Antiepileptics for Indications Other than Epilepsy

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Produced by:
The Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry Street SE Salem, OR 97301 Phone: 503.373.1629
Health Resources Commission
Chair: James MacKay, MD
Vice Chair: Dan Kennedy, RPh
Manny Berman
Dean Haxby, PharmD
Justin Leonard, JD.
Diane Lovell
John Muench, MD
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Rich Clark, MD
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Beckie Child

Health Resources Commission Staff
Director: David Pass M.D.
Assistant: Tina Huntley

Health Resources Commission
The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.
The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview
The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee consist of three Physicians, a Nurse Practitioner, a PhD, MPA and a PharmD and for this review a mental health advocate. All meetings were held in public
with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University’s (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria. The EPC’s report, *Antiepileptic Drugs for Indications Other Than Epilepsy*, October 2008, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony. This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center’s draft report, “*Antiepileptic Drugs for Indications Other Than Epilepsy*” is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: [www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml](http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml)


You may request more information including copies of the draft report from:

David Pass, MD
Director, Health Resources Commission
Office for Oregon Health Policy & Research
1225 Ferry St. SE
Salem, Oregon 97301
Phone: 503-373-1629 (HRC Assistant)
Fax: 503-378-5511
Email: [HRC.info@state.or.us](mailto:HRC.info@state.or.us)
Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
Alison Little, MD
Assistant Director for Health Projects
Oregon Health & Science University
Center for Evidence-based Policy
2611 SW Third Avenue, MQ280
Portland, OR 97201-4950
Phone: 503-494-2691
E-mail: littlea@ohsu.edu
There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy
Senate Bill 819
− “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission
− “Clinical outcomes are the most important indicators of comparative effectiveness”
− “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview
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.

**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%).

The incidence of bipolar I disorder is estimated to be fairly low, between 2 and 21 per 100 000 per year. 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. 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 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 medications (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.

**Quality of the Evidence**

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC’s ratings of “good, fair or poor” for grading the body of
evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial. Internal validity of each trial was based on:
1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:
1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

**Weighing the Evidence**
A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

**Scope and Key Questions**
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 HRC report “Drugs for Neuropathic Pain” [http://www.oregon.gov/OHPPR/HRC/docs/HRC.Reports/NP.3.2008.pdf](http://www.oregon.gov/OHPPR/HRC/docs/HRC.Reports/NP.3.2008.pdf) now encompasses evidence for this indication, neuropathic pain was removed from this review of antiepileptic drugs.

For this report, for bipolar disorder and fibromyalgia the EPC searched PsychINFO from 1806 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, the EPC 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).

**Key Questions (KQs)**
KQ 1. For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in effectiveness?
KQ 2. For adult outpatients with bipolar disorder, fibromyalgia, migraine, or chronic pain, do antiepileptic drugs differ in safety or adverse events?

KQ 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?

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

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Bipolar disorder</th>
<th>Fibromyalgia</th>
<th>Chronic pain</th>
<th>Migraine Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Tegretol®, Carbatio®, Equetro®</td>
<td>acute only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Depakote®, Epival®</td>
<td>acute only</td>
<td></td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Ethotoin</td>
<td>Peganone®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurontin®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal®</td>
<td>maintenance only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Keppra®</td>
<td></td>
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<tr>
<td>Oxcarbazepine</td>
<td>Trileptal®</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td>Dilantin®</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Lyrica®</td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Gabitril®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topamax®</td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Depakene®, Depacon®</td>
<td>acute only</td>
<td></td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Zonegran®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Also known as valproate.

* Not available in Canada.

* Canadian trade name.

Conclusions:
Bipolar Disorder

Acute Manic

1. Evidence suggests that valproate, carbamazepine, and lithium are comparably effective in the treatment of acute manic/mixed episodes.

2. Available evidence does not support the use of phenytoin, gabapentin, lamotrigine, oxcarbazepine, or topiramate for stabilization of acute manic/mixed episodes.

3. Maintenance

1. Benefit of gabapentin, oxcarbazepine, and phenytoin is not supported for maintenance therapy of manic/mixed bipolar disorder.

2. Evidence supports the use of lamotrigine and older forms of carbamazepine and valproate as comparable to lithium in maintenance treatment of patients whose most recent episode was manic/mixed.
Rapid Cycling
1. Valproate was comparable to lithium in 20 month relapse prevention in one small trial (n=60)
2. Lamotrigine showed no benefit over placebo for median time to intervention in patients with rapid cycling bipolar disorder in two trials.

Bipolar Depression
1. Evidence supports a benefit of lamotrigine monotherapy in treating acute bipolar depression over 7 to 10 weeks.
2. Available evidence does not support the use of valproate and topiramate for treatment of acute bipolar depression.
3. In maintenance of response to lamotrigine in patients with bipolar depression, lamotrigine and lithium were similar in time to intervention for any mood episode.
4. Limited evidence suggests valproate was not superior to placebo in preventing relapse of depressive symptoms.

Fibromyalgia
1. Evidence suggests that pregabalin and gabapentin are comparable and may be effective in reducing pain compared to placebo in patients with fibromyalgia but the duration of the effect is unclear.

Migraine Prophylaxis
1. Placebo controlled evidence suggests that topiramate and valproate are comparable and may be effective for migraine prophylaxis.
2. There is limited placebo controlled evidence supporting the use of carbamazepine and gabapentin in migraine prophylaxis.
3. Placebo controlled evidence suggests that lamotrigine and oxcarbazepine are not effective for migraine prophylaxis.

Chronic Pain
1. Limited placebo controlled evidence supports the short term efficacy of topiramate and gabapentin in chronic pain.

Harms
1. Some data suggests an increased risk of suicidal ideation or behaviors with lamotrigine, topiramate, valproate, and carbamazepine.
2. There is an increased risk of Stevens-Johnson syndrome with valproate, phenytoin, and carbamazepine at ≤ 8 weeks.
3. There is an increased risk of aplastic anemia/agranulocytosis with carbamazepine (Odds Ratio approximately equal to 10)
4. Incidence of adverse effects varied among drugs in this class but most commonly included, tremor, rash, diarrhea, nausea and headache, weight change and somnolence.
5. An increased risk of birth defects have been reported with valproate, carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and lamotrigine.
6. “Black Box Warnings” See package inserts for full information.
a. Carbamazepine: risk of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), Agranulocytosis, Aplastic Anemia
b. Divalproex: hepatotoxicity (potentially fatal), teratogenicity, pancreatitis (life threatening)
c. Lamotrigine: serious rashes (life threatening)
d. Valproic acid: hepatotoxicity (potentially fatal), teratogenicity, pancreatitis (life threatening)

Subgroups
1. There is insufficient evidence to determine any comparative differences for subgroups for any of the studied medications or indications.

Supporting Evidence:

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 ethosuximide, levetiracetam, pregabalin, tiagabine or zonisamide in patients with bipolar disorders.

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. 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

Outcomes data from trials conducted through 2002 comparing valproate with placebo, lithium, or haloperidol were previously analyzed in a Cochrane review by Macritchie and others. 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.

Macritchie included data from a trial of 28 children, which did not meet our criterion of only adults. However, when the EPC 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 a trial designed to investigate whether valproate could be as rapidly effective as a conventional antipsychotic in the initial treatment of acute psychotic mania associated with bipolar disorder 30 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.

A fair-quality trial placebo controlled study 24 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 105.30135 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).

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; \(P=0.97\)).

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.38-40 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.

**Carbamazepine compared to antipsychotics**

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**

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.

**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 trials51, 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

**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**
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. One trial enrolled only patients with rapid-cycling bipolar disorder. And another trial enrolled only women with borderline personality disorder and comorbid bipolar II depression. Although the trials were clinically heterogeneous, 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.

One trial included in the meta-analysis reported not only relapse outcomes but quality-of-life outcomes. 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.

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.

Patients with recent mania who had previously achieved response with valproate were randomized to valproate, lithium, or placebo and were followed for 1 year to evaluate the ability to prevent bipolar depression in patients treated for manic/mixed episodes. 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 or placebo 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. 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 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. 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

**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 Lack of information about the comparison groups 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.

**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. 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 the EPC did not think that any were poor quality.

The EPC pooled analysis based on intention to treat populations 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). 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.

In 2 studies the primary outcome measure was improvement on the HAM-D 17, in the other 3 studies the primary outcome measure was the mean change in MADRS score. While none of the studies individually found a statistically significant difference in mean change on HAM-D 17, the EPC 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 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). Three studies evaluated the short-term efficacy of lamotrigine and non-antiepileptic drugs over 7 to 12 weeks in patients with mainly bipolar depression. Across the 3 studies response rates with lamotrigine 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.
The combination product olanzapine/fluoxetine was found to be statistically significantly superior to lamotrigine on CGS-S, MADRS, and YMRS final scores. 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.

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).

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. Of these, 1 was a very small study (N=20), 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. Neither study found statistically significant differences between lamotrigine and tranylcypromine, risperidone, or inositol on response or recovery rates. 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. 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. The mean change on 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) and a mean percent change in HAM-D of -44% for valproate compared with -27% for placebo (P=0.0002). In both studies, valproate and placebo groups had similar rates of early discontinuation of assigned treatment. 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.

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. Statistically significant proportions of patients achieved response and remission in both groups; differences between the drugs were not
statistically significant. Mania ratings also improved in both groups, without a statistically significant difference between groups.

**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. 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 (93 days; \( P=0.029 \) for each comparison).

**Carbamazepine**

We included 1 trial that compared the general efficacy of carbamazepine (immediate-release) with that of placebo in the prophylaxis of bipolar disorder. 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, only 1 of which is fully published. In that trial 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).

**Valproate**

A single trial compared monotherapy with valproate or lithium in patients with rapidly cycling bipolar disorder and found that valproate was no better than lithium in preventing relapses in this difficult-to-treat population. 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**

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 105-107 (6.7 to 7.1). The three pregabalin studies were larger than the gabapentin study 104 (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.

**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. 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

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. Both studies 105, 106 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. 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. In the Crofford study, pregabalin 300 mg/d did not result in a final score that was statistically significantly lower than with placebo. Differences in mean pain score at endpoint did not reach statistical significance for pregabalin 150 mg/d.

**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, \( P=0.067 \). On HADS neither the depression nor anxiety scores were significantly different between pregabalin and placebo groups, with the exception of anxiety symptoms with pregabalin 600 mg/d (difference from placebo -0.79; \( P=0.014 \)). 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.

**Relapse**
Crofford and colleagues reported the only long-term (6-month) trial that studied relapse of symptoms of fibromyalgia. All patients underwent a 6-week open-label phase in which their optimal dose of pregabalin was determined. 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. Chronicle and colleagues conducted meta-analyses by drug for migraine frequency and for the proportion of patients achieving ≥50% reduction in migraine frequency. Only lamotrigine was not statistically significantly superior to placebo. Sodium valproate and divalproex sodium were addressed separately in the Chronicle review. The only data for divalproex sodium related to the proportion of individuals with a ≥50% reduction in migraine frequency. Divalproex had 4 studies (n=574) and an OR (95% CI) of 3.34 (1.46 to 7.67). Much of the included literature in the review had several methodologic limitations. Differences across these studies make qualitative indirect comparisons unwise. However, pooled effects for antiepileptic drugs were still 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. 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.

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.

Additional trials
We identified 10 trials not included in the Chronicle review.

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.

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**

Only 3 topiramate trials120-122 and 1 oxcarbazepine trial118 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 adults120, 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 (n=818) trial112 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.

63% continued to the double blind phase with 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**

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, \( P=0.01 \).

**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.

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 (75% male, mean age=49) with chronic low-back pain who had never undergone back surgery.\(^{124, 126}\) 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 (All Female, Mean age=34) with moderate to severe chronic pain of the masticatory muscles of at least 6 months’ duration.\(^{123}\) 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

**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, lamotrigrine, 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 multiple factors the hazard ratio for divalproex relative to lithium was 2.7 (95% CI, 1.1 to 6.3) for suicide death. 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).

Comparing the hazard ratio estimates and confidence intervals for valproate and carbamazepine for suicide attempts leading to hospitalization, one cannot conclude there is a difference between the 2 drugs for this outcome.

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. 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. The risk increased with duration of use, greatest at 12 years of use, but the study was in an epileptic patient group and the results may not be applicable to a non-epileptic population.

**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. The first provided comparative data for 5 antiepileptic drugs. It was conducted in hospitals in France, Germany, Italy, and Portugal. 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. 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). A total of 177 case subjects and 586 matched controls was included with 5 cases and 1 control having been exposed to carbamazepine, and 2 cases and 1 control that were exposed to phenytoin. The risk for phenytoin was not calculated due to the small number of cases, but the risk of agranulocytosis associated with recent use of carbamazepine gave an odds ratio of 10.96; (95% CI, 1.17 to 102.64).

A similar study used data from the UK General Practitioners Research Database to identify 173 cases and 497 matched controls. 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

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%. The review also confirms the belief that antiepileptic drug monotherapy is associated with somewhat lower risk of birth defects than antiepileptic drug polytherapy. Differences in rates of birth defects among infants exposed in utero to carbamazepine, phenytoin, and phenobarbital were not found. 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 and phenytoin. In a single retrospective study the risk for valproate was higher than for carbamazepine, oxcarbazepine and phenytoin.

A very small study in women taking topiramate for unspecified reasons153 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 levetiracetam have only very limited evidence, such that conclusions cannot be drawn.

**Polycystic ovary syndrome**

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).

**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.
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.

Pooled estimates 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.

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 the analysis of placebo-controlled trials 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, 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 only consistent finding in the EPC meta-analysis 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.

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**

**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. 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. There was no statistically significant difference in response between gabapentin and placebo. These results need to be evaluated in the light of some methodological factors which may limit their usefulness.

Another trial showed no demographic factors to be predictors of a differential response between valproate and lithium. 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.

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. 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. There were baseline differences between these groups. 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.”

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.

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.

Arnold and colleagues studied the effect of anxiety and depression on improvement in pain in the pregabalin trial. 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.

Their 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 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 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.