mostly moderate to severe pain) may reflect a common occurrence in actual clinical practice. Future trials are needed to evaluate whether topiramate and other AEDs are as effective in actual clinical practice as they are efficacious under controlled trial conditions.

The efficacy of AEDs in mixed neuropathic pain types also remains to be demonstrated. The inability to show that AEDs produce either statistically significant or clinically relevant analgesic effects in study populations with various types of neuropathic pain syndromes underlines the need to determine the specific indications for which AEDs are effective. At this time, the evidence is most convincing for gabapentin and pregabalin, which produce a modest analgesic benefit in patients with painful diabetic neuropathy or postherpetic neuralgia.

One of the limitations of this review was the inclusion of only published trials. Some data from a large 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.⁹⁴ The failure to show a benefit with gabapentin in a large trial makes the results with gabapentin less consistent in the treatment of painful diabetic neuropathy. Another unpublished study was a pooled analysis of 4 double-blind placebo-controlled RCTs which reported that topiramate (200 to 600 mg daily) was ineffective for bipolar I disorder with recent mania (Janssen dossier, 2005). Other unpublished trials have failed to show significant efficacy of lamotrigine in acute treatment of bipolar mania or mixed episodes (2 trials) and depression (2 trials), and in time to intervention for a mood episode during maintenance treatment of rapid cycling, although lamotrigine was efficacious in reducing relapse rates and prolonging time to depressive episodes (1 trial) (online communication, L. McKay, GlaxoSmithKline, 19 January 2006). In only 1 of 2 replicate trials, a dose of 400 mg daily of lamotrigine showed significant benefit in relieving pain due to diabetic neuropathy, and in another trial, lamotrigine was ineffective in reducing pain in adults with mixed neuropathic pain that was inadequately relieved by other antineuropathic analgesics (online communication, L. McKay, GlaxoSmithKline, 19 January 2006).

Another limitation was the criterion to evaluate outpatient trials; this stipulation limited the scope of our review for bipolar disorder to mainly maintenance therapy trials, since most of the inpatient trials dealt with acute therapy. Any comparisons of acute AED therapy for bipolar disorder should be interpreted with caution since the trials included in this report represent only a

portion of available trials evaluating acute therapy. We made an exception to the criterion and evaluated three trials in inpatients after finding no head-to-head trials in outpatients and consulting with an expert in psychiatry. Even with the inclusion of these three 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 4 good-quality systematic reviews, 1 fair-quality head-to-head trial (reported in 2 papers) in inpatients, and 7 active control trials and 10 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 2 good-quality systematic reviews showed that carbamazepine and valproate are similar in effectiveness, based on lack of differences relative to lithium. There was also evidence from 2 poor-quality head-to-head trials that valproate is superior to carbamazepine, and topiramate is similar to divalproex / valproate (in combination with risperidone), in improving manic symptoms; however, these findings should be considered inconclusive. Carbamazepine was the only AED that decreased mania scores to a statistically significant degree in either acute or maintenance therapy (2 fair-quality trials). One fair-quality placebo-controlled trial showed that gabapentin is not effective as add-on therapy. Neither divalproex (1 trial) nor lamotrigine (1 trial) was effective in improving mania symptoms in patients with bipolar I disorder with recent depressive episode.

Acute depressive episodes: In bipolar I disorder with recent depressive episode, both divalproex and lamotrigine 200 mg were efficacious in improving depressive symptoms, whereas lamotrigine 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, mixed episodes, or depression: Indirect comparisons from 3 fair-quality lithium- and 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 5 fair-quality active-control trials do not support that carbamazepine, divalproex, and lamotrigine are different in achieving remission, based on lack of treatment differences with lithium. Based on indirect comparisons from 4 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 did not support that carbamazepine, divalproex, and lamotrigine are different 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 have similar efficacy in preventing recurrence. Four trials (3 lithium- and placebo-controlled trials and 1 placebo-controlled trial) showed inconsistent relative treatment effects between divalproex and lamotrigine in terms of functional capacity. Divalproex had similar efficacy 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 had a greater effect 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. In 4 fair-quality placebo-controlled trials, divalproex and lamotrigine had similar 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 27 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.¹²¹ There was no evidence that one agent was better than the other.

In painful diabetic neuropathy, there is fair-quality evidence from placebo-controlled trials that gabapentin, pregabalin (≥ 300 mg daily), topiramate, and valproate have comparable analgesic effects. However, the evidence for the effectiveness of topiramate in painful diabetic neuropathy is conflicting and the effectiveness of valproate has not been confirmed. In postherpetic neuralgia, gabapentin, pregabalin (≥ 150 mg daily), and divalproex appear to have similar analgesic effectiveness relative to placebo. The evidence of the effectiveness of gabapentin for mixed neuropathic pain syndromes is less robust, with population mean reductions in pain falling short of thresholds for clinically relevant changes and responder rates no better than those of placebo. In acute treatment of mixed neuropathic pain types, intravenously administered phenytoin was shown to produce some benefit but neither lamotrigine nor valproate were shown to be effective. Only carbamazepine had fair-quality evidence to support its use in trigeminal neuralgia. In HIV-related painful sensory neuropathy, gabapentin was shown to produce significant relative percentage changes in pain scores but the difference between gabapentin and

placebo in absolute reduction in pain scores was small. Lamotrigine did not show an analgesic effect in the total cohorts of patients with HIV-related distal sensory polyneuropathy. Subgroup analyses, however, showed inconsistent results in HIV-related polyneuropathy. Additional controlled trials are needed to determine the effectiveness of gabapentin and lamotrigine in HIV-related neuropathy.

It was difficult to make indirect comparisons of the AEDs for most of the outcomes of interest because of methodological differences. Gabapentin and pregabalin have similar improvements in 11-point NRS pain scores relative to placebo for patients with painful diabetic neuropathy and postherpetic neuralgia. When the overall treatment responses observed in fair-quality placebo-controlled trials in neuropathic pain are considered, gabapentin (10 trials) and pregabalin (4 trials) have been shown to have beneficial analgesic effects, whereas the effects of lamotrigine (3 trials), topiramate (4 trials), and valproate/divalproex (2 trials) are inconsistent and the effectiveness of carbamazepine (1 trial) has not been confirmed.

One trial showed that pregabalin produced a significant analgesic effect 2 days after the start of therapy. While this suggests that pregabalin may have an earlier onset than the other AEDs, analyses of daily pain scores within the first week of treatment were not available with the other agents. Indirect comparisons of AEDs, based on results of fair-quality placebo-controlled trials reporting pain measurements on a weekly or monthly basis, do not support that gabapentin (6 trials) and pregabalin (3 trials) are different in onsets of effect, and they both may have earlier onsets than lamotrigine (1 trial) and topiramate (1 trial). Gabapentin (1 trial), lamotrigine (3 trials), and valproate (1 trial) have had similar effects in reducing concomitant analgesic use. Gabapentin (4 of 6 trials) and pregabalin (4 trials) are similar, and each is better than lamotrigine (2 trials) 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 consistent evidence of at least fair quality to support the use of pregabalin for neuropathic pain (≥ 150 mg daily for postherpetic neuralgia and ≥ 300 mg daily for painful diabetic neuropathy). We also noted that, in a population of patients with painful diabetic neuropathy or postherpetic neuralgia, the magnitudes of improvement in pain with gabapentin and pregabalin seem to be slightly more than the threshold for clinically relevant changes defined by Farrar, et al.¹⁷ The population data show that pain relief with gabapentin and pregabalin are 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, 7 active control trials, 10 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. Indirect comparisons based on results of placebo-controlled trials suggest that overall adverse event rates may be higher with carbamazepine (2 trials) than with divalproex (1 trial) and lamotrigine (1 trial). Carbamazepine (2 trials), divalproex (2 trials), and lamotrigine (3 trials) have had similar rates of withdrawals due to adverse events in placebo-controlled trials. However, the nature of adverse events leading to withdrawal was notable for lamotrigine, which was associated with toxic epidermal necrolysis in one patient. Carbamazepine, divalproex, gabapentin, and lamotrigine have had similar rates of serious adverse events; however, the comparisons are based on a small number of events. For specific adverse events, dizziness may occur more frequently with carbamazepine than gabapentin, lamotrigine, or valproate. 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, whereas the data from 8 placebo-controlled trials suggest that carbamazepine may be more likely than gabapentin, lamotrigine, and divalproex / valproate to be associated with sedation, somnolence, or fatigue. Rash was reported with lamotrigine and carbamazepine, and not with gabapentin or valproate. Lamotrigine caused weight loss while gabapentin caused weight gain (1 head-to-head trial). In patients with bipolar disorder without a concurrent primary diagnosis of alcohol dependence, weight gain as an adverse event may be more frequent on divalproex (1 placebo-controlled trial) than carbamazepine and gabapentin, neither of which were reported to be associated with weight gain (1 trial each). 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 carbamazepine, divalproex, and lamotrigine differ. Nervous system and gastrointestinal adverse events were common during carbamazepine therapy (2 trials). Headache, rash, and weight loss or gain tended to occur with lamotrigine. Weight gain and adverse events affecting the nervous system, digestive system, and platelet count were reported 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 26 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. In indirect comparisons of AEDs relative to placebo, gabapentin and pregabalin (at lower doses) have had similar tolerability, and gabapentin and valproate may be better tolerated than lamotrigine, pregabalin (≥ 300 mg daily), and topiramate. However, the lamotrigine results were inconsistent. Gabapentin, pregabalin, and topiramate were each similar to placebo in terms of their risk of serious adverse events, which suggests that these three AEDs are similar in this respect. Gabapentin and pregabalin are more likely than topiramate to be associated with dizziness. Somnolence may be more common with gabapentin, pregabalin, and topiramate than with carbamazepine, lamotrigine, phenytoin, and valproate. There is more

convincing evidence that topiramate therapy results in clinically important weight loss ($\geq 5\%$ from baseline to 4.5 to 5.5 months) than there is evidence of weight changes with other AEDs. Indirect comparisons were otherwise limited and inconclusive. Our pooled analysis of adverse events associated with AEDs relative to placebo showed gabapentin and pregabalin, but not lamotrigine, were associated with a greater likelihood of dizziness relative to placebo; however, differences between agents could not be definitely concluded.

Comparative safety of AEDs in other diagnoses

One good-quality case-control study showed that the risk for any or site-specific fracture may be greater for carbamazepine, lamotrigine, oxcarbazepine, and valproate than for phenytoin, tiagabine, and topiramate; however, these treatment differences cannot be definitely concluded. The results of 2 fair-quality case-control studies 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, and similar for carbamazepine and phenytoin, although confidence intervals were wide. The results of a good-quality case-control study suggest that the risk of agranulocytosis may be greater with carbamazepine than phenytoin; however, this finding is uncertain.

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.

Patients experiencing a manic episode may obtain a better response (decreased manic or depressive symptoms) with carbamazepine relative to placebo; however, results of the subanalyses were inconsistent. 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 gabapentin is ineffective, whereas carbamazepine, lamotrigine, and valproate / divalproex are effective in bipolar disorder. For neuropathic pain, there was indirect evidence from overall results that gabapentin and pregabalin are similar in analgesic effects, whereas lamotrigine, topiramate, and valproate/divalproex showed inconsistent results. There was no conclusive (i.e., head-to-head) evidence of differences between AEDs. Our conclusion that gabapentin and pregabalin are effective for neuropathic pain (specifically, painful diabetic neuropathy and postherpetic neuralgia) is stronger than our conclusion for other AEDs. Limited comparative data on the safety and tolerability of the AEDs suggest that the agents differ in their adverse event profiles. Except for fair-quality evidence that topiramate is associated with clinically significant weight loss ($\geq 5\%$ from baseline) in one fourth to one third of patients, we did not detect clearly discernible differences between any of the AEDs in the rates of adverse events or withdrawals due to adverse events. 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	<p>No head-to-head trials and no good-quality trials in outpatient populations. Four good-quality systematic reviews, 1 fair-quality head-to-head trial in inpatients, and 7 active control trials and 10 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.</p> <p><i>Acute manic episodes:</i> Indirect comparisons from 2 good-quality systematic reviews 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. Neither divalproex (1 trial) nor lamotrigine (1 trial) was effective in improving mania symptoms in patients with bipolar I disorder with recent depressive episode. Carbamazepine was the only AED that significantly decreased mania scores.</p> <p><i>Acute depressive episodes:</i> Divalproex (1 trial) and lamotrigine 200 mg are efficacious in improving depressive symptoms, whereas lamotrigine 50 mg showed no treatment benefit (1 trial). There were no trials of at least fair quality for other AEDs.</p> <p><i>Acute rapid cycling:</i> 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.</p> <p><i>Maintenance therapy, bipolar I disorder with recent mania or depression:</i> Indirect comparisons from 3 fair-quality lithium-controlled trials and 1 placebo-only-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 5 fair-quality active-</p>

		<p>control trials do not support that carbamazepine, divalproex, and lamotrigine are different in achieving remission, based on lack of treatment differences with lithium. Based on indirect comparisons from 4 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 do not support that carbamazepine, divalproex, and lamotrigine are different 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 had similar effects in preventing recurrence. Four trials (3 lithium- and placebo-controlled trials and 1 placebo-controlled trial) 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 4 fair-quality placebo-controlled trials that divalproex and lamotrigine are not different in rates of hospitalization. Results with divalproex, however, were inconclusive because of methodological weaknesses in one trial.</p> <p>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.</p>
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1b. Neuropathic pain	Fair (gabapentin, pregabalin) Poor (other AEDs)	<p>One good-quality systematic review and 27 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 convincing evidence that one agent was better than the other. There is fair evidence that gabapentin and pregabalin are effective in neuropathic pain, specifically painful diabetic neuropathy and postherpetic neuralgia. The effectiveness of topiramate in painful diabetic neuropathy is conflicting and the effectiveness of valproate has not been confirmed. In postherpetic neuralgia, gabapentin, pregabalin, and divalproex have not had different analgesic effectiveness, based on treatment effects relative to placebo. Verification from at least fair-quality trials is needed for the effectiveness of gabapentin in phantom-limb pain, spinal cord injury, and neuropathic cancer pain, and lamotrigine in central post-stroke pain (1 trial each). Only carbamazepine had fair-quality evidence (1 trial) to support its use in trigeminal neuralgia. The effectiveness of gabapentin and lamotrigine in HIV-related neuropathy need to be determined in additional controlled trials. Intravenously administered phenytoin showed some benefit in acute treatment of neuropathic pain. Pregabalin was shown to have an onset of 2 days in postherpetic neuralgia (1 trial). Indirect comparisons based on fair-quality placebo-controlled trials reporting pain measurements on a weekly or monthly basis suggested that gabapentin (6 trials) and pregabalin (3 trials) may have earlier onsets than lamotrigine (1 trial) and topiramate (1 trial). Gabapentin (4 of 6 trials) and pregabalin (4 trials) are likely similar, and each appears to be better than lamotrigine (2 trials), in improving functional capacity in patients with neuropathic pain.</p>
Key Question 2: Safety	Overall Quality of Evidence	Conclusion
2a. Bipolar disorder	Fair	<p>One good-quality systematic review; 1 head-to-head, 7 active control, and 10 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</p>

		<p>events overall. Indirect comparisons based on results of placebo-controlled trials suggest that overall adverse event rates may be higher with carbamazepine than with divalproex and lamotrigine (1 trial per agent). Carbamazepine (1 trial), divalproex (2 trials), and lamotrigine (3 trials) had similar rates of withdrawals due to adverse events relative to placebo. Limited indirect comparisons do not support that carbamazepine, divalproex, gabapentin, and lamotrigine are different in terms of serious adverse events; however, the comparisons are based on a small number of events. For specific adverse events, indirect comparisons of AEDs based on effects relative to placebo, suggest that dizziness may occur more frequently with carbamazepine than gabapentin, lamotrigine, or valproate. 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, whereas the data from 8 placebo-controlled trials suggest that carbamazepine may be more likely than gabapentin, lamotrigine, and divalproex / valproate to be associated with sedation, somnolence, or fatigue. Rash was reported with lamotrigine and carbamazepine, and not with gabapentin or valproate. Lamotrigine caused weight loss while gabapentin (1 head-to-head trial) caused weight gain. In patients with bipolar disorder without a concurrent primary diagnosis of alcohol dependence, weight gain as an adverse event may be more frequent on divalproex (1 placebo-controlled trial) than carbamazepine and gabapentin, neither of which were reported to be associated with weight gain (1 trial each). 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 carbamazepine, divalproex and lamotrigine differ (nervous system and gastrointestinal adverse events occur with carbamazepine; headache, rash, and weight loss or gain with lamotrigine; 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.</p>
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2b. Neuro-pathic pain	Fair / Poor	One good-quality systematic review, and 1 active control and 26 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. There is no evidence to support that tolerability is different for the three AEDs. In indirect comparisons of AEDs relative to placebo, gabapentin and pregabalin (at lower doses) did not have different tolerability, and gabapentin and valproate may be better tolerated than lamotrigine, pregabalin (≥ 300 mg daily), and topiramate. Gabapentin, pregabalin, and topiramate were each similar to placebo in terms of their risk of serious adverse events, suggesting that these three AEDs are similar in this respect. Gabapentin and pregabalin are more likely than topiramate to be associated with dizziness. Somnolence may be more common with gabapentin, pregabalin, and topiramate than with carbamazepine, lamotrigine, phenytoin, and valproate. There is more convincing evidence that topiramate therapy results in protocol-defined clinically important weight loss ($\geq 5\%$ from baseline to 4.5 to 5.5 months) than there is evidence of weight changes with other AEDs. Indirect comparisons were otherwise limited and inconclusive.
2c. Other diagnoses	Fair	One good-quality case-control study showed that the risk for any or site-specific fracture may be greater for carbamazepine, lamotrigine, oxcarbazepine, and valproate than for phenytoin, tiagabine, and topiramate; however, these treatment differences cannot be definitely concluded. The results of 2 fair-quality case-control studies 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, and similar for carbamazepine and phenytoin, although confidence intervals were wide. The risk of agranulocytosis may be greater with carbamazepine than phenytoin; however, this finding is uncertain.
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. Search Strategy and Update History

SEARCH STRATEGY FOR ORIGINAL REPORT (DATED NOVEMBER 2004)

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

SEARCH STRATEGY FOR REPORT UPDATE #1

Search #1 (Original drugs + original diagnoses)

PubMed (2004–2005)

Other limiters

English

Human

Search strategy

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 anticonvulsants OR anti-convulsive* OR antiepileptic* OR anti-epileptic* OR levetiracetam OR keppra OR phenytoin OR dilantin OR tiagabine OR gabitril OR topiramate OR topamax

AND

depressive disorders OR bipolar disorder OR mood disorders OR mood OR antimanic OR manic OR depressive OR depression OR pain OR neuralgi* OR migraine*

AND

randomi* OR randomized clinical trials OR randomized controlled trial[pt] OR meta analys* OR meta analysis OR meta analysis[pt] OR systematic review)

Number of items retrieved: 356

SEARCH #2 (Fibromyalgia + original and new drugs)

PubMed (1966–2005)

Other limiters

English

Human

Search strategy

fibromyalgia OR fibrositis

AND

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 anticonvulsants OR anti-convulsive* OR antiepileptic* OR anti-epileptic* OR levetiracetam OR keppra OR phenytoin OR dilantin OR tiagabine OR gabitril OR topiramate OR topamax OR pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

Number of items retrieved: 29

SEARCH #3 (New drugs + original diagnoses)

PubMed (1966–2005)

Other limiters

English

Human

Search strategy

pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

AND

depressive disorders OR bipolar disorder OR mood disorders OR mood OR antimanic OR manic OR depressive OR depression OR pain OR neuralgi* OR migraine*

Number of items retrieved: 17

SEARCH #4 (Original drugs + original diagnoses)

Embase (2004–2005)

Other limiters

English

Human

Search strategy:

levetiracetam or keppra or phenytoin or dilantin or tiagabine or gabitril or topiramate or topamax or 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 anticonvulsant? or anti(2w)convulsive? or anti(2w)convulsant? or antiepileptic? or anti(2w)epileptic?

AND

depression! or depression/ti,ab or depressive or mood disorder! or mood?(2n)disorder? or bipolar disorder! or bipolar/ti,ab or manic depressive psychosis or antimanic or anti(2w)manic or antimania or anti(2w)mania or pain! or neuralgia! or migraine or headache(2w)facial()pain

AND

(randomi?/ti,ab or randomized controlled trial? or systematic()review? or metaanaly? or meta(2w)analy?)

Number of items retrieved: 640

SEARCH #5 (Original and new drugs + fibromyalgia)

Embase (1974–2005)

Other limiters:

English

Human

Search strategy:

levetiracetam or keppra or phenytoin or dilantin or tiagabine or gabitril or topiramate or topamax or 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 anticonvulsant? or anti(2w)convulsive? or anti(2w)convulsant? or antiepileptic? or anti(2w)epileptic? OR pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

AND

fibromyalgia or fibrositis

NOT

results of Search #4

Number of items retrieved: 175

SEARCH #6 (New drugs + original diagnoses)

Embase (1974–2005)

Other limiters

English

Human

Search strategy

pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

AND

depression! or depression/ti,ab or depressive or mood disorder! or mood?(2n)disorder? or bipolar disorder! or bipolar/ti,ab or manic depressive psychosis or antimanic or anti(2w)manic or antimania or anti(2w)mania or pain! or neuralgia! or migraine or headache(2w)facial()pain

NOT

results of Searches #4 OR #5

Number of items retrieved: 269

SEARCH #7 (Original drugs + original diagnoses)

Cochrane (2004–2005)

Search strategy

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 anticonvulsants OR anti-convulsive* OR antiepileptic* OR anti-epileptic* in All Fields OR levetiracetam OR keppra OR phenytoin OR dilantin OR tiagabine OR gabitril OR topiramate OR topamax

AND

depressive disorders OR bipolar disorder OR mood disorders OR mood OR antimanic OR manic OR depressive OR depression OR pain OR neuralgi* OR migraine*

Number of items retrieved: 136

SEARCH #8 (New drugs + original diagnoses)

Cochrane (1966–2005)

Search strategy

pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

AND

depressive disorders OR bipolar disorder OR mood disorders OR mood OR antimanic OR manic OR depressive OR depression OR pain OR neuralgi* OR migraine*

Number of items retrieved: 2

SEARCH #9 (New drugs + new diagnosis)

Cochrane (1966-2005)

Search strategy:

pregabalin OR 3-isobutyl gaba OR lyrica OR ethotoin OR peganone

AND

fibromyalgia OR fibrositis

Number of items retrieved: 4

ADVERSE EVENTS SEARCH

PubMed (April 2004–2005)

Other limiters

English

Human

Search strategy

epidemiol* OR pharmacoepidemiolog*

AND

observational OR prescription database evaluation* OR patient database evaluation* OR prescription event monitor* OR 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

AND

antiepileptic drug*/adverse effects OR anticonvulsants/adverse effects

Number of items retrieved: 26

Cochrane Database of Systematic Reviews, DARE, Controlled Trials Register via OVID (2004–2005)

Search strategy

(antiepileptic\$ OR anti epileptic\$ OR anticonvuls\$ OR anti convuls\$).mp.

AND

adverse.mp.

AND

epidemiol\$.mp. OR pharmacoepidemiolog\$.mp.

AND

(spontaneous adverse drug reaction OR Phase iv OR postmarketing surveillance OR cohort OR long-term OR odds ratio OR relative risk OR case-control OR observational OR prescription database evaluation\$ OR patient database evaluation\$ OR prescription event monitor\$).mp.

Number of items retrieved: 26

Embase (2004–2005)

Other limiters

English

Human

Search strategy

[anticonvulsive agent! OR anticonvulsive therapy OR anticonvuls?/ti,ab OR anti(2w)convuls?/ti,ab OR antiepileptic?/ti,ab

AND

adverse drug reaction! OR side(2w)effect? OR toxic? OR drug response OR adverse(2w)effect? OR adverse(2w)event?] OR anticonvulsant therapy/ae

AND

epidemiol? OR pharmacoepidemiolog?

AND

observational OR prescription()database()evaluation? OR patient()database()evaluation?

OR prescription()event()monitor? OR spontaneous()adverse()drug()reaction()report?

OR 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

Number of items retrieved: 125

Appendix B. Included Studies

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Appendix D. Criteria for Rating Observational Studies of Adverse Events

For use with controlled trials (designed to assess efficacy or adverse events) and observational studies of adverse events.

1. Non-biased selection

Yes (RCT or observational study with inception cohort in which all patients were assessed for adverse events.)

Not clear

No

2. Low overall loss to follow-up

Yes

Not clear (withdrawn not reported, or no patients reported withdrawn although other studies of studies of patients on similar drugs report high withdrawal)

No (overall proportion depends on topic)

3. Adverse events pre-specified or defined

Yes (study reports definitions used for adverse events in an explicit, reproducible fashion)

No

4. Ascertainment techniques adequately described

Yes (Study reports methods used to ascertain complications, including who ascertained, timing, and methods used)

No

5. Non-biased and accurate ascertainment of adverse events

Yes (patients and assessors blinded to intervention, and ascertainment techniques valid)

No

6. Statistical analysis of potential confounders

Yes (study examines relevant confounders/risk factors using standard acceptable statistical techniques)

No

7. Adequate duration of follow-up

Yes (study reports duration of follow-up and duration of follow-up adequate to identify expected adverse events)

No

8. Overall quality score (Either use a point system, or Good=meets all criteria, Poor=fatal flaw, Fair= all other)

Good, Fair, Poor