Drug Class Review

Antiepileptic Drugs for indications other than Epilepsy

Final Report Update 2

October 2008

Original Report Date: December 2004
Update 1 Report Date: May 2006
A literature scan of this topic is done periodically

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.

Update 2
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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report based on the information contained in the scan. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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Suggested Citation for this Report:

McDonagh M, Peterson K, Lee N, Thakurta S. Drug class review: Antiepileptic drugs for indications other than epilepsy. Update 2.
http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

Acknowledgments:

Leah Williams and Arkady Mak, PhD, MD, contributed to this report by formatting and editing the manuscript. Laurie Huffman, MS, Brittany Burda, BS, Trish Thieda, MA, Miranda Walker, MA, and Tracy Dana, MLS assisted with data abstraction and quality assessment of studies. Theresa Nguyen and Allison Low assisted through article retrieval, and assistance with editing and formatting.

Funding:

The Drug Effectiveness Review Project, made up of 15 organizations including 14 state Medicaid agencies, commissioned and funded this report. These organizations selected the topic of the report and had input into its Key Questions. Content and conclusions of the report were determined entirely by researchers at the Evidence-based Practice Center. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in the report.

INTRODUCTION

Antiepileptic drugs have been used beyond treatment of seizure disorders since the 1960s, when they first became available. All antiepileptic drugs can depress 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, and blockade of N-methyl-D-aspartate receptors. Inactivation of sodium channels by antiepileptic drugs may reduce ectopic discharge from injured nerve endings and neurons of dorsal root ganglia.

Conventional pharmacotherapy for bipolar disorder, migraine prophylaxis, chronic pain, and fibromyalgia has typically been suboptimal and limited by drug-related toxicity. Often, multimodal approaches using combinations of pharmacologic and nonpharmacologic therapies are used. For example, in bipolar disorder a combination of antidepressive, antimanic, and mood stabilizing agents is often required to treat and prevent recurrences of mood episodes. And in fibromyalgia syndrome, pharmacotherapy often requires the use of multiple agents to treat the various symptoms associated with the disorder. As new antiepileptic drugs have become available, there has been interest in how their effectiveness, tolerability, and safety compare with existing therapies (carbamazepine, phenytoin, and valproate) used in these populations. The US Food and Drug Administration (FDA) already expanded the indication for some of these drugs beyond treatment of seizure disorders to treatment of bipolar I disorder, prophylaxis of migraine, and management of chronic pain (Table 1). Yet the relative efficacies of the newer and older antiepileptic drugs in the treatment of these disorders, as monotherapy or in combination with another antiepileptic drug or other agent, remain unclear. The objective of this report is to evaluate the comparative effectiveness, safety, tolerability, and response predictors of antiepileptic drugs used for bipolar disorder, fibromyalgia, migraine prophylaxis, and chronic pain.

Table 1. FDA-approved non-epilepsy indications for antiepileptic drugs

Generic name	Trade name(s)	Bipolar disorder	Fibromyalgia	Chronic pain	Migraine Prophylaxis
Carbamazepine	Tegretol®, Carbatrol®, Equetro®,	acute only			
Divalproex sodium[a]	Depakote®[b], Epival®[c]	acute only			yes
Ethotoin[b]	Peganone®				
Gabapentin	Neurontin®				
Lamotrigine	Lamictal®	maintenance only			
Levetiracetam	Keppra®				
Oxcarbazepine	Trileptal®				
Phenytoin	Dilantin®				
Pregabalin	Lyrica®		yes		
Tiagabine[b]	Gabitril®				
Topiramate	Topamax®				yes
Valproic acid[a]	Depakene®, Depacon®[b]	acute only			yes
Zonisamide[b]	Zonegran®				

[a] Also known as valproate.
[b] Not available in Canada.
[c] Canadian trade name.

Indications Addressed

This report addresses the evidence on benefits and harms associated with the use of antiepileptic drugs for bipolar disorder, fibromyalgia, chronic pain, and migraine prophylaxis, all briefly described below. Earlier versions of the report also addressed the use of antiepileptic drugs to treat neuropathic pain. However, as the Drug Effectiveness Review Project's "Drug Class Review on Drugs for Neuropathic Pain" (http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/NP_Final_Report_Original.pdf) now encompasses evidence for this indication, neuropathic pain was removed from this review of antiepileptic drugs.

Bipolar Disorder

Bipolar disorder is a spectrum of symptoms characterized by cycles of manic or hypomanic episodes. It may include depressive episodes and mood-congruent psychotic features. 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 (4 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. Because patients do not necessarily dislike the symptoms of mania, 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 a review of 31 studies of 9389 patients with bipolar disorder, the estimated lifetime prevalence of suicide ranged from 9% to 60% (weighted mean, 18.9%).[1]

The incidence of bipolar I disorder is estimated to be fairly 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.

Fibromyalgia

Fibromyalgia syndrome is a sometimes disabling condition characterized by chronic, widespread musculoskeletal pain. Its estimated worldwide prevalence is 0.5% to 5.0%, with women affected 4 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's diagnostic criteria for fibromyalgia require a history of spontaneous pain along the spine and all 4 quadrants of the body for more than 3 months and pain on digital palpation at 11 of 18 tender point sites. Other comorbid conditions are common in patients with fibromyalgia, although they are not part of the American College of Rheumatology diagnostic criteria. These conditions 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 hypothesis 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.

Migraine Prophylaxis

Migraine is a common and disabling neurological disorder affecting approximately 6% of men and 15% to 18% of women in the United States and other industrialized countries; many cases are undiagnosed or undertreated.[2-4] It is a chronic condition that usually affects children and young to middle-aged adults, and its repeated acute attacks cause considerable disability, loss of work, and disruption of daily functioning.[2, 4]

Treatment of migraines includes both preventive and acute drug therapies. Preventive treatment aims to reduce frequency, severity, and duration of attacks and to improve responsiveness to acute treatment, reduce disability, improve patient functioning, and reduce the overall cost of treating migraine.[2, 3] Studies suggest that approximately one-third of migraine sufferers ought to use preventive therapy, but only 3% to 13% currently do.[3] Preventive treatment should generally be considered for patients (1) who have with frequent migraines (2 or more per month); (2) who have prolonged or severe attacks; (3) who experience intolerable adverse events with acute therapy; (4) in whom acute medication is contraindicated; (5) who have been unresponsive to acute therapy; (6) who are at risk of overusing acute mediations (taken more than twice per week); or (7) who have uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.[2, 4] When preventive therapy is prescribed, it should be given an adequate trial of at least 6 weeks at the

maximally tolerated dose; however, the full benefit of the medication may not be attained for 6 months on this dose.[3]

Chronic Pain

Chronic pain is often defined as pain that persists or progresses for longer than 3 to 6 months. Chronic pain may begin as acute pain associated with a specific injury or condition, but it outlasts the expected period needed for the body to heal. Also included in the chronic category is pain associated with cancer, degenerative conditions, neuropathies, and other illnesses. In some cases, chronic pain lacks an identifiable physical cause. Intensity of chronic pain can range from mild to severe and can become a source of significant disability for its sufferers. Chronic pain can also lead to other psychosocial difficulties, including depression, fatigue, poor sleep, and reduced functional capacity and quality of life.

In the United States chronic pain has long been recognized as a major public health concern. According to findings from multiple studies done in North America, Europe, and Australia, the prevalence of chronic pain has been estimated to range from 10% to 55%.[5] According to the National Institutes of Health, the American public spends over $100 billion annually on the combined expenses of medical care, lost workdays, and litigation associated with chronic pain.

Scales and Tests Used to Measure Outcomes

In patients with bipolar disorder, migraine, fibromyalgia, and chronic pain, outcomes are measured using a variety of rating scales. For the sake of brevity we reported results using common acronyms for outcomes rating scales. The full names of the rating scales are listed in Appendix A. Terms commonly used in reports produced by the Drug Effectiveness Review Project, such as statistical terms, are defined as they apply to these reports in Appendix B.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. A systematic review focuses on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with a careful formulation of research questions. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are emphasized over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat, often referred to as the NNT, is the number of patients who would have to be treated with an intervention for 1

additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed, randomized, controlled trials are considered better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, cohort designs are preferred when conducted well and for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to the generalizability of *efficacy studies* performed in controlled or academic settings. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in typical practice settings. And these studies often restrict options that are of value in actual practice, such as combination therapies or switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as either an efficacy or an effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient

population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much of it there is, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The main goal of this report was to compare the effectiveness and adverse event profiles of antiepileptic drugs in the treatment of bipolar disorder, migraine, chronic pain, and fibromyalgia. The Oregon Evidence-based Practice Center wrote preliminary Key Questions, identifying the populations, interventions, outcomes of interest, and, based on these, the eligibility criteria for studies. A draft of these questions and inclusion and exclusion criteria were posted on the Drug Effectiveness Review Project website for public comment. The draft was reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project, taking into consideration comments received from the public. The participating organizations of Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. The participating organizations approved the following Key Questions to guide the review for this updated report:

1. For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in effectiveness?

2. For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in safety or adverse events?

3. Among these patient populations, are there subgroups of patients based on demographics (age, racial groups, and gender), other medications, or comorbidities for which one antiepileptic drug is more effective or associated with fewer adverse events?

METHODS

Inclusion Criteria

Populations

Adult outpatients with one of the following diseases or conditions:

- Bipolar disorder (any) diagnosed according to Diagnostic and Statistical Manual of Mental Disorders criteria.[1]
- Fibromyalgia or fibromyalgia syndrome diagnosed according to the American College of Rheumatology's diagnostic criteria for fibromyalgia.
- Migraine including any level of severity (mild, moderate, severe), with or without aura. Other types of headache (such as tension headache) were excluded.
- Chronic pain defined as continuous or recurring pain of at least 6 months' duration. Neuropathic pain was excluded.

Drugs

Only oral formulations of the drugs listed in Table 1 (above) were included. These are carbamazepine, divalproex sodium, ethotoin (not available in Canada), gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, tiagabine (not available in Canada), topiramate, valproic acid, zonisamide (not available in Canada). In this report we referred to divalproex sodium and valproic acid collectively as "valproate," except in the evaluation of adverse events and where extended-release formulations were used.

Effectiveness outcomes

Bipolar Disorder

- Danger to self (suicide attempts and completions, suicidal ideation)
- Functional capacity (quality of life, work productivity)
- Hospitalization rates or duration

[1] We excluded trials that included heterogeneous patient populations unless data were presented separately for patients with bipolar disorder.

- Response (rate, degree, speed of onset, duration). Response reported as defined by studies' protocols.
- Remission (rate, speed of onset, duration). Remission reported as defined by studies' protocols.
- Maintenance of response or remission (rate of recurrence or relapse, time to recurrence or relapse). Both reported as defined by studies' protocols.
- Use of other medications for acute episodes

Fibromyalgia and Chronic Pain

- Functional capacity (quality of life, work productivity)
- Response (pain intensity and pain relief, change from baseline and proportion achieving relief)
- Relapse
- Speed and duration of response
- Use of rescue medications

Migraine prophylaxis

- Quality of life
- Functional outcome (for example, change in days of work lost)
- Attack frequency
- Days with migraine
- Response (intensity, duration, proportion of patients achieving)
- Use of acute treatments

Safety Outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious harms. A serious harm is one that results in death or long-term health effects. An increase in rates of suicide or suicidal ideation was considered here as a serious harm. Reduction in these rates was considered with other effectiveness outcomes.
- General adverse effects or withdrawals due to specific adverse events (for example, dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, hyperammonemia)

Study Designs

For effectiveness, controlled clinical trials and good-quality systematic reviews directly comparing one antiepileptic drug with another were preferred. If none existed, trials comparing an included antiepileptic drug with placebo or another drug were considered.

For safety, in addition to controlled clinical trials, observational studies were included. Observational studies were defined as comparative cohort and case-control studies. Studies without a control group were included only if the duration of follow-up was 1 year or longer and serious harms were reported. Studies investigating potential harm to fetuses as a result of exposure to an antiepileptic drug were included only if the population exposed included women who did not have epilepsy, such that studies including only women with epilepsy were not reviewed.

Literature Search

The Original and Update 1 versions of this report, previously produced by the Southern California Evidence-based Practice Center at RAND, provided the basis for identification of included studies in bipolar disorder and fibromyalgia patients through 2005. Their searches included the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects, MEDLINE/PubMed (1966–2005), and Embase (1974–2005). For Update 2, for bipolar disorder and fibromyalgia we searched PsychINFO from1806 to week 2 of March 2008 and searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews only back to 2005. For chronic pain and migraine, we searched MEDLINE (1996 to week 1 of June 2008), the Cochrane Central Register of Controlled Trials (2nd Quarter 2008), and Cochrane Database of Systematic Reviews (2nd Quarter 2008). We also checked reference lists of included review articles. In electronic searches for efficacy trials, we combined terms for antiepileptic drugs, bipolar or mood disorder, fibromyalgia, migraine, chronic pain, randomized clinical trials, systematic reviews, and meta-analyses. For adverse event studies, we combined terms for antiepileptic drugs, adverse effects, and various types of observational studies. All searches were limited to English language and human studies. (See Appendix C for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote® X1, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because lack of detail prevented quality assessment.

Data Abstraction

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) and comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix D. These criteria were based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria for assessing study quality.[6, 7] In rating the internal validity of each trial we assessed the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups

at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality. The remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses; the results of some fair-quality studies were likely to be valid, while others were only possibly valid. Poor-quality trials were not valid: The results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items on the quality assessment checklist.

External validity of trials was assessed based on whether the publication adequately described the study population, whether patients were similar enough to the target population in whom the intervention would be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix D also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of 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 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria, and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on predefined criteria (see Appendix D), which assessed the research questions(s) and inclusion criteria, adequacy of search strategy and validity assessment, adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

The overall strength of evidence for a particular Key Question or outcome reflected the risk of bias of the studies (based on quality and study design) and the consistency, directness, and precision of the studies relevant to the question. Strength of evidence was graded as insufficient, low, moderate, or high.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy-of-evidence approach, in which the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one antiepileptic drug against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data (from direct comparisons) were the primary focus; direct comparisons were preferred over indirect comparisons. Similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare antiepileptic drugs to other drug classes or placebos can also provide evidence about effectiveness. This approach is known as an indirect comparison. Indirect comparisons can be difficult to interpret for a number of reasons, mainly heterogeneity between trial populations, interventions, and assessments of outcomes. Data from indirect comparisons are used to support direct comparisons, where they exist, and also are used as the main comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

In addition to qualitative discussion of studies' finding, this report contains quantitative analyses that were conducted using meta-analyses on outcomes reported by a sufficient number

of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and their heterogeneity in design, patient population, interventions, and outcomes.

Random-effects models were used to estimate pooled effects.[8] Forest plots are presented to graphically summarize the study results and the pooled results.[9] The Q-statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity between the effects from the studies.[10, 11] Heterogeneity was examined with subgroup analysis by factors such as study design, study quality, variations in interventions, and patient population characteristics.

Meta-Analysis of Specific Adverse Events

We aggregated the more commonly documented (or expected) adverse events using patient-level data (Appendix E). We included only trials that specifically reported events at the patient level. Use of patient-specific data can underestimate prevalence and/or eliminate low-level signals of events that occur rarely, because the inclusion criteria for the studies are narrower than in the general population with any given disease.

Data for the adverse events, such as diarrhea, headache, nausea, and rash, were extracted, and an odds ratio was calculated for subgroups that had only 1 trial. For subgroups of events that had at least 2 trials, at least 1 event in the medication group, and at least 1 event in the placebo group, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95% confidence interval. Because 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 apply the usual asymptotic methods that assume normality. Asymptotic methods require correction 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 assume continuity of effects. 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 (Cytel).[21]

Any significant pooled odds ratio greater than 1 indicated that the odds of the adverse event associated with an antiepileptic drug (the intervention group) was larger than the odds associated with the comparison (placebo, lithium, or other antiepileptic drug). If no events were observed in the comparison group, but events were observed in the intervention group, the odds ratio was infinity and the associated confidence interval was bounded from below only. We report the lower bound of this confidence interval. If no events were observed in either group, the odds ratio was undefined, which we denote as "Not calculated" (NC) in the results tables. We did not observe any subgroups of studies for which no events were reported for the intervention group but events were observed in the comparison group.

Since only 1 bipolar disorder trial directly compared adverse events between antiepileptic drugs, for bipolar disorder we assessed only 2 comparisons, antiepileptic drug compared with placebo and antiepileptic drug compared with lithium. We looked for overlap between the confidence intervals of the pooled odds ratios (or single study odds ratio if only 1 trial was available) for each antiepileptic drug. If the confidence intervals overlapped, then we could not conclude that the odds between antiepileptic drugs were significantly different.

Peer and Public Review

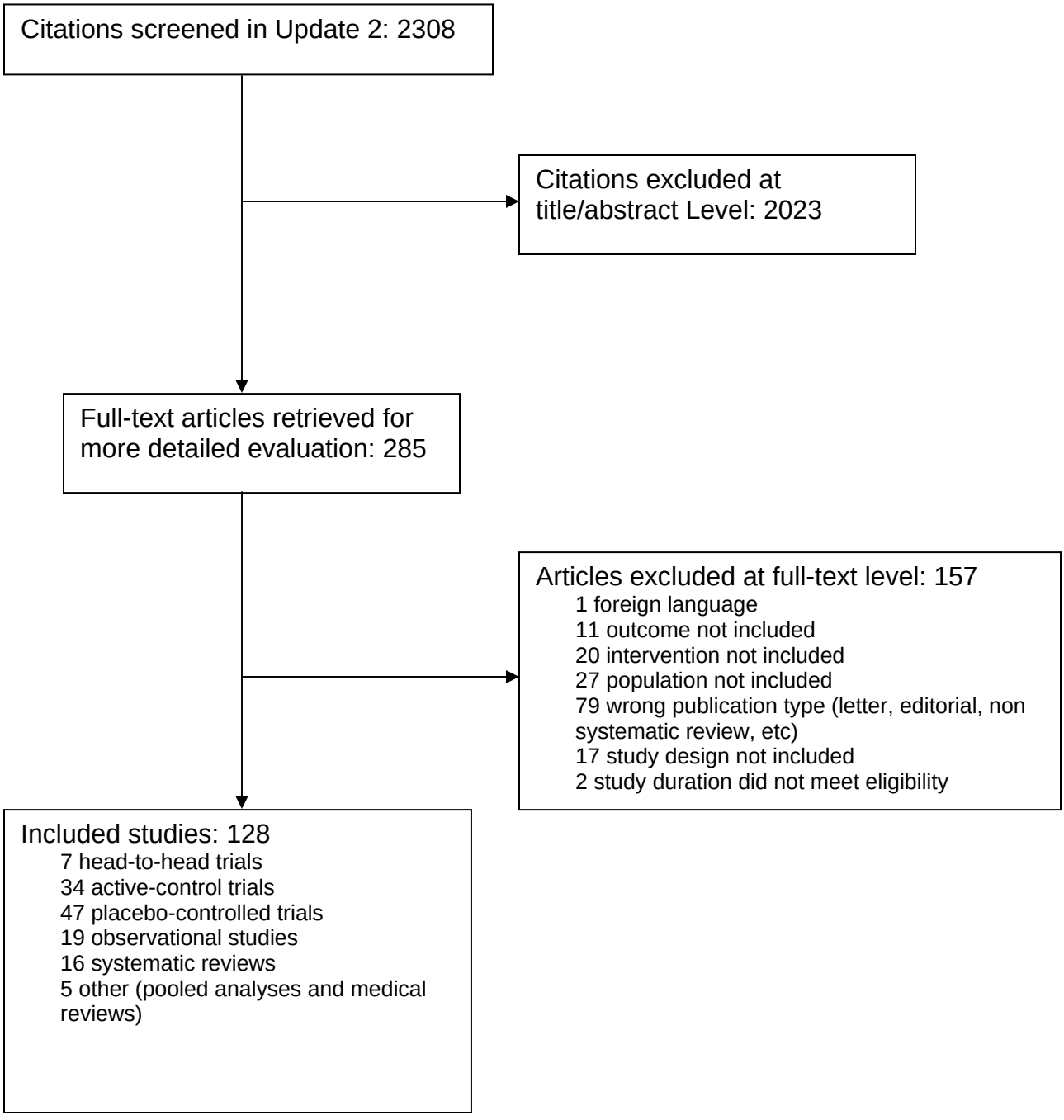
The Original report underwent a review process that involved solicited peer review from 3 clinical experts. Their comments were reviewed and, where possible, incorporated into the final document. The comments received and the author's proposed actions were reviewed by the representatives of the participating organizations of the Drug Effectiveness Review Project prior to finalization of the report. Names of peer reviewers for Drug Effectiveness Review Project reports are listed at www.ohsu.edu/drugeffectiveness.

RESULTS

Overview

Our literature searches identified 2308 new citations for Update 2: 540 from the Cochrane Central Register of Controlled Trials, 25 from the Cochrane Database of Systematic Reviews, 1254 from Medline, 441 from PsychINFO, and 48 from hand-searching. We received no new pharmaceutical company dossier submissions for Update 2. Figure 1 shows results of our study selection process for Update 2. Appendix F lists the excluded studies.

Figure 1. Results of literature search (Update 2)



Summary of Findings

Bipolar Disorder

Stabilization of acute manic/mixed episodes

- Evidence supports the use of immediate- and extended-release forms of carbamazepine and valproate for stabilization of *acute* manic/mixed episodes.
    - Efficacy of older forms of carbamazepine and valproate was comparable to lithium, in that 27% to 62% of all patients had 50% or greater improvements in symptoms ("response").
    - In more-recent placebo-controlled trials, up to 61% of patients responded after treatment with the newest extended-release forms of either carbamazepine (Equetro®) or valproate (Depakote ER®) compared with only up to 34% of placebo-treated patients.
    - Consistent evidence of differences between the 2 antiepileptic drugs is lacking.
- Available evidence largely does not support use of phenytoin, gabapentin, lamotrigine, oxcarbazepine, or topiramate for stabilization of acute manic/mixed episodes.
- No evidence was found regarding the efficacy of other antiepileptic drugs for acute manic/mixed episodes.

Maintenance treatment of manic/mixed episodes

- Evidence supports the use of lamotrigine and older forms of carbamazepine and valproate as maintenance treatment in patients whose most recent episode was manic/mixed.
    - Valproate reduced odds of any relapse by half compared with placebo and had comparable odds of any relapse compared with lithium.
    - Across most of numerous small trials comparing carbamazepine with lithium, differences in relapse outcomes did not reach statistical significance, but their trends generally favored lithium.
    - Compared with placebo, lamotrigine and lithium both improved median time to intervention for recurrence of any mood episode from 85 days to 141 and 292 days, respectively. Differences between lamotrigine and lithium did not reach statistical significance *(P*=0.46).
- Available evidence largely does not support use of gabapentin, oxcarbazepine, or phenytoin for maintenance treatment of manic/mixed episodes.
- No evidence was found regarding the efficacy of other antiepileptic drugs for maintenance treatment of manic/mixed episodes.

Rapid cycling

- Both valproate and lithium prevented relapse for 20 months in just over half of 60 patients with rapid cycling bipolar disorder.
- Lamotrigine consistently did not significantly extend median time to intervention (pharmacotherapy or electroconvulsive therapy) compared with placebo across 2 trials.
- No evidence was found regarding the efficacy of other antiepileptic drugs for rapid cycling bipolar disorder.

Bipolar depression

- Evidence supports a benefit of lamotrigine monotherapy in treating acute bipolar depression over 7 to 10 weeks. The mean response rate based on the MADRS was 51%

for lamotrigine and 41% for placebo, with a pooled number needed to treat of 13. Benefit was also found based on the mean change in depression scale score.
- Evidence does not support a difference in response rates with lamotrigine compared with olanzapine/fluoxetine combination, citalopram, or lithium. Across the 3 studies, response rates with lamotrigine ranged from 45% with adjunctive treatment to 67.5% with monotherapy. The combination of olanzapine/fluoxetine was found superior on some other measures, but not all.
- Rates of switch into hypomania with lamotrigine as monotherapy or adjunctive therapy ranged from 1% to 8% (weighted mean 2.3%) compared with 1.9% with lithium, 1% with citalopram, 4% with olanzapine/fluoxetine, and 2% (weighted mean) with placebo.
- In maintenance of response to lamotrigine in patients with bipolar depression, lamotrigine and lithium were similar in time to intervention for *any* mood episode (for lamotrigine, 200 days; for lithium, 170 days; *P*=0.915), and both were superior to placebo.
- Valproate has mixed evidence for treatment of acute bipolar depression, in that valproate was found superior to placebo in mean change on depression scale scores but not in response or remission rates. Limited evidence suggests valproate was not superior to placebo in preventing relapse of depressive symptoms.
- Topiramate and extended-release bupropion resulted in similar improvements in a single small study comparing the drugs as adjunctive therapies to mood stabilizers in patients with bipolar disorder whose most recent episode was depression.
- Limited evidence finds that lamotrigine is similar to tranylcypromine, risperidone, and inositol in response or recovery rates among patients with treatment resistant bipolar depression.

Fibromyalgia

- Using a definition of 30% or more reduction in pain, pregabalin showed statistically significantly greater rates of response compared with placebo for 300, 450 and 600 mg per day (pooled estimate of relative risk 1.39; 95% CI, 1.26 to 1.53; number needed to treat=8). Gabapentin also showed a greater response rate than placebo (51% compared with 31%; *P*=0.014; our calculated number needed to treat = 5). Pregabalin 600 mg/d recorded the highest responder rate compared with placebo (30% versus 15%; *P*=0.0010; number needed to treat=6.62), using a definition of 50% or greater reduction in pain. The mean pain scores for gabapentin 1800 mg/d and pregabalin 450/d and 600 mg/d were statistically significantly greater than placebo at endpoint..
- In patients who responded to pregabalin during acute treatment with a 50% or more reduction in pain, the time to loss of therapeutic response, defined as <30% reduction in pain from open-label baseline or worsening of fibromyalgia requiring alternate treatment, was statistically significantly longer with pregabalin than placebo over a 6-month period.

Migraine Prophylaxis

- There is evidence to support the use of topiramate or valproate for migraine prophylaxis, in that these drugs reduce migraine frequency compared with placebo. Direct comparisons between the drugs are insufficient to make conclusions.

- The evidence supporting the use of carbamazepine or gabapentin for migraine prophylaxis is weaker than the evidence base for topiramate and valproate but indicates that these drugs also may be superior to placebo in reducing headache frequency.
- There is little evidence to support the use of lamotrigine or oxcarbazepine for migraine prophylaxis. These drugs were not found to be superior to placebo in reducing headache frequency.

Chronic Pain

- Limited evidence supports the short-term efficacy of topiramate and gabapentin compared with placebo for treatment of chronic pain.
- Differences were not found between tiagabine and gabapentin based on pain scores, although tiagabine was found superior in sleep ratings.

Harms Associated with Antiepileptic Drugs

- Antiepileptic drugs may be associated with an increased risk of suicidal ideation or behaviors; however, the risk associated with specific drugs, patient populations, and treatment regimens is unclear.
    - FDA analysis of placebo-controlled trials indicates that lamotrigine and topiramate are associated with statistically significant increases in risk, while valproate is not. For other drugs the evidence was weaker.
    - Evidence suggests that risk of suicide death, suicide attempts resulting in hospitalization, and suicide attempts diagnosed in the emergency department are higher with valproate than lithium. Carbamazepine has a significantly increased risk of suicide attempts resulting in hospitalization compared with lithium.
- The risk of fracture at any site is increased by use of antiepileptic drugs. Adjusted odds ratios for any fracture in patients who used antiepileptic drugs were significantly increased with exposure to carbamazepine (1.18; 95% CI, 1.10 to 1.26), oxcarbazepine (1.14; 95% CI, 1.03 to 1.26), and valproate (1.15; 95% CI, 1.05 to 1.26). The odds ratios were nonsignificant but increased for lamotrigine (1.04; 95% CI, 0.91 to 1.19), phenytoin (1.20; 95% CI, 1.00 to 1.43), tiagabine (0.75; 95% CI, 0.40 to 1.41), and topiramate (1.39; 95% CI, 0.99 to 1.96) compared with no exposure.
- The relative risk of Stevens-Johnson syndrome or toxic epidermal necrolysis for $\leq$ 8 weeks of use was 91 (26 to infinity) for phenytoin, 120 (34 to infinity) for carbamazepine, and 24 (5.9 to infinity) for valproate. The numbers for lamotrigine were too small for meaningful analysis.
- In 2 case-control studies the risk of agranulocytosis associated with recent use of carbamazepine gave odds ratios of 11.0 (95% CI, 1.2 to 102.6) and 10.3 (95% CI, 2.0 to 101.0). In both studies the risk with phenytoin was low and not statistically significant, and in 1 study the risk associated with valproate was 18.2 (odds ratio; 95% CI, 2.5 to infinity). With both drugs the numbers of cases were too low for precise estimates.
- Exposure to older antiepileptic drugs during the first trimester of pregnancy is associated with an increase in risk of birth defects compared with the general population, 4%-10% compared with 2%-5%. Risks associated with newer drugs are less clear.

  - Antiepileptic drug monotherapy is associated with somewhat lower risk compared with antiepileptic drug polytherapy.
  - Valproate was associated with a higher risk compared with carbamazepine, lamotrigine, or all other antiepileptic drugs combined with odds ratios of 2 to 4.
  - Risk of birth defects was similar between carbamazepine and phenytoin, oxcarbazepine, carbamazepine and phenytoin, and lamotrigine and carbamazepine.
  - Evidence suggests a dose-dependent relationship with valproate doses of 800 to 1000 mg/d associated with higher risk. Lamotrigine doses larger than 200 mg/d were associated with risk approaching that of valproate 1000 mg/d in one study, but no association was found in another study.
  - Gabapentin, levetiraetam, and topiramate have only very limited evidence available and conclusions cannot be drawn.
- In short-term monotherapy trials, topiramate and carbamazepine resulted in significantly greater rates of overall reports of adverse events than placebo and carbamazepine. Valproate and topiramate had higher rates of withdrawal than placebo.
  - In head-to-head comparisons, only carbamazepine had significantly higher rates of adverse events than valproate. No difference was found between topiramate and valproate. Topiramate was not directly compared with carbamazepine.
- Comparisons of rates of specific adverse effects:
  - Diarrhea: Lamotrigine (2 trials), but not valproate (1 trial), was significantly less likely than lithium to be associated with diarrhea (pooled odds ratio 0.30; 95% CI, 0.14 to 0.59).
  - Tremor: Lamotrigine (1 trial, odds ratio 0.28; 95% CI, 0.11 to 0.68) and carbamazepine (2 trials, odds ratio 0.00; 95% CI, 0.0 to 0.30), but not valproate (1 trial), were associated with significantly lower odds of tremor than lithium. Valproate (1 trial), but not lamotrigine (1 trial), was associated with significantly higher odds of tremor than placebo (odds ratio 4.76; 95% CI, 2.38 to 10.26).
  - Headache: Lamotrigine (4 trials), but not carbamazepine (1 trial) or gabapentin (1 trial), was more likely than placebo to be associated with headache (odds ratio 1.59; 95% CI, 1.14 to 2.25).
  - Nausea: Carbamazepine (2 trials), but not divalproex (1 trial) or lamotrigine (2 trials), was more likely than placebo to be associated with nausea (odds ratio 5.16; 95% CI, 2.73 to 10.30).
  - Rash: Lamotrigine (2 trials), but not carbamazepine (1 trial), was associated with significantly higher odds of rash relative to placebo (odds ratio 2.23; 95% CI, 1.06 to 5.28).
  - Somnolence: Carbamazepine (2 trials), but not gabapentin (1 trial) or lamotrigine (3 trials), was more likely than placebo to be associated with somnolence (odds ratio 2.71; 95% CI, 1.48 to 5.36).
  - Weight change: Only valproate was reported to cause weight gain as a treatment-emergent adverse event (odds ratio 3.26; 95% CI, 1.36 to 9.03). 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 among 31 evaluable patients; calculated difference, –2.79 kg; P=0.02). There were no significant differences between lamotrigine and placebo or between gabapentin and placebo.

Weight change data should be interpreted with caution, since it was not based on randomized patients.
    - Analysis of reports of depression, headache, rash, somnolence, or weight gain did not show statistically significant differences between drugs.

Subgroups

- In bipolar disorder
    - Demographic factors were not found to be associated with response to valproate or lithium.
    - Among males, response to lamotrigine may be better in patients who had fewer trials of prior medications compared with those with many previous trials. Analysis of data on females did not find this difference to be significant.
    - Response to gabapentin appeared to be better in younger patients with lower baseline weight.
    - Carbamazepine may benefit patients experiencing manic episodes more than patients experiencing mixed episodes.
    - Valproate has better efficacy than lithium for patients experiencing mixed manic episodes. The drugs were similar in patients with mania alone.
    - Patients with bipolar I disorder, recent mania, and previous psychiatric hospitalization may have a longer time to depressive relapse with valproate than lithium.
    - Patients with rapid-cycling bipolar II disorder may have better response with lamotrigine maintenance therapy than placebo. This difference was not seen in the subgroup with bipolar I disorder.
    - Patients 55 years and older did not differ from the overall trial population in their response to lamotrigine in preventing relapse of depressive symptoms or other mood episodes.
- In fibromyalgia, pain relief appears to be independent of improvement in anxiety or mood.
- In chronic pain and migraine prophylaxis, insufficient evidence is available for meaningful assessment of subgroups.

Detailed Assessment

Key Question 1

For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in effectiveness?

Bipolar disorder

We found no trials of ethotoin, levetiracetam, pregabalin, tiagabine[12, 13] or zonisamide in patients with bipolar disorders. A large proportion of included trials in patients with bipolar disorder were previously evaluated in a number of prior systematic reviews.[12-22] However, findings from only the most recent and comprehensive systematic reviews are discussed in detail here.[16, 17, 20]

Manic/mixed episodes

Carbamazepine compared with valproate

We found 1 fair-quality, head-to-head trial that compared carbamazepine with valproate in 30 patients with bipolar disorder (DSM-III-R) and YMRS scores of ≥ 20 at a single center in India.[23] After 4 weeks of therapy, valproate was superior to carbamazepine in the reduction of YMRS scores (-32.8 compared with -20.8 points; *P*=0.023). There was no statistically significant difference in rates of response (> 50% decrease in YMRS total score from baseline to endpoint) between carbamazepine (53.3%) and valproate (73.3%). These results should be considered preliminary, however, until they are confirmed in larger-scale, multicenter trials.

Valproate

For treatment of acute manic/mixed episodes using immediate- and extended-release forms of valproate, we included 5 trials that evaluated comparisons with placebo,[24-28] 2 with comparisons to lithium,[24, 29] and 1 with a comparison to haloperidol.[30] A number of trials conducted to evaluate olanzapine as an even newer alternative for treatment of bipolar disorder used valproate as a control.[31-34] However, these were considered to be outside of the scope of this review. Discussion of their results can be found in the Drug Effectiveness Review Project's systematic review of atypical antipsychotics.

Outcomes data from trials conducted through 2002 comparing valproate with placebo, lithium, or haloperidol[25, 26, 28-30] were previously analyzed in a Cochrane review by Macritchie and others.[216] Their findings are summarized here: Pooled results of 3 short-term trials suggest that valproate was more effective than placebo and comparable to lithium in the treatment of acute bipolar manic and mixed episodes. To assess how valproate compared to placebo and lithium, Macritchie calculated pooled relative risks using fixed-effects models of the outcome "failure to respond by end of study," which is the inverse of "response." The relative risk of failure to respond for valproate compared with placebo was 0.62 (95% CI, 0.51 to 0.77), and 1.05 (95% CI, 0.74 to 1.50) compared with lithium. For the meta-analysis of the comparison of valproate to lithium, Macritchie included data from a trial of 28 children, which did not meet our criterion of only adults. However, when we repeated their analysis and excluded the study in children, a similar relative risk was found (relative risk 1.16; 95% CI, 0.77 to 1.75). Macritchie did not express any serious concerns about methods of randomization, allocation concealment, blinding, or handling of withdrawals.

In addition, another trial investigated whether valproate could be as rapidly effective as a conventional antipsychotic in the initial treatment of acute psychotic mania associated with bipolar disorder.[30] In this trial, 36 patients hospitalized with bipolar disorder with psychotic features were randomized to receive 6 days of treatment with oral loading dosages of valproate 20 mg/kg/d or haloperidol 0.2 mg/kg/d. Oral loading of valproate was found to be comparable to haloperidol in reducing both manic and psychotic symptoms as measured by mean changes in scores on the YMRS (-42% compared with -35%) and the on the global and subscale SAPS.

After the original studies of valproate immediate- and extended-release (included in the Macritchie review) results from a placebo-controlled trial of the newer, once-daily, extended-release form of valproate were published.[24] This fair-quality trial compared valproate extended-release 3057 mg (final mean dose) with placebo in 377 adults who were hospitalized for an acute manic or mixed episode of bipolar disorder. For the protocol-specified primary efficacy endpoint of change on the SADS-C MRS, valproate extended-release produced significantly greater improvement than placebo (-11.5 points compared with -9.0; *P*=0.013). In addition, significantly

more patients treated with valproate extended-release experienced at least a 50% improvement from baseline on SADS-C MRS than with placebo (48% compared with 34%; *P*=0.012), and more patients treated with valproate extended-release were in remission at endpoint (time point the patient left the study; 48% compared with 35%; *P*=0.015).

Carbamazepine

Monotherapy with carbamazepine extended-release was more efficacious than placebo in the acute treatment of patients with bipolar I disorder in 2 identically designed, pivotal trials (105.301 and 417.304)[35, 36] included in the New Drug Application (NDA) submitted to the FDA in 2004 and summarized in an FDA review document.[37] Mean final daily doses of carbamazepine extended-release were 756 mg (8.9 µg/mL) in study 105.301[35] and 643 mg (mean plasma drug level not recorded) in study 417.304.[36] Both trials were 3 weeks long. Compared with the placebo groups in both trials, patients in the carbamazepine extended-release groups had significantly greater improvements in mean YMRS total scores and more patients were considered responders at endpoint (the time point at with the patient left the study, Table 2). In the FDA review of the NDA, we also found results from a third, non-pivotal, failed placebo-controlled trial of carbamazepine extended-release in lithium-resistant patients with bipolar disorder that, to our knowledge, has not yet been fully published.[37] Very little information was provided about this trial, except that its design was identical to the others; it involved 59 randomized patients; and there were no significant differences between carbamazepine extended-release and placebo on the primary outcomes of mean change in YMRS total score (-8.9 compared with -8.7; *P*=0.97).

Table 2. Efficacy outcomes in acute treatment of bipolar disorder with carbamazepine extended-release compared with placebo

Trial	Mean change in YMRS total score	Response rate (≥ 50% decrease in YMRS total scores)
105.301	-8.7 compared with -5.2; *P*<0.05	42% compared with 22%
417.304	-15.1 compared with -7.1; *P*<0.0001	61% compared with 29%; *P*<0.0001

From older evidence supporting use of acute monotherapy with carbamazepine immediate-release, we included 3 trials published between 1987 and 1991 that involved comparisons with lithium (Table 3).[38-40] In all 3 trials, included patients were diagnosed with bipolar disorder based on DSM-III or DSM-III-R criteria; most exhibited manic episodes. Trials were 4 to 8 weeks long and the dosage ratio between carbamazepine and lithium was approximately 1:1 in 2 of 3 trials[39, 40] and 1:1.5 in the other. Methods of outcome assessment were heterogenous across trials, but there were no significant differences between carbamazepine immediate-release and lithium regardless of how outcome was measured. However, these findings should be interpreted with caution given that (1) patients assigned to the lithium groups were significantly older in the 2 largest trials,[39, 40] and this may have biased their results; and (2) the other trial of only 34 patients may not have been large enough to reliably detect differences between the 2 drugs.

Table 3. Efficacy outcomes in acute treatment of bipolar disorder with carbamazepine compared with lithium

Study N	Carbamazepine dose	Lithium dose	Efficacy outcomes
Lerer 1987 N=34	1400 mg/d (8.8 µg/mL)	2100 mg (0.87 µg/mL)	% improvement in mean CGI score: 26.8% compared with 45.6%; *P*=NS
Okuma 1990 N=101	614 mg/d (7.5 µg/mL)	635 mg (0.39 µg/mL)	Marked/moderate improvements on CGI (% patients): 62% compared with 59%; *P*=NS
Small 1991 N=52	1036 mg/d (37 µmol/L)	1155 mg (0.73 mmol/L)	% improvement in mean YMRS score: 28% compared with 32%; *P*=NS

Other miscellaneous trials of acute therapy with carbamazepine immediate-release were included; but, because their comparisons were with antipsychotics, they have limited usefulness here.[41-45] Two trials indicated that carbamazepine had antimanic efficacy comparable to chlorpromazine.[41, 43] Two trials supported the use of carbamazepine in 2 combination therapy situations.[42, 44] Results from 1 trial indicated that carbamazepine showed superior efficacy to placebo when combined with haloperidol in patients with "excited psychoses, " including mania.[42] Results from two other trials indicated that carbamazepine and haloperidol provided similar benefit when added to lithium or other neuroleptics.[44, 45]

Topiramate

In a small (N=74), 6-week, open-label trial comparing topiramate with valproate, both in combination with risperidone,[46] 75.8% of topiramate-treated patients had a 50% or more reduction in YMRS score, which was comparable to the response rate in the valproate group, 70.7%. In the second trial, topiramate 254.7 mg/d was compared with placebo in 287 patients with bipolar I disorder experiencing a manic or mixed episode who were already on ongoing therapy with lithium or valproate.[47] After 12 weeks, there was no significant difference between topiramate and placebo on the primary efficacy measure of reduction in YRMS total score (-10.1 compared with -9.6), in overall response rate, or on any other secondary efficacy outcomes as measured by the CGI-S, BPRS, MADRS, or GAS.

Results from 4 identically designed trials of topiramate monotherapy were reported in a single publication.[48] All were 3 weeks long and collectively randomized 110 patients to topiramate 200 mg, 447 to topiramate 400 mg, 102 to topiramate 600 mg, 227 to lithium, and 429 to placebo. Based on intention-to-treat analyses of mean reduction in YRMS total score, the therapeutic benefit of topiramate was significantly lower than lithium and was not significantly different from placebo. YMRS mean reductions were -5.8 points for the topiramate 200-mg group, -7.9 points for the 600-mg group, and ranged from -5.1 to -8.2 points in the 400-mg groups, from -12.9 to -13.8 in the lithium groups, and from -6.4 to -8.4 in the placebo groups. Limited information was provided in an abstract format regarding a fifth trial that compared topiramate 256 mg (N=33), topiramate 512 mg (N=33), and placebo (N=31) in patients with bipolar I disorder.[49] There, too, no statistically significant differences were reported for either dose of topiramate compared with placebo in the primary efficacy analysis of the mean change from baseline in YMRS total score, but no data were provided.

Lamotrigine

In the only published trial of lamotrigine for patients with bipolar I acute mania, 15 patients each were randomized to receive lamotrigine 100 mg or lithium 800 mg for 4 weeks.[50] Results indicated no significant differences between lamotrigine and lithium for rate of improvement in mean MRS scores (58% compared with 58%; *P*=NS). However, these results should be interpreted with caution in light of the low dose of lithium.

We also identified 2 unpublished trials[51, 52] of treatment of acute manic/mixed episodes with lamotrigine as either monotherapy (SCAA2008/GW609) or adjunct therapy (SCAB2009/GW610), with comparisons to lithium and placebo The only information we found about the results of these studies comes from a review of the use of lamotrigine in bipolar disorder, which stated that there were no significant differences between lamotrigine and placebo in either trial on the primary outcome of change in the 11-item MRS score based on data on file from GlaxoSmithKline.[51] In addition, Appendix B of the FDA Medical Review of the NDA materials for lamotrigine in bipolar disorders provides brief summaries of studies of lamotrigine, including SCAA2008 and SCAB2009, but these were not available to us as those pages were withheld from the online report with reasons given as "Trade Secret/Confidential."

Gabapentin

Two studies of gabapentin involved patients with treatment-resistant symptoms of bipolar mania.[53, 54] One compared gabapentin 900 to 3600 mg/d with placebo as add-on treatment in 117 patients with persistent bipolar disorder symptoms despite ongoing therapy with standard mood stabilizers.[53] After 10 weeks, improvement in YMRS scores were significantly greater in the placebo group (-9.9 compared with -6.5; *P*=0.03), and there were no other differences between gabapentin and placebo for the remainder of efficacy outcomes. The second trial used a crossover design to compare 6-week treatment periods with gabapentin 3987 mg, lamotrigine 274 mg, and placebo monotherapies in 31 patients refractory or intolerant to prior treatments with standard mood stabilizers.[54] Patients received all 3 agents sequentially, divided by 1-week washout periods. On the basis of an overall CGI score much or very much improved, response rates for gabapentin (26%) were significantly lower than for lamotrigine (52%; *P*=0.011) and were not significantly different from placebo (23%; *P*=0.700).

Phenytoin

A single trial evaluated the acute antimanic effects of phenytoin when used for 5 weeks in combination with haloperidol in patients with either bipolar I disorder, manic type (N=12), or schizoaffective disorder, manic type (N=18).[55] The results were stratified by diagnosis, allowing for isolation of phenytoin's effect in the subset of patients with bipolar I disorder. Interpretation of findings is limited by lack of information about whether or not the comparison groups were similar at baseline. At week 5, in the subset of patients with bipolar disorder there was added improvement with phenytoin compared with placebo for scores on the BPRS (23.7 compared with 34.5; *P*=0.01), the CGI (2.5 compared with 4.0; *P*=0.001), and the YMRS (9.5 compared with 19.7, *P* not reported).

Hypomania

Oxcarbazepine

The outcomes of treating hypomania with oxcarbazepine 1350 mg monotherapy or adjunct therapy were compared with valproate 1167 mg in 1 small, open-label, outcome assessor-blinded

trial of 30 patients.[56] A variety of concomitant medications were used by 53% of patients in the oxcarbazepine group and 40% in the valproate group. Twice as many patients in the oxcarbazepine group were using concomitant antidepressants (40% compared with 20%), and patients in the oxcarbazepine group were significantly younger (30 compared with 37 years; P=0.05). After 8 weeks, mean reduction in YMRS score with oxcarbazepine (-13.3 points) was comparable to that with valproate (-12.4). However, these results should be interpreted with caution, as it is unclear how the between-groups imbalances at baseline may have biased patient outcomes.

Maintenance of response: Manic/mixed episodes

Valproate

We included 8 trials of maintenance treatment comparing valproate monotherapy with placebo[57-62] or lithium[57, 63, 64] in patients previously experiencing acute mania. A summary of results from all but 2[60, 61] of the included trials was available in a good-quality systematic review and we will summarize those findings here.[20] We will separately summarize the findings of the 2 remaining trials, [60, 61] one of which was carried out in patients with comorbid alcoholism.[61]

Collectively, 6 trials included in a review by Soares-Weiser and colleagues randomized 347 patients to valproate, 231 to lithium, and 102 to placebo and ranged from 6 to 20 months in duration. Populations were diverse across trials. Two trials enrolled only patients with bipolar I disorder.[57, 64] One trial enrolled only patients with rapid-cycling bipolar disorder.[58] And another trial enrolled only women with borderline personality disorder and comorbid bipolar II depression.[59] To determine the efficacy of valproate in preventing relapse in patients with bipolar disorder, Soares-Weiser and colleagues combined data across trials using a fixed-effects model. Findings from these meta-analyses are reported in Table 4. All but 1 trial[64] measured relapse outcomes. Although the trials were clinically heterogenous, no statistical heterogeneity was detected. Compared with placebo, valproate significantly reduced the odds of depressive, but not manic, outcomes. The effectiveness of valproate in reducing odds of all relapses was comparable to lithium. Additionally, results of a secondary analysis from one of the individual trials indicated that the comparability of valproate and lithium did not differ based on whether initial symptoms were euphoric or dysphoric.[65]

Table 4. Odds ratios for relapse of bipolar disorder treated with valproate (Soares-Weiser 2007)

Treatment comparison	Number of studies	N	Odds ratio (95% CI)
Valproate compared with placebo			
All relapses	1	281	0.51 (0.30 to 0.87)
Manic relapses	1	281	0.74 (0.40 to 1.38)
Depressive relapses	2	311	0.32 (0.15 to 0.69)
Valproate compared with lithium			
All relapses	2	327	1.37 (0.84 to 2.24)
Manic relapses	2	327	1.18 (0.67 to 2.08)
Depressive relapses	2	327	1.47 (0.73 to 2.96)

One trial included in the meta-analysis reported not only relapse outcomes but quality-of-life outcomes.[64] This was an open-label trial that randomized 201 adults with bipolar disorder to either valproate 1504 mg or lithium 1213 mg and measured quality of life using the SF-36. At the end of 12 months no difference in quality-of-life outcomes was found between valproate and lithium. However, these analyses appeared to be based on only the 40% of patients that actually completed the study and for that reason should be interpreted with caution.

While several trials looked at monotherapy, 1 trial has evaluated potential benefits of combining valproate with lithium.[60] In a trial that was not included in the meta-analysis above, 12 patients with bipolar I disorder were randomly assigned to open-label valproate plus lithium or placebo plus lithium and followed for up to 12 months. Although significantly fewer patients assigned to valproate plus lithium experienced a relapse compared with placebo plus lithium (0% compared with 71%; P=0.014), no definitive conclusions can be drawn from these results due to small sample size, lack of blinding, and significant between-group differences in mood polarity of patients at baseline.

Prevention of bipolar depression in patients treated for manic/mixed episodes. Patients with recent mania who had previously achieved response with valproate were randomized to valproate, lithium, or placebo and were followed for 1 year.[57, 62] While statistically significant differences were not found between the 3 groups in the primary outcome (time to recurrence of any mood episode), the difference between valproate and lithium reached a P value of 0.06. A difference favoring valproate over lithium was also seen for time to a depressive episode, but again statistical significance was not achieved (P=0.08). Similar results were found for discontinuations due to any mood episode (mania or depression) except that valproate was found to have significantly fewer discontinuations due to depression than placebo (6% and 16%, respectively; P=0.017).

Carbamazepine

We included trials comparing carbamazepine monotherapy with lithium[66-78] or placebo[79] and evaluated efficacy for prophylaxis of recurrence of symptoms in bipolar disorder. Most trials involving lithium enrolled patients diagnosed with any bipolar disorder (I, II, or unspecified) and were heterogeneous with regard to duration, sample size, quality of methods, and method of outcome assessment (Table 5). Regardless of sources of heterogeneity, however, most trials indicated no significant difference between carbamazepine and lithium in preventing relapse, with their trends generally favoring lithium. The exceptions came from 2 of the 3 shortest trials, which followed patients for only 1 year; they reported nonsignificant trends favoring carbamazepine.[66, 69]

In order to more precisely estimate the comparative effectiveness of carbamazepine and lithium in preventing relapse in persons with bipolar disorder, a recent good-quality Health Technology Assessment conducted by Soares-Weiser calculated odds ratios for each of a majority of these same trials[66, 68-70, 80] and, where appropriate, pooled results across trials.[20] Pooled analyses were stratified by whether investigators defined relapse events as hospitalizations only or as assessed changes in symptoms. Additional subgroup analyses were conducted to evaluate the potential effects of type of bipolar disorder and inclusion of patients who were randomized during an acute episode. However, interpretation of the findings from subgroup analyses was limited by small sample sizes. In the main analyses lithium was favored as the more effective agent for preventing relapse-related psychiatric hospitalizations (odds ratio 0.63; 95% CI, 0.33 to 1.2) and relapse-related changes in symptoms assessed by investigators

(odds ratio 0.48; 95% CI, 0.27 to 0.84). In contrast, in a subgroup of 40 bipolar II disorder patients from 1 trial, carbamazepine tended to be more effective in preventing relapse-related hospitalizations (odds ratio 2.50; 95% CI, 0.54 to 11.62) and had an efficacy more comparable to lithium in preventing relapses as assessed by investigators (odds ratio 0.82; 95% CI, 0.24 to 2.83).[80]

Table 5. Relapse outcomes in bipolar disorder treated prophylactically with carbamazepine or lithium

Trial N	Duration in years	Outcome	Result (carbamazepine compared with lithium)
Watkins 1987 N=37	Unclear	Additional time in remission	3.3 months compared with 9.3 months; *P*<0.001
Lusznat 1988 N=54	1	Relapse - hospitalization	18.5% compared with 37%, NS
Coxhead 1992 N=31	1	Relapse	46% compared with 53%, NS
Denicoff 1997[a] N=52	1	Time to first manic episode	66.2 days compared with 89.8 days; *P*=0.024
Simhandl 1993[a] N=84	2	Relapse - hospitalization	36% compared with 14%, NS
Hartong 2003 N=94	2	Relapse - as stated for (1) overall; (2) subgroup prophylactically randomized; (3) subgroup acutely randomized	(1) 42% compared with 27%, NS (2) 47% compared with 13%, *P*<0.05[b] (3) 35% compared with 43%, NS
Greil 1997 N=144	2.5	(1) Relapse - "hospitalization" (2) Relapse - as stated ("recurrence")	(1) 20% compared with 17%, NS (2) 29% compared with 23%, NS
Placidi 1986[a] N=83	3	Relapse - as stated	27.6% compared with 25.9%, NS

[a] Excluded 33% to 58% of patients from analyses due to early discontinuation.
[b] Calculated by the Oregon Evidence-based Practice Center using StatsDirect v2.7.0.

Phenytoin

A single trial evaluated the prophylactic effects of phenytoin added to ongoing therapy of lithium, carbamazepine, valproate, or conventional antipsychotic in 23 patients with a manic type of either bipolar I disorder or schizoaffective disorder.[81] Results were not stratified by diagnosis. Interpretation of findings was limited by lack of information about whether or not the comparison groups were well balanced at baseline; this raises the question of whether between-group differences in patient outcomes were due mainly to true differences in treatment effects or to significant differences among patients. After 6 months, only 30% of patients treated with phenytoin had a relapse event, compared with 61.5% on placebo; *P*=0.53.

Lamotrigine

We included 1 trial comparing lamotrigine for maintenance treatment of manic or hypomanic patients with bipolar I disorder with lithium and placebo.[82] Of the original 349 patients enrolled in this trial, only 184 (53%) were eligible for randomization based on their completion of the 8- to 16-week run-in phase of open-label lamotrigine 100 to 200 mg and on meeting the criterion for response, defined as a CGI-S scale score of 3 or less maintained for at least 4 continuous weeks. Results indicated that lamotrigine improved median time to intervention for recurrence of any mood episode more than placebo (using survival analysis methods, 141 days compared with 85 days; P=0.02) and about as much as lithium (141 compared with 292 days; P=0.46).

Gabapentin

Adjunct treatment with gabapentin or placebo was compared in 25 patients being treated with mood stabilizers who were in clinical remission at study entry.[83] After 1 year, improvements in scores on the modified version of the CGI-BP were significantly greater for gabapentin (-2.1 compared with -0.6; P=0.0046), but gabapentin did not significantly reduce time to first new episode compared with placebo (hazard ratio 1.34; CI not reported).

Oxcarbazepine

Due to methodological limitations, insufficient evidence was provided for drawing any strong conclusions about the general efficacy of oxcarbazepine in two small prophylaxis trials (N=33) of mixed populations (bipolar depression, schizoaffective psychosis, bipolar affective disorders, unipolar mania).[21, 84, 85]

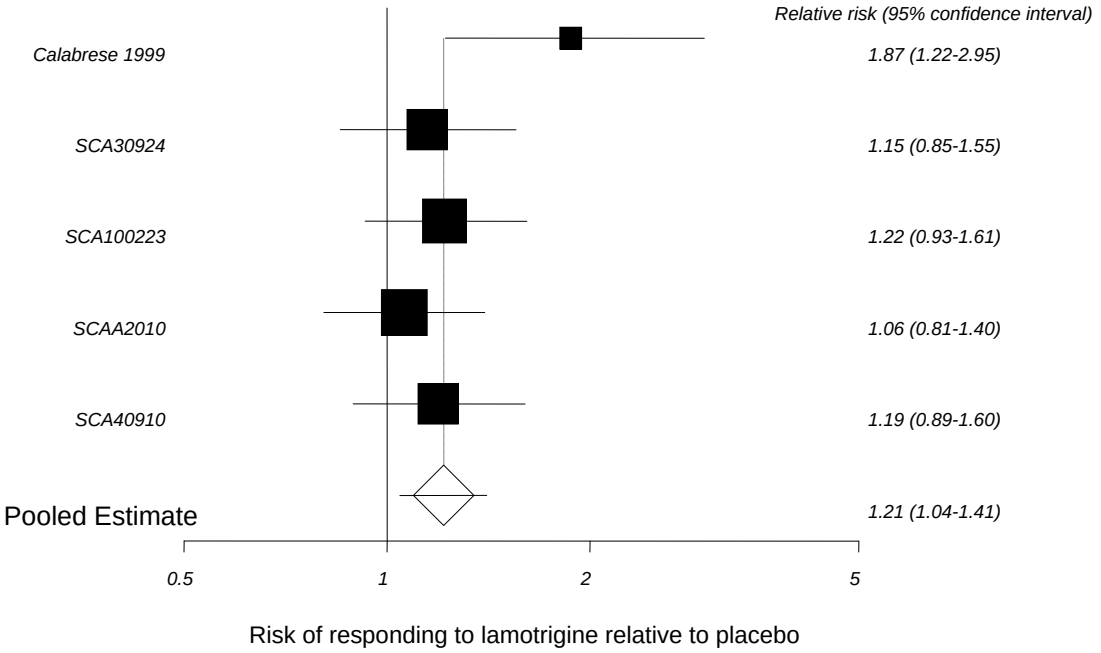
Acute bipolar depression

Lamotrigine

We identified 5 short-term (7 to 10 weeks) completed trials comparing lamotrigine with placebo for acute treatment of bipolar depression. Only 1 has been fully published,[86] although some information on the others has been published in a combined format.[87] Additional details of the results of these unpublished trials are available through the GlaxoSmithKline Trials Registry and at ClinicalTrials.gov.[88-91] These studies included a total of 1138 patients, primarily with bipolar I disorder, who either were depressed or had recently experienced a depressive episode. While we rated the published study fair quality, it was difficult to rate the quality of the others without complete publication. However, based on the available information we do not think that any were poor quality.

Our pooled analysis indicates that lamotrigine was superior to placebo based on response rate, with response defined as a mean change of 50% from baseline HAM-D 17 or MADRS. The pooled relative risk for response on the HAM-D 17 was 1.20 (95% CI, 1.04 to 1.39) and on the MADRS was 1.21 (95% CI, 1.04 to 1.41) (Figure 2). This analysis was based on intention-to-treat populations and used a DerSimmonian-Laird random-effects model. The corresponding numbers needed to treat for 1 additional person to have a response when treated with lamotrigine for 7 to 10 weeks were 13 and 11, respectively.

Figure 2. Response of bipolar depression to lamotrigine based on 50% improvement in MADRS (random-effects model)



In 2 studies[86, 91] the primary outcome measure was improvement on the HAM-D 17, and power calculations were based on finding a 5-point difference in the mean change in score on the outcome measure between groups. In the other 3 studies[88-90] the primary outcome measure was the mean change in MADRS score; again, power calculations were based on finding a 5-point difference on the outcome measure between groups. While none of the studies individually found a statistically significant difference in mean change on HAM-D 17, our pooled analysis indicates a significant benefit of lamotrigine, with a weighted mean difference of -0.99 (95% CI, -1.61 to -0.36). Similarly, only 1 study[86] found a statistically significant difference in the mean change on the MADRS, but our pooled analysis indicates a significant benefit of lamotrigine, with a weighted mean difference of -1.11 (95% CI, -1.49 to -0.74).

There was no difference between lamotrigine and placebo in the risk of patients switching mood from depressed to manic, hypomanic, or mixed in 3 of the 5 trials (relative risk 1.21; 95% CI, 0.40 to 3.62).[86, 88, 91]

Three studies evaluated the short-term efficacy of lamotrigine and non-antiepileptic drugs over 7 to 12 weeks in patients with mainly bipolar depression.[92-94] The largest study (N=410) compared lamotrigine monotherapy with a combination product containing olanzapine and fluoxetine over 7 weeks in patients with bipolar I depression.[92] Across the 3 studies, response rates with lamotrigine ranged from 45% in adjunct treatment[93] to 68 in monotherapy[94] but were not statistically significantly different from placebo or other regimens. Similarly, remission rates were not statistically significantly different between lamotrigine and citalopram, olanzapine/fluoxetine, or lithium. However, some of the differences in response or remission rates were large (for example, remission rates of 35% with lamotrigine and 60% with

citalopram); and, because the sample sizes were small, type II error may explain the lack of significant findings.

While response and remission rates did not identify statistically significant differences among the compared drugs, assessment of mean change in score on various symptom scales did identify some differences. The combination product olanzapine/fluoxetine was found to be statistically significantly superior to lamotrigine on CGS-S, MADRS, and YMRS final scores.[92] Differences were not found between lamotrigine and either citalopram or lithium in mean change on the HAM-D 17, MADRS, or YMRS, although numerical differences were evident; a larger study would be required to clarify the significance of these differences.[93, 94] In the study of lamotrigine and lithium, subgroup analysis among patients with rapid cycling did not indicate a statistically significant difference, and patients with hypomanic symptoms improved in both groups (YMRS ratings).[94]

Rates of switch into hypomania were low overall. Switch into treatment-emergent hypomania (reported as an adverse event by investigators) was not statistically significantly different in any of the comparisons, with a pooled rate of 3.5% for lamotrigine, 1.9% for lithium, 1% for citalopram, and 4% for olanzapine/fluoxetine. However, differences in definitions of switching indicate that this evidence should be interpreted cautiously.

Treatment-resistance in bipolar depression. Two trials compared lamotrigine with other drugs as adjunct therapy in patients whose symptoms were resistant to or who had not tolerated previous treatments given for at least 6 to 12 weeks.[95, 96] Of these, 1 was a very small study (N=20),[96] and the other was part of an NIH-funded study called STEP-BD, which used an equipoise randomization to allow patient preference to be taken into account.[95] Neither study found statistically significant differences between lamotrigine and tranylcypromine, risperidone, or inositol on response or recovery rates, although response rates were numerically higher with tranylcypromine in the small, underpowered study (36.4% compared with 62.5%),[96] and recovery rates (response maintained for 8 weeks) were larger with lamotrigine than risperidone in the other (23.8% compared with 4.6%).[95] The findings of STEP-BD suggest that patients taking lamotrigine stayed on drug longer and had statistically significantly better final depression scores than patients taking inositol and better GAF scores than patients taking risperidone.

An additional study and its related extension study included patients with refractory bipolar and unipolar affective illness, comparing lamotrigine with gabapentin or placebo in a crossover design of 6 weeks each.[54, 97] In this study, 8% of the subjects had unipolar disease. Lamotrigine resulted in more patients having a response, defined as much or very much improved on CGI (lamotrigine, 45% responded; gabapentin, 26%; and placebo, 19%; *P*=0.031). Analysis of only the first randomized drug, in order to avoid carryover effects, showed similar results. Post hoc comparisons of lamotrigine and gabapentin gave a *P* of 0.011.

Valproate

Two placebo-controlled trials of valproate monotherapy in patients with acute bipolar depression found statistically significant benefits for valproate on some, but not all, efficacy outcomes.[98, 99] The studies defined the primary outcome measures as the mean change on the MADRS or HAM-D 17. The mean change on these depression scales was statistically significantly greater in the valproate groups, with a final mean MADRS score of 15.3 for valproate and 22.5 for placebo (*P*= 0.003)[99] and a mean percent change in HAM-D of -44% for valproate compared with -27% for placebo (*P*=0.0002).[98] Both studies also reported greater improvements on HADS and CGI

with valproate, but in only 1 study was statistical significance achieved. [99] In both studies, valproate and placebo groups had similar rates of early discontinuation of assigned treatment.

Only 1 study reported rate of treatment-emergent mania; the rate was higher with placebo (17% compared with 8%), but the difference was only 1 patient.[98] Mania rating scales showed a statistically significant deterioration in the placebo group in 1 study,[99] but no difference in the other.[98] Withdrawal due to increased or continuing symptoms of depression occurred at about the same rate in valproate and placebo groups.

Response and remission were defined very similarly in the studies. Greater than 50% improvement on MADRS indicated response in 1 study,[99] while in the other >50% improvement and score <9 on the HAM-D 17 indicated remission.[98] Valproate was not found to be statistically significantly superior to placebo in response or remission, although the small sample sizes (N=18 and 25) may have been underpowered to find a difference. We are aware of a small unpublished study very similar to these; it found that "43% of valproate-treated patients and 27% of placebo-treated patients achieved recovery, defined as an improvement of ≥50% in score on the 16-item HAM-D in the absence of hypomania (YMRS score <10)."[100]

In a small 6-month study of women with bipolar II disorder and comorbid borderline personality disorder, valproate was not statistically significantly better than placebo on the Symptom Checklist-90 depression subscale.[59] These patients were not experiencing acute symptoms of bipolar disorder at the time of enrollment, so we considered this to be maintenance therapy. We also identified an ongoing maintenance trial of valproate added to lamotrigine treatment for patients with bipolar depression (ClinicalTrials.gov; study code NCT00183469). The trial is expected to be completed in June 2008.

Topiramate

A single, small, 8-week trial compared topiramate with bupropion extended-release as adjunct therapy with mood stabilizers in patients with bipolar disorder whose most recent episode was depression.[22, 101] Statistically significant proportions of patients achieved response and remission in both groups; differences between the drugs were not statistically significant. Other assessments, such as the mean change on HAM-D 17, also indicated significant within-group changes, but no statistically significant differences between groups. Mania ratings also improved in both groups, without a statistically significant difference between groups. Rates of discontinuation due to any reason and due to adverse events were numerically greater in the topiramate group (44% and 33%, respectively) than the bupropion extended-release group (28% and 22%, respectively), but the difference did not reach statistical significance.

Maintenance of response: Bipolar depression

Lamotrigine

Patients who had been successfully treated for acute bipolar depression with lamotrigine were subsequently randomized to lamotrigine, lithium, or placebo in an 18-month maintenance study.[102] Differences were not found between lamotrigine and lithium on the primary outcome measure, time to intervention for *any* mood episode (lamotrigine, 200 days; lithium, 170 days; *P*=0.915), although both were superior to placebo[87] (93 days; *P*=0.029 for each comparison). Similar results were found for discontinuation from study for any reason. Depressive symptoms were the reason for intervention more often than manic symptoms. While lamotrigine was superior to placebo for time to intervention for depressive episodes, and lithium was superior to

placebo for time to a manic episode, differences were not found between the drugs on either measure.

Carbamazepine
We included 1 trial that compared the general efficacy of carbamazepine (immediate-release) with that of placebo in the prophylaxis of bipolar disorder.[79] This was a trial conducted in Japan which enrolled 22 patients diagnosed with bipolar- or manic-type endogenous manic-depressive psychosis according to ICD-9 criteria. Patients were randomized to either carbamazepine 200-1200 mg or placebo and followed for 1 year. Results indicated that carbamazepine completely inhibited or markedly reduced manic-depressive episodes in 60% of patients (compared with 22% for placebo; $P<0.10$). However, our re-analysis of findings from this trial using Fisher's exact test indicated a *P* value of 0.13, suggesting that the difference between carbamazepine and placebo was not statistically significant.

Maintenance of response: Rapid cycling

Lamotrigine
For maintenance treatment of rapidly cycling bipolar disorder, we identified 2 placebo-controlled trials of lamotrigine,[52, 103] only 1 of which is fully published.[103] In the fully published trial,[103] patients entering the 26-week randomized phase consisted of only those who were initially responsive to a preliminary phase of monotherapy with open-label lamotrigine 100 to 300 mg and scored no higher than 14 on the HAM-D and 12 on the MRS (N=182 of an original 324 patients). The main finding of this trial was that lamotrigine did not significantly improve the primary outcome, median time to additional pharmacotherapy for emerging symptoms of any mood episode compared with placebo (18 weeks compared with 12 weeks). For the second, unpublished trial, assessment of methodological quality was limited due to a lack of adequate detail provided by the FDA Medical Review and another narrative review.[51, 52] Our review of the limited data found that this trial did not involve an initial run-in phase; it randomized patients with rapid-cycling bipolar I or II disorder to receive lamotrigine 50 to 400 mg (N=68) or placebo (N=69) as monotherapy or adjunct therapy for 32 weeks. The trial found that lamotrigine did not significantly extend median time to intervention with pharmacotherapy or electroconvulsive therapy compared with placebo (142 days compared with 133 days; $P=0.73$).[51, 52]

Valproate
A single trial compared monotherapy with valproate or lithium in patients with rapid-cycling bipolar disorder and found that valproate was no better than lithium in preventing relapses in this difficult-to-treat population.[58] The trial was designed to test the hypothesis that valproate, at minimum blood levels of 50 µg/mL, would be more effective than lithium, at minimum blood levels of 0.8 mEq/L, in patients who were initially responsive to the combination of the 2 mood stabilizers. Of the 254 patients who initially enrolled in the open-label phase of combination therapy with valproate plus lithium, only 60 patients (23%) responded and were randomly assigned to monotherapy with either agent. After 20 months, just over half of the patients had relapsed, with no significant difference in rate between valproate and lithium, regardless of episode type. Relapses into depressive episodes were more common (31.7%) than relapses into manic episodes (21.7%).

Fibromyalgia

Four placebo-controlled trials assessed short-term (8 to14 weeks) treatment of fibromyalgia, 1 for gabapentin[104] and 3 for pregabalin,[105-107] and 1 placebo-controlled trial of pregabalin assessed relapse over 6 months following response to 6 weeks of treatment with pregabalin.[108]

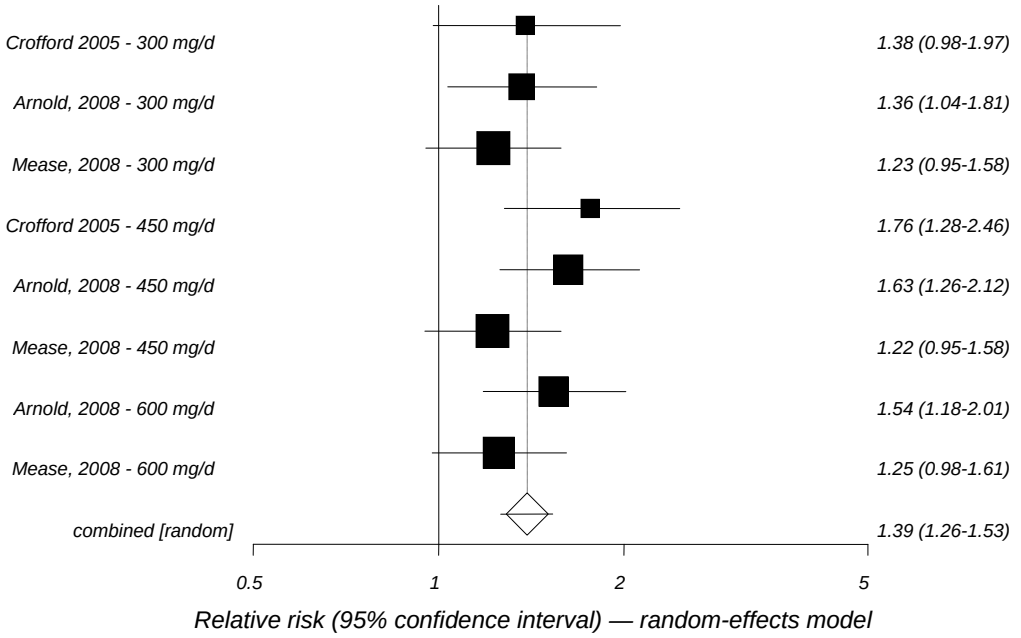
Patient populations were similar across trials, with the overwhelming majority of patients being white females in their late 40s. However, patients in the gabapentin study had lower mean pain scores at baseline (5.8 on an 11-point scale) than those in the pregabalin studies (6.7 to 7.1). The three pregabalin studies were larger than the gabapentin study (N=745, 748, 530 and N=150, respectively). These studies were rated fair quality; although they were double-blind studies, used an intent-to-treat-analysis, and reported attrition, they did not report methods of randomization or allocation concealment. The results and quality of all these trials are summarized in Evidence Tables 5 and 6.

Acute treatment

Response rate

Response was defined as a 30% reduction in pain score in all short-term trials. Our pooled analyses indicate that pregabalin resulted in statistically significantly greater rates of response compared with placebo at 300 mg/d (relative risk 1.31; 95% CI, 1.11 to 1.54), 450 mg/d (relative risk 1.50; 95% CI, 1.20 to 1.87), and 600 mg/d (relative risk 1.38; 95% CI, 1.13 to 1.89). Although the 450 mg/d dose may have the highest response, overlapping confidence intervals preclude making this conclusion. Pooling the 300 mg/d, 450 mg/d and 600 mg/d data indicates a relative risk of response of 1.39 (95% CI, 1.26 to 1.53) with a number needed to treat of 8 (Figure 3). The 150 mg/d dose was not found superior to placebo.[105] Gabapentin showed a greater response rate than placebo (51% compared with 31%; *P*=0.014; our calculated number needed to treat=5).[104]

Figure 3. Response to pregabalin relative to placebo



Using a more stringent definition of 50% or greater reduction in pain, more people responded with pregabalin 450 mg/d than placebo (28.9% compared with 13.2%; *P*=0.003; our calculated number needed to treat=6.4), but again at the lower doses response rates were not significantly greater than for placebo (13% and 18.9%).[105] Pregabalin 600 mg/d recorded the highest responder rate compared with placebo (30% versus 15%; *P*=0.0010; number needed to treat=6.62), and the other treatment arms, 300 mg/d and 450 mg/d, were statistically significantly superior to placebo.[106] Mease and colleagues[107] did not report 50% responder rate.

Quality of life

While all 3 studies of pregabalin measured health-related quality of life using the SF-36, reporting was inconsistent, such that pooled analyses could not be undertaken. Overall, pregabalin improved scores on some, but not all, SF-36 domains with some variation based on dose, relative to placebo in 2 studies.[105, 106] Both studies found that social functioning and vitality scores improved statistically significantly more with pregabalin 450 mg/d than placebo. The third study did not report the change from baseline in health-related quality of life but stated that there were no statistically significant differences at endpoint in any of the pregabalin treatment groups compared with placebo.[107]

Pain

Mean pain score at endpoint was the primary outcome measure in all 4 short-term studies, all using an 11-point numerical rating scale where 0=no pain and 10=worst possible pain.[104-107] Mean pain scores at endpoint in the gabapentin 1800 mg/d groups (3.2) was significantly lower than in the placebo group (4.6; *P*=0.015). Pregabalin 300, 450, and 600 mg/d resulted in statistically significantly lower scores than placebo, with one exception (see Table 6). In the Crofford study, pregabalin 300 mg/d did not result in a final score that was statistically

significantly lower than with placebo.[105] Differences in mean pain score at endpoint did not reach statistical significance for pregabalin 150 mg/d.

Table 6. Change in average pain score in fibromyalgia treated with an antiepileptic drug compared with placebo

Trial	Antiepileptic drug	Baseline pain	Endpoint pain	Between-groups difference
Arnold 2007 12 weeks	gabapentin 1800 mg/d	5.8	3.2 compared with 4.6 *P*=0.015	-0.92[a]
Crofford 2005 8 weeks	pregabalin 300 mg/d pregabalin 450 mg/d	7.0	5.47 compared with 5.88 (NS) 4.94 compared with 5.88 *P*=0.0009	-0.41 -0.93
Mease 2008 13 weeks	pregabalin 300 mg/d pregabalin 450 mg/d pregabalin 600 mg/d	7.1	5.26 compared with 5.7 *P*=0.0449 5.23 compared with 5.7 *P*=0.0449 5.04 compared with 5.7 *P*=0.0070	-0.43 -0.47 -0.66
Arnold 2008 14 weeks	pregabalin 300mg/d pregabalin 450 mg/d pregabalin 600 mg/d	6.7	4.93 compared with 5.64 *P*=0.0009 4.66 compared with 5.64 *P*< 0.0001 4.64 compared with 5.64 *P*< 0.0001	-0.71 -0.98 -1.00

[a] Difference is calculated based on a model including a treatment by time factor.

Other outcomes

Numerous secondary outcomes were reported in all trials. In general, results from these analyses found significant improvements for gabapentin and pregabalin compared with placebo. One of the exceptions was that gabapentin was not superior to placebo in improving associated depressive symptoms. On MADRS gabapentin measured 9.1 compared with placebo 13.9, *P*=0.067.[104] On HADS neither the depression nor anxiety scores were significantly different between pregabalin and placebo groups,[105, 106] with the exception of anxiety symptoms with pregabalin 600 mg/d (difference from placebo -0.79; *P*=0.014).[106] In the other pregabalin study by Mease, it was noted that other than sleep, secondary efficacy measures did not show any statistically significant difference between any of the treatment groups compared with placebo at endpoint.[107]

Relapse

Crofford and colleagues[108] reported the only long-term (6-month) trial that studied relapse of symptoms of fibromyalgia. The objective of the trial was to study the duration of efficacy of pregabalin in treating fibromyalgia. All patients underwent a 6-week open-label phase in which they received escalating doses of pregabalin to determine their optimal dosages. At the end of the open-label phase, responders (greater than 50% reduction in pain using a 100-mm visual analog scale and a self-rating of "much" or "very much" improved on PGIC) entered a double-blind

phase in which patients in one arm received placebo and patients in the other arm received their optimal pregabalin dosage. The primary outcome was the time to loss of therapeutic response, defined as <30% reduction in pain from open-label baseline or worsening of fibromyalgia, requiring alternate treatment.

Of 1051 patients enrolled in the open-label period, 566 were responders (53.8%). The discontinuation rate in this double-blind trial was very high, with 81% of the placebo group and 62% of the pregabalin group discontinuing the study prior to 6 months. Time to loss of therapeutic response was longer for pregabalin than placebo ($P<0.001$). Comparing the first quartile, the median time to loss of therapeutic response was 7 days for placebo and 34 days for pregabalin. At end of the 6-month double-blind phase, 61% of placebo patients met loss of therapeutic response criteria, compared with 32% of pregabalin patients.

Because all patients who withdrew from the study were counted as *not* having loss of therapeutic response in the primary analysis, sensitivity analysis was done counting these patients as having *had* loss of therapeutic response. This sensitivity analysis resulted in similar results, with a $P<0.0001$, although the time to event in the first quartile was 6 days for placebo and 18 days for pregabalin, a difference of 12 days compared with a difference of 27 days in the primary analysis. Several other sensitivity analyses were conducted; all found pregabalin superior to placebo.

Migraine prophylaxis

Previous systematic review

A Cochrane review by Chronicle and colleagues[2] of antiepileptic drugs for migraine prophylaxis assessed the efficacy of carbamazepine, valproate, lamotrigine, gabapentin, and topiramate compared with placebo. Patients with chronic migraine, transformed migraine, or chronic daily headache were excluded from the Chronicle review. Reasons for excluding chronic migraine included concerns with inconsistencies in classification of chronic migraine and concerns with variability of response to treatment due to severity. Further discussion of these issues can be found in the publication.

Chronicle and colleagues conducted meta-analyses by drug for migraine frequency and for the proportion of patients achieving ≥50% reduction in migraine frequency. Table 7 summarizes the results from placebo-controlled trials: Only lamotrigine was not statistically significantly superior to placebo. Before putting significant weight on the pooled estimates from their review, the authors point out that much of the included literature had several methodologic limitations. These included selective outcome reporting, misrepresentation of intention-to-treat analyses, and inadequate measures to minimize carryover effect in crossover studies. Differences across these studies make qualitative indirect comparisons unwise. Despite these caveats, however, pooled effects for antiepileptic drugs were likely more robust in their estimates than effects estimated for agents with 1 trial. Therefore, more evidence supports use of valproate or topiramate for migraine prophylaxis than carbamazepine, lamotrigine, or gabapentin (Table 7). Furthermore, results from active-control trials that compared valproate and topiramate with propranolol or flunarizine (2 agents with evidence on efficacy) provided additional support for this conclusion. Sodium valproate and divalproex sodium are reported separately in this review (see Table 7).

Table 7. Pooled results of antiepileptic drugs compared with placebo for reduction of migraine frequency (Chronicle 2004)

Antiepileptic agent	Reduction in migraine frequency per month		Proportion with ≥50% reduction in migraine frequency	
	N studies/ subjects	SMD (random), 95% CI	N studies/ subjects	Odds ratio (95% CI)
Divalproex sodium	---	---	4/574	3.34 (1.46 to 7.67)
Sodium valproate	2/126	-0.87 (-1.24 to -0.50)	1/68	4.67 (1.54 to 14.14)
Topiramate[a]	4/534	-0.37 (-0.54 to -0.20)	6/898	3.34 (2.36 to 4.73)
Gabapentin	1/63	-1.94 (-2.55 to -1.33)	1/87	4.51 (1.51 to 13.43)
Lamotrigine	1/77	0.09 (-0.36 to 0.53)	---	---
Carbamazepine	---	---	1/48	11.77 (3.92 to 35.32)

Abbreviation: SMD, standardized mean difference.
[a] Results for topiramate 100 mg/d.

Many of the included trials studied various doses of antiepileptic drugs (Table 8). Chronicle and colleagues assessed the impact of various doses for valproate and topiramate. No clear dose-response was found for the drugs, although the 50 mg/d dose of topiramate resulted in the lowest standardized mean difference in migraine frequency among topiramate doses (50, 100, or 200 mg/d). However, the number of studies in these analyses was few, and the resulting confidence intervals were wide, such that these findings should be used with caution. Also, many of the active-control trials used dose comparisons that could be considered unequal.

Table 8. Studied doses of antiepileptic drugs for migraine prophylaxis

Antiepileptic drug	Daily dose (mg/d)
Carbamazepine	Not reported
Sodium valproate	400 – 1500
Divalproex sodium	500 – 1500
Gabapentin	1200 – 2400
Lamotrigine	50 – 200
Oxcarbazepine	1200

Additional trials

We identified 10 trials not included in the Chronicle review: 1 valproate,[109] 1 carbamazepine,[110] 7 topiramate[111-117] (including 1 trial with lamotrigine and placebo comparisons),[113] and 1 oxcarbazepine.[118] The carbamazepine trial[110] was rated as having poor internal validity due to inadequate randomization, allocation, and blinding, and lack of an intention-to-treat analysis. Four topiramate trials were conducted in patients with chronic migraine,[111, 114, 116, 117] a population excluded from Chronicle, and 1 topiramate trial[112] assessed cessation compared with

continuation of therapy. The results from these trials will be discussed briefly here. We also independently evaluated all trials for quality-of-life information.

Direct comparisons of antiepileptic drugs

We identified 2 trials directly comparing one antiepileptic drug with another.[113, 119] In 2 small (N=60 and N=64) crossover studies topiramate was compared with lamotrigine, and topiramate was compared with valproate and placebo. At the end of 20 weeks, a larger portion of the topiramate group than the placebo group achieved ≥50% reduction in migraine frequency (63% compared with 30%; 95% CI, 0.18 to 0.46). Similar to the findings of Chronicle, there was no statistically significant difference in the proportion of patients with ≥50% reduction in migraine frequency for lamotrigine compared with placebo (46% compared with 34%; 95% CI, 0.02 to 0.26). However, when topiramate was compared with lamotrigine, more patients had a response with topiramate than with lamotrigine, although the confidence interval was wide (63% compared with 46%; 95% CI, 3% to 31%).[113]

In the direct comparison of valproate and topiramate, analysis of the first drug assigned found no statistically significant difference in headache frequency, but topiramate was better at reducing headache intensity (mean difference on 10-point visual analog scale 2.1; 95% CI, 1.4 to 2.9) and headache duration (mean difference 8.4 hours; 95% CI, 4.5 to 12.3). In analysis of the second randomized period, topiramate was superior in reducing the number of headaches (mean difference 1.2 per month; 95% CI, 0.2 to 2.1), but no difference was found in severity or duration. Using ANOVA to analyze the first and second randomized periods combined, the authors found no statistically significant differences. However, the conflicting findings of the first and second periods raises the question of carryover effects, such that data from the first period is preferred.

Comparisons with placebo

For topiramate, 2 studies published since the Chronicle review reported conflicting findings: The larger study was unable to find a statistically significant difference compared with placebo, while the smaller study did.[113, 115] Pooling these studies with the previous studies indicates a statistically significant benefit of topiramate (odds ratio 3.04; 95% CI, 1.95 to 4.74). This compares with the pooled odds ratio for topiramate compared with placebo reported by Chronicle of 3.34 (95% CI, 2.36 to 4.73). The mean change in migraine frequency was quite different in the 2 trials, and inadequate data were reported to allow pooling with the previously reported studies (see Table 9).

Table 9. Topiramate compared with placebo for prophylaxis of migraine

Trial	N	Reduction in mean number of migraines per month (change from baseline)	Proportion of group with ≥50% reduction in migraine frequency
Silberstein 2006	211	-1.43 compared with -1.04, *P*=0.29	39.9% compared with 34.2%, *P*=0.27
Gupta 2007	113	-4.21 compared with -2.71, *P*<0.001	63% compared with 30%, *P*<0.001

Treatment with oxcarbazepine was not superior to placebo in reducing migraine frequency (change from baseline, -1.10/mo compared with -1.16/mo; *P*=0.82) or in achieving ≥ 50% reduction in frequency (27.1% compared with 23.5%; *P*=0.557) over 19 weeks of therapy in 170 adults.[118] No additional placebo-controlled trials were identified for carbamazepine, valproate, or gabapentin.

One new active-control trial that compared valproate with subcutaneous histamine was identified.[109] No significant difference in treatment effect for lowering migraine frequency or MIDAS scores was observed in 92 adults randomized to valproate or subcutaneous histamine injection at the end of 12 weeks.

Quality-of-life and disability outcomes

Among all studies from the Chronicle review and an updated search, only 3 topiramate trials[120-122] and 1 oxcarbazepine trial[118] assessed quality-of-life outcomes. There were no significant differences between oxcarbazepine-treated and placebo-treated patients in improvement of quality-of-life scores using the SF-36 assessment tool.[118] In 2 trials of 937 adults[120, 122], patients treated with topiramate 50-200 mg reported significantly better improvement in the performance of daily activities limited by migraine headaches per MSQ-RR than patients treated with placebo. Similar findings were observed with MSQ-RP scores as well.

Topiramate more greatly reduced the number of disability days due to headache than placebo.[121] Baseline mean days with disability was approximately 7. At the end of 16 weeks, the reduction in disability days was significant for topiramate and not placebo (change from baseline -4.3 days compared with -1.0 days, *P*<0.001).

Topiramate cessation compared with continuation

One new topiramate trial[112] compared cessation with continued therapy in a study that began with a 26-week open-label phase and followed with a 26-week double-blind phase. Of 818 adults enrolled in the open-label phase using topiramate, 63% remained and were randomized to continue with topiramate or switch to placebo in the double-blind phase. The primary objective was to evaluate rebound effect after discontinuation of migraine prophylaxis by comparing the number of migraine days during the last month of the double-blind phase with the number of migraine days in the last month of the open-label phase. Patients who switched from topiramate to placebo after 26 weeks experienced an increase in the number of migraine days in a month by 1.19 (95% CI, 0.71 to 1.66). In contrast, patients who continued topiramate experienced minimal change in migraine days (+0.10 days/mo; 95% CI, -0.36 to 0.56). Despite worsening control of migraines, the number of migraine days in the placebo group during the last month of the double-blind phase (5.82 days/mo) did not return to baseline (8.9 days/mo, *P*<0.001).

Chronic migraine

Chronicle and colleagues excluded chronic migraine studies from their review due to concerns with significant differences in disease severity relative to patients without chronic migraines. We identified 3 placebo-controlled trials of topiramate[114, 116, 117] and 1 head-to-head trial[111] evaluating topiramate and valproate and decided to review the results independently and assess whether the results were significantly different between those with and without chronic migraine.

A small (N=49), open-label, active-control trial comparing topiramate 75 mg/d with divalproex sodium 750 mg/d found that at the end of 12 weeks, topiramate-treated and valproex-treated patients exhibited similar reductions in headache frequency (change from baseline, -23.3

headaches/mo with topiramate compared with -23.8 headaches/mo with valproate; between-group *P* value, not reported).[111] The results from this poor-quality study should be considered with caution since about 10% of the population were not included in the analyses. Two placebo-controlled trials showed topiramate was more effective than placebo in reducing migraine frequency and monthly migraine days.[116, 117] In a study of 306 adults [116] the change in mean monthly migraine days for topiramate was -6.4 and for placebo was -4.7, *P*=0.01. An additional trial showed similar findings but was rated poor.[121]

Although the collective result shows that topiramate is more effective than placebo, it is unclear whether the findings in patients with chronic migraine headache should be combined with results in patients without chronic headaches.

Chronic pain

Very little evidence was found to support the short-term use of tiagabine, topiramate, or gabapentin for treatment of chronic pain conditions.[123-125] No evidence was found for other antiepileptic drugs. Full details are given in Evidence Tables 7 and 8.

Open-label tiagabine and gabapentin were directly compared in 91 patients with various types of chronic pain despite ongoing treatment with analgesics or antidepressants.[125] Most patients were diagnosed with either musculoskeletal headache or cervical pain. Most of the population was female (78%), and the mean age was 44 years. Study medications were available only at the patients' expense and were given in addition to ongoing treatment regimens. After 3 months, tiagabine and gabapentin were associated with similar reductions in pain score (-2.3 compared with -1.2 points on an 11-point scale; not statistically significant). Tiagabine (-3.0 points; *P*=0.04) resulted in significantly greater improvement in ratings for sleep quality than gabapentin (-1.54 points).

Topiramate improved pain and associated difficulties significantly more than placebo in a 10-week, fair-quality, double-blind trial of 96 patients with chronic low-back pain who had never undergone back surgery.[124, 126] Overall, 75% of patients were male and their mean age was 49 years. Patients were required to discontinue analgesic or anti-inflammatory medications 1 week before randomization but were allowed to continue any prestudy antidepressant medications. Compared with placebo, topiramate significantly improved pain, associated disability, anger, and quality of life based on scores on the MPQ (-0.1 compared with -1.2 points; *P*<0.001), STAXI, OLBPQ, and SF-36.

Gabapentin was found to have significant analgesic effect compared with placebo in a 12-week, fair-quality, double-blind trial of 50 patients with moderate to severe chronic pain of the masticatory muscles of at least 6 months' duration.[123] All patients enrolled in this trial were female, with a mean age of 34 years. Although ongoing use of muscle relaxants and/or anti-inflammatory drugs was prohibited during the trial, acetaminophen was allowed for breakthrough pain. Patients were also allowed to continue ongoing psychotropic medication regimens (for example, tricyclic antidepressants, benzodiazepines, selective serotonin reuptake inhibitors). In addition to superior reductions in pain compared with placebo (51% compared with 24% reduction based on visual analog scale; *P*=0.037), gabapentin also resulted in greater reduction in number of tender palpation sites from 9.5 at baseline (-6.46 compared with -1.90; *P*=0.002) and greater reduction in impact of pain on daily functioning as measured using a visual analog scale (-53% compared with -19%; *P*=0.026).

Key Question 2

For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in safety or adverse events?

The adverse event profiles of the antiepileptic drugs vary considerably, with overlap only in adverse effects that may affect tolerability, such as somnolence.[127, 128] Comparative assessments of common, overlapping adverse effects were undertaken where possible based on direct evidence from the populations of interest in this review. Emphasis was on the comparison of rates of any adverse event, withdrawals due to adverse events, and longer-term evidence in "real-life" populations (observational studies). For the purposes of this review, side effects that are unique to individual antiepileptic drugs are summarized based on existing reviews, including rare but serious adverse events such as birth defects. Because epilepsy and its treatment are complex and may affect the adverse events experienced with an antiepileptic drug, evidence relating to the population of patients with epilepsy was not reviewed other than to provide basic estimates of rates of adverse events or to provide evidence on harms with long-term effects, such as suicidal ideation.

Suicide

An FDA advisory to healthcare professionals warning of potentially increased risk of suicidality with antiepileptic drugs was published in February 2008. In May 2008 the FDA completed an initial analysis of data on suicide relating to antiepileptic drugs, in preparation for an advisory committee meeting to be held in July 2008 (http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm). Their analysis included 11 drugs: carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide. The meta-analysis was based on 199 placebo-controlled trials, with reports of completed suicides or suicidal ideation/behavior as the primary outcomes. The conclusions of this report are that as a group, these drugs are associated with an increased risk of the patient experiencing a suicidal ideation or behavior; odds ratio compared with a placebo patient was 1.80 (95% CI, 1.24 to 2.66). The number of suicide deaths was small (N=4) but greater than in the placebo groups (N=0), although numbers were insufficient to show statistical significance.

Based on these results, the FDA asked for an advisory committee review to consider regulations requiring "black box" warnings be added to *all* antiepileptic drugs based on the fact that 8 of 11 drugs had a numerically increased odds ratio with only 2 (lamotrigine and topiramate) reaching statistical significance. Three drugs (carbamazepine, divalproex, and tiagabine) did not have odds ratios greater than 1, and the authors of the report note that carbamazepine and tiagabine have had relatively few patients studied (N=502 and 1443, respectively), such that the risk is less certain. For felbamate, no cases were found in either group, with a total of 340 patients studied.

The advisory committee voted against adding a black box warning across the class at this time (http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4372t1.pdf). The committee was not convinced of a class effect and wanted to see an analysis that looked at the drugs individually; assessed geographic differences, differences among indications, longer treatment periods (the analysis was limited to studies of 24 weeks or less), and use in monotherapy versus polytherapy; and used sensitivity analyses to test assumptions about zero events and ascertainment of suicidality. Much of the discussion centered on these issues, particularly how

they had been handled in the previous FDA analysis of suicidality associated with newer antidepressant drugs and the impact of the black box warning added to those drugs.

A cohort study with a mean follow-up period of 2.9 years provided data on suicide risk with carbamazepine, divalproex, and lithium in patients with bipolar disorder.[129] This fair-quality study used a large, computerized, prescription database to retrospectively identify a cohort of 20 638 patients with bipolar disorder. 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) 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) for suicide attempts resulting in hospitalization and 1.8 (95% CI, 1.4 to 2.2) 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). 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 2 drugs 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). An analysis for time-dependent risk differences between valproate 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 revealed little difference in risk in switching from divalproex to lithium and vice versa. Therefore, it appeared that any medication switch was associated with a higher, roughly 2-fold risk of suicide attempt.

Bone fractures

A good-quality case-control study included 124 patients who had sustained a fracture as identified in the National Hospital Discharge Register of Denmark and 373 962 randomly selected gender- and age-matched controls.[130] Adjusted odds ratios (odds ratio; 95% CI) for any fracture in patients who used antiepileptic drugs were significantly increased 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 odds ratios were nonsignificant but increased 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, or valproate. There was a significant dose-response relationship for carbamazepine, oxcarbazepine, and valproate, and no significant dose-response relationship for lamotrigine, phenytoin, tiagabine, or 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 that there are differences between antiepileptic drugs, because the confidence intervals overlapped. No data were available for gabapentin and levetiracetam.

A second case-control study of 1018 cases and 1842 matched controls also found that exposure to antiepileptic drug increased risk of fracture.[131] The risk increased with duration of exposure, with the strongest association at greater than 12 years of use (adjusted odds ratio 4.15; 95% CI, 2.71 to 6.34), with higher risk among women and no difference between antiepileptic drugs that do or do not induce the hepatic cytochrome P450 system. It should be noted that this study was done within a cohort study of epilepsy patients; the data may or may not translate to nonepileptic patients.

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.[132, 133] The first provided comparative data for 5 antiepileptic drugs. It was conducted in hospitals in France, Germany, Italy, and Portugal.[133] 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 (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 antiepileptic drugs was a potential confounder for an association with valproate. Therefore, the risks of these serious skin reactions appear to be increased for short-term (≤ 8 weeks) use of phenobarbital, phenytoin, and carbamazepine. The numbers for lamotrigine were too small for meaningful analysis.

The second 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.[132] 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.

Aplastic anemia and agranulocytosis

A good-quality, population-based, case-control study of antiepileptic drug–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).[134] A total of 177 case subjects and 586 matched controls was 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 (odds ratio 10.96; 95% CI, 1.17 to 102.64). The odds ratio was not calculated for phenytoin because of the small number of exposures. 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.

A similar study used data from the UK General Practitioners Research Database to identify 173 cases and 497 matched controls.[135] The study covered the years 1987 to 2002, when carbamazepine, phenytoin, and valproate were the most commonly used antiepileptic drugs, and lamotrigine saw only limited use. Only 16 of the 173 cases were using an antiepileptic drug prior to the event, although use of any antiepileptic drug was statistically significantly associated with aplastic anemia (odds ratio 9.5; 95% CI, 3.0 to 39.7). The odds ratios for individual drugs were carbamazepine 10.3 (95% CI, 2.0 to 101), phenytoin 3.5 (95% CI, 0.4 to 44), and valproate 18.2 (95% CI, 2.5 to infinity). The broad confidence intervals reflect the small number of cases.

Birth defects

We found 19 studies reporting the risk of birth defects among women treated with antiepileptic drugs during pregnancy.[131, 136-153] Of these, 9 are studies of only women with epilepsy and are not considered here due to the complex nature of both the disease and use of multiple antiepileptic drugs concurrently, potentially resulting in drug interactions and drug-disease interactions that may have complex adverse impact on fetal development.[131, 136-138, 140, 145, 147, 148, 152] The subject of whether epilepsy is associated with birth defects has been debated and reviewed elsewhere.[154] Five studies[138, 139, 142-144, 146] examined the relationship between birth defects and exposure to antiepileptic drugs among broader populations of patients, 2 of which combined data for all antiepileptic drugs.[142, 143] These studies are reviewed here.

In 2005, a review of the relationship between birth defects and exposure to antiepileptic drug during pregnancy (for any reason) found that exposure to older antiepileptic drugs during the first trimester is associated with an increased risk compared with the general population, 4%-10% compared with 2%-5%.[155] The review also confirms the belief that antiepileptic drug monotherapy is associated with somewhat lower risk of birth defects than antiepileptic drug polytherapy. While specific rates vary among studies, differences in rates of birth defects among infants exposed in utero to carbamazepine, phenytoin, and phenobarbital were not found. However, valproate was associated with a higher risk, with odds ratios of 2 to 4, than carbamazepine, lamotrigine, and all other antiepileptic drugs combined. Some studies indicate a dose-dependent relationship, with valproate doses of 800 to 1000 mg/d associated with higher risk. A more recent case-control study found an increased risk of cleft palate among infants exposed to phenytoin during the second and third month of pregnancy and increased risk of posterior cleft palate among infants exposed to carbamazepine during the third and fourth months of pregnancy.[144]

Of the newer antiepileptic drugs, only lamotrigine has been well studied, through 2 registries. In the review conducted in 2005, analysis of data from one of these registries indicated a potential dose-response association for lamotrigine, with doses of > 200 mg/d associated with risk approaching that of valproate 1000 mg/d.[155] However, in an analysis of the manufacturer's registry a dose-effect was not seen in doses up to 400 mg/d. Data on doses above 400 mg/d were too limited for meaningful analysis.[138] Studies did not indicate a significant difference in risk between lamotrigine and carbamazepine. Oxcarbazepine had a risk similar to carbamazepine and phenytoin in a single retrospective study; the risk for valproate was higher. Studies of topiramate exposure during pregnancy are limited to 2 small registry studies, one including only women with epilepsy[152] and the other a very small study in women taking topiramate for unspecified reasons.[153] This study found the rate of nongenetic major malformations to be 4.9% with

topiramate, compared to 3.4% in a control group not exposed to topiramate. This difference was not statistically significant. Gabapentin and levetiraetam have only very limited evidence, such that conclusions cannot be drawn.

Polycystic ovary syndrome

Polycystic ovary syndrome is an endocrine disorder with increased androgen production, abnormal gonadotropin secretion, anovulation, and menstrual dysregulation. Valproate has been identified as a drug that is potentially associated with polycystic ovary syndrome, although there is debate about the relationship between polycystic ovary syndrome and the underlying disease states, such as epilepsy or bipolar disorder. In a study that enrolled women taking valproate for bipolar disorder, with no preexisting polycystic ovary syndrome, new-onset oligomenorrhea that could not be explained by other reasons was identified and compared with a group of women being treated with another mood stabilizer, including other antiepileptic drugs. The resulting sample size was small, N = 230. The rate of new-onset oligomenorrhea with hyperandrogenism was 10.5% in the valproate group and 1.4% in the control group (P=0.002).

While we found 3 other studies examining the effects of valproate in women with bipolar disorder, concerns over study design limits their usefulness in this report.[156-158] One is a cross-sectional study using interviews to obtain menstrual histories; another is a related study with a cross-sectional component and a 17 month follow-up of 56% of the original cohort. The third is an extension of the cohort study discussed above, but this one reports only on women who developed polycystic ovary syndrome while on study or were considered at risk. This is also a very small study, with only 14 women participating.

Delirium

Valproate was not found to be associated with a statistically significant increase in diagnosis of delirium compared with lithium among older patients (age > 65 years) being treated for mood disorders.[159] Using 4 databases, the study found that the hazard ratio of a diagnosis of delirium during a hospitalization was 1.07 (95% CI, 0.67 to 1.70) for valproate compared with lithium.

Overall adverse event rates

Seven head-to-head trials compared topiramate with sodium valproate for migraine prophylaxis; 1 compared topiramate with divalproex for acute mania; 1 compared topiramate with lamotrigine for migraine prophylaxis; 1 compared lamotrigine with gabapentin for refractory mood disorders; 1 compared gabapentin with tiagabine for chronic pain; and 1 compared carbamazepine with sodium valproate for acute mania.[23, 46, 54, 111, 113, 119, 125] Rates of any adverse event and withdrawals due to adverse events were reported in most of these trials, and those data provided the basis for evaluation of direct comparative safety among the antiepileptic drugs (Table 10).

In the trial of carbamazepine and divalproex, a larger number of patients reported an adverse event with carbamazepine than divalproex, with no difference in withdrawals. None of the other trials individually showed statistically significant differences in rate of overall adverse events or withdrawals due to adverse events. Two studies compared sodium valproate and topiramate; again, the pooled analysis did not indicate a significant difference between the drugs. However, these were small fair- to poor-quality studies, with the largest enrolling only 91 patients; it is unlikely that these studies would find statistically significant differences.

Table 10. Risk of any adverse event in head-to-head trials of antiepileptic drugs

Study	Comparison	Relative risk of any adverse event (95% CI)	Relative risk of withdrawal due to adverse event
Bahk 2005	Divalproex and topiramate	Not reported	None reported
Bartolini 2005	Sodium valproate and topiramate	Not reported	1.00 (0.35 to 2.86)
Shaygannejad 2006	Topiramate and sodium valproate	Not reported	Zero withdrawals in both groups
	Pooled risk difference of withdrawals (Bartolini and Shaygannejad) = 0 (-0.06 to 0.06)		
Frye 2000	Lamotrigine and gabapentin	0.63 (0.33 to 1.13)	2 (0.27 to 14.94)
Gupta 2007	Topiramate and lamotrigine	1.5 (0.63 to 3.65)	1 (0.11 to 9.33)
Todorov 2005	Tiagabine and gabapentin		0.98 (0.28 to 3.39)
Vasudev 2000	Carbamazepine and divalproex	**4.00 (1.29 to 14.81)**	None reported

Adverse events were reported in 51 placebo-controlled trials. Of these, 31 reported the number of patients with any adverse event, and 47 reported the number of withdrawals due to adverse events, allowing comparisons to be made. Specific adverse event rates are discussed elsewhere, but because the antiepileptic drugs differ so greatly in their adverse effects, it may be more useful to compare the overall rates of adverse events and rates of withdrawal from study drug due to adverse events. Withdrawal due to adverse events is an appealing measure, because it incorporates the severity of the events. Pooled estimates (Table 11) show that in nonepileptic populations, only topiramate and carbamazepine result in significantly greater rates of adverse event reports than placebo. Withdrawal from study drug due to adverse events is also statistically significantly greater with carbamazepine and topiramate, and also with valproate (immediate-release). These results apply when these drugs are used primarily as short-term monotherapy.

Table 11. Risk of adverse events with antiepileptic drugs compared with placebo

Drug	Relative risk of any adverse event (95% CI)[a]	Relative risk of withdrawal due to adverse events (95% CI)[a]
Carbamazepine	**1.63 (1.14 to 2.33)** **ER 1.40 (1.04 to 1.88)**	**ER 1.98 (1.02 to 3.86)**
Gabapentin	1.38 (0.97 to 1.95)	1.63 (0.93 to 2.84)
Lamotrigine	1.03 (0.93 to 1.13)	1.30 (0.96 to 1.77)
Phenytoin	NR	23.12 (0.26 to 2033)
Pregabalin	1.23 (0.98 to 1.53)	1.81 (0.95 to 3.43)
Topiramate	**1.15 (1.04 to 1.27)**	**2.22 (1.76 to 2.80)**
Valproate	1.14 (0.96 to 1.35) IR 1.33 (0.90 to 1.97) ER 1.07 (0.89 to 1.29)	**2.23 (1.47 to 3.40)** **IR 2.95 (1.66 to 5.26)** ER 1.68 (0.53 to 5.33)

Abbreviations: ER, extended release; IR, immediate release.
[a] DerSimmonian and Laird random-effects model.

Results of all studies are shown by drug in the forest plot in Figure 4. For studies in which zero events occurred in one group, a correction factor was used in the analysis and the resulting confidence intervals extend to infinity. For studies in which zero events occurred in both groups, no point estimate could be calculated. For rates of any adverse events, there is 1 outlier, a small study of valproate (N=74) in which no adverse events were reported in the placebo group and adverse events were experienced by 54% of patients in the valproate group.

Based on crude indirect comparisons of the antiepileptic drugs, no difference in the overall rate of adverse events is apparent, although the rate relative to placebo is higher for carbamazepine and topiramate. In Figure 5, withdrawals across all studies show that although most point estimates indicate higher rates (relative to placebo) with the study drug, the differences are not statistically significant. The graph supports the pooled estimates: Carbamazepine, valproate, and topiramate have higher rates of withdrawal than placebo.

Figure 4. Relative risk of any adverse event: Antiepileptic drug compared with placebo

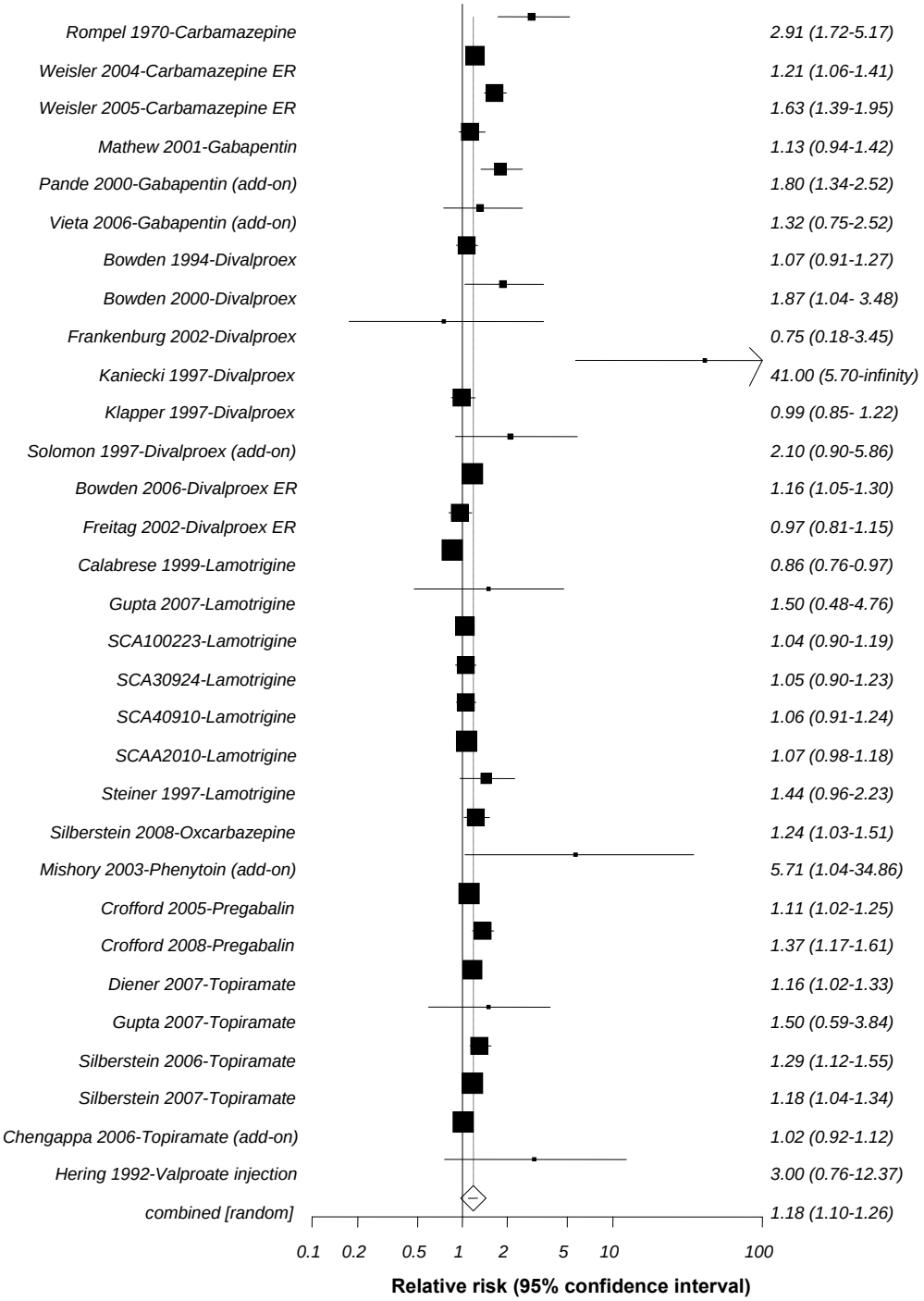
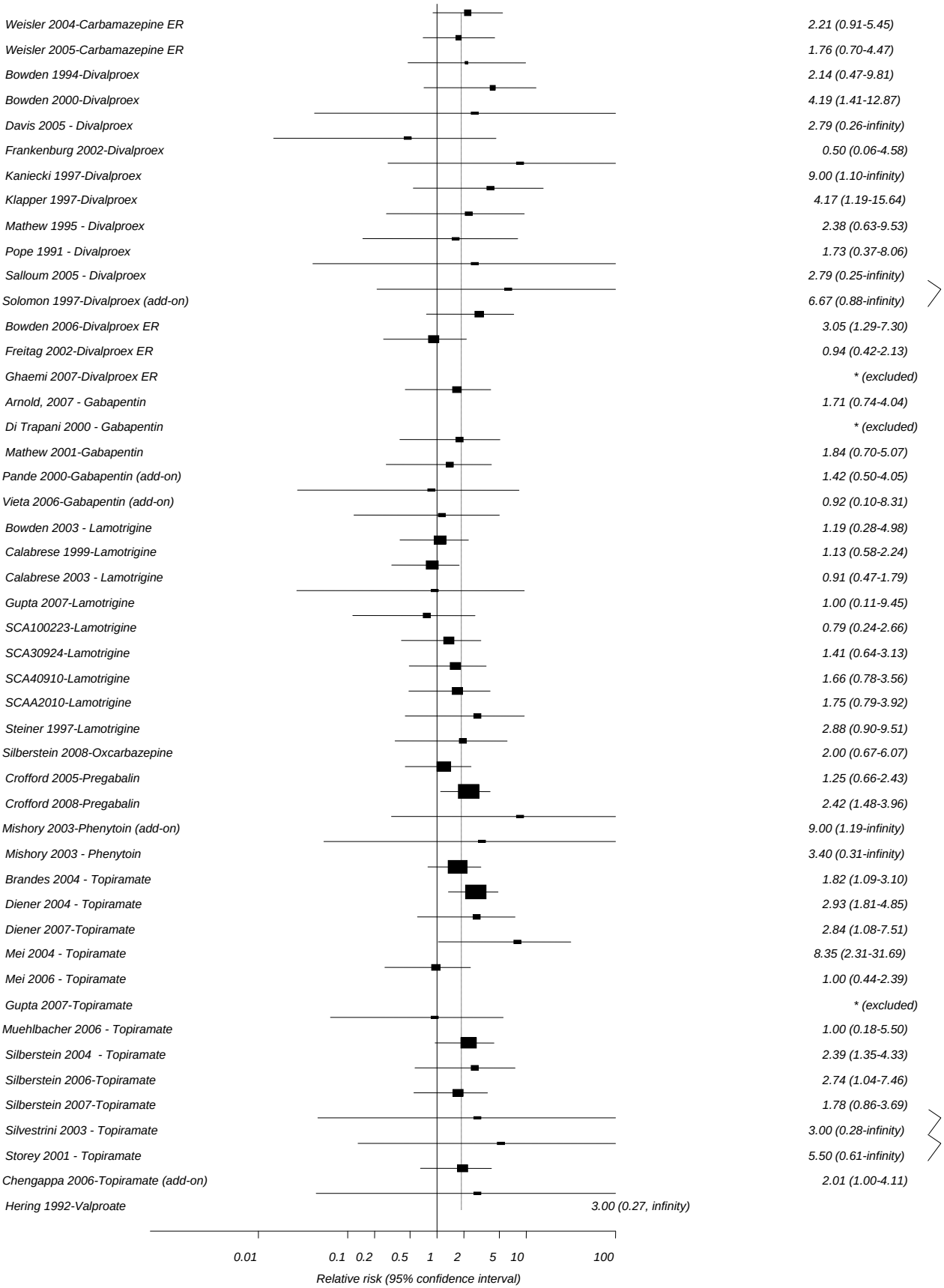


Figure 5. Risk of discontinuing treatment due to adverse effects relative to placebo



In the analysis of placebo-controlled trials (above) the 3 drugs with higher rates of adverse events or withdrawals due to adverse events were carbamazepine, divalproex, and topiramate. In head-to-head comparisons, only carbamazepine had significantly higher rates of adverse events than divalproex. Topiramate was not found different from divalproex or sodium valproate, but was not directly compared with carbamazepine.

We found 1 good-quality systematic review providing comparative data on adverse events with carbamazepine and valproate relative to lithium. Based on 2 randomized controlled trials of acute (4-week) treatment of mania,[160] no statistically significant difference was seen in the risk of adverse events between carbamazepine (relative risk compared with lithium 0.71; 95% CI, 0.49 to 1.02; N=139) and valproate (relative risk 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 comparison treatment, lithium.

Specific adverse events

In an analysis of adverse events we included 14 trials and evaluated 8 specific adverse events (diarrhea, dizziness, headache, nausea, rash, somnolence, tremor, and weight gain). There were no reports of hepatotoxicity, thrombocytopenia, or hyperammonemia in any of the placebo-controlled trials.

The results of our meta-analysis are shown in Appendix E. The only consistent finding was a higher likelihood of tremor with valproate than lamotrigine, based on data from lithium- and placebo-controlled trials. However, the 95% confidence intervals overlapped in both analyses (0.61 to 1.77 for valproate compared with lithium and 0.11 to 0.68 for lamotrigine compared with lithium; 2.38 to 10.26 for valproate compared with placebo and 0.33 to 3.79 for lamotrigine compared with placebo). Therefore, we cannot conclude that valproate and lamotrigine definitely differ in their association with tremor. One of the limitations of the evaluation of specific adverse events and pooled analyses of adverse events is inconsistency among trials in the definition of common adverse event. That is, *common* was defined as occurring in at least 5%, 8%, or 10% of patients in different trials. This variation in reporting of common adverse events may influence indirect comparisons of antiepileptic drugs.

Our statistical analysis of the 1 small trial that compared carbamazepine with valproate found that carbamazepine was significantly more likely than valproate to be associated with dizziness, with an odds ratio of 15.50; however, the 95% confidence interval was wide, 1.53 to 826.43.[23] The incidence of rash was not found to be different and was low in both groups.

We analyzed data for carbamazepine, valproate, and lamotrigine relative to lithium. The numbers of trials and patients were small, and the 95% confidence intervals were wide. However, 2 findings reached statistical significance. Lamotrigine (2 trials),[82, 102] but not valproate (1 trial),[57] was significantly less likely than lithium to be associated with diarrhea (pooled odds ratio 0.30; 95 % CI, 0.14 to 0.59). Lamotrigine (1 trial; odds ratio 0.28; 95% CI, 0.11 to 0.68)[102] and carbamazepine (2 trials; odds ratio 0.00; 95% CI, 0.0 to 0.30),[38, 161] but not valproate (1 trial),[57] was also associated with significantly lower odds of tremor than lithium. Analysis of reports of depression, headache, rash, somnolence, or weight gain did not result in statistically significant differences. (See Appendix E for complete results).

Similarly, we pooled data for carbamazepine, valproate, gabapentin, and lamotrigine compared with placebo. Again, the numbers of trials and patients were small, and the 95% confidence intervals were wide. Lamotrigine (4 trials),[82, 86, 102, 162] and not carbamazepine (1 trial)[35] or gabapentin (1 trial),[53] was more likely than placebo to be associated with headache

(odds ratio 1.59; 95% CI, 1.14 to 2.25). Carbamazepine (2 trials),[35, 36] and not valproate (1 trial)[57] or lamotrigine (2 trials),[82, 86] was more likely than placebo to be associated with nausea (odds ratio 5.16; 95% CI, 2.73 to 10.30). Lamotrigine (2 trials),[82, 86] and not carbamazepine (1 trial),[36] was associated with a significantly higher odds of rash relative to placebo (odds ratio 2.23; 95% CI, 1.06 to 5.28). Carbamazepine (2 trials),[35, 36] and not gabapentin (1 trial)[53] or lamotrigine (3 trials),[82, 86, 163] was more likely than placebo to be associated with somnolence (odds ratio 2.71; 95% CI, 1.48 to 5.36). Valproate (1 trial),[57] and not lamotrigine (1 trial),[102] was associated with significantly higher odds of tremor compared with placebo (odds ratio 4.76; 95% CI, 2.38 to 10.26). Only valproate was reported to cause weight gain as an adverse event (odds ratio 3.26; 95% CI, 1.36 to 9.03).[57]

In 31 evaluable patients, lamotrigine was associated with weight loss (mean change from baseline at 6 weeks, –0.96 kg), while gabapentin was associated with weight gain (+1.83 kg; calculated difference, –2.79 kg; *P*=0.02).[54] There was no significant difference between lamotrigine and placebo (–0.40 kg) or between gabapentin and placebo. The findings should be interpreted with caution, since they were not based on randomized patients.

Key Question 3

Are there subgroups of patients based on demographics (age, racial groups, and gender), other medications, or comorbidities for which one antiepileptic drug is more effective or associated with fewer adverse events?

Bipolar disorder

Patient characteristics

Subtype

A fair-quality trial in a hospitalized inpatient population evaluated possible predictors of clinical response to lamotrigine and gabapentin in 45 patients with bipolar or unipolar mood disorder.[97] Responder rates were higher for lamotrigine (51%) than gabapentin (28%) or placebo (21%). Univariate analyses and linear regression showed 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. Another trial showed no demographic factors to be predictors of a differential response between valproate and lithium.[62] However, for patients with bipolar I disorder with recent mania and previous psychiatric hospitalization, valproate was associated with a longer time to depressive relapse than lithium.[62]

Two placebo-controlled trials evaluated the impact of bipolar subtype, 1 with carbamazepine and 1 with lamotrigine. The trial evaluating carbamazepine showed no differential effect of bipolar subtype by YMRS total score. However, when depressive symptoms were measured on HAM-D, patients with manic episodes appeared to benefit more greatly from carbamazepine than patients with mixed episode; improved symptoms were not consistently of the same type(s). Similarly, valproate was found to have superior efficacy compared with lithium for patients experiencing mixed manic episodes, while in a systematic review of valproate in

bipolar disorder, response to the drugs was similar in patients with mania alone.[15] These authors also found that irritability was more responsive to valproate than lithium or carbamazepine.

Subgroup analyses by bipolar subtype were performed in a trial that compared lamotrigine with placebo maintenance therapy in patients who had bipolar I or II disorder with rapid cycling. The bipolar II subgroup consistently responded better to lamotrigine than placebo on time to premature discontinuation for any reason, proportion of patients who were stable without relapse for 6 months, and GAS score.[162] However, while time to relapse (the primary efficacy measure) was also longer with lamotrigine than placebo in the bipolar II subgroup (17 weeks compared with 7 weeks), this difference between treatments was not statistically significant (P=0.073). The bipolar I subgroup showed no significant difference between lamotrigine and placebo for any outcome. According to the authors, this finding was unexpected, since lamotrigine had previously been shown to be effective in bipolar I disorder. A high rate of response to placebo was observed in bipolar I patients and may be a confounder or an indication of other possible confounders. The factors accounting for different responses between the 2 bipolar subtypes need further clarification.

Age

We found 2 reports on the effect of antiepileptic drugs on symptoms of bipolar disorder in older patients.[14, 164] A pooled analysis evaluated data on 98 patients ≥ 55 years who had been randomized to lamotrigine, lithium, or placebo in these 2 studies of lamotrigine maintenance therapy for which the primary outcome measure was time to intervention for a mood episode.[164] Because the subgroups were small and not stratified at randomization, differences at baseline were present, such as mean lifetime hospitalizations, which were 11.2 in the lamotrigine group, 4.8 for lithium, and 6.3 for placebo. Similar to the findings of the results across all ages, compared with placebo lamotrigine delayed the time to intervention for any mood disorder (manic, mixed manic, or depressive episode), while lithium delayed time to intervention for manic and mixed episodes only. The mean age in these subgroups was 61 years, older than the typical bipolar population but not elderly. Because these are post hoc subgroup analyses, they should be interpreted with caution.

In a 2006 systematic review of evidence on antiepileptic drugs for bipolar disorder in patients > 60 years, Aziz and colleagues reported that there were no "published, controlled studies with these medications that focus on late-life bipolar disorder."[14] The authors went on to report results of observational reports, primarily case series, in older patients with bipolar disorder.

Comorbidity

A small placebo-controlled trial in patients with both bipolar disorder and alcoholism found that valproate as adjunct treatment to lithium was no different from placebo in treating manic or depressive symptoms. Valproate did reduce the number of heavy drinking days; the number of drinks per day on heavy drinking days was about the same as with placebo.[61]

Fibromyalgia

Typically, trial populations were about 90% women. Pregabalin at 450 mg/d was statistically more efficacious than placebo in the primary analyses that included both men and women, as well as a secondary analysis including only women.[105]

In a companion paper[165] Arnold and colleagues studied the effect of anxiety and depression on improvement in pain in the pregabalin trial. Significantly more patients reported symptoms of anxiety (71%) than depression (56%; $P<0.0001$). The pain treatment did not depend on baseline HAM-D score, suggesting that pregabalin improves pain in patients with or without symptoms of depression and anxiety. These analyses indicate that much (75%) of the pain reduction appears to be independent of improvements in anxiety or mood symptoms.

The results of the gabapentin trial[104] might not apply to patients with some comorbid psychiatric disorders, such as psychosis or bipolar disorder; rheumatologic or other musculoskeletal disorders; or unstable psychiatric or medical disorders, because patients with these conditions were excluded from the trial. Similarly the pregabalin trial[105] might have excluded the most severely affected patients and patients with psychiatric comorbidity.

Migraine prophylaxis

Included trials did not provide sufficient evidence to determine comparative efficacy or safety in patients with migraine.

Chronic pain

Included trials did not provide sufficient evidence to determine comparative efficacy or safety in patients with chronic pain.

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90. Study SCA100223 GSK Clinical Trial Registry. A Multicenter, Double-Blind, Placebo-Controlled, Fixed-Dose, 8-Week Evaluation of the Efficacy and Safety of Lamotrigine in the Treatment of Major Depression in Patients with Type II Bipolar Disorder.
91. Study SCAA2010 GSK Clinical Trial Registry. A Multicenter, Double–Blind, Placebo–Controlled, Flexible Dose (100–400mg) 10 Week Evaluation Of the Safety and Efficacy of LAMICTAL (Lamotrigine) in the Treatment of a Major Depressive Episode in Patients with Bipolar Disorder.
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Appendix A. Rating scales

Acronym	Scale name
BPI	Brief Pain Inventory
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Assessment
CGI-BP	Clinical Global Impression for Bipolar Disorder
CGI-S	The Clinical Global Impressions Severity Scale
FIQ	Fibromyalgia impact questionnaire
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Depression Rating Scale
HAM-D 17	Hamilton Depression Rating Scale
HRQoL	Health-related quality of life
MADRS	Montgomery Ashberg Depression Rating Scale
MAF	Multidimensional Assessment of Fatigue
MIDAS	Migraine Disability Assessment questionnaire
MOS	Medical Outcomes Study-Sleep Scale
MPQ	McGill Pain Questionnaire
MRS	Mania Rating Scale
MSQ	Migraine-Specific Quality of Life questionnaire
MSQ-RP	Migraine-Specific Quality of Life questionnaire - role prevention
MSQ-RR	Migraine-Specific Quality of Life questionnaire– role restrictive
MTPS	Manual Tender Point Survey
OLBPQ	Oswestry Low Back Pain Disability Questionnaire
PGIC	Patient Global Impression of Change
PGI	Patient Global Impressions scale
SADS-C MRS	Schedule for Affective Disorders and Schizophrenia-Change Version Mania Rating Scale
SADS-C MSS	Schedule for Affective Disorders and Schizophrenia-Change Version Manic Syndrome Subscale
SAPS	Scale for Assessment of Positive Symptoms
SF-36	Short-form 36
SF-36-RP	Short-form 36 --role physical
SF-36-VT	Short Form-36—vitality
SF-MPG	Short from McGill Pain Questionnaire
SGIC	Subject's Global Impression of Change
STAXI	The State-Trait Anger Expression Inventory Scale
VAS	Visual Analog Scale
YMRS	Young Mania Rating Scale

Appendix B. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Adverse event: An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Blinding: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. Trials are frequently referred to as "double-blind" without further describing if this refers to patients, caregivers, investigators, or other study staff.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report is hypothetically repeated on a collection of 100 random samples of studies, the 100 resulting 95% confidence intervals will include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administration (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Estimate of effect: The observed relationship between an intervention and an outcome. Estimate of effect can be expressed in a number of ways, including number needed to treat, odds ratio, risk difference, and risk ratio.

Equivalence level: The amount that an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount that an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

External validity: The extent to which reported results are generalizable to a relevant population.

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2*:* A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as

(Q-(n-1))/Q, where n is the number of studies.

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on those data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke.

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to treat: An estimate of how many persons need to receive a treatment before 1 person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Point estimate: An estimate of what is true for a population based on results (for example, mean, weighted mean difference, odds ratio, risk ratio, or risk difference) obtained in a sample (a study or a meta-analysis) of that population.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk difference: The difference in size of risk between two groups.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Statistically significant: A result that is unlikely to have happened by chance.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: Unpleasant adverse effects of drugs that are usually transient and not clinically significant, although they can affect a person's quality of life and willingness to continue a treatment.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Appendix C. Search strategy and update history

Search Strategy : Original Report

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-epileptic* 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: 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

Search Strategy: Update 2

Database: Ovid MEDLINE(R) <1950 to March Week 1 2008>
Search Strategy:

---

1 exp Bipolar Disorder/dt [Drug Therapy] (8112)
2 carbamazepine.mp. or exp Carbamazepine/ (10771)
3 tegretol.mp. (328)
4 divalproex.mp. or exp Valproic Acid/ (7679)
5 valproic acid.mp. (8616)
6 depakote.mp. (39)
7 ethotoin.mp. (33)
8 peganone.mp. (12)
9 gabapentin.mp. (2513)
10 neurontin.mp. (96)
11 lamotrigine.mp. (2491)
12 lamictal.mp. (51)
13 levetiracetam.mp. (726)
14 keppra.mp. (53)
15 oxcarbazepine.mp. (833)
16 trileptal.mp. (27)
17 phenytoin.mp. or exp Phenytoin/ (14459)
18 dilantin.mp. (447)
19 pregabalin.mp. (401)
20 lyrica.mp. (19)

21 tiagabine.mp. (655)
22 gabitril.mp. (18)
23 topiramate.mp. (1818)
24 topamax.mp. (45)
25 depakene.mp. (34)
26 depacon.mp. (10)
27 zonisamide.mp. (593)
28 zonegran.mp. (11)
29 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (34217)
30 1 and 29 (1616)
31 limit 30 to (English language and humans and yr="1966 - 2008" and "all adult (19 plus years)" and (clinical trial, all or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial)) (320)
32 from 31 keep 1-320 (320)

Database: PsycINFO <1806 to March Week 2 2008>
Search Strategy:
---
1 carbamazepine.mp. or exp Carbamazepine/ (2272)
2 tegretol.mp. (44)
3 divalproex.mp. or exp Valproic Acid/ (1247)
4 valproic acid.mp. (1188)
5 depakote.mp. (15)
6 ethotoin.mp. (4)
7 peganone.mp. (0)
8 gabapentin.mp. (559)
9 neurontin.mp. (13)
10 lamotrigine.mp. (794)
11 lamictal.mp. (7)
12 levetiracetam.mp. (210)
13 keppra.mp. (11)
14 oxcarbazepine.mp. (231)
15 trileptal.mp. (4)
16 phenytoin.mp. or exp Phenytoin/ (691)
17 dilantin.mp. (79)
18 pregabalin.mp. (88)
19 lyrica.mp. (5)
20 tiagabine.mp. (155)
21 gabitril.mp. (2)
22 topiramate.mp. (618)
23 topamax.mp. (5)
24 depakene.mp. (5)
25 depacon.mp. (1)
26 zonisamide.mp. (104)
27 zonegran.mp. (3)

28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (5546)
29 Bipolar Disorder.mp. or exp Bipolar Disorder/ (14161)
30 28 and 29 (1410)
31 limit 30 to (human and English language and ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0452 retrospective study" or "0800 literature review" or "0830 systematic review" or 1200 meta analysis or 1800 quantitative study or "2000treatment outcome/randomized clinical trial") and adulthood <18+ years> and yr="1966 - 2008") (649)
32 from 31 keep 1-649 (649)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2008>
Search Strategy:
---
1 carbamazepine.mp. or exp Carbamazepine/ (1138)
2 tegretol.mp. (74)
3 divalproex.mp. or exp Valproic Acid/ (549)
4 valproic acid.mp. (629)
5 depakote.mp. (26)
6 ethotoin.mp. (2)
7 peganone.mp. (0)
8 gabapentin.mp. (365)
9 neurontin.mp. (35)
10 lamotrigine.mp. (447)
11 lamictal.mp. (49)
12 levetiracetam.mp. (106)
13 keppra.mp. (10)
14 oxcarbazepine.mp. (158)
15 trileptal.mp. (11)
16 phenytoin.mp. or exp Phenytoin/ (798)
17 dilantin.mp. (29)
18 pregabalin.mp. (83)
19 lyrica.mp. (0)
20 tiagabine.mp. (118)
21 gabitril.mp. (7)
22 topiramate.mp. (322)
23 topamax.mp. (1)
24 depakene.mp. (6)
25 depacon.mp. (4)
26 zonisamide.mp. (48)
27 zonegran.mp. (4)
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (3470)
29 Bipolar Disorder.mp. or exp Bipolar Disorder/ (1646)
30 28 and 29 (335)

31 limit 30 to ((clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) and yr="1966 - 2007") (192)
32 from 31 keep 1-192 (192)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2008>
Search Strategy:
---
1 carbamazepine.mp. or exp Carbamazepine/ (90)
2 tegretol.mp. (4)
3 divalproex.mp. or exp Valproic Acid/ (16)
4 valproic acid.mp. (28)
5 depakote.mp. (3)
6 ethotoin.mp. (1)
7 peganone.mp. (0)
8 gabapentin.mp. (51)
9 neurontin.mp. (0)
10 lamotrigine.mp. (39)
11 lamictal.mp. (2)
12 levetiracetam.mp. (12)
13 keppra.mp. (0)
14 oxcarbazepine.mp. (21)
15 trileptal.mp. (4)
16 phenytoin.mp. or exp Phenytoin/ (62)
17 dilantin.mp. (1)
18 pregabalin.mp. (12)
19 lyrica.mp. (0)
20 tiagabine.mp. (19)
21 gabitril.mp. (2)
22 topiramate.mp. (28)
23 topamax.mp. (1)
24 depakene.mp. (4)
25 depacon.mp. (2)
26 zonisamide.mp. (16)
27 zonegran.mp. (0)
28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (146)
29 Bipolar Disorder.mp. or exp Bipolar Disorder/ (69)
30 28 and 29 (21)
31 from 30 keep 1-21 (21)

Database: Ovid MEDLINE(R) <1996 to May Week 4 2008>
Search Strategy:
---
1 exp Anticonvulsants/ae, po, to [Adverse Effects, Poisoning, Toxicity] (7185)
2 exp Clinical Trials, Phase IV as Topic/ or phase iv.mp. (758)

3 exp Case-Control Studies/ or case control.mp. (289134)
4 exp Cohort Studies/ or cohort.mp. (434363)
5 long term.mp. (202223)
6 exp Product Surveillance, Postmarketing/ (5332)
7 ((postmarket$ or post-market$) adj5 (surveill$ or monitor$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2964)
8 ((prescri$ or patient$) adj5 (database$ adj3 evaluat$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (50)
9 exp Drug Monitoring/ (7153)
10 observational.mp. (25729)
11 (prescri$ adj5 monitor$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (658)
12 (adverse drug reaction$ adj5 report$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3256)
13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (818199)
14 1 and 13 (1616)
15 (epidemiol$ or pharmacoepidem$ or pharmacovigil$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (115772)
16 (ep or eh or mo).fs. (582353)
17 15 or 16 (633513)
18 14 and 17 (299)
19 (2005$ or 2006$ or 2007$ or 2008$).ed. (2190369)
20 18 and 19 (129)
21 from 20 keep 1-129 (129)

Database: Ovid MEDLINE(R) <1996 to June Week 1 2008>
Search Strategy:
---
1 "147".fc_vol. and "Chou$".fc_auts. and "2007".fc_pubyr. and "505".fc_pg. (1)
2 *"Low Back Pain"/ (5566)
3 "22".fc_vol. and "Muehlbacher$".fc_auts. and "2006".fc_pubyr. and "526".fc_pg. (1)
4 "Chronic Disease"/ (72695)
5 low back pain {No Related Terms} (870)
6 pain {No Related Terms} (565)
7 chronic pain {No Related Terms} (517)
8 pain.sh. (41969)
9 pain/ or back pain/ or facial pain/ or neck pain/ or pain, intractable/ or pain, referred/ (51006)
10 carbamazepine.mp. or exp Carbamazepine/ (5064)
11 divalproex.mp. or exp Valproic Acid/ (3954)
12 ethotoin.mp. (2)
13 gabapentin.mp. (2394)
14 lamotrigine.mp. (2242)
15 levetiracetam.mp. (739)
16 oxcarbazepine.mp. (704)
17 phenytoin.mp. or exp Phenytoin/ (3439)
18 pregabalin.mp. (414)

19 tiagabine.mp. (590)
20 topiramate.mp. (1801)
21 valproic acid.mp. or exp Valproic Acid/ (4537)
22 zonisamide.mp. (496)
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (15804)
24 9 and 23 (589)
25 limit 24 to (English language and humans) (400)
26 from 25 keep 11-20 (10)
27 from 25 keep 1-400 (400)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2008>
Search Strategy:
---
1 carbamazepine.mp. or exp Carbamazepine/ (1145)
2 tegretol.mp. (74)
3 divalproex.mp. or exp Valproic acid/ (560)
4 valproic acid.mp. (638)
5 depakote.mp. (28)
6 ethotoin.mp. (2)
7 peganone.mp. (0)
8 gabapentin.mp. (380)
9 neurontin.mp. (43)
10 lamotrigine.mp. (458)
11 lamictal.mp. (51)
12 levetiracetam.mp. (123)
13 keppra.mp. (10)
14 oxcarbazepine.mp. (159)
15 trileptal.mp. (14)
16 phenytoin.mp. or exp Phenytoin/ (802)
17 dilantin.mp. (29)
18 pregabalin.mp. (92)
19 lyrica.mp. (2)
20 tiagabine.mp. (118)
21 gabitril.mp. (7)
22 topiramate.mp. (336)
23 depakene.mp. (7)
24 depacon.mp. (4)
25 zonisamide.mp. (50)
26 zonegran.mp. (4)
27 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (3540)
28 fibromyalgia.mp. or exp Fibromyalgia/ (449)
29 fibrositis.mp. (29)
30 28 or 29 (460)
31 27 and 30 (6)
32 limit 31 to yr="2005 - 2008" (5)

33 from 32 keep 1-5 (5)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2nd Quarter 2008>
Search Strategy:
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1 carbamazepine.mp. or exp Carbamazepine/ (95)
2 tegretol.mp. (4)
3 divalproex.mp. or exp Valproic acid/ (17)
4 valproic acid.mp. (29)
5 depakote.mp. (3)
6 ethotoin.mp. (1)
7 peganone.mp. (0)
8 gabapentin.mp. (54)
9 neurontin.mp. (0)
10 lamotrigine.mp. (42)
11 lamictal.mp. (2)
12 levetiracetam.mp. (12)
13 keppra.mp. (0)
14 oxcarbazepine.mp. (22)
15 trileptal.mp. (4)
16 phenytoin.mp. or exp Phenytoin/ (66)
17 dilantin.mp. (1)
18 pregabalin.mp. (16)
19 lyrica.mp. (1)
20 tiagabine.mp. (20)
21 gabitril.mp. (2)
22 topiramate.mp. (29)
23 depakene.mp. (4)
24 depacon.mp. (2)
25 zonisamide.mp. (17)
26 zonegran.mp. (0)
27 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (154)
28 fibromyalgia.mp. or exp Fibromyalgia/ (24)
29 fibrositis.mp. (1)
30 28 or 29 (24)
31 27 and 30 (4)
32 limit 31 to yr="2005 - 2008" (4)
33 from 32 keep 1-4 (4)

Appendix D. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination[1, 2] criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw is reflected in failing to meet combinations of criteria that may be related in indicating the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
   - Adequate approaches to sequence generation:
     - Computer-generated random numbers
     - Random numbers tables
   - Inferior approaches to sequence generation:
     - Use of alternation, case record number, birth date, or day of week
   - Not reported

2. Was the treatment allocation concealed?
   - Adequate approaches to concealment of randomization:
     - Centralized or pharmacy-controlled randomization
     - Serially-numbered identical containers
     - On-site computer based system with a randomization sequence that is not readable until allocation
     - Other approaches sequence to clinicians and patients
   - Inferior approaches to concealment of randomization:
     - Use of alternation, case record number, birth date, or day of week
     - Open random numbers lists
     - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
   - Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Study should give number excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.)

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Was the duration of follow-up reasonable for investigated events? (Did it meet the stated threshold?)

Assessment of External Validity

1. Was the population described adequately?

2. How similar was the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (The study should give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References

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Appendix E. Meta-analysis of specific adverse events associated with antiepileptic drugs in the treatment of bipolar disorder

The patient-level adverse event analysis included 14 trials and evaluated 8 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 1 and 2 of this appendix. In Table 1, three antiepileptic drugs (carbamazepine, valproate, and lamotrigine) are assessed against lithium. Because the numbers of trials and patients are small, and the 95% confidence intervals are wide, the lack of statistically significant evidence for a specific adverse event cannot be taken to mean that an antiepileptic drug did not cause that adverse event. Lamotrigine (2 trials), but not valproate (1 trial), was significantly less likely than lithium to be associated with diarrhea. Lamotrigine (1 trial) and carbamazepine (2 trials), but not valproate (1 trial), were associated with a significantly lower odds of tremor than lithium.

Table 1. Adverse event analysis at patient level, mood: Antiepileptic drug compared with lithium

			Lithium		Intervention Groups			
Adverse Events	Drug	No. of studies	No. of patients with event	Sample size	No. of patients with event	Sample size	Pooled OR	95% CI
Depression	Carbamazepine	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	1	42	94	65	187	0.66	(0.39 to 1.13)
Diarrhea	Lamotrigine	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	2	25	166	42	228	1.27	(0.71 to 2.28)
Nausea	Carbamazepine	1	1	14	0	14	0.00	(0.00 to 39.00)
Nausea	Divalproex	1	41	94	79	187	0.95	(0.56 to 1.61)
Nausea	Lamotrigine	2	33	166	32	228	0.65	(0.37 to 1.16)
Rash	Carbamazepine	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	2	22	166	21	228	0.66	(0.33 to 1.32)
Tremor	Carbamazepine	2	7	40	0	72	0.00	(0.0 to 0.30)
Tremor	Divalproex	1	38	94	77	187	1.03	(0.61 to 1.77)
Tremor	Lamotrigine	1	20	120	9	169	0.28	(0.11 to 0.68)
Weight gain	Carbamazepine	1	5	16	0	15	0.00	(0.0 to 1.01)
Weight gain	Divalproex	1	12	94	39	187	1.80	(0.86 to 3.99)
Weight gain	Lamotrigine	0	NR	NR	NR	NR	NC	NC

Abbreviations: CI, confidence interval; Inf, infinity; NC, not calculable; NR, not reported; OR, odds ratio (odds of antiepileptic drug / odds of lithium)

Table 2 pools data comparing antiepileptic drugs (carbamazepine, valproate, gabapentin, and lamotrigine) with placebo. Again, the numbers of trials and patients are small, and the 95% confidence intervals are wide. In general, the same cautions as mentioned for Table 1 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 valproate (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 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. Valproate (1 trial), and not lamotrigine (1 trial), was associated with significantly higher odds of tremor as compared with placebo. Only valproate was reported to cause weight gain as an adverse event.

Table 2. Adverse events analysis at patient level, mood: Antiepileptic drug compared with placebo

			Placebo		Intervention Groups			
Adverse Events	Drug	No. of studies	No. of patients with event	Sample size	No. of patients with event	Sample size	Pooled OR	95% CI
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

Abbreviations: 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 valproate 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 valproate and 0.11 to 0.68 for lamotrigine, antiepileptic drug compared with lithium; and 2.38 to 10.26 for valproate and 0.33 to 3.79 for lamotrigine, antiepileptic drug compared with placebo). Therefore, we cannot conclude that there is a definite difference between valproate and lamotrigine in their association with tremor.

One limitation of the evaluation of specific adverse events and the pooled analyses of adverse events is inconsistency in the definition of common adverse events among trials. For example, trials may consider an adverse event to be common if it occurs in at least 5%, 8%, or 10% of patients. Variation in reporting of common adverse events may influence indirect comparisons between antiepileptic drugs.

Meta-analyses similar to the ones presented for bipolar disorder were done for neuropathic pain for the original version of this report. Although Update 2 does not include neuropathic pain, we present its adverse event analysis. 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 3 presents the results of our pooled analyses of placebo-controlled trials. Gabapentin (7 trials) and pregabalin (4 trials), but not lamotrigine (1 trial), was associated with a significantly higher likelihood of dizziness compared with placebo. The 95% confidence intervals overlapped; therefore, we cannot conclude that the odds of dizziness were different for the 3 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). Again, the 95% confidence intervals overlapped, and so we cannot conclude that the odds of each adverse event are different for the two agents.

Table 3. Adverse events analysis at patient level, pain: Antiepileptic drug compared with placebo

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

			Placebo		Intervention Groups			
Adverse Events	**Drug**	**No. of studies**	**No. of patients with event**	**Sample size**	**No. of patients with event**	**Sample size**	**Pooled OR**	**95% CI**
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	1	1	70	3	76	2.82	(0.22 to 150.99)

Abbreviations: CI, confidence interval; Inf, Infinity; NC, not calculable; NR, not reported; OR, odds ratio (odds of antiepileptic drug / odds of placebo)

Appendix F. Excluded studies

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Excluded studies Update 2

A total of 87 studies (Head to head trials, Active control trials, Placebo-controlled trials and Observational studies).

Reasons for exclusion are:

1=Foreign language, 2=Wrong outcome, 3=Wrong Intervention, 4=Wrong population, 5=Wrong publication type, 6=Wrong study design, 7=Insufficient duration.

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Okuma T. Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology Vol 27(3) 1993, 138-145. 1993.	2
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Thomas SV, Sukumaran S, Lukose N, George A, Sarma PS. Intellectual and language functions in children of mothers with epilepsy. Epilepsia. Dec 2007;48(12):2234-2240.	4
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Excluded studies	Codes
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