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

Final Report
EVIDENCE TABLES

May 2006

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

Francine Goodman, PharmD, BCPS
Peter Glassman, MBBS, MSc
Margaret Maglione, MPP
Marika Suttorp, MS
Additional authors of the original report:
Shannon Rhodes, MPH, Qiufei Ma, MA, Cony Rolón, BA

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

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

OHSU

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Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

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

Systematic Review Table 1. Bipolar Disorder

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Bridle, 2004{ID 2034}	To evaluate the clinical and cost-effectiveness of quetiapine, olanzapine, and divalproex in the treatment of mania associated with bipolar disorder	Up to July 2002	RCTs that assessed the effectiveness of quetiapine, olanzapine, or divalproex as monotherapy or adjunctive therapy for treatment of acute manic episodes. Economic evaluations that compared two or more options, and considered both costs and consequences.	For divalproex: 734 adults (42 children) (Data not shown for quetiapine and olanzapine vs. non-AED)	6 RCTs in adults --5 double-blind RCTs (including 1 abstract) --1 single-blind RCT (1 RCT in children)

Systematic Review Table 1. Bipolar Disorder

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results
Bridle, 2004{ID 2034}	Diagnosis of bipolar I or II disorder, manic or mixed phase with or without psychotic features. Diagnoses made by DSM-III-R, DSM-IV, or Research Diagnostic Criteria; 3 RCTs also used mania (Mania Rating Scale [MRS] or Young Mania Rating Scale [YMRS]) scores > / = 14 as diagnostic criteria. A total of 186 patients were hospitalized in 2 RCTs.	Divalproex (150 mg/d) vs. Placebo for 1 to 3 wk (1 RCT) Divalproex loading (30 mg/kg/d x 2 d then 20 mg/kg/d) vs. Divalproex nonloading (750 mg/d x 2 d then titration) vs. Lithium 30 mg/kg/d x 2 d then 20 mg/kg/d; total treatment duration 10 d (1 RCT) Divalproex (750 to 1000 mg/d) vs. Lithium 750 to 1000 mg/d vs. Placebo for 3 wk (1 RCT) Divalproex 20 mg/kg/d vs. Haloperidol 20 mg/kg/d for 6 d (1 RCT) Divalproex (500 to 2500 mg/d) vs. Olanzapine 5 to 20 mg/d for 3 wk (1 RCT) Divalproex 20 mg/kg/d vs. Olanzapine 20 mg/kg/d for 3 and 12 wk (1 RCT abstract) Treatment duration: 6 d to 8 wk	Divalproex was --better than placebo in reducing manic symptoms, but may cause adverse gastrointestinal effects. --similar to lithium in clinical effectiveness and adverse events. --similar to haloperidol in patients with psychotic features in terms of efficacy and was associated with fewer extrapyramidal effects. --inferior to olanzapine in reducing mania; however, it was associated with more dry mouth, increased appetite, edema, somnolence, speech disorder, Parkinson-like symptoms, and weight gain whereas nausea was more common with divalproex than olanzapine. One small trial in children (N = 42) showed that divalproex and carbamazepine were similar in efficacy and safety.

Systematic Review Table 1. Bipolar Disorder

Author, year	Main results (cont'd)	Subgroups	Adverse events
Bridle, 2004{ID 2034}		---	*Selected Adverse Events, RR (95% CI) (values < 1 favor divalproex)* *Divalproex vs. Lithium* --Early discontinuation due to intolerance to treatment, any adverse event, dizziness, and somnolence: NSD for each --Fever: 0.10 (0.01 to 0.86; p = 0.04) --Pain: 6.78 (0.92 to 49.80; p = 0.06) *Divalproex vs. Haloperidol* --Extrapyramidal symptoms (EPS): 0.04 (0.00 to 0.69) *Divalproex vs. Olanzapine* -- Early discontinuation due to adverse events: 0.90 (0.47 to 1.74; NSD) --Somnolence: 0.55 (0.41 to 0.76; p = 0.0002) --Dizziness: 0.74 (0.40 to 1.39) --Weight gain: 0.53 (0.30 to 0.93; p = 0.03) --Increased appetite: 0.20 (0.06 to 0.67) --Dry mouth: 0.19 (0.09 to 0.39) --Nausea: 2.75 (1.53 to 4.93) --Speech disorder / slurred speech: 0.10 (0.02 to 0.53; p = 0.007) --Edema: 0.05 (0.00 to 0.90) *Divalproex vs. Placebo* -- Early discontinuation due to intolerance to treatment, any adverse event, and sedation/fatigue/somnolence: each NSD --Dizziness: 2.95 (0.99 to 8.83) --GI discomfort/nausea/vomiting: 1.66 (1.04 to 2.67; p = 0.03)

Systematic Review Table 1. Bipolar Disorder

Author, year	Comments
Bridle, 2004{ID 2034}	In comparison with lithium, no significant differences were found between quetiapine, olanzapine, and divalproex in terms of effectiveness. Each agent was better than placebo, and all of the agents were associated with adverse events. Economic review not reported here.

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

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

Systematic Review Table 2. Neuropathic Pain

Author, year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Dubinsky, 2004 {ID 2030}	To answer the following clinical question: In patients with postherpetic neuralgia, which treatments provide benefit in terms of decreased pain and improved quality of life?	1960 to August 2003, updating in January 2004	Studies that addressed alleviation of pain in postherpetic neuralgia, with duration of at least 8 wk after healing of herpetic rash; were prospective, retrospective, or case series studies that provided clinical information on subjects who received treatment; provided detailed methodology and a clear outcome measure; aimed to demonstrate a decrease of pain related to postherpetic neuralgia; evaluated treatment feasible for an outpatient setting.	559 patients from 2 class I (prospective, outcome-assessor-blinded, randomized controlled) trials evaluating gabapentin 173 patients from 1 class I trial evaluating pregabalin Total of 6 trials were included (3 class I trials were discussed further)	3 multicenter double-blind placebo-controlled RCTs: 2 gabapentin (Rowbotham, 1998 and Rice, 2002), 1 pregabalin (Dworkin, 2003)

Systematic Review Table 2. Neuropathic Pain

Author, year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Subgroups
Dubinsky, 2004 {ID 2030}	Gabapentin vs. Placebo (2 trials): 256 males, 479 females; range of mean ages 71.5 to 75.3; duration of symptoms 27.4 to 33.8 mo. One trial included patients who had benefited from open-label gabapentin. Pregabalin vs. Placebo (1 trial): 81 males, 92 females; mean age 71.5; duration of symptoms 33.8 mo	Gabapentin up to 3600 mg/d vs. Placebo Gabapentin 1800 mg/d vs. 2400 mg/d vs. Placebo Pregabalin 600 mg/d vs. Placebo	Gabapentin vs. Placebo (Rowbotham 1998) Change in pain score on 11-point Likert scale: -2.1 vs. 0.5 Improved on global impression of change scale: 66/94 (70.2%) vs. 25/79 (31.6%) NNT = 2.2 for any benefit (95% CI 1.7 to 3.0) NNT = 2.8 for moderate to much improved Gabapentin vs. Placebo (Rice 2002) Experienced >/= 50% decrease in pain on 11-point Likert scale: 74/223 (33.2%) vs. 16/111 (14.4%) NNT = 5.3 (95% CI 3.6 – 10.2) NSD between gabapentin 1800 mg/d and 2400 mg/d Pregabalin vs. Placebo (Dworkin 2003) Experienced > 50% decrease in pain on 11-point Likert scale: 45/89 (50.6%) vs. 17/84 (20.2%) NNT 3.3 (95% CI 2.3 – 5.9)	---

Systematic Review Table 2. Neuropathic Pain

Author, year	Adverse events	Comments
Dubinsky, 2004 {ID 2030}	Gabapentin vs. Placebo (Rowbotham 1998) Withdrawals due to somnolence: 4.4% vs. 1.7% NNH for somnolence = 10.3 Gabapentin vs. Placebo (Rice 2002) Withdrawals due to AEs: 34/223 (15.2%) vs. 7/111 (6.3%) NNH = 11.2 (Calculated 95% CI: 6 to 42) Pregabalin vs. Placebo (Dworkin 2003) Withdrawals due to AEs: 32% vs. 5% NNH 3.7 Calculated NNH (95% CI) based on withdrawals due to AEs: 4 (3 to 6) (see Dworkin 2003 in Evidence Table 6)	This was a report of the Quality Standards Subcommittee of the American Academy of Neurology. Findings for other agents evaluated (tricyclic antidepressants, opioids, topical and intradermal agents, and NMDA antagonist) are not reported here. Financial disclosure was not given. Additional data for the 3 class I AED trials were available at www.neurology.org (Table E-1). Data on the other 3 included trials were not reported.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout Period	(6) Allowed other medications/ interventions
Bahk (2005) South Korea (Poor)	Multicenter (8 sites), open-label RCT University-based hospitals, tertiary care unit, and chronic mental health institute	DSM-IV bipolar I disorder with current manic episode and requirement for antipsychotic treatment; age 18 to 65 y; minimum score on Young Mania Rating Scale (YMRS) of 20; medicosurgically stable	Topiramate + Risperidone vs. Divalproex + Risperidone, flexibly dosed for 6 wk Recommended starting dose (and titration rate every 2 to 5 d): Topiramate 50 mg/d (rate: 25 to 50 mg/d); Divalproex 750 mg/d (rate: 250 to 500 mg/d); Risperidone 0.5 to 2 mg/d (clinician's judgment)	3-d washout of prior medications	Oral lorazepam < / = 4 mg/d; injectable lorazepam except within 24 h before completing rating scales; antiparkinsonian drugs

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

Author, year Country Trial name (Quality score)	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Bahk (2005) South Korea (Poor)	YMRS, Clinical Global Impression (CGI), Simpson-Angus Rating Scale (SARS, neurologic adverse events) at baseline, wk 1, wk 3, and wk 6 / endpoint; reduction in YMRS and CGI scores of > / = 50% at end point vs. baseline; vital signs and adverse events at all assessment periods; ECG and blood tests at baseline and end point. Remission defined as YMRS < / = 12.	Topiramate vs. Divalproex (each combined with Risperidone) Age, mean, y: 37.5 vs. 37.6 Male, n (%): 15 (56.6%) vs. 22 (53.7%) Ethnicity: Not reported	YMRS: 35.2 vs. 33.9 CGI-s: 5.3 vs. 5.5 SARS: 0.2 vs. 0.5 Age at onset, y: 29.3 vs. 38.8 Body mass index (BMI), kg/m^2: 24.1 vs. 24.6 Weight, kg: 65.4 vs. 67.3 Drug use within 1 y prior to study, n (% of total patients): --Mood stabilizer: 44 (59.5%) --Antipsychotic: 14 (18.9%) --Antianxiety: 56 (75.7%) --Antidepressant: 8 (10.8%) Most common drug used within 1 y prior to study --Mood stabilizer, lithium, n: 15 vs. 17 --Antipsychotic, olanzapine: 2 vs. 4 --Anxiolytic, alprazolam: 17 vs. 21 --Antidepressant, paroxetine: 2 vs. 3	81 screened / number eligible not reported / 74 enrolled and randomized	10 withdrew / 3 lost to follow-up / 74 analyzed

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

Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Bahk (2005) South Korea (Poor)	Topiramate (N = 33) vs. Divalproex (N = 41) Doses, mean, mg/d --Mood stabilizer: 220.6 vs. 908.3 --Risperidone: 3.4 vs. 3.3 (NSD) --Lorazepam: 1.8 vs. 1.5 (NSD) --Benztropine: 1.4 vs. 1.8 (NSD) Absolute (Relative) decrease in scores --YMRS: 23.9 (67.9%) vs. 21.6 (63.7%) (NSD) --CGI: 3.0 (56.6%) vs. 3.2 (58.2%) (NSD)	Responder rates (Patients with > / = 50% reduction), n (%) --YMRS: 25 (75.8%) vs. 29 (70.7%) (NSD) --CGI-s: 24 (72.7%) vs. 30 (73.2%) (NSD)	Patients entering remission (YMRS < / = 12), n (%): 21 (63.6%) vs. 25 (61.0%) (NSD)

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

Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Bahk (2005) South Korea (Poor)	Monitoring	**Topiramate (N = 33) vs. Divalproex (N = 44) (each in combination with Risperidone)** AEs reported in > / = 10% of patients in either treatment group, n (%) --Dizziness: 7 (21.2%) vs. 0 (0%) --Headache: 6 (18.2%) vs. 2 (4.9%) --Nausea: 4 (12.1%) vs. 5 (2.4%) --Paresthesia: 3 (6.8%) vs. 0 (0%) --Sedation: 1 (3.0%) vs. 8 (19.5%) --Concentration difficulty: 1 (3.0%) vs. 6 (14.6%) Other AEs: --Extrapyramidal symptom: 9 (27.3%) vs. 13 (31.7%) --Increased alanine aminotransferase (ALT): 1 (3.0%) vs. 2 (4.5%) SARS score, mean change from baseline to end point: Values not reported (NSD) Patients showing weight change at end point, n (%) --Weight loss in topiramate group: 15 (45.5%) --Weight gain in divalproex group: 30 (73.2%) Mean change from baseline to end point --Weight, kg (%): -0.25 (0.5%) vs. 2.25 (3.6%) (p < 0.0001) --BMI, kg/m^2 (%): -0.1 (0.4%) vs. 0.75 (3.3%) (p < 0.0001)	Total withdrawals, n: 5 vs. 8 (NSD) Withdrawals due to AEs: Not reported by group	AE rates reflect combination therapy; no monotherapy control group for comparison. In post hoc analyses, no correlation was found between weight loss with topiramate and topiramate dose, initial weight, BMI, and gender. Possible observer biases due to multicenter design. Possible carryover effects of prior treatments due to relatively short washout period.

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Hartong, 2003 The Netherlands (Fair)	Mean age (SD) 41.9 (13.9) 45.7% male, 54.3% female Ethnicity not reported	Bipolar I 72/94 Bipolar II 22/94 Rapid Cycling 10/94 Non-rapid cycling 84/94	--/--/150/144	46 withdrawn/0 lost to follow-up/94 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Lusznat, 1988 U.K. (Poor)	Not reported	DSM-III diagnosis, n: Schizoaffective (2), bipolar without psychotic features (35) Carbamazepine vs. Lithium History of alcohol abuse, n: 8 vs. 4 B-R MRS score: 15.8 vs. 14.6	128 screened / 54 eligible / 54 enrolled / 54 randomized	25 withdrawn / Lost to follow-up none / Number analyzed for B-R MRS scores not reported

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Bowden, 2000 Canada, U.S. (Fair)	Divalproex vs. Lithium vs. Placebo Mean (SD) age, y: 38.9 (12.7) vs. 40.3 (9.8) vs. 38.7 (11.9) 48.8% Male, 51.2% Female 91.3% White, 4.1% Black, 4.6% Other	Divalproex vs. Lithium vs. Placebo MRS, mean (SD): 3.4 (3.7) vs. 3.2 (3.7) vs. 3.4 (3.4) Prior manic episodes 1 to 10: 48.9% 11 to 20: 13.3% > 20: 36.6% Prior depressive episodes 0: 4.9% 1 to 10: 44.7% > 10: 48.8% 61% had at least one previous hospitalization 18% hospitalized for the index episode	4758/--/571/372	256 withdrew / Number lost to follow-up not reported / 369 analyzed

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Tohen, 2002 U.S. (Fair)	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian	Nonpsychotic 54.6% Mixed Episode 43.0% Manic Episode 57.0% Rapid Cycling 57.4%	330/--/--/251	79/ Not reported /248

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Tohen, 2003 U.S. (Fair)	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian	Mean (SD) YMRS total score: 27.7 (5.9; severe) Mixed bipolar 43.0% Rapid cycling 57.4% Psychotic 45.4% Treatment resistant (did not respond to previous adequate treatment for acute mania with lithium, valproate, or carbamazepine) 21.1%	--/--/251/251	187 / 25 / 248

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Zajecka, 2002 U.S. (Fair)	Divalproex (N = 63) vs. Olanzapine (N = 57) Age, mean (SD), y: 38.9 (12.1) vs. 38.1 (12.2) Male / Female: 56% / 44% vs. 53% / 47% Ethnicity, n (%) --Asian/Pacific Islander: 2 (3) vs. 1 (2) --White: 50 (79) vs. 40 (70) --Black: 8 (13) vs. 14 (25) --Other: 3 (5) vs. 2 (4)	DSM-IV diagnosis Mixed mania: 31 (49%) vs. 26 (46%) Rapid cycling: 19 (30%) vs. 16 (28%)	Numbers screened, eligible, enrolled not reported / 120 randomized	67 / 16 / 115

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(8) Age Gender Ethnicity	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed
Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Open-label Lamotrigine; Double-blind Lamotrigine, Lithium, and Placebo Mean (SD) age: 40.7 (11.8); 40.6 (12.6), 41.9 (11.3) vs. 40.9 (11.0) Male: 50%; 45%, 48% vs. 49% Ethnicity not reported	Open-label Lamotrigine; Double-blind Lamotrigine, Lithium, and Placebo Mean (SD) MRS: 22.9 (6.7); 22.3 (6.8), 22.3 (5.6) vs. 22.4 (7.8) History of psychotic episodes: 46%; 38%, 46% vs. 41% Ever hospitalized for mood-related disturbance: 66%; 60%, 67% vs. 61% Ever attempted suicide: 29%; 28%, 41%, 19% (Lithium vs. Placebo, p=0.01)	--/--/349/175	Open-label phase (N=349): 135/30/184 (completed) Double-blind phase: 41/5/171

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 2. Active-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Solomon, 1997 U.S. (Poor)	Number of lifetime mood episodes, range: 2 to 51 vs. 3 to 30 (mean data not reported; NSD) Past lithium treatment, n (%): 1/5 (20.0%) vs. 6/7 (85.7%) Major depression at intake, n (%): 4/5 (80.0%) vs. 2/7 (28.6%) (NSD) Mania episode at intake, n (%): 1/5 (20.0%) vs. 5/7 (71.4%) (NSD)	Numbers screened and eligible not reported / 12 enrolled / 12 randomized	4 withdrew / None lost to follow-up / 12 analyzed	Divalproex vs. Placebo Partial remission, n: 5/5 (100%) vs. 6/7 (85.7%) (1 divalproex patient recovered prior to randomization; 1 placebo patient recovered abruptly in wk 4 with no intervening period of partial remission) Time to partial remission, range, wk: 0 to 1 vs. 1 to 11 Relapse or recurrence, n (%): 0/5 (0.0%) vs. 5/7 (71.4%) (p = 0.014)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Solomon, 1997 U.S. (Poor)				Monitored

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Solomon, 1997 U.S. (Poor)	Most common adverse events on divalproex (+ lithium): gastrointestinal distress, tremor, cognitive impairment, alopecia Adverse events on placebo (+ lithium): not reported	Total withdrawals: 2/5 (40.0%) vs. 2/7 (28.6%) Withdrawals due to adverse events: 2/5 (40.0%) vs. 0/7 (0.0%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Solomon, 1997 U.S. (Poor)	Results are inconclusive (pilot study). Small sample size, confounding co-medications, nonblinded research psychiatrist.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Chloral hydrate, lorazepam, temazepam. oxazepam during first 3 wk of treatment	HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS); Mania Rating Scale (MRS), Clinical Global Impressions scale for Severity (CGI-S) at baseline and weekly for 7 wk, and Clinical Global Impressions scale for Improvement (CGI-I) from day 4 onward. Response was defined as 50% or more reduction on the 17-item HAM-D or MADRS scales or a rating of very much improved or much improved on the CGI-I scale.	Lamotrigine 50 mg/d (N = 66) vs. Lamotrigine 200 mg/d (N = 63), vs. Placebo (N = 66) Age, mean, y: 41 vs. 42, vs. 42 Male / Female: 33% / 67% vs. 44% / 56% vs. 41% / 59% Ethnicity not reported

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Age of onset of affective symptoms, mean, y: 22 vs. 21 vs. 21 No. of mood episodes in last 12 mo per patient, mean (SD): 2.2 (0.8) vs. 2.2 (0.9) vs. 2.2 (0.8) Duration of current episode --2 to 8 wk: 39% vs. 37% vs. 29% --> 8 to 24 wk: 44% vs. 41% vs. 42% --> 24 wk: 17% vs. 22% vs. 29% Moderate intensity of depression: 58% vs. 54% vs. 61% CGI-S score (% of patients) --Mildly ill: 3% vs. 10% vs. 2% --Moderately ill: 64% vs. 51% vs. 65% --Markedly ill: 23% vs. 30% vs. 28% --Severely ill: 11% vs. 10% vs. 11% Melancholic features: 39% vs. 40% vs. 50% Prior hospitalization for mood episode: 44% vs. 51% vs. 62% Prior suicide attempts: 32% vs. 32% vs. 36% Lithium use in last 5 mo: 23% vs. 19% vs. 23%	Numbers screened, eligible, and enrolled not reported / 195 randomized	60 withdrew / None reported / 192 analyzed for efficacy, 194 analyzed for safety	Lamotrigine 50 mg/d (N = 64) vs. Lamotrigine 200 mg/d (N = 63) vs. Placebo (N = 65) (Last observation carried forward [LOCF] analysis) *Change in scores from baseline, mean* 17-item HAM-D (Primary efficacy variable): -9.3 vs. -10.5 vs. -7.8 (p = 0.084) (Analysis for observed change showed a significant treatment difference in change from baseline: -12.6 (N = 43) vs. -13.2 (N = 45) vs. -9.3 (N = 47) (p < 0.05 for both lamotrigine groups vs. placebo) Significant improvement was first noted for lamotrigine 200 mg/d only vs.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Change in scores from baseline, mean MADRS: -11.2 vs. -13.3 vs. -7.8 ($p < 0.05$ for lamotrigine 200 vs. placebo) CGI-S: -1.0 vs. -1.2 vs. -0.7 ($p < 0.05$ for lamotrigine 200 vs. placebo) CGI-I: 3.0 vs. 2.6 vs. 3.3 ($p < 0.05$ for lamotrigine 200 vs. placebo) MRS: 0.9 vs. 0.3 vs. -0.5 (NSD)	Combined week 3 analysis (lamotrigine </= 50 mg/d for both active groups) (N = 127): significant improvements ($p < 0.05$) were seen by week 3 in HAM-D Item 1 and MADRS for LOCF analyses. Subgroup analysis: No significant effect of recent lithium use on treatment group differences for any efficacy measure.	*Responder rate* 17-item HAM-D: 45% vs. 51% vs. 37% (NSD) MADRS: 48% vs. 54% vs. 29% ($p < 0.05$ for each lamotrigine group vs. placebo) CGI-I: 41% vs. 51% vs. 26% ($p < 0.05$ for lamotrigine 200 vs. placebo)	Elicited by investigator

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Lamotrigine 50 mg/d (N = 66) vs. Lamotrigine 200 mg/d (N = 66) vs. Placebo (N = 65) Patients reporting any adverse event: 79% vs. 79% vs. 92% Of the most common (>/= 5%) adverse events, only headache showed a significant treatment difference (n, %): 23 (35%) vs. 20 (32%) vs. 11 (17%) (p < 0.05 for each lamotrigine group vs. placebo) Other common adverse events: --Nausea: 11 (17%) vs. 10 (16%) vs. 10 (15%) --Pain: 5 (8%) vs. 7 (11%) vs. 5 (8%) --Rash: 9 (14%) vs. 7 (11%) vs. 7 (11%) --Dizziness: 6 (9%) vs. 6 (10%) vs. 2 (3%) Manic / hypomanic / mixed episodes (as reported by investigator) (n, %): 2 (3%) vs. 5 (8%) vs. 3 (5%) (NSD) Patients reporting any serious adverse event: 4 vs. 2 vs. 3 Illness-related Serious Adverse Events --Probable suicide: 0 vs. 0 vs. 1 --Attempted suicide: 1 vs. 0 vs. 1 --Suicidal ideation: 1 vs. 1 vs. 0 --Worsening depression: 1 vs. 0 vs. 0 --Psychotic episode: 1 vs. 0 vs. 0 (All illness-related serious adverse events in the lamotrigine 50-mg/d group except for the attempted suicide [3 out of 4 events] were considered to be possibly drug related.)	Lamotrigine 50 mg/d vs. Lamotrigine 200 mg/d vs. Placebo Total withdrawals: 23 (35%) vs. 18 (29%) vs. 19 (29%) Withdrawals due to adverse events: 12 (18%) vs. 10 (16%) vs. 10 (15%) Adverse events accounting for more than one withdrawal --Rash: 3 vs. 4 vs. 2 --Worsening of psychiatric depression: 3 vs. 0 vs. 1 --Pruritus: 0 vs. 1 vs. 1 --Suicidal ideation: 1 vs. 1 vs. 0 --Suicide attempt: 1 vs. 0 vs. 1 --Mania: 0 vs. 2 vs. 0

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Modified ITT analyses were used for efficacy and safety. Dosage escalation was faster than the recommended regimen and may have increased the risk of rash. The fixed-dose titration schedule resulted in unequal treatment durations for the 50-mg group (5 wk) and the 200-mg group (3 wk). The 17-item HAM-D scale (weighted toward somatic symptomatology) may have been less sensitive and reliable for detecting effects on bipolar depression or treatment differences than the MADRS.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Calabrese, 2000 U.S., Canada (Fair)	Open-label phase: Lithium (60, 19%), divalproex (63, 19%), carbamazepine (14, 4%), antidepressants (96, 30%), antipsychotics (24, 7%), and benzodiazepines (88, 27%) Double-blind phase: Lorazepam. Other psychotropics (e.g., lithium, divalproex, antipsychotics, electroconvulsive therapy) could be added only if an increase in lamotrigine dose was not effective or appropriate (i.e., patients reached primary study end point).	Open-label phase: 17-item HAM-D, MRS, Clinical Global Impressions-Severity scale (CGI-S), Global Assessment Scale (GAS), and retrospective life chart at screening (within -14 d), day 1, then weekly till randomization. Double-blind phase: HAM-D, MRS, CGI-S, GAS, and prospective life chart on day 1, then wk 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 26. *Relapse* was operationally defined as the need for additional pharmacotherapy for a mood episode or one that was thought to be emerging.	Open-label Lamotrigine (N = 324); Double-blind Placebo (N = 88) vs. Lamotrigine (N = 92) Age, mean, y: 38.6; 37.4 vs. 38.5 Female, n (%): 190 (59%); 52 (59%) vs. 51 (55%) Ethnicity: Not reported

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Calabrese, 2000 U.S., Canada (Fair)	Age at onset of first episode of depression / mania, mean, y: 17.5 / 20.2; 17.0 / 19.1 vs. 17.3 / 20.7 Bipolar I, n (%): 225 (69%); 60 (68%) vs. 68 (74%) Bipolar II, n (%): 98 (30%); 28 (32%) vs. 24 (26%) No. of mood episodes in last 12 mo, mean: 6.3; 5.9 vs. 6.3 Prior hospitalizations for mood episode, mean: 1.8; 1.3 vs. 1.5 Prior suicide attempt, n (%): 117 (36%); 34 (39%) vs. 25 (27%) Lifetime prevalence of psychosis, n (%): 88 (27%); 21 (24%) vs. 25 (27%) Type of mood episode at screening, % --Depression: 57%; 56% vs. 55% --Mania/Hypomania: 20%; 19% vs. 20% --No episode: 18%; 17% vs. 21% --Mixed: 5%; 9% vs. 4%	Numbers screened and eligible not reported / 324 enrolled / 182 randomized	Open-label phase: 142 withdrew / 19 lost to follow-up / 324 analyzed for safety Double-blind phase: 28 withdrew / 10 lost to follow-up / 177 analyzed for efficacy, 180 for safety	Lamotrigine vs. Placebo Time to relapse (Primary Efficacy Measure), median survival time, wk: 18 vs. 12 (p = 0.177) --In bipolar I subgroup (N = 125): 18 vs. 14 (estimated; p = 0.738) --In bipolar II subgroup (N = 52): 17 vs. 7 (p = 0.073) Required additional pharmacotherapy for emerging mood episode, n (%): 45 (50%) vs. 49 (56%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Calabrese, 2000 U.S., Canada (Fair)	Time to premature discontinuation for any reason, median survival time, wk: 14 vs. 8 (p = 0.036) --In bipolar I subgroup: 10 vs. 12 (estimated; p = 0.426) --In bipolar II subgroup: 16 vs. 5 (estimated; p = 0.015) Stable without relapse for 6 mo, n (%): 37/90 (41%) vs. 23/87 (26%) (p = 0.03) --In bipolar I subgroup: 39% vs. 31% (NSD) --In bipolar II subgroup: 46% vs. 18% (p = 0.04)	CGI-S, change from baseline: NSD (data not reported) --In bipolar I subgroup: NSD --In bipolar II subgroup: NSD GAS, change from baseline: NSD (data not reported) --In bipolar I subgroup: NSD --In bipolar II subgroup: p </= 0.03 at wk 3, 6, and 12 17-item HAM-D, change from baseline: NSD (data not reported) MRS, change from baseline: NSD (data not reported)		Monitored

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Calabrese, 2000 U.S., Canada (Fair)	Double-blind phase--Lamotrigine (N = 92) vs. Placebo (N = 88) Serious adverse events, n: 1 vs. 2 Adverse events considered reasonably related to study treatment: 24 (27%) vs. 28 (30%) (NSD); most common: nausea (4, 4% vs. 4, 5%) and headache (6, 7% vs. 8, 9%) Most Common (>/= 10%) Treatment-emergent Adverse Events: headache (21, 23% vs. 15, 17%), nausea (13, 14% vs. 10, 11%), infection (11, 12% vs. 10, 11%), pain (9, 10% vs. 7, 8%), and accidental injury (10, 11% vs. 4, 5%). Rash occurred in 3 (3%) vs. 2 (2%) patients. Treatment-related rash: 0 (0%)	Double-blind phase Total withdrawals: 11/93 (12%) vs. 17 (19%) Withdrawals due to adverse events: 1 (1%) vs. 2 (2%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Calabrese, 2000 U.S., Canada (Fair)	The analyses for double-blind treatment were based on a selective cohort of patients who were more likely to be lamotrigine responders and less prone to develop rash. The primary efficacy measure, time to relapse, depended on the investigator's discretion of whether additional psychotropic medication was necessary to treat an emerging mood episode.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Mishory, 2003 Israel (Poor)	Ongoing prophylactic treatment remained unchanged (lithium, carbamazepine, valproate, or neuroleptic)	Brief Psychiatric Rating Scale (BPRS), Young Mania Scale (YMS), Hamilton Depression Scale (HMS), and Global Clinical Impression at baseline and monthly thereafter Primary outcome measure was time to 'event,' an affective relapse. Criteria for an 'event' were need for hospitalization or emergent symptoms of sufficient severity to require addition of a neuroleptic or antidepressant, according to the masked clinical psychiatrist.	Age. mean (SD), y: 45.2 (9.6) Male / Female: 9 / 14 Ethnicity not reported

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Mishory, 2003 Israel (Poor)	Age of onset of illness, mean (SD), y: 26.5 (9.0) Number of affective episodes, mean (SD): 13.8 (8.5) Time in remission before entering trial, mo: 4.0 (range: 1 to 13) Last affective episode --Mania: 11 --Depression: 7 --Mixed: 5	Number screened, eligible, enrolled not reported / 23 randomized	4 withdrew (and were replaced with new enrolled patients) / None lost to follow-up / 23 analyzed (30 6-mo observation periods)	Phenytoin vs. Placebo Time to clinical relapse (event), median (estimated from figure), mo: > 6 vs. 5 (p = 0.02) Relapsed during first 6 mo: 3/10 (30.0%) vs. 8/13 (61.5%) (p = 0.053) Data for rating scales were not reported.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Mishory, 2003 Israel (Poor)				Not reported

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Mishory, 2003 Israel (Poor)	Phenytoin (n = 14) vs. Placebo (n = 16) Common adverse events during 30 observation periods Slight weakness and sleepiness: 1 (7.1%) vs. 1 (6.2%) Temporary dizziness, resolved without change in treatment: 3 (21.4%) vs. 0 (0.0%) Psoriasis-like symptoms: 1 (7.1%) vs. 0 (0.0%)	Phenytoin vs. Placebo Total withdrawals: 9/23 (39.1%) vs. 7/23 (30.4%) (if 4 dropouts during the first 3 wk of phenytoin treatment are counted, total for phenytoin would be 13/27, 48.1%) Withdrawals due to adverse event: 1/23 (4.3%) vs. 0/23 (0.0%) (psoriasis-like symptoms due to concomitant lithium treatment)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Mishory, 2003 Israel (Poor)	Small sample size; dropouts excluded from analyses; short study duration; incomplete reporting of data. Results reflected a selective population of compliant patients because any post-randomization dropout was excluded from analyses and replaced with a new patient who was assigned the dropout's randomization number.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

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

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Pande, 2000 U.S. (Fair)	Ongoing treatment for bipolar disorder --Lithium only, n: 22 vs. 17 --Valproate only, n: 26 vs. 31 --Both, n: 10 vs. 11	Numbers screened and eligible not reported / 117 enrolled / 117 randomized	48 withdrawn / None lost to follow-up / 114 analyzed	Gabapentin vs. Placebo Adjusted means included treatment and center in ANCOVA model and YMRS baseline score as covariate YMRS, adjusted mean: -6.5 vs. -9.9 (difference -3.34; 95% CI: -6.35 to -0.32; p = 0.03) HAM-D, adjusted mean: 0.01 vs. -1.3 (difference -1.32; 95% CI: -4.40 to 1.77; p = 0.40)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Pande, 2000 U.S. (Fair)	Change in score from baseline to last observation carried forward HAM-A, total score: 0.36 vs. -1.05 (p = 0.24) CGI-S: -0.63 vs. -0.98 (p = 0.10) ISS, % of patients --Manic (>/= 70): 9 vs. 8 --Depressed (</= 30): 17 vs. 17 --Normal (31 to 69): 74 vs. 75	CGIC "much improved" or "very much improved" (responders), % : 37 vs. 47 (p = 0.30)		Monitoring

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Pande, 2000 U.S. (Fair)	Gabapentin vs. Placebo Serious adverse events: 6 vs. 5 (3 of the 6 serious adverse events in the gabapentin group started during the placebo lead-in) Most frequent adverse events, % --Somnolence: 24.1 vs. 11.9 --Dizziness: 19.0 vs. 5.1 --Diarrhea: 15.5 vs. 11.9 --Headache: 10.3 vs. 11.9 --Amnesia: 10.3 vs. 3.4	Gabapentin vs. Placebo Total Withdrawals: 27/58 (46.6%) vs. 21/59 (35.6%) Withdrawals due to adverse events: 7/58 (12.1%) vs. 5/59 (8.5%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Pande, 2000 U.S. (Fair)	Primary efficacy variables were the YMRS and HAM-D. Placebo was superior to gabapentin in terms of changes in YMRS scores. A post hoc analysis determined that more lithium dosage adjustments were made during the placebo lead-in in the placebo group (n = 12) than in the gabapentin group (n = 4; p < 0.01). When the data from these 16 patients were excluded from analysis, the treatment difference in YMRS change score was no longer significant.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Multicenter (24 sites) double-blind, placebo-controlled, parallel-group RCT Inpatient then outpatient setting	Age at least 18 y; bipolar I disorder with current manic or mixed episodes (DSM-IV); history of at least 1 previous manic or mixed episodes; minimum screen and baseline total score of 20 on Young Mania Rating Scale (YMRS); enrollment of treatment-resistant patients was discouraged	Carbamazepine extended-release capsules (CBZ ERC) started at 400 mg/d then titrated based on investigator discretion to 200 to 1600 mg/d vs. Placebo for 4 wk --Mean final daily dose of CBZ ERC: 756 mg --Median final dosage range (N=192, ITT): 800 to 1000 mg --Mean plasma drug concentration: 8.9 mcg/ml	Single-blind placebo lead-in for first 7 days

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Lorazepam, acetaminophen, and ibuprofen; other less commonly used allowed co-medications were not reported	YMRS, Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales; Hamilton Rating Scale for Depression (HAM-D), adverse events, and adherence, every week; physical examination, hematology, blood chemistry, and urinalysis at screening, baseline, and termination visit Responder rate defined as percentage of patients with at least 50% decrease in YMRS scores from baseline to last observation	CBZ ERC (N = 101) vs. Placebo (N = 103) Age, mean, y: 38.0 vs. 38.1 (NSD) Female, n: 41 (40.6%) vs. 56 (54.4%) (p = 0.0489) White, n: 73 (72.3%) vs. 75 (72.8%) (p = 0.2924)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Mixed episode, n: 60 (59.4%) vs. 48 (46.6%) (p = 0.0670)	Numbers screened, eligible, enrolled not reported / 204 randomized	Of 204 randomized: 108 (52.9%) withdrew / 6 lost to follow-up / 192 analyzed (ITT)	CBZ ERC (N = 94) vs. Placebo (N = 98) YMRS total score, mean --Baseline: 27 vs. 28 --Day 21, primary end point (Calculated change from baseline): 18 (-8.70) vs. 23 (-5.17) (calculated difference, -4; p < 0.033) --First statistically significant difference seen at day 14 Responder rate --Day 21: 69% vs. 30% (p < 0.003) Calculated NNT: 3 (2 to 4) --End point: 41.5% vs. 22.4% (p < 0.0074) Calculated NNT: 5 (3 to 16) --First statistically significant difference seen at day 14

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Subgroup analyses YMRS total score --By gender, 3 age groups, white vs. nonwhite, manic vs. mixed episode: similar moderate treatment effects in favor of CBZ ERC in all subgroups Change in YMRS total score from baseline to end point --Manic episode patients: -6.44 vs. -1.8 (p = 0.0092) --Mixed episode patients: -10.31 vs. -9.8 (NSD)	CGI-S score, change (improvement) from baseline to end point / day 21: 4.07 vs. 3.66 (p = 0.0254) CGI-I score, mean % change at day 21: 66.7% vs. 35.3% (p = 0.0035) CGI-I score, mean % change at end point: 43.6% vs. 24.0% (p = 0.0067) HAM-D score, mean change from baseline to day 21: -5.35 vs. -1.58 (p = 0.09) Post hoc subgroup analysis of change in HAM-D score from baseline in mixed-episode patients remaining on CBZ ERC treatment at day 21: -7.62 vs. -2.44 (p = 0.01)	Took allowed co-medication: 89.1% vs. 90.3% --Lorazepam: 71.3% vs. 67.0% (NSD) --Lorazepam dose (n = 83), mg: 2.2 vs. 2.2 Daily adherence rate, mean: 92.4% vs. 93.4%	Monitoring

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	CBZ ERC (N = 101) vs. Placebo (N = 103) Serious AEs, n: 4 (4.0%) vs. 4 (3.9%) --Worsening/Exacerbation of bipolar symptoms, n: 4 vs. 3 --Suicidality with rehospitalization, n: 0 vs. 1 --Deaths: None Total AEs, n: 89 (88.1%) vs. 75 (72.8%) (p = 0.0078) Possibly related / related AEs, n: 78 (77.2%) vs. 59 (57.3%) (p = 0.0029) Notable Treatment-emergent AEs with a significant treatment difference, n --Dizziness: 49 (48.5%) vs. 13 (12.6%) --Nausea: 38 (37.6%) vs. 11 (10.7%) --Somnolence: 33 (32.7%) vs. 16 (15.5%) --Vomiting: 22 (21.8%) vs. 4 (3.9%) --Dyspepsia: 19 (18.8%) vs. 5 (5.8%) --Dry mouth: 12 (11.9%) vs. 3 (2.9%) --Pruritus: 9 (8.9%) vs. 2 (1.9%) --Speech disorder: 7 (6.9%) vs. 0 (0.0%) Other selected AE, n --Rash: 9 (8.9%) vs. 6 (5.8%) (NSD)	CBZ ERC (N = 101) vs. Placebo (N = 103) Total withdrawals: 51 (50.5%) vs. 57 (55.3%) (NSD) Withdrawals due to serious AEs: 3 (treatment group(s) not reported) Withdrawals due to AEs: 13 (12.9%) vs. 6 (5.8%) (p = 0.0959) --Nausea, dizziness, mania, pruritus: each 2 (2.0%) vs. 0 (0.0%) --Rash: 2 (2.0%; 1 severe) vs. 2 (1.9%) --Diarrhea: 0 (0.0%) vs. 2 (1.9%) Laboratory results showing significant treatment differences --Alkaline phosphatase, mean absolute (relative %) change, U/l: 8.035 (12%) vs. 1.686 (2%) (p = 0.0108) --Cholesterol, mean change, mg/dl: 21.4 vs. 1.1 (p < 0.0001) --White blood cell count, mean change (final value), 103/µl: -1.151 vs. -0.053 (p < 0.0001) Vital signs showing significant treatment differences, mean change from basline to end point --First supine diastolic blod

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Subgroup analysis of change in YMRS scores showed statistically significant treatment difference only in manic patients because of a greater placebo response in mixed-episode patients. Authors note that an antidepressant effect would not be expected to occur in a 3-wk trial. Trial was not powered to detect rare AEs, such as agranulocytosis (1.4 per 1 million patients treated per year) and aplastic anemia (5.1 per 1 million patients treated per year).

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Weisler, 2005 U.S., India SPD417 Study (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Inpatient then outpatient (after day 7 of double-blind treatment, patient could be discharged at physician's discretion)	Age > / = 18 y; DSM-IV criteria for bipolar I disorder with current manic or mixed episodes; history of at least one previous manic or mixed episode; minimum prestudy and baseline Young Mania Rating Scale (YMRS) total score of 20	Carbamazepine extended-release capsules (CBZ ERC) started at 400 mg/d then titrated based on investigator discretion to 200 to 1600 mg/d vs. Placebo for 21 d (double-blind treatment phase) then 30-d follow-up (for safety) --Most patients titrated to final daily dose of CBZ ERC 400 to 1000 mg	5-day single-blind placebo run-in to ensure washout of previous bipolar treatment and exclusionary medications

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Weisler, 2005 U.S., India SPD417 Study (Fair)	Lorazepam--through, and not after, the second week of double-blind treatment	YMRS, Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales, Hamilton Rating Scale for Depression (HAM-D), time to outpatient status, physical examination, electrocardiogram, laboratory assessments, adverse event reporting Responder rate was the percentage of patients with > / = 50% decrease (improvement) in YMRS scores from baseline to last observation	Carbamazepine ERC (N = 122) vs. Placebo (N = 117) Age, mean, y: 37 Male,%: 70% From U.S.: 62% From India: 38% Caucasian: 46% Manic episode: 79.1%

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Weisler, 2005 U.S., India SPD417 Study (Fair)	Mixed episodes: 21% Received prior bipolar treatment: 90%	Numbers screened, eligible, enrolled not reported / 239 randomized	95 (39.7%) withdrew / 4 lost to follow-up / 235 analyzed	CBZ ERC (N = 120) vs. Placebo (N = 115) Mean change from baseline to day 21 --YMRS total score: -15.1 vs. -7.1 (p < 0.0001) --CGI-S score (improvement): 1.5 vs. 0.6 (p < 0.0001) --HAM-D total score: -2.7 vs. -1.0 (p = 0.008) --HAM-D depressed mood item number 1 score: NSD at any time point (data not reported) Responder rate: 73/120 (61%) vs. 33/115 (29%) (p < 0.0001) Calculated NNT: 3 (2 to 5)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Weisler, 2005 U.S., India SPD417 Study (Fair)	Outpatient status: 48.3% vs. 38.4% ($p < 0.05$) Time to discharge: 14.1 d in both groups Onset (time to first statistically significant effect): 7 d Withdrawals due to lack of efficacy: 6.6% vs. 23.1% ($p = 0.0004$)	Subgroup analyses by age, gender, country, manic or mixed episode --YMRS total scores: similar decreases (data not reported) --HAM-D: significant treatment difference in manic subgroup ($p < 0.05$); NSD in mixed episode subgroup ($p = 0.0607$)	Concomitant medications: 91.8% vs. 86.3% (mostly lorazepam, ibuprofen, acetaminophen) Concomitant lorazepam: 73.8% vs. 78.6%	Monitoring

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Weisler, 2005 U.S., India SPD417 Study (Fair)	CBZ ERC (N = 122) vs. Placebo (N = 117) Serious AEs: 3.3% vs. 5.1% (NSD) --One SAE was considered to be possibly related to study treatment: fever, erythematous macular rash over trunk and lower extremities and low white blood cell count --No deaths Any treatment-emergent AE: 91.8% vs. 56.4% (p < 0.0001) AEs occurring at a significantly higher rate on CBZ ERC than Placebo: dizziness, somnolence, nausea, ataxia, vomiting, and blurred vision --Dizziness: 39.3% vs. 12.0% (p < 0.0001) --Somnolence: 30.3% vs. 10.3% (p = 0.0001) Other selected AEs: --Rash: 4.9% vs. 2.6% (NSD) --Pruritus: 8.2% vs. 2.6% (NSD) Percent change from baseline to end point --WBC count: -11.7% vs. 0.3% (p=0.0001) --Total cholesterol: 13.2% vs. 2.0% (p<0.0001) --Low-density lipoprotein (LDL): 28.1% vs. 11.5% (p<0.0001) --High-density lipoprotein (HDL): 9.7% vs. 3.2% (p<0.01) Clinically significant increase in LDL, n: 1 vs. 0 Clinically significant increase in triglycerides, n: 1 vs. 0	Total withdrawals: 34.4% vs. 45.3% (NSD) Withdrawals due to AEs: 9.0% vs. 5.1% (NSD)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Weisler, 2005 U.S., India SPD417 Study (Fair)	All patients were hospitalized during the run-in period and for at least the first 7 days of double-blind treatment, after which patients could be discharged if stable.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Salloum, 2005 U.S. (Fair)	Two-center double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Age 18 to 65 y; after clearing of acute withdrawal symptoms (using Revised Clinical Institute Withdrawal Assessment for Alcohol Scale), met 4 of 7 DSM-IV alcohol dependence criteria; actively drank alcohol in past month; concurrent acute episode of bipolar I disorder (manic, mixed, or depressed)	Divalproex started at 750 mg/d then titrated to serum concentration of 50 to 100 mcg/ml (mean, 51.5 mcg/ml) vs. Placebo for 24 wk (as add-on to lithium)	None

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Salloum, 2005 U.S. (Fair)	Lithium (to trough concentration of 0.7 to 1.2 mEq/l); perphenazine; benztropine; sertraline; trazodone; dual diagnosis recovery counseling; participation in self-help groups (e.g., Alcoholics Anonymous; dual Recovery Anonymous; manic-depressive support group)	Timeline Follow-back for Recent Drinking; Modified Quantitative Alcohol Inventory / Craving Scales; Weekly Self-Help Activity Questionnaire; Somatic Symptoms Checklist; Medication Adherence Form; breath alcohol concentration, urine drug screen; number of drinks consumed; proportion of heavy drinking days (> / = 4 drinks/d for women; > / = 5 drinks/d for men); number of drinks per heavy drinking day; time to relapse to sustained heavy drinking (3 consecutive heavy drinking days); Hamilton Rating Scale for Depression (HRSD-25); Bech-Rafaelsen Mania Scale (BRMS); Global Assessment Scale (GAS); remission of mania (score of </=7 on BRMS); remission of depression (score of </=7 on HRSD-25) every 2 wk for 24 wk	Divalproex vs. Placebo Age, mean, y: 37 vs. 38 Male, n: 21 (72%) vs. 23 (77%) African American, n: 8 (28%) vs. 7 (23%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Salloum, 2005 U.S. (Fair)	Mixed bipolar, n: 30 (58%) Manic: 11 (21%) Depressed: 11 (21%) Attempted suicide during index episode: 6 (17%) (of inpatient recruits) Other substance use disorders, n: 26 (50%) Social class V, n: 13 (45%) vs. 11 (37%) Drinking to intoxication in past 30 d, mean, d: 12.3 vs. 16.3 No. of drinks per week, mean: 88 vs. 104 HRSD-25 score, mean: 20.3 vs. 21.2 BRMS score, mean: 15.2 vs. 15.3 Global Assessment of Functioning score, mean: 38.1 vs. 38.4 Duration of bipolar disorder, mean, y: 13.0 vs. 15.6	Numbers screened and eligible not reported / 72 enrolled / 59 randomized	32 withdrew / 7 lost to follow-up (number lost to follow-up for mood outcomes not calculable) / 52 analyzed (for alcohol use outcome; not reported for mood outcome)	*Alcohol Use Outcome* Divalproex (N = 27) vs. Placebo (N = 25) Divalproex was superior to placebo in improving drinking behavior (data not shown here) *Mood Outcome* Divalproex (N = 27) vs. Placebo (N = 25) Overall mean scores (Mixed model estimate; p-value) --BRMS (Mania) --baseline: 15.2 vs. 15.3 --final: 5.56 vs. 6.10 (-0.03; NSD) --calculated change from baseline: -9.64 vs. -9.20 --HRSD-25 (Depression) --baseline: 20.3 vs. 21.2 --final: 16.3 vs. 14.4 (0.12; NSD) --calculated change from baseline: -4.0 vs. -6.8

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Salloum, 2005 U.S. (Fair)	Time to remission from mania (BRMS score < / = 7): 2 to 3 wk; earlier with divalproex but time not reported by treatment group (p = 0.07 for difference between treatment groups) Time to remission from depression (HRSD-25 score < / = 7): 8 to 9 wk; not reported by treatment group Remission from mania, n: 21 (78%) vs. 20 (80%) (calculated p = 0.86) Remission from depression, n: 17 (63%) vs. 12 (48%) (calculated p = 0.42) Global Assessment of Functioning score --Baseline / Final score, mean: 38.1 / 57 vs. 38.4 / 57 --Calculated change (improvement) from baseline: 18.9 vs. 18.6	Mixed model estimate for association between the following: Valproate serum concentration and improvements in --HRSD-25 scores: -0.11 (p = 0.06) --Functioning: 0.15 (p = 0.06) Manic and depressive symptoms and alcohol use outcomes and functioning (p = 0.006 to p < 0.001) Functioning and alcohol use outcomes (p < 0.001)	*Medication Adherence and Adjunctive Treatment* Divalproex vs. Placebo --Self-reported medication adherence rate: 87% vs. 86% (NSD) --Lithium serum / red blood cell concentration, mean, mEq/l: 0.68 / 0.27 vs. 0.66 / 0.32 (NSD) --Valproate serum concentration, mcg/ml: 51.5 vs. Not reported / applicable --Participated in any psychosocial treatment, n: 21 (78%) vs. 19 (76%) --Received adjunctive antidepressants, n: 11 / 23 (48%) vs. 10 / 21 (48%) --Received adjunctive antipsychotics: 8 (35%) vs. 6 (29%) --Received trazodone as a hypnotic, n: 2 (9%) vs. 9 (43%) (p = 0.03)	Monitoring

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Salloum, 2005 U.S. (Fair)	Serious AEs: 0 Divalproex (N = 27) vs. Placebo (N = 25) Treatment-emergent AEs: NSD between treatment groups for individual AEs (not listed here) Selected treatment-emergent AEs (NSD for any AE) --Nausea or vomiting: 9 (39.1%) vs. 2 (9.5%) (p = 0.07) --Tremor: 11 (47.8%) vs. 14 (66.7%) --Fatigue: 7 (30.4%) vs. 10 (47.6%) --Weight gain: 3 (14.3%) vs. 5 (23.8%) ALT and AST levels did not differentiate between groups in mixed-model analysis Gamma-GTP, IU/l: 66 vs. 81 (estimate, -62.08; p = 0.045) Gamma-GTP correlated with weekly alcohol use (estimate, 0.49; p = 0.02)	Divalproex vs. Placebo Total withdrawals: 15 (56%) vs. 17 (68%) --Required psychiatric hospitalization: 3 / 29 (10.3%) vs. 5 / 30 (16.7%) (calculated p = 0.924) Withdrawals due to AEs: 1 (3.7%) vs. 1 (4.0%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Salloum, 2005 U.S. (Fair)	Authors state this is the first double-blind placebo-controlled trial of valproate in alcoholic patients with bipolar I disorder. Adjunctive medications and psychotherapy may have obscured treatment differences in mood symptoms and dropout rates. Inclusion of patients with a mixture of bipolar I mood states and a small sample size may have reduced the study's power to detect treatment differences in mood symptoms.

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Davis, 2005 U.S. (Fair)	Single-center double-blind, placebo-controlled, parallel-group RCT Outpatient setting	DSM-IV diagnosis of bipolar I disorder, currently in depressed phase; score > / = 16 on 17-item Hamilton Rating Scale for Depression (HRSD); stable general medicine condition; no significant abnormal laboratory values	Divalproex 500 to 2500 mg/d titrated to serum concentration of 50 to 100 mcg/ml (mean, 80 to 81 mcg/ml) vs. Placebo for 8 wk	2-wk washout of previous psychotropic medication (6 wk for fluoxetine)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Davis, 2005 U.S. (Fair)	Diphenhydramine or hydroxyzine	17-item HRSD, Hamilton Rating Scale for Anxiety (HRSA), Clinical Global Impression (CGI), Clinician Administered Rating Scale for Mania (CARS-M) at baseline then weekly; adverse events recorded weekly; valproate serum concentrations and liver function tests at 4 and 8 wk	Not reported by treatment group Age, mean 9range), y: 41 (25 to 54) M / F: 89% / 11% Caucasian: 81%

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to follow-up /analyzed	(12) Results
Davis, 2005 U.S. (Fair)	Veterans; otherwise characteristics not reported	Numbers screened and eligible not reported / 25 enrolled / 25 randomized	13 withdrew / 0 lost to follow-up / 25 analyzed	Divalproex (N = 13) vs. Placebo (N = 12) HRSD (Primary Efficacy Measure), mean percentage change from baseline to 8 wk: -43.51 vs. -27.00 (calculated difference, -16.51; p = 0.0002) HRSD, mean change from baseline to 8 wk (estimated from Figure 1 in original report): -11.5 vs. -6.8 (calculated difference, -4.7; p = 0.0002) Mixed-effects model repeated measures (MMRM) analysis of results over time were significant in favor of divalproex (p=0.033)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Davis, 2005 U.S. (Fair)	HRSA, mean percentage change: -35.21 vs. -5.25; calculated difference, 29.96; p = 0.0001) HRSA, mean change from baseline at wk 8 (estimated from Figure 2 of original report): -7 vs. -1.4 (calculated difference, -5.6) (p=0.033) MMRM analysis of results over time were significantly in favor of divalproex (p=0.0001)	Rate of HRSD improvement (change over time using random regression analysis), points improvement per time unit on square root scale: 5.5 vs. 2.6 (calculated difference, 2.9; p = 0.0227) Rate of HRSA improvement: 3.4 vs. 0.7 (calculated difference, 2.7; p = 0.009)	CARS-M and CGI: NSD (data not reported)	Monitoring

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Davis, 2005 U.S. (Fair)	Not reported	Divalproex vs. Placebo Total withdrawals: 6 / 13 (46.2%) vs. 7 / 12 (58.3%) Withdrawals due to AEs: 1 / 13 (7.7%) vs. 0 / 12 (0.0%)

Evidence Table 3. Placebo-Controlled Trials: Bipolar Disorder

(1) Author, year Country Trial name (Quality score)	(16) Comments
Davis, 2005 U.S. (Fair)	Most of the outpatient subjects were moderately ill. This trial is unique for monitoring anxiolytic effects (which are not typically evaluated in bipolar clinical trials). Results need to be confirmed in larger, well-designed trials before one can conclude efficacy of divalproex for acute treatment of bipolar depression.

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

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

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

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

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

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

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

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Phenytoin vs. Carbamazepine			
Skelton, 1991 U.S. (Poor)	Not reported	Phenytoin vs. Carbamazepine Total withdrawals: 3/7 (42.8%) vs. 3/5 (60.0%), all due to adverse events (no statistical analysis)	Small sample size; can't infer one medication is superior to the other.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Leijon, 1989 Sweden (Poor)	Acetaminophen 2000 mg/d (n = 1) and Transcutaneous Electrical Nerve Stimulation (n = 2, one for nociceptive knee pain and the other for CPSP)	10-point verbal scale for pain intensity, daily; 5-point global assessment scale fo pain relief (1 = pain worsened, 5 = pain-free) on day 28 of each treatment period; 10-item Comprehensive Psychopathological Rating Scale (CPRS) for depression before each treatment and on day 28 of each treatment period. Responders on the daily pain rating scale were defined as patients who obtained a pain reduction of at least 20% as compared with the placebo period.	Mean age (range), y: 66 (53 to 74) 80% Male, 20% Female Ethnicity not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Leijon, 1989 Sweden (Poor)	Location of cerebrovascular lesion, n: brainstem (7), thalamic (5), supratentorial, extrathalamic (2), unidentified (1) Duration of pain, mean (range), mo: 54 (11 to 154) Dominant pain qualities: burning, aching, and throbbing Other types of chronic pain, n: low back pain (3), chronic tension headache (1), sciatica (1)	27/15/15/15	1 discontinued carbamazepine on day 25 because of interaction with warfarin (included in analyses); 1 not randomized to carbamazepine because of allergy / none lost to follow up / 14, 15, and 15 analyzed for carbamazepine, amitriptyline, and placebo, respectively	Carbamazepine vs. Amitriptyline vs. Placebo Week 4 Daily Pain Rating, mean: 4.2 vs. 4.2 vs. 5.3 ($p < 0.05$ for amitriptyline vs. placebo)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Leijon, 1989 Sweden (Poor)	Improved on Global Assessment of Change in Pain: 5/14 (36%) vs. 10/15 (67.8%) vs. 1/15 (6.7%) ($p < 0.05$ for amitriptyline vs. placebo; NSD between amitriptyline and carbamazepine)	Depression Scores at end of each treatment period, mean (range): 3.0 (0 to 7) vs. 2.2 (0 to 8) vs. 2.6 (0 to 6) (NSD) Almost all patients had low baseline depression scores (mean 2.9; range 0 to 6.5) and no patients appeared to be depressed	Monitored	Most frequent AEs-- On carbamazepine: vertigo, tiredness, gait disturbances On amitriptyline: tiredness and dry mouth

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Leijon, 1989 Sweden (Poor)	Total withdrawals: 1 (carbamazepine) Withdrawals due to adverse events: None	Pain rating scores at baseline and change from baseline were not reported.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Gomez-Perez, 1996 Mexico (Poor)	Not reported	Vertical visual analogue scale for pain and paresthesia at baseline and every 15 d	Sequence A (Nortriptyline / Fluphenazine first) vs. Sequence B (Carbamazepine first) Mean (SD) age, y: 51.5 (8.4) vs. 43.1 (19.4) (p > 0.05) 50.0% vs. 37.5% Male (p > 0.05) Ethnicity not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Gomez-Perez, 1996 Mexico (Poor)	Sequence A (Nortriptyline / Fluphenazine first) vs. Sequence B (Carbamazepine first) Mean (SD) diabetes mellitus duration, y: 8.9 (7.8) vs. 9.9 (4.4) Mean (SD) neuropathy duration, y: 2.0 (1.9) vs. 2.3 (2.8) (p > 0.05) Mean (SD) HgA1c, %: 10.2 (2.8) vs 9.5 (1.9)	--/--/16/16	2/0/14	Carbamazepine vs. Nortriptyline / Fluphenazine Mean % change in pain at 30 d: Sequence A: -53.7 vs. -56.1 (NSD) Sequence B: -44.4 vs. -77.0 (NSD)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Gomez-Perez, 1996 Mexico (Poor)	Carbamazepine vs. Nortriptyline / Fluphenazine Mean % change in paresthesia at 30 d: Sequence A: -68.2 vs. -62.2 (NSD) Sequence B: -48.0 vs. -82.0 (NSD)			Not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gomez-Perez, 1996 Mexico (Poor)	Nortriptyline / Fluphenazine Adverse events (units not reported): 8 vs. 3 Dryness of the mouth and dizziness reported with nortriptyline / fluphenazine Epigastric pain reported with carbamazepine	Carbamazepine vs. Nortriptyline / Fluphenazine Total withdrawals: 1/16 (6.3%) vs. 1/16 (6.3%) Withdrawals due to adverse events: 1/16 (6.3%) vs. 0/16 Limited by small sample size.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Lechin, 1989 Venezuela (Poor)	Not reported (see eligibility criteria)	Number screened and eligible not reported / 68 enrolled / 59 randomized	9 withdrew during placebo washout before randomization / Not reported / 48 analyzed (11 excluded from analyses)	Carbamazepine vs. Pimozide Reduction in total trigeminal neuralgia score at wk 6, mean: 49.7% vs. 78.4% ($p < 0.001$) Similar results were obtained at wk 7 and 8 ($p < 0.001$ for each analysis). (It is unclear whether percentages are relative or absolute changes.)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Lechin, 1989 Venezuela (Poor)	Onset of significant improvement, wk: 4 vs. 2 "Improved" (It is unclear whether "improved" was based on 20% or more reduction in the trigeminal neuralgia score.) --Before crossover: 14 (58%) vs. 24 (100%) --After crossover: 13 (54%) vs. 24 (100%)	Dose achieving maximal response, mg/d: 900 vs. 12	Monitored	Serious toxic effects of carbamazepine: sluggishness (mental and physical) (18/48, 37.5%); related to blood elements [*sic*]; liver function abnormalities; inappropriate secretion of vasopression in association with a decreased ability to excrete a water load; erythematous exanthem (resolved after trial ended) (1 patient, 2.1%, each) Frequent adverse events during pimozide therapy: physical and mental retardation, hand tremors, memory impairment, involuntary jerking movements during sleep, and slight Parkinson's disease manifestations (attenuated by small doses of biperiden or dosage reduction) (total 40/48, 83.3%). Despite experiencing adverse events on pimozide, all patients refused interruption of pimozide therapy.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Lechin, 1989 Venezuela (Poor)	Total withdrawals: 9 (before randomization) Withdrawals due to adverse events: None	Exclusion of placebo responders before randomization may have resulted in treatment responses smaller than those that might be seen in clinical practice. Although patients had obtained partial and temporary improvement followed by "total failure" of prior

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Keczkes, 1980 U.K. (Poor)	Parallel-group RCT (blinding not reported) Inpatient for 2 wk then outpatient setting	Inclusion criteria unclear; patients described as being over 50 years old with early, severe painful herpes zoster (mean duration of rash before treatment was 5.0 days for carbamazepine and 5.3 days for prednisolone-treated patients.	Carbamazepine (acting as placebo) 400 mg/d for 4 wk vs. Prednisolone 40 mg/d for 10 d then gradually tapering off over next 3 wk. Treatments were given prophylactically.	None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Keczkes, 1980 U.K. (Poor)	Topical neomycin plus gramicidin ointment; talcum powder; analgesics allowed only in posthperpetic neuralgia phase (not acute phase)	Presence or absence of postherpetic neuralgia recorded every 2 wk Postherpetic neuralgia was defined as pain in the affected area that lasted beyond 2 mo from the onset of pain.	Age, mean (range), y: 66.4 (50 to 81) Male / Female: 14 / 6 in both groups Ethnicity not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Keczkes, 1980 U.K. (Poor)	Duration of rash before study treatment: 5 days (carbamazepine) and 5.3 days (prednisolone)	Numbers screened and eligible not reported / 40 enrolled / 40 randomized	None withdrew / None lost to follow-up / 40 analyzed	Carbamazepine vs. Prednisolone (no statistical analyses) Developed postherpetic neuralgia (pain lasting > 2 mo): 13/20 (65%) vs. 3/20 (15%)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Keczkes, 1980 U.K. (Poor)	Duration of postherpetic neuralgia, mo: > 3 to 18 vs. 4 to 6 Duration of postherpetic neuralgia >/= 1 y, n (%): 4 (20%) vs. 0 (0%)		Not reported	Not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Keczkes, 1980 U.K. (Poor)	No withdrawals; No withdrawals due to adverse events	Blinding was not reported. Spontaneous resolution of postherpetic neuralgia may have confounded treatment response rates. Treatment regimens differed, with a tapering schedule for prednisolone and stable dosing for carbamazepine. Double-dummy was not used

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Lindström, 1987 Sweden (Poor)	DB CO RCT Double-blind, crossover RCT	Active, typical idiopathic trigeminal neuralgia; seeral attacks daily over a long period of time	Carbamazepine in maximum tolerated dose vs. Tocainide 20 mg/kg/d	None

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Lindström, 1987 Sweden (Poor)	None	11-point scale for pain frequency and severity daily; patient activity pattern, pain precipitation factors twice weekly by telephone interview	Age range, y: 41 to 78 42% Male, 58% Female Ethnicity not reported

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Lindström, 1987 Sweden (Poor)	Disease duration: 5 to 19 y	--/--/12/12	0/0/12	No Medication (N = 8) vs. Carbamazepine (N = 11) vs. Tocainide (N = 11) Range of Mean Pain Scores for the Last 10 Days of Each 2-wk Treatment Period: 4 to 10 vs. 0.6 to 7.9 vs. 0.8 to 8.1 Number of mean pain scores </= 4.0: 1/8 (12.5%) vs. 9/11 (81.8%)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Lindström, 1987 Sweden (Poor)			Monitored	No adverse events reported for carbamazepine. Tocainide: nausea, apical paresthesias, skin rash

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Lindström, 1987 Sweden (Poor)	Total withdrawals: 1 (due to rash on tocainide)	Limited by small sample size and problems with internal validity. Serious hematologic side effects of tocainide infrequently cause death.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Dallocchio, 2000 Italy (Poor)	Duration of pain, mean (SD or SE, not specified), mo: 34 (11) vs. 22 (12) (p = 0.026) Duration of diabetes, mean (SD or SE, not specified), y: 12 (4) vs. 9 (7)	Number screened not reported / Number eligible not reported / 25 enrolled / 25 randomized	None withdrawn / None lost to follow-up / 25 analyzed	Gabapentin vs. Placebo Mean change in pain score (scale, 0 to 4): -1.9 (0.8) vs. -1.3 (0.6) (p = 0.026)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Dallocchio, 2000 Italy (Poor)	Achieved goal pain intensity score of 1 or less: 10/13 (76.9%) vs. 8/12 (66.7%) (no statistical analysis)		Not reported	Gabapentin vs. Amitriptyline Total patients reporting >/= 1 adverse event: 4/13 (30.8%) vs. 11/12 (91.7%) Most common adverse events: Dizziness: 2/13 (15.4%) vs. 5/12 (41.7%) Somnolence: 1/13 (7.7%) vs. 6/12 (50.0%) Dry mouth: 0/13 (0.0%) vs. 5/12 (41.7%) Constipation: 0/13 (0.0%) vs. 4/12 (33.3%)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Dallocchio, 2000 Italy (Poor)	None of the patients withdrew	Dissimilarity in duration of pain at baseline (a difference of 1 yr), while probably not clinically relevant, suggests that randomization may have been inadequate. Open-label design introduces possibility of bias. On the 5-point pain scale, the mean changes in pain scores were equivalent to reducing pain from moderate-to-severe to mild pain for gabapentin as compared with reducing pain from moderate-to-severe to mild-to-moderate for amitriptyline.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Morello, 1999 U.S. (Fair)	Mean (SD) duration of diabetes, y: 13.4 (11.3) Mean (SD) initial hemoglobin A1c: 0.071 (0.005) Mean (SD) duration of pain: 5.7 (4.2)	--/28/25/25	4/0/19 or 21 (2 Early Crossovers)	Mean difference in pain intensity scores at 6 wk: 0.091 units (95% CI: -0.074 to 0.256; p = 0.26) (Note: 0.35 units was the difference between moderate and mild pain) Gabapentin vs. Amitriptyline Patients with moderate or greater pain relief: 11/21 (52%) vs. 14/21 (67%) (p > 0.1)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Morello, 1999 U.S. (Fair)			Not reported	More common on amitriptyline than gabapentin: weight gain (6 vs. 0; p = 0.01) No statistically significant difference (top 10 adverse events): sedation, dry mouth, dizziness, postural hypotension, ataxia, constipation, lethargy, edema, headache, pruritus

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Morello, 1999 U.S. (Fair)	Gabapentin vs. Amitriptyline Total Withdrawals: 2 vs. 2 Withdrawals due to adverse event: 2 vs. 1 Early Crossover Because of Intolerable Adverse Events: 2 vs. 1	The limited number of patients enrolled introduces the possibility of a type II error. Post hoc analysis revealed that a sample size of 260 patients per paired crossover study would be necessary to provide 80% power to detect a significant treatment difference of one third of the difference between mild and moderate pain.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

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

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Lockman, 1973 U.S. (Poor)	7 hemizygotes, 1 heterozygote for Fabry's disease	Numbers screened and eligible not reported / 8 enrolled / 8 randomized	None withdrawn / None lost to follow-up / 8 analyzed	Phenytoin vs. Aspirin vs. Multivitamin Pain relief score, mean (range): 2.7 (1.0 to 3.0) vs. 0.5 (0 to 2.1) vs. 0.9 (0 to 2.6) ($p < 0.001$ for phenytoin vs. aspirin or multivitamin; NSD for aspirin vs. multivitamin)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Lockman, 1973 U.S. (Poor)	Adherence (percentage of doses taken), median (range): 95 (55 to 100) vs. 75 (28 to 95) vs. 81 (71 to 98)		Monitoring	Dizziness, drowsiness, and headache: 1 patient on phenytoin (serum concentration 33 mcg/ml)

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Lockman, 1973 U.S. (Poor)	No withdrawals	Adherence (percentage of doses taken) seemed to be lower with aspirin than the other two treatments. No washout before crossovers; possible carryover effects.

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Gilron, 2005 Canada (Poor)	Single-center, double-blind, double-dummy, 4-period crossover RCT Outpatient setting implied	Daily moderate pain for 3 months or more, age 18 to 89 y, serum alanine aminotransferase or aspartate aminotransferase level < 1.2 times normal; creatinine < 1.5 upper limit of normal; sufficient language skills to communicate with staff	Gabapentin 900 mg/d vs. Morphine sustained-release 60 mg/d vs. Combination (Gabapentin 900 mg/d + Morphine SR 30 mg/d) vs. Active Placebo (Lorazepam 0.7 mg/d), each given for 5 wk (maximally tolerated dose given in fourth week); doses were titrated to adverse events and target doses of 3200 mg/d (Gabapentin monotherapy), 120 mg (Morphine monotherapy), 2400 mg/d + 60 mg/d (Gabapentin + Morphine SR), 1.6 mg/d Lorazepam; lower doses were given for patients > 60 y old or < 60 kg (i.e., Morphine SR 30 mg/d; target doses adjusted downward for Morphine SR (60 mg/d) and Gabapentin (2400 mg/d)).	3-day washout before crossover

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Gilron, 2005 Canada (Poor)	Stable doses of nonopioid analgesic drugs other than gabapentin	Self-rated scales and research nurse assessments. 11-point numerical rating scale for pain intensity (0 = no pain, 10 = worst pain imaginable); adverse events; Short-form McGill Pain Questionnaire (SF-MPQ); Brief Pain Inventory (BPI); Beck Depression Inventory (BDI); SF-36 Health Survey (SF-36); Mini-mental State Examination (MMSE); and Global pain relief at baseline and during each treatment period at maximal tolerated doses; "blinding" questionnaire taken by patients and research nurses when patients were taking maximal tolerated doses of study drugs.	Patients with Diabetic Neuropathy (N = 35) and Patients with Postherpetic Neuralgia (N = 22) Age, median (range), y: 60 and 68 (40 to 75 and 47 to 81) Male / Female: 51% / 49% and 64% / 36% Ethnicity, White / Other: 97% / 3% and 100% / 0%

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/ randomized	(11) Number withdrawn/ lost to fu/analyzed	(12) Results
Gilron, 2005 Canada (Poor)	Duration of pain or time since onset of herpes zoster, y: 4.5 and 4.6 Duration of diabetes, y: 10.8 Allodynia, %: 49% and 64% Concomitant medications, None / Tricyclic antidepressant / Selective serotonin reuptake inhibitor / antiepileptic drug / acetaminophen or nonsteroidal antiinflammatory drug, %: 63% / 11% / 6% / 3% / 23% and 77% / 9% / 5% / 0% / 9%	86/--/--/57	16/ Not reported /44	Mean weekly pain intensity scores (Primary efficacy outcome): NSD between treatment sequences Gabapentin vs. Morphine vs. Gabapentin+Morphine vs. Placebo Mean pain intensity scores at maximally tolerated dose (Primary efficacy outcome): 4.15 vs. 3.70 vs. 3.06 vs. 4.49

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?	(14) Adverse events reported
Gilron, 2005 Canada (Poor)	Total SF-MPQ score: 10.7 vs. 10.7 vs. 7.5 vs. 14.4 ($p < 0.05$ for Gabapentin+Morphine vs. other treatment groups) BPI score (pain-related interference): All 3 active treatments better than placebo ($p < 0.05$) for all 7 domains except with gabapentin and morphine for social relations, and morphine for walking. SF-36: All 3 active treatments better than placebo ($p<0.05$) for all 8 domains except for general health, and morphine for role-emotional.	BDI score: 6.4 vs. 6.7 vs. 6.0 vs. 8.5 ($p < 0.05$ for all 3 active treatments vs. placebo) MMSE score: 28.8 vs. 29.0 vs. 29.0 vs. 28.9 Achieved at least moderate pain relief, n: 27 (61%) vs. 35 (80%) vs. 32 (78%) vs. 13 (31%) ($p < 0.05$ for all 3 active treatments vs. placebo) Mean maximal tolerated dose as single agent vs. in combination, mg: Morphine--45.3 vs. 34.4	Monitored	Gabapentin vs. Morphine vs. Gabapentin+Morphine vs. Placebo Adverse events showing significant differences between study treatment and gabapentin+morphine (*) or placebo (**), % of patients: During Dose Titration (Wk 1 to 3) --Constipation 4.2* vs. 43.2** vs. 44.2** vs. 4.7 --Sedation 10.4* vs. 36.4 vs. 39.5 vs. 18.6 --Dry mouth 8.3* vs. 11.4 vs. 32.6** vs. 2.3 --Insomnia 4.2** vs. 13.6 vs. 2.3** vs. 25.6 --Vomiting 0.0** vs. 9.1 vs. 16.3 vs. 0.0 At Maximal Tolerated Dose (Wk 4) --Constipation 2.1* vs. 38.6** vs. 20.9** vs. 4.7 --Dry mouth 6.3 vs. 4.6* vs. 20.9** vs. 0.0

Evidence Table 5. Active-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Gilron, 2005 Canada (Poor)	Gabapentin vs. Morphine vs. Gabapentin+Morphine vs. Placebo Total withdrawals: 4 vs. 5 vs. 6 vs. 1 Withdrawals due to adverse events: Not reported	For the weekly average of daily pain scores, an exploratory analysis showed that the effect of morphine was more likely to carry over to the next treatment period than that of placebo (p = 0.005).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Campbell, 1966 U.K. (Poor)	Not reported	Number screened not reported / Number eligible not reported / 77 enrolled / 77 randomized	7 withdrawn / 3 lost to follow-up and 1 record were lost / 70 analyzed
Dalessio, 1966 only RCT described here U.S. (Poor)	Not reported	Numbers screened and eligible not reported / 10 enrolled / 10 randomized	None withdrawn / None lost to follow-up / 10 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Campbell, 1966 U.K. (Poor)	Carbazepine (C) vs. Placebo (P) Upgrading rates (sum of upgrading / sum of possible upgradings, %) C-P-C-P treatment sequence: 51/89 (58%) - 2/37 (5%) - 38/59 (64%) - 4/26 (15%) P-C-P-C treatment sequence: 22/86 (26%) - 27/66 (41%) - 7/41 (17%) - 28/54 (52%) Difference in upgrading rate in first treatment period (without carryover effects): 32% ($p < 0.01$)	
Dalessio, 1966 only RCT described here U.S. (Poor)	Carbamazepine vs. Placebo Drug effective (pain relief): 10 vs. 0 ($p < 0.002$)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Campbell, 1966 U.K. (Poor)			Elicited by investigator
Dalessio, 1966 only RCT described here U.S. (Poor)			Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Campbell, 1966 U.K. (Poor)	Carbazepine adverse events (placebo AEs not reported) Giddiness, unsteadiness, drowsiness, rash	Total withdrawals: 7 Withdrawal due to adverse event: 1 (rash on carbazepine)
Dalessio, 1966 only RCT described here U.S. (Poor)	Not reported	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Campbell, 1966 U.K. (Poor)	Carryover effects were possible because there was no washout between treatments. Study used a novel system of scoring pain severity (upgrading and downgrading rates).
Dalessio, 1966 only RCT described here U.S. (Poor)	Open-label pilot study, which preceded the RCT, is not described here. Insufficient information and small sample size make it difficult to generalize results.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Harke, 2001 Germany (Poor)	Reactivation of SCS in case of intolerable pain	Numeric Analog Scale (NAS) of pain intensity (ranging from 0 to 10 points) recorded in diary every 2 h	Median age, y: 55 48.8% male, 52.2% female Ethnicity not reported
Nicol, 1969 U.S. (Poor)	Phenytoin	4-point descriptive pain rating scale (Excellent to Unchanged) sent weekly and thereafter every four to eight weeks dependent upon the patients' clinical progress	47.7% Male, 52.3% Female Age and Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Harke, 2001 Germany (Poor)	Median pain duration: 6 y Median pain intensity (NAS range 0 to 10): 9 Median pain increase on NAS of 4.6 after switching off SCS Median duration of SCS switch-off: 145 min Neuropathic diagnoses (n): isolated radiculitis (17), postherpetic thoracic neuralgia (6), phantom limb pain (3), diabetic neuropathy (3), peripheral nerve lesion (7), reflex sympathetic dystrophy (Complex Regional Pain Syndrome I) (7)	Phase I: 77/68/43/43 Phase II: '--/38/38/38	Phase I: 5/0/38 Phase II: 3/--/35
Nicol, 1969 U.S. (Poor)	Not reported	Number screened not reported / 64 eligible / 44 enrolled / 44 randomized (Carbamazepine, N = 20; Placebo, N = 24)	None withdrawn / None lost to follow-up / 44 analyzed; however, treatment groups that were analyzed consisted of Carbamazepine (N = 20), Placebo followed by carbamazepine (N = 17), and Placebo only (N = 7)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Harke, 2001 Germany (Poor)	Phase I Carbamazepine vs. Placebo Mean maximum pain intensity (NAS) Responders (analgesia comparable to SCS): 2.5 vs. no data Partial responders: 5.9 vs. 7.7 (p = 0.04) Nonresponders (reactivated SCS because of severe pain): 7.2 vs. 9.0 (p = 0.06)	Phase II Morphine vs. Placebo Mean maximum pain intensity (NAS) Responders: 1 vs. no data Partial Responders: 6.7 vs. 6.1 (p = 0.41) Nonresponders: 8.3 vs. 8.3 (p = 0.83)
Nicol, 1969 U.S. (Poor)	(I) Carbamazepine vs. (II) Placebo followed by carbamazepine vs. (III) Placebo only At least good clinical response: 8 vs. 12 vs. 6 (no statistical analyses)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Harke, 2001 Germany (Poor)			Not reported
Nicol, 1969 U.S. (Poor)			Reported spontaneously by patient; laboratory tests monitored

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Harke, 2001 Germany (Poor)	Carbamazepine: ataxia, dizziness, vomiting, nausea, fatigue, sweating, headache Morphine: dizziness, vomiting, nausea, fatigue, sweating, headache, constipation Frequency not reported by number of patients	Phase I, Carbamazepine vs. Placebo Total Withdrawals: 5/43 (11.6%) Adverse Event Withdrawals: Not reported Phase II, Morphine vs. Placebo Total Withdrawals: Not reported Adverse Event Withdrawals: 1/19 (5.3%) vs. 2/19 (10.5%)
Nicol, 1969 U.S. (Poor)	Carbamazepine: Generalized pruritis; erythematous skin eruption; drowsiness; staggering gait; minor stomach upset; tremulousness; impaired recent memory; lightheadedness; blurred vision; asymptomatic decrease in white blood cell count; asymptomatic increase in liver transaminases Placebo: Not reported	Carbamazepine Total withdrawals: 2, both due to adverse events (generalized pruritis and generalized erythematous eruption) Placebo: Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Harke, 2001 Germany (Poor)	Method of diagnosing neuropathic pain was not reported. Changes in pain intensity from baseline were not reported by treatment groups.
Nicol, 1969 U.S. (Poor)	Patients were not analyzed in the treatment groups to which they were originally randomized; a third treatment group was added (Placebo followed by carbamazepine) apparently when results were evaluated. Small sample size and unorthodox analyses.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Rockliff, 1966 (--) U.S. (Fair)	Group 1 Previous surgical treatment: 4/9 (44.4%) Previous AED treatment: 7/9 77.8%)	Group 1, Controlled Trial + Extended Open Trial Numbers screened and eligible not reported / 9 enrolled / 9 randomized	Of total 20 patients: 9 withdrew / 1 lost to follow-up / 9 analyzed in controlled trial; 11 in extended open trials
	Group 2 Not reported	Group 2, Additional Patients in Extended Open Trial Numbers screened and eligible not reported / 11 enrolled / Number randomized not applicable	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Rockliff, 1966 (--) U.S. (Fair)	Controlled Trials (Group 1) Preferred carbamazepine: 8/9 (88.9%) (p < 0.05 using a "closed" sequential design method) Both equally effective: 1/9 (11.1%)	Extended Open Trial (Group 1) Major (two thirds of pain relieved or almost pain-free) to complete relief following controlled trial: 7/9 (77.8%) Required addition of phenytoin: 1/9 11.1% Remission, off medication: 3/9 (33.3%) Maintained partial relief (frequency and severity of pain markedly reduced): 2/9 (22.2%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Rockliff, 1966 (--) U.S. (Fair)	Extended Open Trial (Group 2) Partial, Moderate, Marked, or Complete Relief Initially: 11/11 (100%) Relapse of Pain (after 2 d to 4 mo): 5/11 (45.4%) --Relapse, controlled after addition of phenytoin +/- other treatments: 3/11 (27.3%) --Relapsed, elected surgery: 2/11 (18.2%) Partial relief initially, controlled after addition of phenytoin: 1/11 (9.1%) Remission, off medication: 2/11 (18.2%) Maintained on carbamazepine: 3/11 (27.3%)	Combined results from both groups Treatment satisfactory on carbamazepine alone or combined with phenytoin (and mephenesin carbamate in one case): 16/20 (80%) Remained in remission, off medication: 5/20 (25%) Required continuous or intermittent medication: 11/20 (55%)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Rockliff, 1966 (--) U.S. (Fair)	Controlled Trial: Treatment comparisons not reported Extended Open Trial on carbamazepine Any adverse event, n: 14/20 (70.0%) Most common adverse events: drowsiness, dizziness, headache, and nausea	Controlled Trial: No withdrawals Extended Open Trial Total withdrawals: 6/20 (30.0%) Withdrawals due to adverse events: 1/20 (5.0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Rockliff, 1966 (--) U.S. (Fair)	This study used an unconventional statistical method, called a "closed" sequential design, to limit the duration of the trial. The probability of a preference for carbamazepine was based on the assumptions that the response rates would be 80% for carbamazepine and 40% for placebo. A design was then chosen such that if the preference path crossed an outside boundary, then the null hypothesis would be rejected with p = 0.05.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Rull, 1969 Mexico (Poor)	Not reported	Subjective changes in intensity, distribution, and duration of symptoms in comparison with baseline, graded by a blinded author from 0 (no change) to 5↓ (disappearance) or 5↑ (maximal increase); frequency of assessments not reported. Overall results for each patient at end of each 2-wk period were obtained by algebraic summation of all positive and negative changes.	Age, mean (range), y: 54.2 (21 to 81) Male / Female: 9 / 21 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Rull, 1969 Mexico (Poor)	Duration of diabetes, mean (range), y: 10.9 (3 to 24) Degree of control (n) --Good: 11 --Fair: 5 --Poor: 14 Treatment (n) --Diet alone: 2 --Insulin: 10 --Oral hypoglycemic: 18	Numbers screened and eligible not reported / 30 enrolled / 30 randomized (14 to A-B-A and 16 to B-A-B treatment sequence, where A = carbamazepine and B = placebo)	2 withdrawn / 1 lost to follow-up (reason for not attending visit was not reported) / 30 analyzed (with 3 marked as results not recorded)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Rull, 1969 Mexico (Poor)	Carbamazepine (44 patient-periods) vs. Placebo (46 patient-periods) (Results shown here were tallied and calculated from reported data that was presented by treatment period. No statistical analyses were reported.) Change in symptoms (No. of patient-periods. %) --Disappearance (5↓): 2 (4.5%) vs. 2 (4.3%) --Improvement (3↓ to 4↓): 23 (52.3%) vs. 4 (8.7%) --Improvement (1↓ to 2↓): 15 (34.1%) vs. 20 (43.5%) --No change: 2 (4.5%) vs. 4 (8.7%) --Increase (1↑ to 5↑): 0 (0.0%) vs. 15 (32.6%) --Not recorded: 2 (4.5%) vs. 1 (2.2%) (Note: A patient-period represents the patient exposure; i.e., number of patients multiplied by the number of treatment periods for each drug.)	

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Rull, 1969 Mexico (Poor)			Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Rull, 1969 Mexico (Poor)	No treatment comparisons. Adverse events reported during carbamazepine periods or in the first few days of placebo following carbamazepine treatment were the following (n, %): --Somnolence: 16/30 (53.3%) --Dizziness: 12/30 (40.0%) --Gait changes 4/30 (13.3%) --Urticaria: 2/30 (6.6%) --Nausea: 2/30 (6.6%) --Vomiting: 1/30 (3.3%)	Carbamazepine vs. Placebo Total withdrawals: 2/30 (6.6%) vs. 1/30 (3.3%) Withdrawals due to adverse events: 2/30 (6.6%) vs. 0/30 (0.0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Rull, 1969 Mexico (Poor)	Lack of washout between treatment periods resulted in carryover effects, which may have reduced any treatment differences. Double-blinding may have been breached because adverse events tended to occur only during carbamazepine therapy.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Backonja, 1998 U.S. (Fair)	Gabapentin vs. Placebo Duration of neuropathic pain: Not reported Duration of diabetes, mean (SD), y: 12.0 (9.6) vs. 11.2 (8.7)	232 screened / 165 eligible / 165 enrolled / 165 randomized	30 withdrew / None lost to follow-up / 162 analyzed for efficacy, 165 for safety (3 patients excluded from efficacy analyses apparently because they either did not receive study medication or were missing data, and therefore, did not meet the definition of the ITT population)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Backonja, 1998 U.S. (Fair)	Gabapentin (N = 82) vs. Placebo (N = 80) Likert Pain score (Primary efficacy measure) Difference in mean scores at end point (95% CI): -1.2 (-1.9 to -0.6) (p < 0.001) Calculated change (%) in mean scores from baseline to end point: -2.5 (39.1%) vs. -1.4 (21.5%) Gabapentin vs. Placebo At least moderate improvement, n/N (%) CGIC: 39/81 (48.1%) vs. 16/75 (21.3%) (p = 0.001) [Calculated NNT (95% CI): 4 (2-8)] PGIC: 59/79 (74.7%) vs. 25/76 (32.9%) (p = 0.001) [Calculated NNT (95% CI): 2 (2-4)]	Onset of significant analgesic effect: 2 wk Sleep interference score, difference (95% CI): -1.47 (-2.2 to -0.8) (p < 0.001) Total SF-MPQ, difference (95% CI): -5.9 (-8.8 to -3.1) (p < 0.001) SF-MPQ VAS, difference (95% CI): -16.9 (-25.3 to -8.4) (p < 0.001) Calculated change (%) in mean scores from baseline: 30.8 (45.5%) vs. 17.4 (24.4%)]

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Backonja, 1998 U.S. (Fair)	SF-MPQ PPI, difference (95% CI): -0.6 (-0.9 to -0.3) (p < 0.001) SF-36 QoL, [calculated change in means from baseline]; difference at end point (95% CI) Bodily pain: [14.6 vs. 9.9]; 7.8 (1.8 to 13.8) (p = 0.01) Mental health: [3.7 vs. 3.9]; 5.4 (0.5 to 10.3) (p = 0.03) Vitality: [12.0 vs. 2.9]; 9.7 (3.9 to 15.5) (p = 0.001) Note: Increase in score reflects improvement.	POMS, [calculated change in means from baseline]; differences at end point (95% CI) Anger/hostility: [-2.1 vs. -2.4]; -2.2 (-4.1 to -0.3) (p = 0.02) Vigor/activity: [0.7 vs. 0]; 1.96 (0.5 to 3.5) (0 = 0.01) Fatigue/inertia: [-3.5 vs. -1.1]; -1.96 (-3.4 to -0.5) (p = 0.01) Total mood: [-10.2 vs. 8.1]; -9.14 (-17.3 to -1.0) (p = 0.03) Note: Increase in vigor/activity score reflects improvement.	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Backonja, 1998 U.S. (Fair)	Gabapentin (N = 84) vs. Placebo (N = 81) Most frequently reported adverse events with treatment difference, n (%) Dizziness: 20 (23.8%) vs. 4 (4.9%) (p < 0.001) Somnolence: 19 (22.6%) vs. 5 (6.2%) (p = 0.004)	Gabapentin vs. Placebo Total Withdrawals: 14/84 (16.7%) vs. 16/81 (19.8%) Withdrawals due to adverse events: 7/84 (8.3%) vs. 5/81 (6.2%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Backonja, 1998 U.S. (Fair)	The diagnosis of diabetic neuropathy was based on clinical examination. Electrophysiologic studies could have excluded other causes for neuropathy. The calculated change in mean pain intensity scores from baseline (-2.5, -39%) with gabapentin meet criteria for clinically relevant changes in chronic pain by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Bone, 2002 U.K., Ireland (Fair)	Duration since amputation, mean (range), mo: 18 (6 to 51)	Number screened not reported / 33 eligible / 19 enrolled / 19 randomized	5 withdrew / None lost to follow-up / 19 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Bone, 2002 U.K., Ireland (Fair)	Gabapentin vs. Placebo VAS Pain Intensity score, mm Pain Intensity Difference (PID) at wk 6 compared with baseline (Primary efficacy measure): 3.2 vs. 1.6 (p = 0.03) Calculated relative change in pain score from baseline: 52.5% vs. 23.9% Categorical pain, mean Baseline: 1.5 vs. 1.8 (NSD) End of therapy, wk 6: 1.45 vs. 1.6 (NSD)	Rescue medication, no. of tablets, mean: 177 vs. 187 (NSD) Sleep interference, median (interquartile range, IQR) Baseline: 4 (2 to 5) vs. 4 (2 to 5) End of therapy: 3 (1 to 5) vs. 4 (1 to 5) (NSD) HAD depression scale, median (IQR) Baseline: 14 (5 to 25) vs. 15 (25 to 25) End of therapy: 12 (4 to 22) vs. 14 (5 to 25) (NSD)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Bone, 2002 U.K., Ireland (Fair)	Barthel Index, median (IQR) Baseline: 90 (70 to 105) vs. 85 (65 to 100) End of therapy: 85 (70 to 105) vs. 87 (65 to 105) (NSD)		Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Bone, 2002 U.K., Ireland (Fair)	Gabapentin vs. Placebo Most frequently reported adverse events, n (%) [% calculated based on N = 19] Somnolence: 7 (36.8%) vs. 2 (10.5%) Dizziness: 2 (10.5%) vs. 1 (5.3%) Headache: 2 (10.5%) vs. 1 (5.3%) Nausea: 1 (5.3%) vs. 1 (5.3%)	Gabapentin vs. Placebo Total withdrawals: 2/19 (10.5%) vs. 3/19 (15.8%) Withdrawals due to adverse events: None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Bone, 2002 U.K., Ireland (Fair)	The mean categorical pain intensity scores indicated that the patients started and ended with mild to moderate pain. The pain may not have been of sufficient severity to demonstrate a significant improvement on treatment using a 4-point categorical pain scale. The magnitude of change in VAS pain intensity scores (3.2 from a baseline of 6.1 on a 100-mm scale) with gabapentin was sufficient to show a statistically significant treatment difference, but seems small from a clinical standpoint and was not accompanied by improvements in sleep, mood, or function. The small study population limited the power of the study to detect differences in efficacy measures other than the VAS pain score.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Gorson, 1999 U.S. (Fair)	Duration of neuropathic pain, mean (SD), y, range: 4 (3.5), 4 mo to 15 y Previous use of narcotics or other chronic analgesics for pain: 25/40 (62.5%)	Number screened not reported / Number eligible not reported / 40 enrolled / 40 randomized	None withdrawn / None lost to follow-up / 40 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Gorson, 1999 U.S. (Fair)	Gabapentin vs. Placebo (Number randomized, 1st period: 19 vs. 21) Mean reduction (difference) MPQ: 8.9 vs. 2.2 (6.7) (p = 0.03) VAS: 1.8 vs. 1.4 (0.4) (p = 0.42) PPI: 1.2 vs. 0.3 (0.9) (p = 0.2)	Patient Global Assessment, moderate or excellent pain relief, n: 17 vs. 9 (p=0.11) In gabapentin-treated patients, MPQ and VAS scores did not return to baseline after crossover, suggesting that the washout period was inadequate.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Gorson, 1999 U.S. (Fair)			Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Gorson, 1999 U.S. (Fair)	Most common adverse events on gabapentin (n): drowsiness (6), fatigue (4), and imbalance (3). Adverse events not reported for placebo	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Gorson, 1999 U.S. (Fair)	The study had 80% power to detect a 20% reduction in pain scores. Primary efficacy measure was not specified. Carryover of gabapentin effects into the placebo phase may have resulted in underestimation of the treatment benefit.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Stable doses of antidepressants, mild opioids, aspirin (up to 300 mg/d) for cardiovascular prophylaxis, and nonsteroidal antiinflammatory drugs	11-point Likert scale (0 = no pain, 10 = worst possible pain) of pain intensity over the previous 24 h, recorded daily upon waking, and 11-point Likert scale for sleep interference (0 = pain does not interfere with sleep, 10 = pain completely interferes with sleep), both assessed at screening, wk 0, 1, 2, and 7; Short Form McGill Pain Questionnaire (SF-MPQ) and Short Form-36 (SF-36) Health Survey for quality of life, assessed at wk 0 and 7; 7-point Clinician and Patient Global Impression of Change (CGIC and PGIC) scales (ranging from very much improved to very much worse), assessed at wk 7 Response defined as >/= 50% reduction in mean pain score from baseline	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo Age, median, y: 74.8 vs. 76.3 vs. 74.9 Male / Female: 40% / 60% vs. 43% / 57% vs. 41% vs. 59% Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo (N = 111) Years since diagnosis, median (range): 1.9 (0.1 to 19.4) vs. 2.5 (0.3 to 30.7) vs. 2.2 (0.1 to 28.4) Previous number of drugs tried, median: 3 vs. 3 vs. 3 Drug categories tried, n (%) AEDs: 69 (60%) vs. 72 (67%) vs. 62 (56%) Amitriptyline: 83 (72%) vs. 83 (77%) vs. 79 (71%) Mild analgesics: 107 (93%) vs. 100 (93%) vs. 102 (92%) Overall, 16% of patients were newly diagnosed (< 6 mo) and the median duration of postherpetic neuralgia was about 4 years.	411 / 359/ 334/ 334	62 withdrew / None lost to follow-up / 334 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo (N = 111) Change (%) in average daily pain score (Primary efficacy measure), mean [back-calculated from % change]: -2.2 (-34.5%) vs. -2.2 (-34.4%) vs. -1.0 (-15.7%) (p < 0.01 vs. placebo for both gabapentin groups) Onset of earliest analgesic effect: 1 wk	Response rate, % of patients: 32% vs. 34% vs. 14% (p = 0.001 for both gabapentin groups vs. placebo) Additional data from Rice, 2002, Response to Comments (Rice, 2002): Response rate for 30% reduction in pain, n (%): 61/115 (53%) vs. 59/108 (55%) vs. 32/111 (29%). NNT for 30% / 50% reduction: 4.13 / 5.63 for 1800 mg; 3.88 / 5.04 for 2400 mg Sleep interference (0 to 10, Likert scale), difference at final week (95% CI) Gabapentin 1800 mg/d vs. placebo: 0.9 (0.4 to 1.4; p < 0.01) Gabapentin 2400 mg/d vs. placebo: 1.1 (0.7 to 1.6; p < 0.01)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo SF-MPQ, difference in improvements in scores between gabapentin and placebo were statistically significant for the following: Sensory score (0 to 33), mean: 13.9 vs. 15.0 vs. 13.2 ($p < 0.05$ for both doses) Total score (0 to 45), mean: 17.8 vs. 19.6 vs. 17.1 ($p < 0.05$ for both doses) Visual analogue scale (0 to 100 mm), mean: 67 vs. 70 vs. 68 ($p < 0.05$ for 2400 mg only) No significant treatment differences were found for affective scores.	PGIC much or very much improved, n/N (%): 44/107 (41%) vs. 42/98 (43%) vs. 24/105 (23%) ($p </= 0.005$ for both analyses) CGIC much or very much improved, n/N (%): 48/108 (44%) vs. 45/103 (44%) vs. 20/107 (19%) ($p </= 0.002$ for both analyses) SF-36 Quality of Life domains showing statistically ($p < 0.05$) greater improvements in mean score on gabapentin than placebo: vitality (both doses), bodily pain (1800 mg only), and mental health (1800 mg only).	Elicited by investigator

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	Gabapentin 1800 mg/d (N = 115) vs. Gabapentin 2400 mg/d (N = 108) vs. Placebo All adverse events, n (%): 81 (70.4%) vs. 81 (75.0%) vs. 55 (49.5%) Possibly / probably treatment-related, n (%): 65 (56.5%) vs. 65 (60.2%) vs. 31 (27.9%) Serious, nonfatal adverse events, n (types): 3 (fever, infection, retinal vein thrombosis and hemoptysis) vs. 1 (congestive heart failure) vs. 1 (depression) -- all considered to be not related to study drug Common adverse events (> 5% of patients), n (%) Dizziness: 36 (31%) vs. 36 (33%) vs. 11 (9.9%) Somnolence: 20 (17.4%) vs. 22 (20.4%) vs. 7 (6.3%) Peripheral edema: 6 (5.2%) vs. 12 (11.1%) vs. 0 (0%) Asthenia: 7 (6.1%) vs. 6 (5.6%) vs. 4 (3.6%) Dry mouth: 7 (6.1%) vs. 5 (4.6%) vs. 1 (0.9%) Diarrhea: 7 (6.1%) vs. 5 (4.6%) vs. 1 (0.9%)	Gabapentin 1800 mg/d vs. Gabapentin 2400 mg/d vs. Placebo Total Withdrawn: 22/115 (19.1%) vs. 23/108 (21.3%) vs. 17/111 (15.3%) Withdrawals due to adverse events: 15/115 (13.0%) vs. 19/108 (17.6%) vs. 7/111 (6.3%) Most withdrawals (76%) due to adverse events on gabapentin occurred during the first 3 wk. Most common adverse events resulting in withdrawal: dizziness (7% of each dose group) and drowsiness (5% to 6%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Rice, 2001 U.K., Republic of Ireland (Fair) Additional data from response to comments on the article (Rice, 2002)	The absolute and relative reductions in Likert pain intensity scores met criteria for clinically relevant changes by Farrar (Farrar, 2001). There were also significant differences between gabapentin and placebo in terms of improvements in sleep, vitality, mental health, and bodily pain, but not mood, physical functioning, or social functioning. The 2400-mg dose did not appear to confer additional benefits over the 1800-mg dose. The distribution of patients with newly diagnosed (< 6 mo) postherpetic neuralgia (which is more likely to spontaneously resolve than a longer-standing (> 12 mo) condition) among the three treatment groups was not reported. The impact of this possible confounding factor on the treatment effects is uncertain.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Rowbotham, 1998 U.S. (Fair)	Tricyclic antidepressants and narcotics if doses stable before and during study	11-point Likert scale, SF-MPQ with 100-mm VAS at baseline and wk 2, 4, and 8; Short Form 36 (SF-36) Quality of Life Questionnaire and Profile of Mood States (POMS) at baseline and wk 8; Subject's and Investigator's Global Impression of Change Questionnaires at wk 8.	Gabapentin (N = 109) vs. Placebo (N = 116) Median age (range), y: 73 (40 to 90) vs. 74 (39 to 89) Male / Female: 56.9% / 43.1% vs. 48.3% / 51.7% Ethnicity, White / Others: 87.2% / 12.8% vs. 94.0% / 6.0% (p = 0.08)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Rowbotham, 1998 U.S. (Fair)	Median time since last zoster eruption, mo: 27.4 vs. 29.8 Prior postherpetic neuralgia medications, 0 / 1 / 2 to 3: 79.8% / 15.6% / 4.6% vs. 78.5% / 15.5% / 6.0% Concomitant medications, None / Tricyclic antidepressants / Opioid / Combination opioid and tricyclic antidepressants: 65.1% / 11.9% / 17.4% / 5.5% vs. 62.9% / 9.5% / 23.3% / 4.3%	292 screened / number eligible not reported / number enrolled not reported / 229 randomized	45 withdrawn / 5 of these (lost to follow-up or personal reasons) / 225 analyzed for primary efficacy variable, 229 for safety

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Rowbotham, 1998 U.S. (Fair)	Gabapentin vs. Placebo Average daily pain (0 to 10; Primary Efficacy Measure), mean change from baseline to wk 8: -2.1 vs. -0.5 (p < 0.001) Physician's Clinical Global Impression of Change, Moderately or Much Improved at wk 8: 39.5% vs. 12.9%	Mean change from baseline to week 8 Sleep rating score: -1.9 vs. -0.5 (p < 0.001) SF-MPQ for total pain: -5.8 vs. -1.8 (p < 0.001)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Rowbotham, 1998 U.S. (Fair)	SF-36 physical functioning, role-physical, bodily pain, vitality, and mental health measures showed gabapentin to be superior to placebo (p </= 0.01) Improvements in POMS depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment, and total mood disturbance showed gabapentin to be superior to placebo (p </= 0.01)	Onset of significant analgesic effect: 2 wk	Monitored

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Rowbotham, 1998 U.S. (Fair)	Most frequently reported AEs Numerically higher rate on gabapentin than placebo: somnolence (27.4% vs. 5.2%), dizziness (23.9% vs. 5.2%), ataxia (7.1% vs. 0.0%), peripheral edema (9.7% vs. 3.4%), and infection (8.0% vs. 2.6%) Numerically higher rate on placebo than gabapentin: pain (10.3% vs. 4.4%)	Gabapentin vs. Placebo Total Withdrawals: 24/113 (21.2%) vs. 21/116 (18.1%) Adverse Event Withdrawals: 21/113 (18.6%) vs. 14/116 (12.1%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Rowbotham, 1998 U.S. (Fair)	For early terminations, wk 8 assessments were done at the last study visit. ITT population included randomized subjects who took at least 1 dose of study medication and provided at least 1 follow-up efficacy assessment. ITT and efficacy evaluable (per-protocol) analysis results were similar. Change in average daily pain of -2.1 on gabapentin meets the validated definition of clinically relevant improvement (reduction of 2 on 11-point numerical rating scale) in chronic pain by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Serpell, 2002 U.K. and Republic of Ireland (Fair)	Antidepressants if stable for 30 d prior to entering study; aspirin (up to 300 mg/d) for cardiovascular prophylaxis; nonsteroidal antiinflammatory drugs for non-neuropathic pain conditions; mild opioids (e.g., codeine preparations); acetaminophen (up to 4000 mg/d); combination codeine (up to 240 mg/d) plus acetaminophen (up to 4000 mg/d) as rescue medication. 45/305 patients (15%) reported taking no additional medication for neuropathic pain. 6/305 patients (2%) reported taking prohibited medications (carbamazepine, morphine, and sodium valproate); doses were stable for 2 patients but drug was started or stopped in 4 patients during the baseline or treatment evaluation periods and may have affected the estimates of efficacy.	11-point Likert scale for pain intensity (0 to 10), recorded each morning; Visual Analogue Scale (VAS, 0 to 10) for allodynia and hyperalgesia; diary assessment of allodynia, burning pain, shooting pain, and hyperalgesia (pain scale not specified); Short Form-McGill Pain Questionnaire (SF-MPQ); Clinician Global Impression of Change (CGIC); Patient Global Impression of Change (PGIC); Short Form-36 (SF-36) Health Survey for quality of life. Assessments were made very 2 wk. SF-MPQ, CGIC, PGIC, and SF-36 were recorded at wk 7.	Gabapentin (N = 153) vs. Placebo (N = 152) Age, median (range), y: 57.7 (25.9 to 88.4) vs. 56.1 (20.3 to 86.2) Male / Female: 41.2% / 58.8% vs. 51.3% / 48.7% Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Serpell, 2002 U.K. and Republic of Ireland (Fair)	Duration of disease, median (range), y: 5.2 (0 to 30.8) vs. 4.4 (0 to 27.7) Pain < 3 mo, n (%): 18 (12%) vs. 19 (12%) Pain > 5 y, n (%): 47 (31%) vs. 44 (29%) Previous drugs tried, median (range): 1 (0 to 10) vs. 2 (0 to > 10); 1 vs. 3 patients were "not known" Drug categories tried, n (%) AEDs: 53 (35%) vs. 44 (29%) Amitriptyline: 101 (66%) vs. 95 (65%) Mild analgesics: 136 (89%) vs. 142 (93%)	351 screened / 327 eligible / 307 enrolled / 305 randomized	73 withdrew / None lost to follow-up / 305 analyzed (excluded 2 randomized patients who withdrew before receiving study drug)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Serpell, 2002 U.K. and Republic of Ireland (Fair)	Gabapentin vs. Placebo Average daily pain diary score, change from baseline (Primary efficacy measure): 1.5 (21%) vs. 1.0 (14%) (p = 0.048) Mean pain scores showed significant treatment differences for wk 1, 3, 4, 5, and 6 (p < 0.05) but there was no significant difference for wk 7 and 8. Tests for interaction of the treatment effect with baseline pain score and cluster (study centers) were not significant. Response rate (> 50% reduction in mean pain score from baseline): 21% vs. 14% (p = 0.16)	Change in individual pain symptoms from baseline to wk 8 (last observation carried forward), mean (estimated from figure) Allodynia: -1.4 vs. -1.1 (NSD) Shooting pain: -1.8 vs. -1.5 (NSD) Burning pain: -1.6 vs. -1.2 (NSD) Hyperalgesia: -1.7 vs. -1.1 (NSD) Treatment differences were noted at wk 1 and 3 for burning pain (p < 0.05) and wk 3, 4, 5, and 6 for hyperalgesia (p < 0.05). No interactions of treatment with baseline or center. Response rates for individual symptoms (no statistics) Allodynia: 23% vs. 15% Shooting pain: 32% vs. 24% Burning pain: 23% vs. 15% Hyperalgesia: 26% vs. 17%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Serpell, 2002 U.K. and Republic of Ireland (Fair)	SF-MPQ Greater improvement was seen on gabapentin than placebo for sensory score and total score (no data reported; $p < 0.05$) PGIC, much or very much improved: 48/141 (34%) vs. 22/138 (16%) ($p = 0.03$) CGIC, much or very much improved: 53/142 (38%) vs. 25/142 (18%) ($p = 0.01$)	SF-36 Health-related quality of life Mean change from baseline showed significantly ($p < 0.05$) greater improvement on gabapentin than placebo for the following domains (estimated from figure): Bodily pain 10 vs. 5 Social functioning 10 vs. 3 Role-emotional 11 vs. -4 Interaction test showed no differences in treatment effect according to type of pain ($p = 0.29$).	Elicited by investigator

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Serpell, 2002 U.K. and Republic of Ireland (Fair)	Gabapentin (N = 153) vs. Placebo (N = 152), n (%) All adverse events: 117 (76.5%) Possibly/probably treatment related: 88 (57.5%) vs. 56 (36.8%) Deaths: 0 (0%) vs. 2 (1.3%) Serious, nonfatal adverse events: 4 (2.6%) vs. 2 (1.3%) Common adverse events (> 5% of patients) occurring at a rate 5% greater (absolute difference) in either treatment group Dizziness: 37 (24.2%) vs. 12 (7.9%) Somnolence: 22 (14.4%) vs. 8 (5.3%)	Gabapentin vs. Placebo Total Withdrawals: 32/153 (20.9%) vs. 41/152 (27.0%) Withdrawals due to adverse events: 24/153 (15.7%) vs. 25/152 (16.4%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Simpson, 2001 U.S. (Poor)	Mean duration of diabetes, y: 8 vs. 9 Type 1 diabetes, %: 20 vs. 17 Type II diabetes, %: 80 vs. 83	Part 1: --/--/--/60 Part 2: --/12/--/11 Part 3: 42 were considered	Part 1: 6 / 0 / 54 Part 2: 4 / 0 /11 Part 3: 4 / 0 / 38

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Simpson, 2001 U.S. (Poor)	Part 1 Gabapentin vs. Placebo Change in mean pain score, baseline to final: -2.4 vs. -0.5 (p< 0.01) Much / Moderately improved on PGIC and CGIC: 15 (55.5%) vs. 7 (25.9%) Change in mean sleep interference scores, SF-McGill total pain scores, SF-McGill Present Pain Intensity, SF-VAS, POMS, and SF-36 QOL showed significant improvement in the gabapentin group.	Part 2 Gabapentin + venlafaxine vs. gabapentin + placebo Change in mean pain score, baseline to final: -2.0 vs. -0.5 (p < 0.001) Much / Moderately improved on PGIC and CGIC: 3 (75%) vs. 1 (33.3%) Change in sleep interference scores, SF-McGill total pain scores, SF-McGill PPI, SF-McGill VAS, POMS and SF-36 QOL showed significant improvement in the gabapentin + venlafaxine group.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Simpson, 2001 U.S. (Poor)	Part 3 Gabapentin + venlafaxine Change in mean pain score, baseline to final: -2.1		Monitored

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Simpson, 2001 U.S. (Poor)	Gabapentin (N = 27) vs. Placebo (N = 27) Dizziness: 6 (22.2%) vs. 1 (3.7%) Somnolence: 6 (22.2%) vs. 1 (3.7%) Headache 3 (12.3%) vs. 1 (3.7%) Diarrhea: 3 (12.3%) vs. 1 (3.7%) Confusion: 2 (7.4%) vs. 0 (0%) Nausea: 2 (7.4%) vs. 1 (3.7%)	Part 1: 3 total withdrawals from each group; 2 withdrawals due to adverse event from each group Part 2: 2 total withdrawals from each group; 1 withdrawal due to adverse event on gabapentin plus venlafaxine Part 3: 4 total withdrawals; 3 withdrawals due to adverse event

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Simpson, 2001 U.S. (Poor)	Small sample size.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Tai, 2002 U.S. (Poor)	Ongoing AED, antidepressant, and other analgesic medications. As-needed analgesics (i.e., nonsteroidal antiinflammatory drugs, tricyclic antidepressants, and narcotics).	11-point Neuropathic Pain Scale at baseline for both treatment groups and at wk 4 of both treatment periods	Age range, y: 27 to 48 6 Male / 1 Female Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Tai, 2002 U.S. (Poor)	Etiology of injury: 5 motor vehicle crash; 1 fall; 1 diving Duration of injury, range: 1 mo to 20 y (</= 3.5 mo in 5 patients) Short Form Beck Depression Inventory score, median (range): 11 (8 to 16)	Number screened and eligible not reported / 14 enrolled / 14 randomized	6 withdrew / 2 of the 7 were lost to follow-up / 7 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Tai, 2002 U.S. (Poor)	Of 10 items assessed on the Neuropathic Pain Scale, only 1 ("unpleasant feeling") showed a statistically significant treatment difference (p = 0.028). Data presented for individual patients; no descriptive statistical data were reported. Gabapentin vs. Placebo Average Pain Intensity at wk 4, range (estimated from figure): 0 to 7 vs. 2 to 10 (NSD; no descriptive statistical data were reported)	3 patients required additional analgesic medications (oxycodone controlled release, ibuprofen, and amitriptyline, and combination oxycodone plus acetaminophen)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Tai, 2002 U.S. (Poor)			Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Tai, 2002 U.S. (Poor)	1 patient had urinary retention	Total withdrawals: 7 Withdrawals due to adverse events: 1 (urinary retention, treatment group not reported)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Finnerup, 2002 Denmark (Poor)	Duration of pain, median (range), y: 7 (1 to 31) Pain intensity (NRS 0 to 10), median (range): 5 (3 to 8) Allodynia, n: 9 Pain descriptor, n Shooting: 12 Tingling: 11 Taut: 11 Pricking: 10	330 screened / 100 eligible / 30 enrolled / 30 randomized	8 withdrawn / none lost to follow-up / 22 analyzed
McCleane, 1999 U.K. (Fair)	Duration of pain, mean, mo: 87 vs. 61 (p > 0.05)	Number screened not reported / Number eligible not reported / 100 enrolled / 100 randomized	18 withdrew / 8 others failed to attend for end of study review / 74 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Finnerup, 2002 Denmark (Poor)	Lamotrigine vs. Placebo Change in pain score, median All patients: 1 vs. 0 Incomplete SCI lesions (n = 12), estimated from figure: -2 vs. 0 (p = 0.02) Complete SCI lesions (n = 10), estimated from figure: -0.5 vs. -0.5 Difference in pain reduction Incomplete SCI lesions, median (25% CI): 25% (8% to 42%) NNT for 50% pain relief (25% CI): 12 (2 to ∞) NNT for 33% pain relief (25% CI): 3 (1.41 to ∞)	Difference in pain reduction Incomplete SCI lesions, median (25% CI): 25% (8% to 42%) NNT for 50% pain relief (25% CI): 12 (2 to ∞) NNT for 33% pain relief (25% CI): 3 (1.41 to ∞)
McCleane, 1999 U.K. (Fair)	Lamotrigine vs. Placebo Mean change in scores (0 to 10 VAS) from baseline to wk 8 on treatments --Overall pain: -0.01 vs. 0.03 --Mood: -0.08 vs. -0.22 --Sleeping: -0.27 vs. -0.15 --Quality of life: -0.38 vs. -0.15 (p > 0.05 for all analyses)	50% reduction in overall pain, n: 0 vs. not reported Change in analgesic use, baseline to wk 8, no. of tablets: 0.35 vs. 0.29

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Finnerup, 2002 Denmark (Poor)	Categorical pain relief, period preference, sleep interference, acetaminophen use, MPQ, SF-36, and spasticity: NSD Plasma concentration of lamotrigine between responders and nonresponders for whole group or subgroup with incomplete injury: NSD	Predictors of positive outcome: All 7 patients (100%) with evoked pain (brush allodynia or wind-up-like pain) were responders (reduction in pain >/= 2) vs. 1 of 14 patients (7.1%) without evoked pain was a responder ($p < 0.001$).	Elicited by investigator
McCleane, 1999 U.K. (Fair)	Withdrew due to lack of pain relief, n/N: 4/36 (11.1%) vs. 2/38 (5.3%)		Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Finnerup, 2002 Denmark (Poor)	Lamotrigine (N = 27) vs. Placebo (N = 28), n (%) CNS: 12 (44.4%) vs. 9 (32.1%) Skin: 4 (14.8%) vs. 4 (14.3%) Gastrointestinal: 4 (14.8%) vs. 3 (10.7%) Other: 5 (18.5%) vs. 6 (21.4%)	Lamotrigine vs. Placebo Total withdrawals: 4/15 (26.7%) vs. 4/15 (26.7%) Withdrawals due to adverse events: 1/15 (6.7%) vs. 2/15 (13.3%)
McCleane, 1999 U.K. (Fair)	Not reported	Lamotrigine vs. Placebo Total withdrawals: >/= 10/36 (27.8%) vs. >/= 8/38 (21.1%) (8 patients who failed to attend for end of study review were not reported by treatment group) Withdrawals due to adverse events: 6/36 (16.7%) vs. 6/38 (15.8%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Finnerup, 2002 Denmark (Poor)	Only patients whose final dose was at least 200 mg/d for at least 2 wk were to be considered completers and included in analyses. Apparently no patients were excluded because of this criterion.
McCleane, 1999 U.K. (Fair)	Relatively low maximal dose of lamotrigine (200 mg/d) may account for lack of efficacy. Type of neuropathic pain not specified in report. Baseline values only given for overall group, not by treatment group. Inclusion criterion may be questioned ("intractable" not defined).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Simpson, 2000 U.S. (Fair)	Lamotrigine vs. Placebo Baseline CD4 count, cells/mm3, mean (SD), n: 377 (179), 4 vs. 153 (89), 9	Number screened not reported / Number eligible not reported / 42 enrolled /42 randomized	13/42 (31.0%) withdrew before wk 6 (before maximal dose) and 1 withdrew after wk 6 Discrepancy in loss to follow-up between text (5/20, 25.0% Lamotrigine vs. 1/22, 4.5% Placebo; total 6/42, 14.3%) and Figure 1 (2/20, 10.0% vs. 1/22, 4.5%; total 3/42, 7.1%) 29/42 (69.0%) analyzed (9 lamotrigine, 20 placebo)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Simpson, 2000 U.S. (Fair)	Lamotrigine vs. Placebo, ITT Population (N = 42) Mean adjusted change in Gracely pain scores (Primary Efficacy Measure): -0.242 vs. -0.183 Calculated difference: -0.059 (p = 0.65)	Increased / Decreased Use of Concomitant Analgesics at wk 14: 1 / 0 vs. 2 / 0 (p = 0.99) No treatment differences in global pain score and worst pain score (data not reported).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Simpson, 2000 U.S. (Fair)	Subgroup Analysis by Neurotoxin Exposure (ddI, ddC, or d4T) Lamotrigine vs. Placebo Mean change in average pain (difference) --Neurotoxin-yes: -0.54 vs. -0.41 (-0.13) (p = 0.51) --Neurotoxin-no: -0.66 vs. -0.05 (-0.61) (p = 0.03)		Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Simpson, 2000 U.S. (Fair)	Lamotrigine (n): rash (5), gastrointestinal infection (1), fatigue, pneumonia, diarrhea (number not reported). Placebo: no adverse events reported	Lamotrigine vs. Placebo Total withdrawals: 11/20 (55.0%) vs. 2/22 (9.1%) (no statistics) Withdrawals due to adverse events: 6/20 (30.0%) vs. 0/22 (0.0%) (no statistics) Withdrawals due to adverse events on lamotrigine, n: rash (5), gastrointestinal infection (1)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Simpson, 2000 U.S. (Fair)	Higher apparent rates of loss to follow-up and withdrawals were seen in the lamotrigine group compared with the placebo group. Selection bias as well as the small sample size may have produced dissimilar treatment groups and affected the study results. Baseline differences in CD4+ counts between lamotrigine and placebo groups were unexplained. ITT analysis was performed using last value carried forward (LVCF) and a longitudinal analysis with no LVCF. The latter showed pain reduction in both groups (data not given here); however, selection bias may have occurred because of the greater number of lamotrigine dropouts. An extension of this study in a larger population was done by Simpson, 2003.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Simpson, 2003 Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Neurotoxic ART Stratum Lamotrigine vs. Placebo CD4+ Count, median: 278 vs. 250 Karnofsky scale score, mean (SD): 85 (9) vs. 84 (10) HIV-1 RNA, mean log10, copies/ml: 3.16 vs. 2.99 No Neurotoxic ART Stratum Lamotrigine vs. Placebo CD4+ Count, median: 271 vs. 372 Karnofsky scale score, mean (SD): 83 (10) vs. 84 (9) HIV-1 RNA, mean log10, copies/ml: 3.16 vs. 3.23	Numbers screened and eligible not reported / 227 enrolled /227 randomized	43 withdrew / 12 lost to follow up / 172 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Simpson, 2003 Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Neurotoxic ART Stratum Lamotrigine (N = 45) vs. Placebo (N = 23) Gracely Pain Scale score, average daily pain (Primary efficacy measure, based on completers) Mean change, baseline to wk 11 (calculated difference): -0.27 vs. -0.10 (-0.17) (NSD) VAS score Mean change (calculated difference): -27.1 vs. -9.0 (-18.1) (p = 0.003) VAS-30 Responder rate (at least 30% decrease in VAS): 57% vs. 23% (p = 0.02) SF-MPQ Mean change (calculated difference): -6.9 vs. -1.6 (-5.3) (p = 0.02)	Neurotoxic ART Stratum (cont'd) CGIC Moderate improvement: 18% vs. 4% Marked improvement: 30% vs. 9% (p = 0.008) At least moderate improvement (calculated): 48% vs. 13% PGIC Moderate improvement: 24% vs. 26% Marked improvement: 29% vs. 4% (p = 0.02) At least moderate improvement (calculated): 53% vs. 30% Use of Any Analgesic, n (%): 29 (47%) vs. 16 (53%) Most common analgesics: Ibuprofen, Acetaminophen

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Simpson, 2003 Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	Lamotrigine (N = 150) vs. Placebo (N = 77) Most common adverse events, n (%) Rash: 21 (14%) vs. 9 (12%) Nausea: 17 (11%) vs. 8 (10%) Headache: 16 (11%) vs. 8 (10%) Adverse events considered to be drug-related by investigator and reported by at least 5% of patients in either treatment group, n (%) Nausea: 11 (7%) vs. 3 (4%) Rash: 7 (5%) vs. 4 (5%) No cases of serious rash (i.e., associated with hospitalization or discontinuation of study drug)	Lamotrigine vs. Placebo Total Study Population Total withdrawals: 34/150 (22.7%) vs. 21/77 (27.3%) Withdrawals due to adverse events: 10/150 (6.7%) vs. 7/77 (9.1%) Neurotoxic ART Stratum Total withdrawals: 17/62 (27.4%) vs. 7/30 (23.3%) Withdrawals due to adverse events: 5/62 (8.1%) vs. 2/30 (6.7%) No Neurotoxic ART Stratum Total withdrawals: 17/88 (19.3%) vs. 14/47 (29.8%) Withdrawals due to adverse events: 5/88 (5.7%) vs. 5/47 (10.6%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Simpson, 2003 Lamotrigine HIV Neuropathy Study Team U.S. (Fair)	The primary efficacy results showing a beneficial effect of lamotrigine in patients taking neurotoxic ART but not in those with no neurotoxic ART are opposite of the results found in the author's previous study (Simpson, 2000). The authors attribute the discrepancy to the small sample size and high dropout rate in the earlier study. The baseline differences in CD4+ counts between treatment groups were unexplained in both studies. A surprising finding was the difference in magnitude of change in Gracely pain scores between placebo groups in the two strata (-0.10 vs. -0.27 in the Neurotoxic ART vs. No Neurotoxic ART). The magnitude of the placebo effect (-0.27) in the No Neurotoxic ART stratum was similar to the effect achieved by lamotrigine in either stratum (-0.27 and -0.30). It is possible that a difference in an unidentified confounding factor between treatment populations is affecting the study results.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Vestergaard, 2001 Denmark (Fair)	Acetylsalicylic acid 300 mg/d (as antithrombotic) and acetaminophen 500 mg as needed for escape medication	Ongoing Pain: 11-point (0 to 10) Likert scale for average pain recorded daily; escape medication use daily; global pain score for physical pain (0 = no pain to 5 = very strong pain) and degree to which pain affected daily activities (1 = not at all to 5 = very much) recorded at end of each treatment period; area of spontaneous pain and dysesthesia or allodynia; acetaminophen intake Evoked pain: 11-point (0 to 10) scale at baseline and end of each treatment period; digitized circumference and calculated area of painful region	Age, median (range), y: 59 (37 to 77) 60% Male / 40% Female Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Vestergaard, 2001 Denmark (Fair)	Duration of central post-stroke pain (CPSP), median (range), y: 2.0 (0.3 to 12) Nontrial drugs at study start, median (range): 4 (1 to 8) Barthel Index (0 to 100; higher scores reflect greater independence in functional ability), median (range): 100 (50 to 100) Thalamic / Suprathalamic / Brainstem lesion(s), n (%): 12 (40) / 20 (67) / 9 (33) More than one lesion on magnetic resonance imaging (MRI) or computerized tomography (CT), n (%): 20 (67)	Number screened not reported / 31 eligible / 31 enrolled / 30 randomized	Period 1: 3 withdrew, 1 discontinued drug but continued in period 2 / None lost to follow-up / 27 entered period 2 Period 2: 7 withdrawn / None lost to follow-up / 27 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Vestergaard, 2001 Denmark (Fair)	<u>Ongoing Pain</u> Lamotrigine vs. Placebo Likert Pain Intensity score Baseline--All patients (N = 30), median (range): 6 (4 to 10) End of wk 8 (Primary efficacy measure, N = 27), median: 5 vs. 7 (p = 0.01) NSD in pain scores for the other doses (25 to 100 mg)	Lamotrigine Responders (defined as patients who achieved a clinically significant pain reduction in the last week; i.e., >/= 2 points lower than placebo values on 0 to 10 scale,), n/N (%): 12/27 (44.4%) Global pain score Physical Pain, median: 3 (moderate) vs. 4 (strong) (p = 0.02) Pain Affecting Daily Activities, median: 3 (some) vs. 4 (a lot) (p = 0.11) (Reduction of one step on the global nonlinear pain scale was considered to be a clinically significant effect.) Use of Acetaminophen 500 mg as Escape Medication, median: 0 tablets (NSD between the four lamotrigine dosing periods)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Vestergaard, 2001 Denmark (Fair)	<u>Evoked Pain</u> Lamotrigine vs. Placebo Likert Pain Intensity score (0 to 10) (Primary Efficacy Measure), median (range) Acetone Drop: 1 (0 to 10) vs. 2 (0 to 10) (p = 0.01) No significant treatment difference for von Frey hairs and electrical toothbrush Area of Pain / Pain Extension: no significant treatment differences for spontaneous pain or allodynia/dysesthesia		Elicited by investigator

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Vestergaard, 2001 Denmark (Fair)	Lamotrigine vs. Placebo vs. Washout, n (%) (N = 30) Total: 17 (56.7%) vs. 18 (60.0%) vs. 10 (33.3%) (NSD between lamotrigine and placebo) CNS: 8 (26.7%) vs. 13 (43.3%) vs. 3 (10.0%) Skin*: 5 (16.7%) vs. 3 (10.0%) vs. 2 (6.7%) Gastrointestinal: 7 (23.3%) vs. 2 (6.7%) vs. 1 (3.3%) Respiratory: 4 (13.3%) vs. 5 (16.7%) vs. 6 (20.0%) Other: 12 (40.0%) vs. 11 (36.7%) vs. 1 (3.3%) *Rash: 2 (6.7%) vs. 2 (6.7%) vs. Not reported	Lamotrigine vs. Placebo Total withdrawals: 4/30 (13.3%) vs. 6/30 (20.0%) Withdrawals due to adverse events: 3/30 (10.0%) vs. 0/30 (0.0%) (mild rash, severe headache, and severe pain)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Zakrzewska, 1997 U.K. (Poor)	Time since onset of first trigeminal neuralgia, median, y: 10 vs. 6 Time since onset of current episode, median, mo: 4 vs. 3 Carbamazepine therapy, n: 5 vs. 8 Phenytoin therapy, n: 2 vs. 2	Number screened not reported / Number eligible not reported / 14 enrolled / 14 randomized	1 withdrawn (day 14 of placebo) / None lost to follow-up / 13 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Zakrzewska, 1997 U.K. (Poor)	Lamotrigine vs. Placebo Composite Efficacy Index (CEI): 11/13 (85%; 95% CI: 61% to 97%) favored lamotrigine vs. 2/13 (15%) favored placebo (p = 0.011) CEI determined in 2 patients by use of escape medication; for 8 patients by total pain score; and for 3 patients by global evaluation.	Lamotrigine/Placebo vs. Placebo/Lamotrigine sequence Daily Total Pain Scores (Burst + Severity + Relief scores, estimated from figure) Period 1, Day 14: 5.5 vs. 7.3 Period 2, Day 31: 7.5 vs. 6.9

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Zakrzewska, 1997 U.K. (Poor)	Daily activity measure, Day 15 and Day 32 Increases in ability to wash face, comb hair, and brush teeth were apparently reported on lamotrigine. Apparently no treatment differences in chewing, shaving, and talking.	Lamotrigine vs. Placebo Global Evaluations Better or Much Better / Same / Worse or Much Worse: 10 / 3 / 0 vs. 8 / 2 / 4 (p = 0.025 using a randomization test with 100,000 simulations)	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Zakrzewska, 1997 U.K. (Poor)	Lamotrigine vs. Placebo Total: 25 adverse events reported by 7/13 patients (53.8%) vs. 13 adverse events reported by 7/14 patients (50%) Adverse events numerically more frequent on lamotrigine than placebo, n (%): Dizziness 5 (38.5%) vs. 1 (7.1%) Constipation 3 (23.0%) vs. 2 (14.3%) Nausea and Somnolence 3 (23.0%) vs. 1 (7.1%) for each Diplopia and Vomiting 2 (15.4%) vs. 0 (0.0%) for each Abnormal accommodation, Amblyopia, and Ataxia 1 (7.7%) vs. 0 (0.0%) for each	Lamotrigine vs. Placebo Total withdrawals: 0/13 (0.0%) vs. 1/14 (7.1%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Chadda, 1978 India (Poor)	Not reported	Intensity and extent of pain and paresthesia in comparison with pre-treatment symptoms, using a 6-point scale (0 = No improvement; 5 = Complete disappearance of symptoms); frequency of assessments was not reported. Definition of relief (response): moderate improvement of symptoms (i.e., more than score of 2)	Age, mean (range), y: 49.9 (20 to 70) Male / Female: 23 / 17 Ethnicity not reported
McCleane, 1999 U.K. (Fair)	Not reported	11-point linear visual analogue scale (VAS) for total pain, shooting pain, burning pain, numbness, paresthesia, and sensitivity, recorded every 15 min during infusion and daily for 7 d after infusion	Age, mean (range), y: 40 (25 to 60) Male / Female: 9 / 11 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Chadda, 1978 India (Poor)	Duration of diabetes mellitus, mean (range), y: 7.6 (0.25 to 12) Control of diabetes --"Good": 25 --"Poor": 15 Group A (Phenytoin - Placebo) vs. Group B (Placebo - Phenytoin) --Pain: 20/20 (100%) vs. 20/20 (100%) --Paresthesias: 16/20 O80.0%) vs. 18/20 (90.0%)	--/--/40/40	2 withdrawn / 2 lost to follow-up (reasons for withdrawal were not reported) / 40 analyzed
McCleane, 1999 U.K. (Fair)	Duration of neuropathic pain, mean (range), mo: 70 (13 to 132) Diagnosis (n) --Lumbar radiculopathy (6) --Sacral neuritis (3) --Brachial neuritis (2) --Digital neuroma (2) --Diabetic neuropathy (3) --Cervical radiculopathy (4)	Numbers screened and eligible not reported / 20 enrolled / 20 randomized	None withdrawn / None lost to follow-up / 20 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Chadda, 1978 India (Poor)	Phenytoin vs. Placebo Group A Pain Improved (at least moderate improvement or score > 2): 14/20 (70.0%) vs. 5/20 (25.0%) ($p < 0.02$) Paresthesia improved: 12/16 (75.0%) vs. 5/16 (31.2%) ($p < 0.05$)	Group B Pain Improved: 14/18 (77.8%) vs. 5/18 (27.8%) ($p < 0.01$) Paresthesia Improved: 11/16 (68.8%) vs. 3/16 (18.8%) ($p < 0.02$)
McCleane, 1999 U.K. (Fair)	Phenytoin vs. Placebo Calculated change in mean overall pain score, baseline to 2 h: -1.37 vs. 0 (no statistical analysis)	Calculated change in mean overall pain score, baseline to 1 d / 7 d: -1.34 / -0.55 vs. 0.36 / 0.56 (no statistical analysis)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Chadda, 1978 India (Poor)	Group A Complete Pain Relief (score of 5): 4/20 (20.0%) vs. 0/20 (0.0%) Complete Paresthesia Relief (score of 5): 5/20 (25.0%) vs. 0/20 (0.0%)	Group B Complete Pain Relief: 5/18 (27.8%) vs. 1/18 (5.6%) Complete Paresthesia Relief: 4/16 (25.0%) vs. 0/16 (0.0%) No improvements were seen in sensory deficit, motor strength, or deep reflexes on either treatment.	Not reported
McCleane, 1999 U.K. (Fair)	Patients indicating a reduction in pain scores: 14/20 (70.0%) vs. 0 (0%) Patients rating treatment to be of significant benefit: 8/20 (40.0%) vs. Not reported	No predictive factors for response to phenytoin were apparent.	Reported spontaneously by patient

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Chadda, 1978 India (Poor)	Phenytoin vs. Placebo Group A (Phenytoin - Placebo) Giddiness: 2/20 (10.0%) vs. 0/20 (0.0%) Group B (Placebo - Phenytoin) Giddiness: 2/18 (11.1%) vs. 0/18 (0.0%)	Total withdrawals: 2/20 (10.0%), after 2 wk in group B (during washout/neither treatment?) Withdrawals due to adverse events: None
McCleane, 1999 U.K. (Fair)	Adverse events on phenytoin, n --Lightheadedness: 20 --Nausea for > 24 h: 4 --Skin rash: 2 No reported adverse events on placebo	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Chadda, 1978 India (Poor)	Pain assessments were relative to baseline levels, suggesting that they may have been confounded by patient's recall. Glucose control was poor in 15 (37.5%) of 40 patients; potential differences in glucose control between treatment groups may have affected responses to study drugs. The authors noted that the majority of patients responded within 4 d. Also, there was no correlation between duration of diabetes and relief of symptoms after phenytoin.
McCleane, 1999 U.K. (Fair)	Effects of baseline differences in overall pain scores on results were not explained. Magnitude of decrease in pain scores on phenytoin do not meet Farrar's criteria for clinically relevant changes (Farrar, 2001); however, 40% of patients considered phenytoin beneficial. Heterogeneous sample population in terms of neuropathic pain types. Patients were not clearly having pain exacerbations; therefore, results may apply to acute treatment, but not necessarily to pain in flare.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Saudek, 1977 U.S. (Poor)	Not reported	Self-assessed linear analogue scale (range: "None" to "Severe"; score measured as distance in mm from "None" to patient's mark) for pain, numbness, and pins and needles symptoms, recorded daily. Blood glucose.	Age, mean (range), y: 55 (30 to 75) Male / Female: 5 / 7 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Saudek, 1977 U.S. (Poor)	All patients had insulin-dependent diabetes for a mean of 15 y (range 1 to 39) Retinopathy: 6 Arteriosclerotic heart disease: 4 Hypertension: 1 Nephropathy: 1	Numbers screened, eligible, and enrolled not reported / Number randomized is unclear (12?); may be number completed	2 withdrawn / Number lost to follow-up not reported / 12 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Saudek, 1977 U.S. (Poor)	Phenytoin (serum concentration > 5 mg/l) vs. Placebo Symptom level, mean, mm (no. of individual symptom evaluations) --All symptoms: 14.4 vs. 16.2 (246 vs. 299) --Last 3 days: 15.5 vs. 15.9 (137 vs. 135) --Pain only: 7.2 vs. 8.0 (83 vs. 102) NSD for all comparisons	Phenytoin (serum concentration < 5 mg/l) vs. Placebo Symptom level, mean, mm (no. of individual symptom evaluations) --All symptoms: 22.8 vs. 23.5 (144 vs. 174) --Last 3 days: 20.5 vs. 24.1 (54 vs. 81) --Pain only: 19.1 vs. 20.0 (48 vs. 58)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Saudek, 1977 U.S. (Poor)			Method not reported for symptoms Blood glucose after fasting and 30, 60, 90, and 120 min after a standard meal (100 gm carbohydrate) was monitored

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Saudek, 1977 U.S. (Poor)	Phenytoin vs. Placebo Adverse events (no. of occurrences): 16 vs. 4 --Ataxia: 5 vs. 3 --Blurry vision: 3 vs. 0 --Dizziness: 2 vs. 0 --Rash: 3 vs. 0 --Other: 3 vs. 1	Phenytoin vs. Placebo Total withdrawals: 2/12 (16.7%) vs. 0 (0%) Withdrawals due to adverse events: 2!2 (16.7%) vs. 0 (0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

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

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Gilron, 2001 U.S. (Poor)	Double-blind, two-period, crossover RCT ("main study") followed by a double-blind, triple crossover RCT ("confirmatory study") Outpatient setting implied	Not reported per se; patients described as having idiopathic trigeminal neuralgia (which included recurrent trigeminal neuralgia following invasive peripheral nerve or intracranial procedures) and entered the trial after maintaining a stable dose of other pain medications for 2 wk. Patients with a pain score favoring topiramate over plaebo by at least one unit on the 0-to-10 overall pain measure could enter the confirmatory study.	Main Study: Topiramate titrated from 25 to 800 mg/d vs. Placebo for 12 wk Confirmatory Study: Topiramate at maximally tolerated dose from main study (range 75 to 600 mg/d) vs. Placebo for 4 wk per treatment in three 8-wk segments (crossovers)	Main Study: 2-wk washout before crossover and end of study Confirmatory Study: Washout not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Gilron, 2001 U.S. (Poor)	Carbamazepine, baclofen, clonazepam, tricyclic antidepressants, gabapentin	11-point Numeric Rating Scale (NRS) (0 = No pain, 10 = Most pain imaginable for 1 day); 0 to 20 numeric scoring grid with 13 verbal pain intensity descriptors (for intensity of worst pain paroxysms in previous 24 h); frequency and duration of paroxysms; all recorded daily. The means from the last 2 wk of each treatment period were used in analyses.	Age, range, y: 40 to 66 Male / Female: 1 / 2 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Gilron, 2001 U.S. (Poor)	Duration of pain, range, y: 5 to 32	Numbers screened and eligible not reported / 3 enrolled / 3 randomized. 3 entered confirmatory study	Main Study: None withdrew / None lost to follow-up / 3 analyzed Confirmatory Study: 1 / 0 lost to follow-up / 2 appeared to be analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Gilron, 2001 U.S. (Poor)	Topiramate vs. Placebo Range of treatment differences for the 3 patients, Topiramate - Placebo (% difference) Main Study --Overall Daily Pain: -1.2 to -2.1 (-31.8% to -64.3%) (p = 0.04) --Paroxysm Frequency (no./d): -3.2 to -59.6 (-10.2% to -93.3%) (NSD) --Paroxysm Intensity: -0.4 to -5.8 (-2.5% to -31.6%) (NSD) --Paroxysm duration (sec): -54.8 to 8.5 (-76.6% to 290.2) (NSD)	Confirmatory Study and Main Study Plus Confirmatory Study: NSD between treatments in any pain measures when data was analyzed by individual patient or together through all completed treatment periods (data not shown here). Responses sometimes varied between treatment periods; for instance, a reduction in pain scores could occur in one period and an increase in the next period.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Gilron, 2001 U.S. (Poor)			Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Gilron, 2001 U.S. (Poor)	Adverse events of at least moderate severity during topiramate but not placebo (Main Study) (n): --Irritability and diarrhea (2) --Fatigue/sedation, hyperactivity, nausea, abdominal cramps, lightheadedness, and cognitive impairment (1 each)	1 apparent withdrawal during Confirmatory Study (reason not reported) Withdrawals due to adverse events were not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Gilron, 2001 U.S. (Poor)	Baseline pain scores were not reported; therefore, change from baseline could not be assessed. Complete data were available for analysis from only 2 of the 3 patients from crossover treatment periods #2 and #3. Multiple crossovers and repeated measures over time may have increased the power of the study; however, the sample size is still extremely small (N = 3). Failure to confirm the positive results in the main study may be due to chance variation or development of tolerance to topiramate.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Drewes, 1994 Denmark (Poor)	Double-blind, crossover RCT Hospitalized (n = 3) or outpatients (n = 17) at the spinal cord injury center	Older than 18 y, nonprogressive spinal cord injury, central pain (pain distal to level of injury in area with loss of normal feeling) for > 1 mo, failed to respond to conventional treatments	Valproate 600 to 2400 mg/d titrated to serum concentration and clinical response vs. Placebo for 3 wk each	Washout for 2 wk before crossover
Kochar, 2002 India (Poor)	Double-blind, placebo-controlled, parallel-group RCT Diabetes clinic setting	Not reported; patients described as having type 2 diabetes mellitus with painful neuropathy	Sodium valproate 600 to 1200 mg/d vs. Placebo for 4 wk	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Drewes, 1994 Denmark (Poor)	Analgesics (not otherwise specified)	Verbal rating scale (1 to 5) of present pain intensity (PPI) by telephone assessment, weekly; Danish version of McGill Pain Questionnaire (MPQ) before and after each treatment series (3 wk apart). MPQ consisted of a Pain Rating Index (PRI), subscales for sensory, affective, evaluate, and miscellaneous dimensions of pain); Number of Words Chosen (NWC); PPI; and pain localization (affected area as percentage of total body area).	Median age (range), y: 32.5 (18 to 75) 75% Male, 25% Female Ethnicity not reported
Kochar, 2002 India (Poor)	Analgesics (not otherwise specified) -- no changes were allowed	Short Form McGill Pain Questionnaire (SF-MPQ) at baseline, day 7, and end of 1 mo.	Valproate (N = 28) vs. Placebo (N = 24) Age, y (statistical units not reported): 58.5 (7.6) vs. 53.9 (8.3) Male / Female: 57.1% / 42.9% vs. 54.2% / 45.8% Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Drewes, 1994 Denmark (Poor)	16 (80%) paraplegic, 4 (20%) tetraplegic 19 (95%) traumatic injury; 1 (5%) spinal stenosis	Number screened not reported / 20 eligible / 20 enrolled / 20 randomized	1 withdrawn from MPQ analysis / None lost to follow-up / 19 analyzed
Kochar, 2002 India (Poor)	Duration of type 2 diabetes, y, statistical units not reported: 9.2 (6.2) vs. 8.1 (6.2)	60 screened / Number eligible, enrolled, and randomized not reported / 57 treated	8 withdrawn / Number lost to follow-up not reported / 52 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Drewes, 1994 Denmark (Poor)	Valproate vs. Placebo Patients improved (definition and denominator not reported): 6 vs. 4 (not statistically different) PPI (mean change from baseline to 3 wk): 0.2 vs. -0.1 (not statistically different)	MPQ subscores Not statistically different
Kochar, 2002 India (Poor)	Valproate (N = 28) vs. Placebo (N = 24) SF-MPQ, mean: Baseline: 5.0 vs. 4.9 1 mo: 3.4 vs. 4.6 (p = 0.028) Calculated change (%) in mean score from baseline to 1 mo: 1.6 (31.8%) vs. 0.3 (6.1%) Calculated difference between changes in mean scores: 1.3	Patients with at least moderate pain relief: 24/28 (85.7%) vs. 5/24 (20.8%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Drewes, 1994 Denmark (Poor)			Method used in telephone assessments not reported; laboratory tests monitored
Kochar, 2002 India (Poor)	Electrophysiologic studies showed significant ($p < 0.05$) deterioration in isolated ulnar (placebo only) and sural (both treatment groups) sensory conduction studies. Significant ($p < 0.05$) improvement was seen in isolated tibial motor conduction on valproate.		Elicited by investigator

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Drewes, 1994 Denmark (Poor)	Valproate: Gastroenteritis (authors retrospectively believed this was not a side effect); dizziness Placebo: none of the patients had adverse events	Total withdrawals: 1 Withdrawal due to adverse event: 1 on valproate
Kochar, 2002 India (Poor)	Valproate: 1/28 (3.6%) with increased liver function tests (bilirubin 3.5 mg%, AST 80 ku/ml, ALT 90 ku/ml; normal ranges not reported) Placebo: none	Valproate vs. Placebo Total Withdrawals: 2/30 (6.7%) vs. 4/30 13.3%) and 2 unaccounted for Withdrawals due to adverse events: 1/30 (3.3%) vs. 0 (0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Drewes, 1994 Denmark (Poor)	Authors reported that there was no statistical evidence of carry-over effect or regression towards the mean.
Kochar, 2002 India (Poor)	Primary efficacy variable was not defined. Adjustment for multiple statistical tests was not done.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Kochar, 2004 India (Fair)	Double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Diabetes for at least 6 mo; stable dosage of insulin or oral hypoglycemic agent; HgA1c < 11; daily neuropathic pain of at least moderate severity for > 3 mo that interfered with daily activity or sleep; pain intensity of > 4 on a visual analogue scale (VAS)	Sodium valproate 500 to 1000 mg/d vs. Placebo for 3 mo	None
Eisenberg, 2001 Israel (Poor)	Single-center, double-blind, placebo-controlled, parallel-group RCT Outpatient setting (physician's office)	Diabetes mellitus type 1 or 2; no change in antidiabetic medications within 3 wk; evidence of peripheral neuropathy as indicated by at least 2 of the following 3 measures: (a) medical history, (b) neurologic examinations, or (c) abnormal nerve conduction test results; pain attributed to diabetic neuropathy for > 6 mo; 11-point numerical pain scale (NPS) score of at least 4	Lamotrigine 25 mg/d x 2 wk, 50 mg/d x 2 wk, then increased weekly by 100 mg/d up to 400 mg/d vs. Placebo for 8 wk	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Kochar, 2004 India (Fair)	None reported	Short Form McGill Pain Questionnaire (SF-MPQ), VAS and present pain intensity (PPI) at baseline, 1 mo, then 3 mo. Motor and sensory nerve conduction studies (MNCV and SNCV) at baseline and 3 mo.	Sodium valproate (N = 21) vs. Placebo (N = 18) Age, units not reported: 54.4 (8.8) vs. 56.2 (8.8) Male / Female: 57.1% / 42.9% vs. 50% / 50% Ethnicity not reported
Eisenberg, 2001 Israel (Poor)	Acetaminophen, dipyrone, nonsteroidal antiinflammatory drugs	11-point NPS (0 = no pain; 10 = worst imaginable pain) for present pain intensity, recorded twice daily; rescue analgesic use recorded daily; McGill Pain Questionnaire (MPQ), Beck Depression Inventory (BDI), and Pain Disability Index (PDI) recorded before and after treatment phase; global assessment of both efficacy and tolerability (on 0 to 10 scale) recorded at end of treatment phase (score of 8 to 10 = high, 4 to 7 = moderate, 0 to 3 = low)	Lamotrigine (N = 27) vs. Placebo (N = 26) Age, mean, y: 52.7 vs. 57.8 Male/ Female: 17 / 10 vs. 16 / 10 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Kochar, 2004 India (Fair)	Duration of type 2 diabetes, statistical units not reported, y: 8.8 (4.2) vs. 8.8 (3.8) HbA1c, %: 8.8 (1.3) vs. 8.6 (1.1) Duration of diabetic neuropathy: not reported	48 Screened / 44 eligible / 43 enrolled / 43 randomized	4 withdrawn / None lost to follow-up / 39 analyzed
Eisenberg, 2001 Israel (Poor)	Diabetes type 1 / type 2: 3 / 24 vs. 2 / 24 Duration of diabetes, mean, y: 13.9 vs. 9.6 (p = 0.04) Previous treatment for neuropathic pain --Antidepressants: 8 vs. 10 --Antiepileptic drugs: 7 vs. 8 --Capsaicin cream: 4 vs. 2 --Other: 2 vs. 3	160 screened / Numbers eligible and enrolled not reported / 59 randomized	13 withdrawn / None lost to follow-up / 53 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Kochar, 2004 India (Fair)	Valproate (N = 21) vs. Placebo (N = 18) Difference at 3 mo SF-MPQ: -8.1 (p < 0.001) VAS: -3.0 (p < 0.001) PPI: -1.28 (p < 0.001)	Change from baseline to 3 mo: SF-MPQ: -9.81 vs. 0.12 VAS: -3 vs. 0.29 PPI: -1.38 vs. 0.04 NCV data: no improvement from baseline to 3 mo
Eisenberg, 2001 Israel (Poor)	Lamotrigine (N = 27) vs. Placebo (N = 26) Change in weekly mean pain intensity from baseline to wk 8 (calculated): -2.2 vs. -1.2 (calculated difference: -1.0; p < 0.001) Relative (%) change in weekly mean pain intensity (calculated): 34.4% vs. 18.5% Maximal pain reduction from baseline: 37% vs. 20% Achieved 50% reduction in pain during the last 3 wk of treatment: 12/25 (48.0%) vs. 5/22 (22.7%) (p = 0.05)	Intake of > 7 tablets/wk of an analgesic --Lamotrigine, baseline / last 4 wk of treatment / calculated change, n: 7 / 2 / 5 --Placebo, baseline / end of treatment / calculated change, n: 3 / 3 / 0

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Kochar, 2004 India (Fair)			Elicited by investigator
Eisenberg, 2001 Israel (Poor)	Calculated change from baseline --MPQ, words: 0.5 vs. -0.4 (NSD) --BDI, total score: 0.4 vs. -1.2 (NSD) --PDI, total score: -0.2 vs. -0.1 (NSD)	Global assessment of efficacy, n (%) --High: 7/22 (32%) vs. 2/21 (10%) --Moderate: 9/22 (41%) vs. 7/21 (33%) --Low: 6/22 (27%) vs. 12/21 (57%) p = 0.07 Global assessment of tolerability, n (%) --Highly tolerable: 18/22 (81%) vs. 18/21 (86%)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Kochar, 2004 India (Fair)	On valproate, n: Nausea (2) Drowsiness (1) Increased liver function tests (bilirubin, AST, ALT) (1, at 1 mo) On placebo: none	Valproate vs. Placebo Total Withdrawals: 1/22 (4.5%) vs. 3/21 (14.3%) Withdrawals due to adverse events: 1/22 (4.5%) vs. 0/21 (0%)
Eisenberg, 2001 Israel (Poor)	Lamotrigine (N = 29) vs. Placebo (N = 30) Reported adverse event, n (calculated %): 17/29 (58.6%) vs. 21/30 (70.0%) Specific adverse events, n --Rash: 2 vs. 0 --Nausea: 4 vs. 4 --Epigastric pain: 3 vs. 1 --Headache: 2 vs. 2 --Drowsiness: 1 vs. 4 --Dizziness: 3 vs. 4 --Other: 2 vs. 6	Lamotrigine vs. Placebo Total Withdrawals, n (calculated %): 5/29 (17.2%) vs. 8/30 (26.7%) Withdrawals due to adverse events: 2/29 (6.9%) vs. 2/30 (6.7%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Kochar, 2004 India (Fair)	Small sample size limits generalizability of results.
Eisenberg, 2001 Israel (Poor)	Method of concealing allocation of treatment appeared to be inadequate (one patient was able to open the emergency blinding code).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Kochar, 2005 India (Fair)	Double-blind placebo-controlled RCT Outpatient	Adults with persistent pain > 6 mo after onset of herpes zoster rash; at least 40/100 mm point on Visual Analogue Scale (VAS) and 4/11 point on Likert scale	Divalproex vs. Placebo; doses not reported; 8 wk	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Kochar, 2005 India (Fair)	None	Short-form McGill Pain Questionnaire (SF-MPQ), present pain intensity (PPI) score, VAS, 11-point Likert scale (11 PLS) at baseline, 2, 4, and 8 wk. Patient's global impression of change (PGIC) at 8 wk. Routine blood test, fasting blood sugar, blood urea, serum creatinine, and complete urine examination at baseline. Serum bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at baseline and each subsequent visit. Adverse events interview and examination at 2, 4, and 8 wk.	Divalproex (N = 22) vs. Placebo (N = 18) Age, y: 57.9 vs. 56.36 Male / Female: 12 / 10 vs. 10 / 8 Ethnicity: Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Kochar, 2005 India (Fair)	Duration of postherpetic neuralgia, mo: 7.7 vs. 8.04	48/48/48	8 withdrawn / 0 lost to follow-up / 40

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Kochar, 2005 India (Fair)	Divalproex (N = 22) vs. Placebo (N = 18) (Per-protocol population) *Calculated* change in mean pain scores from baseline to end of treatment, calculated difference (*Reported* difference *at end point* and p-value) SF-MPQ: -8.57 vs. -2.02, -6.55 (-4.21; p < 0.0001) PPI: -2.05 vs. -0.46, -1.59 (-1.27; p < 0.0001) VAS: -38.90 vs. -8.24, -30.66 (-23.67; p < 0.0001) 11 PLS: -3.34 [47.9%] vs. -0.80 [13.0%], -2.54 (-1.7; p < 0.0001) (Primary efficacy measure was not identified.)	Achieved at least 50% pain relief on VAS (Per-protocol population): 13/22 vs. 2/18 (no p-value reported) Number-needed-to-treat (NNT) (95% CI): 2 (1 to 5) Calculated NNT: 2 (1 to 6); p = 0.001

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Kochar, 2005 India (Fair)	Moderately or much improved on PGIC at 8 wk: 58.2% vs. 14.8% Calculated NNT: 2 (1 to 4); p = 0.002		Monitoring and elicited

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Kochar, 2005 India (Fair)	Divalproex vs. Placebo Patients (calculated %, ITT) reporting adverse event: 4/24 (16.7%) vs. Not reported Specific adverse events on divalproex, n --Nausea, dizziness, drowsiness, mild change in appetite: 3 --Severe vertigo leading to discontinuation: 1	Divalproex vs. Placebo Total withdrawals, n (calculated %, ITT): 2/24 (8.33%) vs. 6/24 (25.0%) Withdrawals due to adverse events, n (calculated %, ITT): 1/24 (4.2%) vs. 0/24 (0.0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Kochar, 2005 India (Fair)	Dosing regimen of divalproex not reported. The calculated magnitude of change in mean pain score on 11 PLS observed with divalproex meets Farrar's criteria for clinically relevant changes (Farrar, 2001). NNT calculations were based on the per-protocol population and may not be comparable to NNTs from other trials that used the ITT population.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Van de Vusse (2004) The Netherlands (Fair)	Single-center, double-blind, placebo-controlled, crossover RCT Outpatient setting implied	Fulfilled IASP criteria for diagnosis of complex regional pain syndrome type I; age 18 to 75 y; pain score > 3 on 11-point visual analog scale (VAS; 0 = No pain; 10 = Worst pain imaginable); functional loss and pain outside the original traumatized area	Gabapentin (titrated from 600 mg/d to 1800 mg/d over 5 d, maintained at 1800 mg/d from day 5 to 21) vs. Placebo	2-wk washout between study treatments

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Van de Vusse (2004) The Netherlands (Fair)	Usual analgesics (not otherwise specified) at stable doses	24-h VAS pain score at baseline and 3, 5, and 8 wk; use of additional analgesics; global perceived effect (GPE; 7-item verbal rating scale); neuropathic pain scale (NPS; 10 items); sensory tests using a Von Frey monofilament skin application (9 areas, cutaneous nerve branches and dermatomes of hands or feet); mechanic allodynia test (brush strokes, static pressure; 9 areas as for touch sensation); edema, discoloration, and changed skin temperature on 3-point rating scale (No, Some, or Overt presence of each sign); Symptom Checklist 90-Revised (SCL-90-R); Brief Pain Inventory adapted for CRPS (BPI-CRPS; 0=CRPS has not interfered; 10=CRPS completely interfered in general on daily life); and range of motion (limb function) at 3, 5 and 8 wk	Gabapentin starter vs. Placebo starter Age, mean, y: 47 vs. 42 M / F, n: 4 / 18 vs. 4 / 21 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Van de Vusse (2004) The Netherlands (Fair)	Duration, mo: 44 vs. 43 Excluded from analysis-- Gabapentin starter vs. Placebo starter Duration, mo: 45 vs. 83	151 screened / 58 eligible, enrolled, and randomized	12 withdrawn / 2 lost to follow-up / 46 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Van de Vusse (2004) The Netherlands (Fair)	Gabapentin starter vs. Placebo starter VAS pain score First treatment period --Baseline: ~69 vs. ~70 --3 wk: ~55 vs. ~72 (p < 0.05) Second treatment period --5 wk: ~70 vs. ~68 --8 wk: ~70 vs. ~65 (NSD) Pain level unexpectedly increased during washout period for both gabapentin and placebo starters.	Global perceived effect on pain, % of patients with effect (defined as "much improvement") --First treatment period: 14% (3/22) vs. 5% (1/24) (NSD) --Second treatment period: 21% (5) vs. 4% (1) (NSD) --Total Gabapentin vs. Total Placebo (from both treatment periods): 17% (8/46) vs. 4% (2/46) (p<0.10) Global perceived effect on pain, % of patients with some or much improvement --Total Gabapentin vs. Total Placebo: 43% (20/46) vs. 17% (8/46) (p < 0.005) Calculated NNT: 4 (2 to 12) 'Aggravation of pain': 13% (6/46) vs. 9% (4/46) (NSD) BPI-CRPS, NPS corrected for multiple tests, Use of co-medication, SCL-90-R: all NSD

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Van de Vusse (2004) The Netherlands (Fair)	Cutaneous sensory thresholds, mean ranking --Hand: 15.6 (N = 15) vs. 12.0 (N = 12) (NSD) --Feet: 12.0 (N = 3) vs. 5.5 (N = 10) (p < 0.011) --Total: 25.0 (N = 18) vs. 16.8 (N = 22) (p < 0.027) Mechanical allodynia, static and dynamic stimuli: NSD Other symptoms: NSD Limb dysfunction, number of responders: NSD	Blinding: treating physician correctly guessed the used medication more often after both treatment phases than can be explained by chance (p = 0.000); blinding was sufficient in the first phase (p = 0.2)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Van de Vusse (2004) The Netherlands (Fair)	Gabapentin (N = 54) vs. Placebo (N = 51) Experienced >/= 1 AE (statistics not reported) 1st tx period: 21 (95%) vs. 14 (58%) 2nd tx period: 15 (63%) vs. 7 (32%) AEs reported in > / = 10% of gabapentin patients --Dizziness: 37.3% vs. 3.9% (p = 0.0000) --Somnolence: 27.8% vs. 5.9% (p = 0.003) --Lethargy: 20.4% vs. 2.0% (p=0.003) --Nausea: 18.5% vs. 9.8% (NSD) --Headache: 14.8% vs. 5.9% (NSD)	Gabapentin vs. Placebo vs. Washout (N=58) Total withdrawals: 4 (6.9%) vs. 6 (10.3%) vs. 2 (3.4%) Withdrawals due to AEs: 3 (5.2%) vs. 0 vs. 0

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Van de Vusse (2004) The Netherlands (Fair)	The NPS has not been adequately validated. Blinding was compromised (probably because of AEs) but did not seem to result in bias favoring gabapentin. An increase in pain above baseline levels was unexpectedly observed during washout for both gabapentin and placebo starters. This "rebound" effect could theoretically be due to a period effect (although regression toward the mean instead of increasing pain would be expected) or reversed placebo effect (expectation and/or actual perception of not receiving gabapentin increased pain intensity). All patients adhered to treatment regimen.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Hahn (2004) Germany (Fair)	Multicenter, double-blind, placebo-controlled RCT Outpatient setting	Symptoms of painful HIV sensory neuropathy (HIV-SN), diagnosed by a neurologist based on history, clinical findings, and neurophysiologic examination; age > / = 18 y; completed baseline pain diary over 1 wk prior to randomization. Diagnosis of HIV-SN made y standard definition including distal sensory symptoms, abnormal sensory signs, and decreased or absent ankle reflexes.	Gabapentin vs. Placebo titrated from 400 mg/d to 1200 mg/d over 2 wk (n = 4) or 2400 mg/d over additional 2 wk (n = 10) depending on clinical response (total duration, 4 wk). Thereafter, treatment was unblinded and gabapentin continued at 1200 (n = 10) or 2400 mg/d (n = 5) or increased to 3600 mg/d if necessary (n = 6).	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Hahn (2004) Germany (Fair)	Nonsteroidal antiinflammatory drugs (NSAIDs) at minimal doses	10-cm Visual Analogue Scale (VAS) (0 = No pain; 10 = Maximal pain intensity) on Short-form McGill Pain Questionnaire (SF-MPQ) recorded twice daily in patient diary; daily sleep interference score using a VAS (0 = Excellent sleep; 10 = No sleep due to pain); adverse events; laboratory tests at baseline and end point	Gabapentin (N = 15) vs. Placebo (N = 11) Age, median, y: 46 vs. 44 M / F, n: 10 / 5 vs. 10 /1 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Hahn (2004) Germany (Fair)	CD4 count, median, cells/µl: 395 vs. 319 Duration of painful neuropathy, median, wk: 48 vs. 28 Neurotoxic antiretroviral drugs, n --Concomitant use: 4 vs. 3 --Previous (within 3 mo): 2 vs. 1 --None: 1 vs. 1	Numbers screened and eligible not reported / 26 enrolled and randomized	2 withdrawn / 0 lost to follow-up / 26 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Hahn (2004) Germany (Fair)	Gabapentin (N = 15) vs. Placebo (N = 11) Weekly median pain score --Baseline / Wk 4: 5.1 / 2.85 vs. 4.7 / 3.3 --Calculated change (Reported % change): - 2.25 (-44.1%) ($p < 0.05$) vs. -1.4 (-29.8%) ($p = 0.646$) --Calculated difference between changes in scores: -0.85 (p-value not reported for treatment difference at 4 wk)	Weekly median sleep interference score --Baseline / Wk 4: 4.5 / 2.3 vs. 5.6 / 4.95 --Calculated change (Reported % change; p-value versus baseline): -2.2 (-48.9%) ($p < 0.05$) vs. -0.65 (-11.6%) ($p = 0.575$) --Calculated difference between changes in scores: -1.55 (p-value not reported for treatment difference at 4 wk)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Hahn (2004) Germany (Fair)	Concomitant NSAID, baseline / wk 4, n: 3 / 1 vs. 2 / 1 (NSD between treatment groups)		Monitoring and elicited by investigator (AE data in diary table)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Hahn (2004) Germany (Fair)	Gabapentin (N = 15) vs. Placebo (N = 11) No serious AEs occurred AEs reported in > / = 10% of gabapentin patients, mild / moderate / severe, n (total n, % of patients) --Somnolence: 4/4/4 (12, 80%) vs. 1/0/1 (2, 18.2%) (p = 0.006) --Dizziness: 3/1/5 (9, 60%) vs. 3/1/1 (5, 45.5%) (NSD) --Gait ataxia: 2/3/2 (7, 46.6%) vs. 2/0/1 (3, 27.3%) (NSD) --Nausea: 3/2/0 (5, 33.3%) vs. 2/0/0 (2, 18.2%) (NSD) Laboratory abnormalities noted on gabapentin --Increased lipase (88 and 94 U/l), n: 2 --Increased blood glucose (135 mg/dl), n: 2	Gabapentin (N = 15) vs. Placebo (N = 11) Total withdrawals: 1 vs. 1 Withdrawals due to AEs: 1 (6.7%) vs. 0 (0.0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Hahn (2004) Germany (Fair)	HIV-SN includes both distal-symmetric polyneuropathy (DSP) caused by HIV infection and antiretroviral toxic neuropathy (ATN). Electrophysiologic tests were not done in this study because both DSP and ATN primarily affect small sensory nerve fibers, which cannot be evaluated with standard electrodiagnostic studies. No patients were treated with opioids during study. High rate of somnolence may have compromised blinding.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Levendoğlu (2004) Turkey (Fair)	Double-blind crossover RCT Outpatient setting implied during stable dosing period; hospitalization during titration	Complete traumatic spinal cord injury (SCI) at thoracic and lumbar level; age between 20 and 65 y; neuropathic pain for more than 6 mo confirmed by physician; Neuropathic Pain Scale (NPS) score > 4 (moderate to severe) on 11-point scale	Gabapentin vs. Placebo for 8 wk per treatment; forced titration from 900 mg/d to 3600 mg/d at end of wk 4	15-d washout of prior analygesics before study; 2-wk washout before crossover

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Levendoğlu (2004) Turkey (Fair)	None reported	Neuropathic Pain Scale (NPS) twice daily for 3 d then daily; Visual Analog Scale (VAS; 0 = No pain to 100 = Worst pain) twice daily for 3 d then biweekly from wk 2 to 18; Lattinen questionnaire (LQ), including subjective pain intensity, frequency of pain, quality of sleep, and disability due to pain at baseline then biweekly from wk 2 to 18; 7-point Ramsay Sedation Scale	Age, mean, y: 35.9 Male / female: 13/7 Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Levendoğlu (2004) Turkey (Fair)	Trauma time, mean, mo: 18.5 Pain onset time after trauma, mean, mo: 2.7 Pain duration, mo: 15.8	Numbers screened and eligible not reported / 20 enrolled / 20 randomized	0 withdrawn / 0 lost to follow-up / 20 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Levendoğlu (2004) Turkey (Fair)	Gabapentin vs. Placebo VAS Pain Intensity score, mm (1st of 2 primary efficacy measures) --Baseline: ~89 vs. ~89 --At 8 wk: ~35 vs. ~80 (p < 0.001) --Calculated change from baseline to 8 wk (calculated difference): -54 vs. -9 (-45) --First statistically significant treatment difference: 2 wk --At 8 wk vs. 6 wk: NSD VAS Pain Relief at 8 wk, mean: 60.7% vs. 10.3% (p = 0.000)	LQ evaluation at 8 wk --Subjective pain intensity: ~1.2 vs. ~3.0 (p < 0.001) --Frequency of pain: ~2.5 vs. ~3.1 (p < 0.05) --Quality of sleep: ~1.3 vs. ~2.6 (p < 0.001) --Disability due to pain: ~0.75 vs. ~2.1 (p < 0.001)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Levendoğlu (2004) Turkey (Fair)	NPS scores at 8 wk; % of pain relief [change from baseline] (2nd of 2 primary efficacy measures) --Pain intensity: 3.2 vs. 7.4 (p = 0.000); -61.9% vs. -13.2% (p = 0.000) --Sharp: 3.0 vs. 6.2 (p = 0.000); -56.7% vs. -8.3% (p=0.000) --Hot: 2.7 vs. 5.2 (p = 0.001); -52.8% vs. -10.9% (p = 0.000) --Dull: 0.3 vs. 0.6 (NSD); % pain relief not reported --Cold: 0.8 vs. 0.8 (NSD); % pain relief not reported --Sensitive: 0.5 vs. 0.8 (NSD); % pain relief not reported --Itchy: 0.0 vs. 0.0 (NSD); % pain relief not reported --Unpleasantness: 3.6 vs. 7.3 (p = 0.000); -55.5% vs. -12.9% (p = 0.000) --Deep pain: 3.5 vs. 6.2 (p = 0.000); -54.0% vs. -7.8% (p = 0.000) --Surface pain: 2.8 vs. 5.5 (p = 0.001); -56.3% vs. -9.0% (p = 0.000)	Dose of gabapentin without AEs, mean (range): 2235 (900 to 2700) Maximum tolerated dose, mean (range): 2850 (1200 to 3600)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Levendoğlu (2004) Turkey (Fair)	Gabapentin vs. Placebo (N = 20 each) Patients experiencing AEs, n (%): 13 (65%) vs. 5 (25%) ($p < 0.05$) Total number of AEs: 17 vs. 6 ($p < 0.05$) AEs reported in > / = 10% of gabapentin patients, n (%) (all NSD) --Weakness: 5 (25%) vs. 2 (10%) --Edema: 3 (15%) vs. 0 --Vertigo: 3 (15%) vs. 1 (5%) --Sedation: 3 (15%) vs. 0 --Itching: 2 (10%) vs. 0	Total withdrawals: 0 vs. 0 Withdrawals due to AEs: 0 vs. 0

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Levendoğlu (2004) Turkey (Fair)	First statistically significant pain relief occurred at 2 wk (time of first statistical analysis). The authors noted that low baseline levels of itchy, dull, sensitive, and cold pain characteristics may have caused lack of gabapentin efficacy.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Caraceni (2004) Italy, Spain (Fair)	Multicenter double-blind, placebo-controlled, parallel-group RCT (randomized 2:1) Outpatient setting implied	Active cancer lesion causing pain by infiltration or compression of nervous structures; at least one of the following signs or symptoms referred to the pain area: burning pain, shooting/lancinating pain episodes, dysesthesias, or allodynia. Age > / = 18 y; 11-point numerical rating scale (NRS) pain intensity score > / = 5 in preceding 24 h; regularly scheduled opioid therapy without sufficient analgesia with significant opioid-related adverse events; stable opioid dose for > 24 h; life expectancy >/= 30 d; Karnofsky performance score (KPS) >/= 40. Patients were withdrawn from the study if they required more than one daily dose of as-needed opioid after visit 1 or chemotherapy, radiotherapy, or surgery for disease control.	Gabapentin titrated from 600 to 1800 mg/d vs. Placebo for 10 d, added on to current opioids and other analgesics	None

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Caraceni (2004) Italy, Spain (Fair)	Previous analgesics (opioid and nonsteroidal antiinflammatory drugs [NSAIDs]) and adjuvant therapies (i.e., steroids, antidepressants, AEDs, anxiolytics, and muscle relaxants) at stable doses; one dose of opioid as needed on visit 1. Stable hormone therapy.	11-point NRS (0 = No pain; 10 = Worst possible pain) of average pain in previous 24 h, intensity of shooting / lancinating pain, burning pain, and dysesthesia (selected by patient from among these types: pins / needles, cold, numbness, tension / constriction) at baseline and 10 d or discontinuation; presence or absence of allodynia at baseline and 10 d or discontinuation; number of lancinating episodes; concomitant opioid use. Pain control defined as Pain Intensity Difference (PID) (change from baseline) >/= 33%.	Gabapentin (N = 80) vs. Placebo (N = 41) Age, mean, y: 59.0 vs. 60.7 Male / Female: 43.7% / 56.3% vs. 43.9% / 56.1% Ethnicity: Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Caraceni (2004) Italy, Spain (Fair)	Oral morphine daily equivalent, mg: 116.5 vs. 106.6 Karnofsky performance score, median (range): 60 (40 to 90) vs. 70 (40 to 100) Concomitant pain medication --NSAID: 58.7% vs. 63.4% --Steroids: 47.5% vs. 36.6% --Antidepressants: 20.0% vs. 14.6% --AED: 7.5% vs. 9.7% --Bisphosphonates: 5.0% vs. 0 Global pain score, mean: 7.0 vs. 7.7 Shooting pain score in previous 24 h, mean (n, 59 vs. 27): 6.0 vs. 6.1 Dysesthesia score in previous 24 h, mean (n, 70 vs. 35): 6.4 vs. 6.0 No. of episodes of lancinating pain in previous 24 h, mean: 6.0 vs. 11.5 Allodynia, n: 15 (19.7%) vs. 14 (35.9%) Neuropathic pain syndrome, most frequent types in both treatment groups, % of patients: --Brachial plexopathy: 28.7%	691 screened / 130 eligible / 121 enrolled and randomized	31 withdrew / 1 lost to follow-up / 120 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Caraceni (2004) Italy, Spain (Fair)	Gabapentin (N = 79) vs. Placebo (N = 41) Global pain score, mean for entire follow-up period (Primary efficacy measure): 4.6 vs. 5.4 (calculated difference, -0.8; p = 0.025) --Calculated absolute (relative %) change from baseline (difference): -2.4 (34.3%) vs. -2.3 (29.9%) (-0.1)	*Secondary efficacy measures* Gabapentin (N = 76) vs. Placebo (N = 39) (Modified intent-to-treat) Dysesthesias score: 4.3 vs. 5.2 (p = 0.0077) Shooting pain: 3.8 vs. 4.3 (NSD) Burning pain: 2.2 vs. 2.3 (NSD) No. of lancinating pain episodes: 4.9 vs. 4.9 (NSD) Allodynia: Data not reported (NSD)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Caraceni (2004) Italy, Spain (Fair)	Use of additional analgesic doses, % of patients: 47.1% vs. 64.7% (p = 0.0999) Use of as-needed opioid doses, % of follow-up days: 21.6% vs. 35.8% (p = 0.0559) Maximum gabapentin dose, median, mg/d: 1800 Patients with pain score > 5 on gabapentin 1800 mg/d at end of study: 22/55 (40.0%)	*Other pain response analyses* Percentage of follow-up days with PID > / = 33%, mean: 51.6% vs. 37.8% (p = 0.039) Never reached 33% PID, % of patients: 15% vs. 40% (p = 0.048) Patients achieving > / = 33% PID by time point --Day 3, % (95% CI): 57% (45% to 69%) vs. 31% (15% to 45%) --Day 10: 62% vs. 64% (95% CIs overlap) --Other time points: 95% CIs overlap --Higher percentage of patients achieved >/=33% PID in first few days of treatment on gabapentin than placebo (p=0.0048)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Caraceni (2004) Italy, Spain (Fair)	Gabapentin (N = 79) vs. Placebo (N = 41) Deaths and other serious AEs: 2 (2.4%) vs. Not reported --Patient with KPS of 50 and liver failure developed sedation and coma, and died after taking 3 doses of gabapentin (600 mg/d) and 24 h after increasing morphine dose, in addition to multiple benzodiazepines --Patient with KPS of 50, history of respiratory depression on methadone (120 mg/d), and complex medication regimen including methadone (90 mg/d) developed respiratory depression after taking gabapentin 1200 mg/d on second study day; symptoms reversed with naloxone Patients experiencing >/= 1 AE: 35 (43.7%) vs. 10 (24.3%) Adverse events related to treatment: 1 (1.2%) vs. 0 (0.0%) for each of the following: sedation (severe), incontinence, tremor, vertigo, maculopapular rash, respiratory depression (severe) Adverse events experienced by >/= 10% of patients in either group --Somnolence: 18 (22.8%) vs. 4 (9.7%) Other selected AEs: --Dizziness: 7 (8.8%) vs. 0 (0.0%)	Gabapentin (N = 80) vs. Placebo (N = 41) Total withdrawals: 22 (27.5%) vs. 9 (22.0%) Withdrawals due to AEs: 6 (7.5%) vs. 3 (7.3%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Caraceni (2004) Italy, Spain (Fair)	The primary efficacy results were robust when sensitivity analyses used different criteria for missing data imputation (last observation carried forward and worst value imputed). The authors concluded that gabapentin (300 mg) in association with opioids was usually safe, but a more cautious dosage titration should be used in patients who are frail, on high opioid doses, and on complex pain regimens, particularly those including benzodiazepines. The primary efficacy results showed a statistically significant but clinically nonrelevant treatment difference (-0.8 on 11-point scale) in mean global pain scores (i.e., average over the entire follow-up period). The calculated change in global pain scores from baseline with gabapentin was similar to the change seen with placebo. The use of 33% PID differs from 30% or 50% PID typically used in other trials.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Age > / = 18 years; type 1 or 2 diabetes mellitus; distal symmetric sensorimotor polyneuropathy for 1 to 5 y; stable antidiabetic medication; completed at least 4 daily pain diaries during baseline phase; average baseline daily pain score > / = 4 (on 0 to 10 scale); score of >/= 40 mm on visual analog scale (VAS) of Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits	Pregabalin 75, 300, or 600 mg/d vs. Placebo for 5 wk (75- and 300-mg doses started without titration; 600-mg dose was titrated over 1 wk, then fixed for 4 wk)	1-wk run-in baseline phase; patients who completed at least 4 daily pain diaries during the baseline phase, had an average baseline daily pain score > / = 4 (on 0 to 10 scale), and had a score of > / = 40 mm on the SF-MPQ VAS at the baseline and randomization visits were randomized.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	Acetaminophen (up to 3 g/d); selective serotonin reuptake inhibitors (stable doses)	11-point numerical rating scale by patient daily diary (0 = No pain; 10 = Worst possible pain); daily sleep interference diary; SF-MPQ (including pain descriptors total score, VAS, and present pain intensity [PPI]) weekly; Clinical Global Impression of Change (CGIC); Patient Global Impression of Change (PGIC) at completion visit; SF-36 Health Survey (SF-36) and Profile of Mood States (POMS) at study randomization and completion	Age, mean (range), y: 59.9 (26 to 85) M / F: 202 / 135 Race, white / black / other, n (%): 318 (94.4) / 12 (3.6) / 7 (2.1)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	Estimated creatinine clearance, mean, ml/min: 98.1 Diabetes type, 1 / 2, n (%): 31 (9.2) / 306 (90.8) Baseline pain score, mean (range): 6.4 (2.9 to 10.0) Antidiabetic medication, Insulin / Oral, n (%): 142 (42.1) / 247 (73.3)	578/Not reported/Not reported/338	36 withdrawn / loss to follow-up not reported / 337 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	Pregabalin 75 mg/d (N = 77) vs. 300 mg/d (N = 81) vs. 600 mg/d (N = 81) vs. Placebo (N = 97) Pain scores (0 to 10 scale) --Baseline mean / Endpoint least squares (LS) mean (Calculated change): 6.7 / 4.91 (-1.79) vs. 6.2 / 3.80 (-2.40) vs. 6.2 / 3.60 (-2.60) vs. 6.6 / 5.06 (-1.54) --Difference from placebo, end point mean pain scores (95% CI): -0.15 (-0.76 to 0.46) vs. -1.26 (-1.86 to -0.65; p=0.0001) vs. -1.45 (-2.06 to -0.85; p=0.0001) vs. 0 Onset of effect (first statistically significant difference from placebo): 1 wk (Pregabalin 300 and 600 mg/d) Responder Rates, Patients with > / = 50% reduction in pain: n Not reported/77 (~25%) vs. 37/81 (41%) vs. 39/81 (48%) vs. 17/97 (18%) > / = 30% reduction in pain: n Not reported/77 (~37%) vs. 50/81 (62%) vs. 53/81 (65%) vs. 32/97 (33%) (calculated p < 0.0001 for 300- and 600-mg doses vs. placebo for both 50% and 30% pain reduction; see calculated NNT under Comments)	Sleep interference score at end point --LS mean: ~3.6 vs. ~2.7 vs. ~2.6 vs. ~4.2 --Difference from placebo: Not reported vs. 1.3 vs. 1.6 vs. 0 (p = 0.0001 for 300- and 600-mg doses) SF-MPQ total score --LS mean: 15.06 vs. 10.17 vs. 9.88 vs. 15.06 --Difference from placebo (95% CI): 0.01 (-2.43 to 2.44; NSD) vs. -4.89 (-7.29 to -2.48; p=0.0001) vs. -5.18 (-7.58 to -2.79; p=0.0001) vs. 0

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	VAS score --LS mean: 49.70 vs. 37.40 vs. 34.48 vs. 53.49 --Difference from placebo (95% CI): -3.79 (-10.90 to 3.32; NSD) vs. -16.09 (-23.11 to -9.08; p = 0.0001) vs. -19.01 (-26.00 to -12.01; p = 0.0001) PPI score --LS mean: 1.67 vs. 1.20 vs. 1.18 vs. 1.79 --Difference from placebo (95% CI): -0.12 (-0.41 to 0.18; NSD) vs. -0.59 (-0.88 to -0.30; p=0.0001) vs. -0.61 (-0.90 to -0.32; p=0.0001) vs. 0	Much improved or very much improved, n/N (%) --PGIC: Not reported vs. 44/79 (55.7%) vs. 54/78 (69.2%) vs. 23/95 (24.2%) (no statistics) --CGIC: Not reported 46/79 (58.2%) vs. 50/78 (64.1%) vs. 25/95 (26.3%) (no statistics) (Note: These proportions are different from those shown in figure 5 of the report for PGIC or CGIC "improvement" for which p = 0.001 for 300- and 600-mg doses for both scales) SF-36 (scores not reported) Pregabalin 300 and 600 mg/d, respectively, were better than placebo in --Social functioning domain: p < 0.05 and p < 0.01 --Bodily pain domain: p < 0.005 and p < 0.0005 Pregabalin 75 and 300 mg/d, respectively, were better than placebo in --Vitality domain: p < 0.05 and p < 0.01 POMS Pregabalin 300 mg/d was better than placebo in Tension-anxiety mood	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	Pregabalin 75 (N = 77) vs. 300 (N = 81) vs. 600 mg/d (N = 82) vs. Placebo (N = 97) AEs that occurred in >/= 10% of patients in any pregabalin group, n (%) --Dizziness: 6 (7.8%) vs. 22 (27.2%) vs. 32 (39.0%) vs. 5 (5.2%) --Somnolence: 3 (3.9%) vs. 19 (23.5%) vs. 22 (26.8%) vs. 4 (4.1%) --Peripheral edema: 3 (3.9%) vs. 6 (7.4%) vs. 11 (13.4%) vs. 2 (2.1%) --Headache: 5 (6.5%) vs. 7 (8.6%) vs. 8 (9.8%) vs. 10 (10.3%) Other selected AEs --Amnesia: 2 (2.6%) vs. 0 (0.0%) vs. 5 (6.1%) vs. 1 (1.0%) --Accidental injury: 4 (5.2%) vs. 2 (2.5%) vs. 4 (4.9%) vs. 0 (0.0%) --Euphoria: 0 (0.0%) vs. 5 (6.2%) vs. 4 (4.9%) vs. 0 (0.0%) Other specific AEs reported in >/= 5% of patients in any pregabalin group: ataxia, neuropathy, pain, amnesia, accidental injury, dry mouth, euphoria, diarrhea, infection	Total withdrawals: Placebo - 8/97 (8.2%) Pregabalin 75 mg - 10/77 (13%) Pregabalin 300 mg - 5/81 (6.2%) Pregabalin 600 mg - 12/82 (14.6%) Withdrawals due to adverse events, n: 2/77 (2.6%) vs. 3/81 (3.7%) vs. 10/82 (12.2%) vs. 3/97 (3.1%) (no statistics)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Lesser, 2004 U.S. Pregabalin Diabetic Neuropathy 1008-29 Study (Fair)	End point LS mean pain scores were derived from patients' last 7 d of diary entries. Rationale was not given for excluding previous nonresponders to gabapentin > / = 1200 mg/d. For pregabalin 300- and 600-mg doses, the calculated changes in mean pain scores on an 11-point numerical rating scale met Farrar's criteria for clinically relevant changes in pain (Farrar, 2001). Calculated NNT (95% CI) for at least 50% improvement in pain as compared with placebo in a 5-wk treatment period was 4 (2 to 7) for pregabalin 300 mg/d and 3 (2 to 6) for pregabalin 600 mg/d. For 30% improvement in pain, the corresponding values were 3 (2 to 7) and 3 (2 to 5), respectively. NNTs were not calculated for pregabalin 75 mg/d because of uncertain number of responders.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Multicenter, double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Pain > 6 mo after healing of herpes zoster rash; age > / = 18 y; completed > 4 daily pain diaries during the 7-d baseline phase; average daily pain score > / = 4; score > / = 40 mm on 100-mm visual analogue scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits	Pregabalin 150 vs. 300 mg/d vs. Placebo for 8 wk (1-wk forced titration, 7-wk fixed dose period)	1-wk run-in baseline phase; patients who completed at least four daily pain diaries during the baseline phase, had an average baseline daily pain score > / = 4, and had a score of > / = 40 mm on the SF-MPQ VAS at the baseline and randomization visits were randomized. Washout of benzodiazepines and AEDs at least 14 d prior to receiving study medication

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Stable regimens of acetaminophen (up to 3 g/d),nonsteroidal antiinflammatory drugs, opioid or non-opioid analgesics, or antidepressants	11-point Numerical Rating Scale (NRS; 0 = No pain; 10 = Worse possible pain or sleep interference) scores recorded daily in pain diaries; sleep interference scores daily; Patient Global Impression of Change (PGIC); Clinical Global Impression of Change (CGIC); SF-36 Health Survey (SF-36); Zung Self-Rating Depression Scale (ZSRDS); VAS of the SF-MPQ; adverse events; laboratory data; physical examination, neurologic examination, 12-lead electrocardiogram. Evaluation occurred every 1 to 3 wk.	Pregabalin 150 mg/d (N = 81) vs. 300 mg/d (N = 76) vs.Placebo (N = 81) Age, mean, y: 71.3 vs. 71.9 vs. 73.2 M / F, n (%): 39 (48%) / 42 (52%) vs. 31 (41%) / 45 (59%) vs. 37 (46%) / 44 (54%) Ethnicity, White / Black: 79 (98%) / 2 (2%) vs. 76 (100%) / 0 (0%) vs. 81 (100%) / 0 (0%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Estimated creatinine clearance, mean, ml/min: 62.9 vs. 58.9 vs. 60.5 Duration of postherpetic neuralgia, mean, mo: 40.9 vs. 40.7 vs. 44.8 Concomitant drugs (patients may be taking > 1) --Analgesics, opioid and non-opioid, n (?): 46 vs. 42 vs. 31 --Antiinflammatories: 21 vs. 17 vs. 12 --Antidepressants: 17 vs. 22 vs. 18	307 / 238 / 253 / 238	46 withdrawn / 0 lost to follow-up / 238 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Pregabalin 150 mg/d (N = 81) vs. 300 mg/d (N = 76) vs. Placebo (N = 81) Pain scores (Primary efficacy measure, ITT) --Baseline mean / End point least squares (LS) mean of weekly score (Calculated change): 6.9 / 5.14 (-1.76) vs. 7.0 / 4.76 (-2.24) vs. 6.6 / 6.33 (-0.27) --Difference from placebo, end point mean pain scores (95% CI): -1.20 (-1.81 to -0.58; p=0.0002) vs. -1.57 (-2.20 to -0.95; p=0.0001) --Earliest statistically significant onset, wk: 1 vs. 1 vs. Not applicable	Responder rate (decrease in mean pain score of at least 50% from baseline to end point), n/N (%): 21/81 (26%) vs. 21/76 (28%) vs. 8/81 (10%) (p = 0.006 and p = 0.003 for pregabalin 150 and 300 mg/d, respectively, vs. placebo) Calculated NNT: 6 (4 to 22) and 6 (3 to 17), respectively Proportion of patients who achieved at least 30% decrease in mean pain score from baseline (post hoc outcome measure): 37% vs. 50% vs. 19% Calculted NNT: 6 (3 to 21) and 4 (3 to 9), respecitively

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Pregabalin 150 mg/d vs. 300 mg/d vs. Placebo End point SF-MPQ VAS pain score --N analyzed: 80 vs. 76 vs. 80 --Least squares mean: 52.03 vs. 62.05 vs. 48.41 --Difference from placebo (95% CI): -10.02 (-17.15 to 2.90; p = 0.0060) vs. -13.64 (-20.87 to -6.40; p = 0.0003) vs. 0 End point mean sleep interference score --N analyzed: 81 vs. 76 vs. 81 --Least squares mean: 3.13 vs. 2.81 vs. 4.24 --Difference from placebo (95% CI): -1.11 (-1.71 to -0.51; p = 0.0003) vs. -1.43 (-2.04 to -0.82; p = 0.0001) vs. 0 --Earliest statistically significant onset, wk: 1 vs. 1 vs. Not applicable	Much improved or very much improved, n/N (%) --PGIC: 25/81 (31%) vs. 29/76 (40%) vs. 11/81 (14%) (p = 0.064 and p = 0.002 for pregabalin 150 and 300 mg/d, respectively, vs. placebo) --CGIC: Not reported Pregabalin 150 vs. 300 mg/d SF-36 Health-related quality of life, LS mean difference from placebo --Mental Health: 5.72 vs. 6.05 (p = 0.043 for each) --Bodily Pain: Not reported vs. 9.58 (p = 0.005) --Vitality: Not reported vs. 7.11 (p = 0.044) Zung Self-rating Depression Scale index, LS mean difference from placebo (95% CI): -2.97 (-6.03 to 0.08; adjusted p = 0.056) vs. -4.01 (-7.13 to -0.89; adjusted p=0.024)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	Pregabalin 150 mg/d (N = 81) vs. 300 mg/d (N = 76) vs. Placebo (N = 81) AEs occurring in > / = 10% of patients in any pregabalin group, n (%) --Dizziness: 10 (12%) vs. 21 (28%) vs. 12 (15%) --Somnolence: 12 (15%) vs. 18 (24%) vs. 6 (8%) --Peripheral edema: 2 (3%) vs. 10 (13%) vs. 0 (0%) --Headache: 9 (11%) vs. 8 (11%) vs. 3 (4%) --Dry mouth: 9 (11%) vs. 5 (7%) vs. 3 (4%) Other selected AE --Infection: 2 (3%) vs. 5 (7%) vs. 0 (0%) % of patients experiencing at least 1 AE: 83% on pregabalin 300 mg/d (not reported for other groups) Significant new ECG findings (all unlikely related to study drug), n: 3 vs. 2 vs. 4 Weight gain > 7% from baseline, % of patients: 4% vs. 14% vs. 4% Serious AEs, n: 4 vs. 1 vs. 3 (total 5/157 [3.2%] vs. 3/81 [3.7%]) --Ventricular extrasystoles considered serious and possibly or probably related to study drug: 2 vs. 0 vs. 1 --Confusion: 1 on Pregabalin 150 mg/d (serious AE resolved after patient discontinued drug)	Total withdrawals, n (%): 10 (12.3%) vs. 16 (21.1%) vs. 20 (24.7%) Withdrawals due to adverse events, n (%): 9 (11.1%) vs. 12 (15.8%) vs. 8 (9.9%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Sabatowski (2004) Australia, Europe (8 countries) 1008-045 Study (Fair)	End point LS mean pain scores were derived from patients' last 7 d of diary entries. Nonresponders to previous treatment with gabapentin > / = 1200 mg/d for postherpetic neuralgia were excluded, in part, because at the time of the study's design, pregabalin and gabapentin appeared to have similar mechanisms. If response to gabapentin predicts response to pregabalin, this exclusion may favor finding beneficial results with pregabalin. The results of this trial may not apply to patients who have failed gabapentin > / = 1200 mg/d. The differences between the baseline mean and LS mean pain scores suggest that treatment with pregabalin 300 mg/d and not 150 mg/d resulted in clinically relevant improvement in pain based on the criteria by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Dworkin (2003) U.S. (Fair)	Multicenter (29), double-blind, placebo-controlled, parallel-group RCT Outpatient setting	Age > / = 18 y; postherpetic neuralgia (pain present for more than 3 mo after healing of a herpes zoster skin rash); pain at least 40 mm on 100-mm visual analog scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits; completed at least four daily pain diaries and had minimum mean daily pain rating of 4 on 11-point numerical rating scale during 1-wk baseline period; normal chest X-ray within preceding 2 y	Pregabalin 300 mg/d (creatinine clearance > 30 and < / = 60 ml/min) or 600 mg/d (creatinine clearance > 60 ml/min) vs. Placebo for 8 wk Pregabalin titration: 150 mg/d for 3 days then increased to 300 mg/d; patients with creatinine clearance > 60 ml/min increased their dose to 600 mg/d starting the second week. Note: The two pregabalin groups were combined into one treatment group for analysis.	1-wk run-in baseline phase; patients who completed at least four daily pain diaries during the baseline phase, had an average baseline daily pain score > / = 4, and had a score of > / = 40 mm on the SF-MPQ VAS at the baseline and randomization visits were randomized. Washout of benzodiazepines, skeletal muscle relaxants, oral steroids, local and topical agents for postherpetic neuralgia, and AEDs (including gabapentin). Injected local anesthetics or steroids prohibited within 1 mo of baseline.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Dworkin (2003) U.S. (Fair)	Stable doses of narcotic and non-narcotic analgesics, acetaminophen (maximum 4 g/d), nonsteroidal antiinflammatory drugs, aspirin, antidepressants	11-point numerical rating scale (NRS; 0 = No pain; 10 = Worst possible pain) of pain recorded daily; SF-MPQ (including pain quality, 100-mm VAS, and 6-point present pain intensity [PPI] scale) at baseline, start of treatment, and at end of wk 1, 3, 5, and 8; daily sleep interference score on 11-point NRS (0=Did not interfere with sleep; 10=completely interfered with sleep); Medical Outcomes Study (MOS) Sleep scale, SF-36 Health Survey (SF-36), and Profile of Mood States (POMS; 5-point scale where 0 = Applies not at all; 4 = Applies extremely) at randomization and termination visits; Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) at termination visit; adverse events; physical and neurologic examinations, vision testing (visual field screening, dilated ophthalmoscopy, and visual acuity); 12-lead electrocardiogram (ECG);	Pregabalin 300/600 mg/d (N = 89) vs. Placebo (N = 84) Age, mean, y: 72.4 vs. 70.5 M / F: 41.6% / 58.4% vs. 52.4% / 47.6% Ethnicity, White / Hispanic / Asian or Pacific Islander, %: 92.1% / 6.7% / 1.1% vs. 97.6% / 1.2% / 1.2%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Dworkin (2003) U.S. (Fair)	Age > / = 65 y, %: 83.1% vs. 79.8% Estimated creatinine clearance, mean, ml/min: 72.9 vs. 80.3 Creatinine clearance strata, % --Low (> 30, < / = 60 ml/min): 33.7 vs. 29.8 --Normal (> 60 ml/min): 66.3 vs. 70.2 Duration of postherpetic neuralgia, mean, mo: 33.3 vs. 34.4 Used concurrent pain medications, n (%): 118 (68%)	245 screened / Number eligible and enrolled not reported / 173 randomized	41 withdrawn / 0 lost to follow-up / 171 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Dworkin (2003) U.S. (Fair)	Pregabalin 300/600 mg/d (N = 88) vs. Placebo (N = 84) Pain scores (Primary efficacy measure) --Baseline mean / End point least squares (LS) mean daily pain (Calculated change): 6.3 / 3.60 (-2.7) vs. 6.4 / 5.29 (-1.11) --Calculated difference in score change: -1.59 --Difference at end point (95% CI): -1.69 (-2.33 to -1.05; p = 0.0001) --Onset of earliest statistically significant difference in weekly mean pain score: 1 wk; in daily pain scores: 2 d --End point LS mean excluding 46 patients taking tricyclic antidepressants, opioids, AEDs, and topical analgesics: 3.17 vs. 5.14 (p = 0.0001) --End point LS mean excluding patients who had any AE reported in > 10% of patients in pregabalin group: 3.60 vs. 5.29; p = 0.0001) --End point LS mean excluding patients who had any AE reported in > 5% of patients in pregabalin group: 3.62 vs. 5.37 (p < 0.05) Responder rates, calculated n/N (reported %); NNT --Achieved >/= 50% reduction in pain: 44/88 (50%) vs. 17/84 (20%) (p < 0.05); NNT = 3.4	End point LS mean (difference; 95% CI) SF-MPQ --Total pain score: 9.85 vs. 14.72 (-4.87; -7.41 to -2.34; p = 0.0002) --VAS: 38.68 vs. 56.30 (-17.62; -25.37 to -9.86; p = 0.0001) --PPI: 1.58 vs. 1.98 (-0.40; -0.71 to -0.09; p = 0.0127)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Dworkin (2003) U.S. (Fair)	End point LS mean (difference; 95% CI) Sleep Interference score: 1.93 vs. 3.51 (-1.58; -2.19 to -0.97; p = 0.0001) MOS Sleep Scale sleep problem index: 26.63 vs. 36.43 (-9.80; -14.49 to -5.11; p = 0.0001) SF-36 (only statistically significant results shown here) --Bodily pain: 55.14 vs. 46.14 (9.00; 3.33 to 14.66; p = 0.0021) --General health perception: 67.61 vs. 63.40 (4.21; 0.02 to 8.40; p = 0.0488) POMS depression-dejection scale: 6.70 vs. 8.47 (not reported; p = 0.051)	Minimally improved, much improved, or very much improved, % PGIC: 84% vs. 26% CGIC: Stated to closely parallel PGIC results Pregabalin 300 mg/d vs. 600 mg/d --Observed plasma pregabalin concentration, range, mcg/ml: 2.44 to 4.8 vs. 0.244 to 18.6 --Time post-dose, range, h: 1.00 to 6.67 vs. 0.75 to 17.8 --Predicted Cavg, mcg/ml: 6.64 vs. 8.36 --Predicted morning CminSS, mcg/ml: 4.69 vs. 5.27	Monitoring and reported by patient, patient's family, or investigator

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Dworkin (2003) U.S. (Fair)	Pregabalin 300/600 mg/d (N = 89) vs. Placebo (N = 84) Reported AEs, % of patients: 87% vs. 63% AEs considered to be related to study drug, % of AEs: 73% vs. 37% AEs reported by at least 10% of patients in the pregabalin group, n (%) --Dizziness: 25 (28.1%) vs. 10 (11.9%) --Somnolence: 22 (24.7%) vs. 6 (7.1%) --Peripheral edema: 17 (19.1%) vs. 2 (2.4%) --Amblyopia: 10 (11.2%) vs. 1 (1.2%) Other selected AEs: --Ataxia: 6 (6.7%) vs. 0 --Confusion: 6 (6.7%) vs. 0 --Speech disorder: 5 (5.6%) vs. 0	Pregabalin 300/600 mg/d vs. Placebo Total withdrawals: 31 (34.8%) vs. 10 (11.9%) Withdrawals due to AEs: 28 (31.5%) vs. 4 (4.8%) Number-needed-to-harm (NNH) based on all AEs: 4.3 (Calculated NNH 4; 95% CI: 3 to 9) Calculated NNH (95% CI) based on withdrawals due to AEs: 4 (3 to 6) Adverse events leading to withdrawal --Somnolence: 10 (11.2%) vs. Not reported --Peripheral edema: 2 vs. Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Dworkin (2003) U.S. (Fair)	End point LS mean pain scores were derived from patients' last 7 d of diary entries. Nonresponders to previous treatment with gabapentin > / = 1200 mg/d for postherpetic neuralgia were excluded. If response to gabapentin predicts response to pregabalin (an assumption that could not be evaluated in this trial), this exclusion may favor finding beneficial results with pregabalin. The results of this trial may not apply to patients who have failed gabapentin > / = 1200 mg/d. The difference between the baseline mean and LS mean pain scores suggests that treatment with pregabalin 300 mg/d and not 150 mg/d resulted in clinically relevant improvement in pain based on the criteria by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Rosenstock (2004) U.S. (Fair)	Multicenter double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Age at least 18 y; type 1 or 2 diabetes mellitus; symmetrical painful symptoms in distal extremities for 1 to 5 y prior to study; symptoms attributable to sensorimotor diabetic peripheral neuropathy; score of at least 40 mm on 100-mm visual analog scale (VAS) of Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomization visits; completion of at least 4 dail diaries during the week preceding randomization; minimum average daily pain score of 4 on 11-point numerical rating scale (NRS) during baseline period; normal chest X-ray within prior 2 y; baseline hemoglobin A1c </= 11%;	Pregabalin 300 mg/d vs. Placebo for 8 wk (fixed-dose regimen without titration)	1-wk run-in baseline; patients who completed at least 4 pain diary entries, had a mean daily pain score > / = 4 over the previous 7 d, and scored at least 40 mm on the SF-MPQ were randomized

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Rosenstock (2004) U.S. (Fair)	Stable antidiabetic medications; acetaminophen up to 4 g/d; aspirin up to 325 mg/d for myocardial infarction or transient ischemic attack prophylaxis; serotonin reuptake inhibitors at stable doses within 30 d prior to randomization or during study; drugs and supplements use for diabetic peripheral neuropathy; AEDs for pain; tricyclic antidepressants; centrally acting analgesics	Pain score on 11-point NRS (0 = No pain; 10 = Worst possible pain) recorded daily; SF-MPQ (quality of pain; 100-mm VAS pain score; present pain intensity (PPI) on 6-point scale (0 = None; 5 = Excruciating) at baseline, start of treatment, and end of wk 1, 3, 5, and 8; Daily sleep interference score (sleep score) on 11-point NRS (0 = Did not interfere with sleep; 10 = Completely interfered with sleep); Patient Global Impression of Change (PGIC; 7-point scale: 1 = Very much improved, 7 = Very much worse) at end of study; Clinical Global Impression of Change (CGIC; 7-point scale as for PGIC) at end of study; SF-36 Health Survey (SF-36) at baseline and end of study; Profile of Mood States (POMS) at baseline and end of study; adverse events; physical, neurologic, and laboratory evaluations	Pregabalin (N = 76) vs. Placebo (N = 70) Age, mean, y: 59.2 vs. 60.3 M / F: 55.3% / 44.7% vs. 57.1% / 42.9% Ethnicity, White / Black / Other: 84.2% / 7.9% / 7.9% vs. 91.4% / 4.3% / 4.3%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Rosenstock (2004) U.S. (Fair)	Duration of diabetes, mean, y: 9.3 vs. 9.4	225 screened / 165 / Enrolled not reported / 146 randomized	19 withdrawn / 1 lost to follow-up / 144 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Rosenstock (2004) U.S. (Fair)	Pregabalin vs. Placebo End point least squares (LS) mean [of daily scores in previous 7 d] (difference; 95% CI) --Mean pain score: 3.99 vs. 5.46 (-1.47; -2.19 to -0.75; p = 0.0001) Mean pain score, baseline / end point: 6.5 / 4.0 vs. 6.1 / 5.3 (p=0.0001 for end point score) --Calculated change, baseline to end point (calculated difference): -2.5 vs. -0.8 (-1.7) --Reported change, baseline to end of wk 1 (calculated difference): -2.2 vs. -0.4 (-1.8; p=0.0001) Responder rates (patients achieving at least 50% reduction in end point mean pain scores): 40% vs. 14.5% (p = 0.001) Calculated NNT: 4 (3 to 9)	Pregabalin vs. Placebo End point least squares (LS) mean (difference; 95% CI) --Mean sleep interference score: 2.78 vs. 4.32 (-1.54; -2.28 to -0.80; p = 0.0001) --SF-MPQ --Total score: 10.51 vs. 14.92 (-4.41; -7.32 to -1.49; p = 0.0033) --VAS score: 40.83 vs. 57.01 (-16.19; 24.52 to -7.86; p = 0.0002) --PPI score: 1.42 vs. 1.79 (-0.72 to -0.02; p = 0.0364) --SF-36, bodily pain: 53.83 vs. 46.95 (6.87; 0.70 to 13.04; p=0.0294) (p > 0.05 for other domains) --POMS, statistically significant differences in the following: --Tension/anxiety: 8.39 vs. 10.49 (-2.10; -3.95 to 0.25; p = 0.0264) --Total mood disturbance: 23.48 vs. 33.43 (-9.95; -18.53 to -1.37; p = 0.0234)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Rosenstock (2004) U.S. (Fair)	PGIC improvement, % of patients: 67% vs. 39% (p = 0.001) Calculated NNT: 4 (2 to 8) CGIC improvement, % of patients: Not reported (p = 0.004 in favor of pregabalin) Onset of first significant pain reduction: 1 wk		Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Rosenstock (2004) U.S. (Fair)	Pregabalin vs. Placebo AEs reported in > / = 10% of patients in the pregabalin group, n (%) --Dizziness: 27 (35.5%) vs. 8 (11.4%) --Somnolence: 15 (19.7%) vs. 2 (2.9%) --Infection: 11 (14.5%) vs. 4 (5.7%) --Peripheral edema: 8 (10.5%) vs. 1 (1.4%) Other selected AEs, n (%) --Constipation: 4 (5.3%) vs. 0 (0.0%) --Euphoria: 4 (5.3%) vs. 0 (0.0%) --Hyperglycemia: 3 (3.9%) vs. 0 (0.0%) AEs considered to be related to study medication, n (%): 47 (62%) vs. 20 (29%)	Pregabalin vs. Placebo Total withdrawals: 11 (14.5%) vs. 8 (11.4%) Withdrawals due to AEs: 8 (10.5%) vs. 2 (2.9%) AEs leading to withdrawal --Somnolence: 2 vs. Not reported --Dizziness: 2 vs. 1

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Rosenstock (2004) U.S. (Fair)	End point LS mean pain scores were derived from patients' last 7 d of diary entries. Nonresponders to previous treatment with gabapentin > / = 1200 mg/d for postherpetic neuralgia were excluded. If response to gabapentin predicts response to pregabalin, this exclusion may favor finding beneficial results with pregabalin. The results of this trial may not apply to patients who have failed gabapentin > / = 1200 mg/d. The change (-2.5) in mean pain scores from baseline to end point meets criteria for clinically relevant improvement in pain based on the criteria by Farrar (Farrar, 2001).

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Raskin (2004) U.S. (Fair)	Multicenter double-blind, placebo-controlled, parallel-group RCT Outpatient setting implied	Age 18 to 75 y; history of symmetric peripheral diabetic neuropathy in lower extremities for > 3 mo and < / = 10 y; diagnosis confirmed by clinical, electrophysiologic, or quantitative sensory testing; stable glycemic control (HgA1c < / = 11%) with insulin, oral hypoglycemics, or diet for > 3 mo before randomization; score of at least 40 mm (moderate or severe) on 100-mm pain visual analogue scale (VAS; 0 = No pain; 100 = Worst possible pain) at end of washout phase	Topiramate titrated from 25 mg/d to 400 mg/d (or maximum tolerated dose, MTD) over 8 wk; maintained at 400 mg/d (or MTD) from wk 8 to 12	Screening / washout period for up to 28 d

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Raskin (2004) U.S. (Fair)	Rescue analgesia with acetaminophen 500 mg or another short-acting medication only during first 6 wk but not within 24 h before any study visit; zaleplon and zolpidem at bedtime as needed up to 3 d / wk	Pain intensity score on 100-mm VAS at baseline and each study visit; current and worst pain on 5-point scale (0 = None; 4 = Extreme) at each study visit; SF-36 Health Survey (SF-36) at baseline and wk 8 and 12; sleep disruption on 11-point scale (0 = Does not interfere; 10=Completely interferes) at baseline and wk 12; global subject assessment scores on 5-point scale (1 = Poor, 5 = Excellent) at wk 12	Topiramate (N = 208) vs. Placebo (N = 109) Age, mean, y: 59.4 vs. 58.9 M / F, %: 47.6% / 52.4% vs. 53.2% / 46.8% Race, White / Black / Other, %: 88.0% / 11.1% / 1.0% vs. 86.2% / 11.9% / 1.8%

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Raskin (2004) U.S. (Fair)	Time since diabetes diagnosis, mean, y: 10.3 vs. 10.0 Time since neuropathy diagnosis, mean, y: 3.2 vs. 3.2 HgA1c, mean, %: 7.7 vs. 7.6	553 screened / 323 eligible and randomized	131 withdrew / 6 lost to follow-up / 317 and 320 analyzed for efficacy and safety, respectively

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Raskin (2004) U.S. (Fair)	Topiramate (N = 208) vs. Placebo (N = 109) Pain scores, baseline / end point, mm: 68.0 / 46.2 vs. 69.1 / 54.0 (p = 0.038) --Calculated change from baseline to end point, mm: -21.8 vs. -15.1 --Calculated difference in score changes, mm: -6.7 --First statistically significant difference: 8 wk (p = 0.028) Responder rates, n (%) --At least 50% decrease in pain VAS score: 74 (35.6%) vs. 23 (21.1%) (p = 0.005) Calculated NNT: 7 (4 to 23) --At least 30% decrease in pain VAS score: 103 (49.5%) vs. 37 (33.9%) (p = 0.004) Calculated NNT: 6 (4 to 23)	Worst pain intensity over previous week at end point, mean: ~2.1 / ~ 2.0 vs. 2.5 / 2.5 (p = 0.026) --First statistically significant difference: 8 wk (p = 0.026) Current pain intensity over previous week at end point, mean: ~1.7 vs. ~1.9 (p = 0.093) --First statistically significant difference: 12 wk

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Raskin (2004) U.S. (Fair)	Sleep disruption score, baseline / end point, mean: 6.5 / 3.9 vs. 6.2 / 4.6 (p = 0.020) SF-36, baseline / end point, mean --Physical component summary: 33.2 / 37.2 vs. 32.4 / 34.9 (p = 0.066) --Mental component summary: 49.0 / 46.9 vs. 49.6 / 49.9 (p = 0.023)	Global assessment of efficacy, n (%) --Good: 48 (24.5%) vs. 14 (13.3%) --Very good: 48 (24.5%) vs. 18 (17.1%) --Excellent: 16 (8.2%) vs. 5 (4.8%)	Monitoring

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Raskin (2004) U.S. (Fair)	Topiramate (N = 211) vs. Placebo (N = 109) Treatment-emergent AEs reported in > / = 10% of topiramate patients, n (%) --Diarrhea: 24 (11.4%) vs. 4 (3.7%) --Loss of appetite: 23 (10.9%) vs. 1 (0.9%) --Somnolence: 21 (10.0%) vs. 4 (3.7%) Other selected AEs: --Headache: 12 (5.7%) vs. 10 (9.2%) --Difficulty with concentration/attention: 11 (5.2%) vs. 1 (0.9%)	Topiramate (N = 214) vs. Placebo (N = 109) Total withdrawals: 102 (47.7%) vs. 29 (26.6%) Withdrawals due to AEs: 52 (24.3%) vs. 9 (8.3%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Raskin (2004) U.S. (Fair)	Forced titration to a relatively high dose (400 mg/d) was not tolerated (high rates of total withdrawals and withdrawals due to adverse events), limits applicability of results to clinical practice, and does not reflect usual clinical practice. The high dropout rate and use of last-observation-carried-forward method of imputation may have led to underestimation of the efficacy of topiramate relative to placebo.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	Pooled analysis of 3 multicenter, double-blind, placebo-controlled trials with identical eligibility criteria and overlapping treatment groups across trials Outpatient setting implied	Adults (18 to 75 y old); type 1 or 2 diabetes mellitus controlled by oral hypoglycemic agents (OHAs) and/or insulin or by diet alone; bilateral and simultaneous symptoms of painful peripheral polyneuropathy for at least 6 mo; antidiabetic regimens stable for at least 3 mo prior to study entry and during study; HbA1c < 11%; creatinine clearance at least 60 ml/min. Present pain intensity >/= 2 on a 5-point Categorical Pain Scale (CPS) (0 = None; 4 = Extreme) at randomization.	Topiramate 100, 200, and 400 mg/d vs. Placebo for 18 (1 RCT) or 22 weeks (2 RCTs) (titration phase: 6 to 10 wk depending on target dose then 12-wk maintenance period) Doses were titrated weekly from 25 mg/d in 25-mg then 50-mg increments. Treatment groups by study (doses in mg/d): NP-001: 100, 200, 400, placebo NP-002: 200, 400, placebo NP-003: 100, 200, placebo	28-day baseline run-in phase on stable therapeutic doses of oral hypglycemics and/or insulin At least 7-day washout of prior opioids and antineuropathic medications before randomization. Patients had to have a CPS score > / = 2 at randomization for present pain intensity.

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	Periodic doses of short-acting, immediate-release breakthrough pain analgesics	CPS (for present pain intensity and worst pain over past week); 100-mm Visual Analog Scale (VAS) (0 = No pain; 100 = The worst pain I can imagine); Sleep Disruption Scale (0 = Does not interfere; 10 = Completely interferes) at baseline/randomization, every 2 wk during titration, and every 1 mo during maintenance. Medical Outcomes Study Short-form 36 (SF-36) at baseline/randomization, after titration, and monthly during maintenance.	Topiramate 100 (N = 253), 200 (N = 372), 400 mg/d (N = 260) vs. Placebo (N = 384) (NB: N = Number of patients in safety, population; i.e., patients who received at least one dose and provided at least one safety measurement; the number of patients randomized was not reported) Age, mean, y: 58, 58, 58 vs. 59 Male/Female, %: 55/45, 58/42, 57/43 vs. 60/40 Ethnicity: Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	Type 2 diabetes, % of patients: 90, 89, 84 vs. 86 Time since diabetes diagnosis, mean, y: 12, 11, 13 vs. 13 Time since diabetic neuropathy diagnosis, mean, y: 4.0, 4.3, 4.1 vs. 4.4 HbA1c, mean, %: 8.0, 7.9, 8.1 vs. 7.9 CPS score (present pain), % of patients with moderate/severe/extreme pain: 68/28/3, 70/25/3, 68/28/3 vs. 67/28/4 CPS score (present pain), mean: 2.3, 2.3, 2.3 vs. 2.3 VAS score, mean, mm: 60, 58, 57 vs. 57 Sleep Disruption Scale score, mean: 5.5, 6.0, 5.8 vs. 5.7 Weight, mean, kg: 96 Body Mass Index (BMI), mean: 33 BMI > 30 (Obese), % of patients: 59 Antidiabetic therapy, % of patients --Insulin: 26, 27, 27 vs. 27 --OHA: 49, 50, 52 vs. 48 --Insulin + OHAs: 24, 18, 20 vs. 21	Not reported.	620 withdrawn / 30 Lost to follow-up / 1259 analyzed for efficacy, 1269 for safety

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	According to the authors of the paper, numerical differences in VAS scores between topiramate and placebo were NSD in NP-001 and NP-002. VAS Scores (Primary efficacy measure) NP-001: Topiramate 100, 200, 400 vs. Placebo --N: 128, 130, 130 vs. 136 --Final visit, mean: 36.1, 38.3, 39.7 vs. 43.1 --95% CI (topiramate groups only): -12.1 to -0.18, -10.4 to 1.45, -7.46 to 4.40 --p-value vs. placebo: 0.043, 0.138, 0.612 --Calculated change from baseline: -24.0, -17.5, -16.6 vs. -14.6 --Calculated difference in score change vs. placebo: -9.4, -2.9, -2.0	VAS Scores (cont'd) NP-002: Topiramate 200, 400 vs. Placebo --N: 116, 129 vs. 119 --Final visit, mean: 37.8, 39.3 vs. 41.6 --95% CI: -10.7 to 2.76, -8.88 to 4.20 --p-value vs. placebo: 0.247, 0.482 --Calculated change from baseline: -20.2, -18.5 vs. -15.9 --Calculated difference: -4.3, -2.6

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	VAS Scores (cont'd) NP-003: Topiramate 100, 200 vs. Placebo --N: 122, 123 vs. 126 --Final visit, mean: 44.7, 44.7 vs. 37.8 --95% CI: -1.88 to 11.63, -1.03 to 12.46 --p-value vs. placebo: 0.156, 0.096 --Calculated change from baseline: -15.7, -14.6 --Calculated difference: 1.8, 2.9	CPS: NSD (data not reported) Sleep Disruption Scales: NSD except scores favored placebo over topiramate 100 (p = 0.02) in NP-003. SF-36: Data not shown Use of rescue medications: Not reported by treatment group All Topiramate (N = 878) vs. Placebo (N = 381), n (%) Withdrawals due to inadequate pain control: 123 (14%) vs. 82 (22%)	Not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	AEs for which absolute difference was > / = 5% between any topiramate group vs. placebo: fatigue, nausea, paresthesia, somnolence, appetite decrease, weight loss, taste perversion, memory difficulty, confusion All Topiramate (N = 885) vs. Placebo (N = 384), % of patients Deaths: None reported Serious AEs: 7% vs. 8% Most common adverse events (frequency >/=10% in any treatment group) --Fatigue: 16% vs. 11% --Nausea: 12% vs. 7% --Paresthesia: 12% vs. 5% --Somnolence: 10% vs. 4% --Appetite decrease: 10% vs. 3% Other selected AEs: --Weight loss: 7% vs. 1% --Hypoglycemia/hypoglycemic reactions: 3% vs. 2% --Clinically significant weight loss (> / = 5% of baseline body weight): 19% to 38% vs. 7% --Clinically significant reduction in HbA1c (> / = 5%): 55% to 62% vs. 29% (NB: No correlation between HbA1c reduction and weight loss was observed.)	All Topiramate (N = 878) vs. Placebo (N = 381) Total withdrawals: 464 (53%) vs. 156 (41%) Withdrawals due to AEs: 213 (24%) vs. 32 (8%) Most common (frequency > / = 3%) treatment-limiting AEs, % of patients --Nausea: 4 vs. 1 --Fatigue: 4 vs. 0 --Dizziness: 3 vs. 2 --Concentration / Attention difficulty: 3 vs. 1 --Somnolence: 3 vs. 1 --Appetite decrease: 3 vs. 0 Other notable treatment-limiting AE, n (%) of patients --Kidney stones: 3 (0.3%) vs. 1 (0.2%)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Thienel (2004) Australia, Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Repubic of South Africa, Spain, Sweden, U.K., U.S. The Topiramate Diabetic Neuropathic Pain Study (Fair) (3 RCTs)	Post hoc analyses of study completers followed the same pattern as the modified intent-to-treat population. The authors explained that these topiramate studies may not have been sensitive to detect statistically significant differences between topiramate and placebo despite statistically-determined adequate sample sizes because use of the CPS for determining patient eligibility versus the VAS for measuring treatment effects led to inclusion of patients with baseline VAS scores < 40 mm (corresponding to less than moderate pain) in 18% of topiramate groups and 20% of placebo group. Post hoc analyses showed a correlation coefficient for the two baseline scores (CPS vs. VAS) of 0.44, suggesting potential for disagreement. The ability of the study to detect treatment effects may also have been affected by the short (7-d) washout period of prior medications and protocol-allowed use of rescue medications (about 33% of patients used simple analgesics; almost 20% used opioids) and the use of nonspecific questions for rating pain with the VAS (i.e., 'How would you rate your pain'). Post

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(2) Study design (optional) Setting	(3) Eligibility criteria	(4) Interventions (drug, dose, duration)	(5) Run-in/Washout period
Otto (2004) Denmark (Fair)	Single-center double-blind crossover RCT Outpatient setting implied	Polyneuropathy > / = 6 mo confirmed by electrophysiologic tests; age > 20 y; median pain rating of at least 4 on 11-point numeric rating scale (NRS) (0 = No pain; 10 = Worst possible pain) for total pain during 1-wk off medications	Valproic acid increased to 1500 mg/d in first 5 d vs. Placebo for 4 wk each (median valproic acid serum concentration, 462 µmol)	1-wk washout of prior medications; 1-wk baseline run-in off prior medications; washout before crossover not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(6) Allowed other medications/interventions	(7) Method of outcome assessment and timing of assessment	(8) Age Gender Ethnicity
Otto (2004) Denmark (Fair)	Acetaminophen	11-point NRS of total pain and specific pain symptoms (pain paroxysms, touch evoked, pressure evoked, constant deep aching, and constant burning pain during daily activities) at baseline and daily; daily number of acetaminophen tablets and 6-point verbal rating scale ("Complete" to "Worse") at end of each treatment period; cold allodynia to acetone, allodynia to stroking with cotton wool, pressure pain thresholds, rating of pain by repetitive pinprick stimulation at end of baseline and treatment periods; cold and warm detection thresholds at baseline; valproic acid serum concentrations and liver enzymes at end of treatment period	Age, median (range), y: 60 (34 to 81) Male / Female, n: 19 (61.3%) / 12 (38.7%) Ethnicity not reported

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(9) Other population characteristics (diagnosis, etc)	(10) Number screened/ eligible/enrolled/randomized	(11) Number withdrawn/ lost to follow up/analyzed
Otto (2004) Denmark (Fair)	Diabetic polyneuropathy, n: 15 Pain duration, median (range), mo: 40 (9 to 120) Previously treated for neuropathic pain, n: 24 --Failed to respond to 1 relevant agents: 12 --Did not respond to 2 or more agents: 0 --Previously treated with valproic acid: 0	95 screened / 59 eligible / 37 enrolled / 37 randomized	3 withdrawn / 0 lost to follow-up / 31 analyzed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results (if continued)
Otto (2004) Denmark (Fair)	Valproic acid vs. Placebo Total pain rating, median daily pain score (primary efficacy measure) --Baseline: 6 --Wk 4, median: 5 vs. 6 (NSD) --Calculated change (%) in median scores from baseline: -1 (16.7%) vs. 0 (0.0%) Total pain rating in subgroups with --Stimulus-evoked pain (n=24): NSD --Spntaneous pain (n=31): NSD --Clinical signs of deafferentation (n=9): NSD --Clinical signs of increased small fiber input (n=4): NSD --Diabetes (n=15): NSD --Without diabetes (n=16): NSD	Deep aching pain, burning pain, pressure-evoked pain, touch-evoked pain, lancinating pain: NSD Acetaminophen, median, tablets/wk --Baseline: 8 --Wk 4: 10 vs. 10 (NSD) --Calculated change from baseline: 2 vs. 2

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(12) Results (if cont.)	(12) Results (if cont.)	(13) Method of adverse effects assessment?
Otto (2004) Denmark (Fair)	Complete, good, or moderate pain relief, n: 3 vs. 8 (no p-value reported) No relation between valproic acid serum concentrations and degree of pain relief (r_s = -0.28; NSD) Valproic acid serum concentrations in responders vs. nonresponders, median, mcmol/l: 519.8 vs. 453.5 (NSD)	Adherence by tablet counts, mean: 100% Carryover effects and period effects for primary effect variable or individual rating of pain symptoms: NSD (not present)	AEs not assessed

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Otto (2004) Denmark (Fair)	AEs not assessed	Valproic acid (N = 19) vs. Placebo (N = 18) Total withdrawals: 2 (10.5%) vs. 1 (5.6%) Withdrawals due to AEs: 2 (10.5%) vs. 1 (5.6%) AEs leading to withdrawal --Valproic acid: Skin rash and flu-like symptoms (n = 1), headache and nausea (n = 1) --Placebo: Headache (n = 1)

Evidence Table 6. Placebo-Controlled Trials: Neuropathic Pain

(1) Author, year Country Trial name (Quality score)	(16) Comments
Otto (2004) Denmark (Fair)	Authors stated that their study probably had an adequate sample size based on their previous studies that showed clinical benefits with similar sample sizes. The levels of significance were 0.05 for the primary efficacy measure and, after applying a Bonferroni correction for multiple tests, 0.0055 for secondary outcome measures. The magnitude of change in pain scores did not meet the criteria for clinically relevant improvement in pain by Farrar (Farrar 2001).

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Goodwin, 2003(2) (Fair)	2 large integrated health plans in California and Washington	Retrospective cohort; mean follow-up of 2.9 y per individual (total 60,060 person-years for cohort)	Plan members aged >/= 14 y; record of outpatient treatment for bipolar I or II disorder (DSM-IV); enrolled in Kaiser Permanente (KP) or Group Health Cooperative (GHC) at any time from Jan. 1, 1994 to Dec. 31, 2001; at least 1 prescription for lithium, divalproex, or carbamazepine filled at a KP or GHC pharmacy	Schizophrenia; schizoaffective disorder recorded before first diagnosis of bipolar disorder; dementia or cognitive disorders occurring before first diagnosis of bipolar disorder. Patients with schizoaffective disorder occurring after the first diagnosis of bipolar disorder were included but censored on the date of the first schizoaffective diagnosis.
Rzany, 1999(80) (Fair)	Inpatient hospital setting; rash developed in outpatient setting Participating countries: France, Germany, Italy, Portugal	Multinational, multicenter matched case-control study with comparison of AEDs Study period: Started February 1989 (in Italy) to March 1992 (in Germany); ended January 1993 (in France) to July 1995 (other countries)	Developed skin reaction when not hospital inpatients; reactions validated and classified as Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) by an expert committee. Controls were patients admitted to the same hospital for an acute illness	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
Goodwin, 2003(2) (Fair)	Treatment exposure (% of all person-years of follow-up, based on computerized pharmacy records): Lithium (27%) Divalproex (18%) Carbamazepine (4%) Combination (4%) None of above (47%)	Number screened not reported / 20,638 eligible / Number "enrolled" not applicable	Numbers withdrawn and lost to follow-up not reported / 20,638 analyzed	KP (n = 16,248) vs. GHC (n = 4390) Age, mean (SD), y: 38.7 (14.6) vs. 37.9 (14.7) Female, n (%): 10,429 (64) vs. 2945 (67) Ethnicity not reported
Rzany, 1999(80) (Fair)	Phenobarbital Phenytoin Carbamazepine Valproate Lamotrigine	Numbers screened and eligible not reported / 352 cases and 1579 controls enrolled	Numbers withdrawn and lost to follow-up not reported / 352 cases and 1579 controls analyzed	Characteristics of 73 patients on AEDs Age, n (%) --0 to 24 y: 16 (22%) --25 to 49 y: 29 (39%) --50 y or older: 28 (39%) Female: 41 (56%) Characteristics of all cases vs. controls Ethnicity, n --France: 117 vs. 498 --Germany: 116 vs. 659 --Italy: 90 vs. 369 --Portugal: 29 vs. 53

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
Goodwin, 2003(2) (Fair)	KP vs. GHC First mood stabilizer, n (%) --Lithium: 7121 (44) vs. 2050 (47) --Divalproex: 7595 (47) vs. 1676 (38) --Carbamazepine: 909 (6) vs. 474 (11) --Combination: 623 (4) vs. 190 (4) Ever exposed to --Lithium: 8935 (55) vs. 2609 (59) --Divalproex: 10,171 (63) vs. 2476 (56) --Carbamazepine: 2265 (14) vs. 1020 (23) --Antidepressants: 12,222 (75) vs. 3337 (76) --Typical antipsychotics: 3420 (21) vs. 1061 (24) --Atypical antipsychotics: 5218 (32) vs. 1110 (25)	Suicide mortality: mortality files from state departments of health using ICD-9 codes Suicide attempts: computerized records of all emergency department (ED) visits or inpatient discharges using ICD-9 codes; also specific suicide terms on ED encounter forms for KP only	Numbers (event rates per 1000 person-years during periods of exposure, both sites (p-values for treatment vs. lithium) Suicide attempts resulting in hospitalization --Lithium: 67 (4.2) --Divalproex: 112 (10.5) (p < 0.001) --Carbamazepine: 39 (15.5) (p < 0.001) --Combination: 30 (12.4) (p < 0.001) --None: 135 (4.8) (p = 0.44) Suicide deaths --Lithium: 9 (0.7) --Divalproex: 14 (1.7) (p = 0.04) --Carbamazepine: 2 (1.0) (p = 0.86) --Combination: 3 (1.5) (p = 0.40) --None: 25 (1.2) (p = 0.20)
Rzany, 1999(80) (Fair)	AED Cases (N = 73/352. 20.7%) vs. Controls (N = 28/1579, 1.8%) Previous adverse drug reaction to AEDs: 6 (8%) vs. 1 (4%) --Previous adverse drug reaction to phenobarbital: 2/6 (33.3%) cases --Previous adverse drug reaction to other AED not taken at time	Expert committee; diagnostic criteria not reported	All cases (N = 352) Stevens-Johnson Syndrome (SJS): 136 cases Toxic Epidermal Necrolysis (TEN): 216 cases Definite diagnosis: 266/352 (76%) Probable diagnosis: 86/352 (24%) AED Cases (N = 73) --SJS: 30 (41%) --TEN: 43 (59%) Deaths among AED cases: 8/73 (11%)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
Goodwin, 2003(2) (Fair)	Divalproex vs. Lithium Risk of Suicide Attempts and Deaths, Hazard Ratio (95% CI) --Suicide attempts ascertained in ED: 1.8 (1.4 to 2.2) (p < 0.001) --Suicide attempts resulting in hospitalization: 1.7 (1.2 to 2.3) (p = 0.002) --Suicide deaths: 2.7 (1.1 to 6.3) (p = 0.03)	Carbamazepine vs. Lithium Risk of Suicide Attempts and Deaths, Hazard Ratio (95% CI) --Suicide attempts ascertained in ED: 1.4 (1.0 to 2.0) (p = 0.09) --Suicide attempts resulting in hospitalization: 2.9 (1.9 to 4.4) (p < 0.001) --Suicide deaths: 1.5 (0.3 to 7.0) (p = 0.6)	Not reported
Rzany, 1999(80) (Fair)	Univariate analysis of individual AEDs identified short-term use for all drugs and long-term use of phenobarbital and valproate as risk factors for SJS / TEN. Multivariate risk estimates for use longer than 8 wk were not significant. Univariate / Multivariate relative risk of SJS TEN for </= 8 wk of use (95% CI) --Phenobarbital: 57 (16 to 360) / 59 (12 to 302) --Phenytoin: 91 (26 to ∞) / Not calculated (NC) --Carbamazepine: 120 (34 to ∞) / NC --Valproate: 24 (5.9 to ∞) / NC --Lamotrigine: 25 (5.6 to ∞) / NC	Univariate / Multivariate relative risk of SJS / TEN for > 8 wk of use (95% CI) --Phenobarbital: 6.2 (2.4 to 17.0) / 2.1 (0.5 to 9.3) --Phenytoin: 1.2 (0 to 5.4) / NC --Carbamazepine: 0.4 (0.02 to 2.1) / NC --Valproate: 7.0 (2.4 to 21.0) / 2.0 (0.3 to 15.0) --Lamotrigine: NC Confounders for association of long-term use of phenobarbital: region, short-term use of other AEDs, recent radiotherapy, intake of glucocorticoids, sulphonamides, anti-infective drugs, all other suspected drugs, and all other drugs. Confounders for the association with valproate: mostly short-term use of other AEDs	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Comments
Goodwin, 2003(2) (Fair)	Adjustments for some confounders were done but not for prior suicide attempts or disease severity. Accuracy and sensitivity of diagnosis and outcome ascertainment methods are uncertain. Actual treatment exposure (adherence) is uncertain. Estimates of drug exposures were based on assumptions. These limitations should apply equally to the main treatment groups and not produce systematic bias; however, potential differences in case mix cannot be adjusted for. No sensitivity analyses for residual confounding were performed.
Rzany, 1999(80) (Fair)	Lamotrigine was not available in every country for the entire study period. It became available in Germany in 1993, and in Italy and Portugal in 1994. It was not available in France at the time of the study. Methods used to identify and diagnose cases were not clear.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Tohen, 1995(78) (Poor)	Inpatient psychiatric hospital	Retrospective cohort; May 1989 to May 1993	Baseline white blood cell count (WBC) of > 4,000/mm3, hematocrit > 30%, and platelet count > 100,000/mm3 before starting an index agent.	Blood dyscrasia associated with a probably causal medical illness or other agents

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
Tohen, 1995(78) (Poor)	Carbamazepine Valproate Imipramine Desipramine	Not reported. 11,720 admitted, 1251 received valproate, 977 received carbamazepine; 65 both agents; 317 both agents at different times	Numbers withdrawn and lost to follow-up not reported / 29 analyzed	Reported for patients with leukopenia (n = 25) Age, range, y: 13 to 63 Male / Female: 6 / 19 Ethnicity not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
Tohen, 1995(78) (Poor)	Major affective disorder: 20/25 (80.0%)	Blood dyscrasias defined as WBC 3000 to 4000/mm3 (moderate leukopenia) or < 3000/mm3 (severe leukopenia); platelet count < 100,000/mm3; hematocrit < 30%. Cases identified from laboratory records. Blood cell counts were required at least weekly for patient	Carbamazepine vs. Valproate All Leukopenia: 21/977 (2.1%) vs. 5/1251 (0.4%) Odds ratio [OR] 5.4 (95% CI: 2.0 to 2.3); p = 0.0001) Moderate leukopenia: OR 6.9 (1.9 to 29.9; p = 0.0003) Severe leukopenia: NSD Combination carbamazepine + valproate vs. carbamazepine All leukopenia: 1/65 (1.5%) (NSD) Thrombocytopenia: 1 vs. 0 Anemia: 0 vs. 0

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
Tohen, 1995(78) (Poor)	Carbamazepine vs. Tricyclic antidepressants All leukopenia: 21/977 (2.1%) vs. 3/1,031 (0.3%); Risk ratio 7.4 (95% CI: 2.2 to 24.7; p = 0.0001) Valproate vs. Tricyclic antidepressants All leukopenia: 0.4% vs. 0.3% (NSD) Latency of onset of leukopenia on carbamazepine, mean / median (range), d: 29 / 16 (3 to 47) Recovery time to WBC >/= 4000/mm3, mean (range), d: 6.5 (2 to 14)		Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Comments
Tohen, 1995(78) (Poor)	Ascertainment of outcome may be biased with respect to risk factor. Laboratory monitoring was required to be at least weekly for AEDs but a similar requirement did not exist for the antidepressants. No statistical analysis of potential confounders. Drug exposure assumed from pharmacy records.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Ibáñez, 2005 {ID 2063} (Fair)	17 hospital hematology units in metropolitan area of Barcelona, Spain (population of 3.3 to 4.1 million inhabitants)	Population-based case control study with blinded review by hematologist (or blinded international hematologic committee from 1980 to 1986), part of a 22-year systematic, multicenter, collaborative surveillance of agranulocytosis and aplastic anemia (International Agranulocytosis and Aplastic Anemia Study, IAAAS)	Granulocyte count < 500 mm3 or total white blood cell count < 3000/microl in 2 consecutive counts; hemoglobin > 10 g/dl; platelet count > 100 x 103/microl; bone marrow aspirate or biopsy generally required but not mandatory if other diagnostic criteria were met and if neutrophil count was within reference range within 30 d.	Primary exclusion criteria (applied to patients receiving chemotherapy for cancer, radiation therapy, or immunosuppressive drugs): hypersplenism, lupus erythematosus, leukemia, lymphoma, megaloblastic anemia, AIDs; asymptomatic cases discovered coincidentally by complete blood cell counts performed for other reasons; age < 2 y Secondary exclusion criteria (applied to patients who could not be interviewed during the first 28 d of hospital stay, to avoid memory bias): psychiatric conditions, blindness, deafness, living in nursing home (because these patients rarely know the names of their drugs) In-hospital cases were excluded from case-control analysis because of difficulty establishing acceptable criteria for selection of adequate controls without incurring selection bias

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
Ibáñez, 2005 {ID 2063} (Fair)	Carbamazepine Phenytoin Data for other agents are not shown here	454 screened (potential) / 396 eligible / 177 cases (admitted to hospital from community) and 586 controls enrolled	0 withdrawn / 0 lost to follow-up / 177 cases and 586 controls analyzed in total Cases / Controls in conditional primary analysis (in unconditional analysis) --Carbamazepine: 5 / 1 (10 / 2) --Phenytoin: 2 / 1 (5 / 6)	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
Ibáñez, 2005 {ID 2063} (Fair)	Not reported	Hematology laboratory results; see Eligibility Criteria for definition of agranulocytosis	Drug exposures within the week before the index day of agranulocytosis, OR (95% CI) Conditional analysis --Carbamazepine: 10.96 (1.17 to 102.64) --Phenytoin: Not done Unconditional analysis --Carbamazepine: 115.24 (23.13 to 574.28) --Phenytoin: 11.62 (3.11 to 43.48)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
Ibáñez, 2005 {ID 2063} (Fair)	Risk and incidence of agranulocytosis for exposure to carbamazepine within the week before the index day --Cases exposed in week before index day, n (%): 5 (2.82%) --Attributable risk, % (95% CI): 2.57 (0.03 to 5.04) --Attributable incidence, no./1 million per year (95% CI): 0.09 (<0.01 to 0.17)		Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Comments
Ibáñez, 2005 {ID 2063} (Fair)	The study population was covered by a universal free health care service. Two analyses were performed, one adjusting for potential confounders and the other without adjustment. Three approaches were used to avoid exposure misclassification, and three approaches were used to minimize information bias due to differential recall between cases and controls.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Vestergaard (2004) {ID 2066} (Good)	Inpatient (1977 onward) and outpatient (1995 onward)	Case-control, large computerized databases	Cases: All subjects who had sustained a fracture from January 1st, 2000 to December 31st, 2000 as identified in the National Hospital Discharge Register of Denmark. Controls: Gender- and age-matched controls who were alive and at risk for fracture diagnosis at the time the corresponding case was diagnosed, randomly selected from the Civil Registration System records of vital status (3 controls for each case)	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
Vestergaard (2004) {ID 2066} (Good)	Carbamazepine Lamotrigine Oxcarbazepine Phenytoin Tiagabine Topiramate Valproate Key AEDs without data: Gabapentin (not used by participants), Levetiracetam Other AEDs: Fosphenytoin, ethosuximide, vigabatrin clonazepam, clobazam, phenobarbital, primidone	Numbers screened and eligible not reported / 124,655 cases and 373,962 controls enrolled	0 withdrawn / 0 lost to follow-up / 124,655 cases and 373,962 controls analyzed	Cases vs. Controls Age, mean?, y: 43.44 vs. 43.44 M / F, n (%): 60,107 (48.2%) / 64,548 (51.8%) vs. 180,321 (48.2%) / 193,641 (51.8%) Ethnicity not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
Vestergaard (2004) {ID 2066} (Good)	Cases tended to have a higher frequency of comorbidity, higher number of comorbid conditions than controls, were more often retired, more likely to be divorced or unmarried, had a lower income than controls, higher frequency of prior fractures (33.1% vs. 15.0%), and more often had used antiosteoporosis drugs (including any antiresorptive drug, bisphosphonates, selective estrogen-receptor modulators (SERMs, e.g., raloxifene), and ever use of any corticosteroid), except for lower use of hormone replacement therapy (p < 0.01 for each analysis; except for prior fractures, specific data not shown here)	ICD10 codes recorded by physician upon patient discharge from hospitals and entered into the National Hospital Discharge Register of Denmark	Any fracture in patients who used AEDs, crude odds ratio (OR) (95% CI) --Carbamazepine: 1.88 (1.78 to 2.00) --Phenytoin: 2.47 (2.12 to 2.88) --Lamotrigine: 2.14 (1.93 to 2.37) --Oxcarbazepine: 2.09 (1.93 to 2.26) --Tiagabine: 2.21 (1.33 to 3.65) --Topiramate: 3.00 (2.36 to 3.82) --Valproate: 1.93 (1.79 to 0.07)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
Vestergaard (2004) {ID 2066} (Good)	Any fracture in patients who used AEDs, Adjusted OR (95% CI) --Carbamazepine: 1.18 (1.10 to 1.26) --Phenytoin: 1.20 (1.00 to 1.43) --Lamotrigine: 1.04 (0.91 to 1.19) --Oxcarbazepine: 1.14 (1.03 to 1.26) --Tiagabine: 0.75 (0.40 to 1.41) --Topiramate: 1.39 (0.99 to 1.96) --Valproate: 1.15 (1.05 to 1.26) Fracture risk associated with use of AEDs at various skeletal sites (hip, Colles', and spine), Adjusted OR (95% CI) Significant (OR does not include 1) for the following: --Carbamazepine - Hip: 1.33 (1.13 to 1.58) --Lamotrigine - Spine: 2.47 (1.13 to 5.39) --Oxcarbazepine - Hip: 1.48 (1.11 to 1.97) Not significant for phenytoin, tiagabine, topiramate, valproate, as well as other skeletal sites for drugs above (data not shown here)	Dose-response relation for AEDs, with any fracture as end point, < 50 DDDs / 50 to 400 DDDs / > 400 DDDs, unadjusted OR (95% CI; Test for trend p-value) Significant for the following: --Carbamazepine: 1.68 (1.53 to 1.84) / 1.81 (1.61 to 2.05) / 2.22 (2.01 to 2.44); p < 0.01 --Oxcarbazepine: 1.81 (1.53 to 2.14) / 2.14 (1.86 to 2.45) / 2.20 (1.95 to 2.47); p = 0.03 --Valproate: 1.94 (1.70 to 2.22) / 1.75 (1.55 to 1.96) / 2.17 (1.90 to 2.47); p = 0.02 Not significant (p > 0.05) for phenytoin, lamotrigine, tiagabine, topiramate (data not shown here) DDD = Sum of all ingested defined daily dosages of drug in question	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Comments
Vestergaard (2004) {ID 2066} (Good)	According to the authors, the National Hospital Discharge Register of Denmark has an almost 100% completeness of registrations and a precision of 97% for fractures. Drug purchases at pharmacies were registered in the National Pharmacological Database. Additional data were available from tax authorities and the National Bureau of Statistics on income, social status, and working status in 1999, and the National Health Organisation Register (contacts with general practitioners and practicing specialists) for the period 1996 to 2000.

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Lin (2005) {ID 2065} (Fair)	Inpatient (university hospital) / Outpatient?? Setting at the time of onset of AE is unclear	Case-control, hospital admission database	Cases: Subjects suspected of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) using hospita discharge ICD-9-CM codes, verified using standardized criteria by dermatologist blinded to drug exposure; *index day* was defined as date of skin reaction; *exposed* was defined as subject took drug that had half-life less than 24 h (e.g., phenytoin) within 1 wk before index day, or within 2 wk for drugs with elimination half-lives between 24 and 72 h (e.g., carbamazepine), or 3 wk for drugs with elimination half-lives longer than 72 h (e.g., phenobarbital) Controls: Subjects with acute illness not suspected of being drug-related, randomly selected from hospital admission database and matched to cases by age (+/- 2 y), sex, and calendar month of admission; *index day* was defined as the date that their illness started	Control subjects with drug-related E-codes (e.g., accidental poisoning, therapeutic use, suicide attempt, assault, undetermined)

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
Lin (2005) {ID 2065} (Fair)	Carbamazepine Phenytoin Other suspect drugs mentioned: allopurinol, chlormezanone, oxicam nonsteroidal antiinflammatory drugs, phenobarbital, sulfa drugs, antibiotics	Numbers screened and eligible not reported / 35 cases and 102 controls enrolled	Numbers withdrawn and lost to follow-up not reported / 35 cases and 102 controls analyzed	Cases (SJS / TEN) vs. Controls N: 35 (30 / 5) vs. 105 Age, mean, y: Overall age not reported (53.4 / 36.0) vs. Not reported Males, n: 19 (16 / 3) vs. Not reported Females, n: 16 (14 / 2) vs. Not reported Ethnicity: Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
Lin (2005) {ID 2065} (Fair)	Average onset of SJS or TEN after initial drug administration: 15 d (only 1 case after 8 wk) Naranjo scores (likelihood that AE was associated with drug in cases) --Definite: 1 (3%) --Probable: 32 (91%) --Possible: 1 (3%) --No: 1 (3%) Exposed to at least one drug: 34/35 (97%) vs. 14/105 (13%) Drug exposed to within exposure interval preceding the index day --Carbamazepine: 11 (31%, 3 coadministered with other suspect drugs) vs. 1 (1%) --Phenytoin: 7 (20%, 2 coadministered with other suspect drugs) vs. 3 (3%)	ICD9-CM codes recorded in computerized hospital discharge file; method of ascertaining patients who died was unclear (medical records?) Potential confounders collected in data: radiotherapy, collagen vascular disease, infections with HIV, recent herpes infection, autoimmune disease	Cases (N = 35: 30 SJS / 5 TEN) vs. Controls (N = 105) No. of cases (%) vs. controls (%) --Carbamazepine: 11 (31%) vs. 1 (1%) --Phenytoin: 7 (20%) vs. 3 (3%) Deaths: 10% SJS / 40% TEN vs. Not reported --Not reported by drug

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
Lin (2005) {ID 2065} (Fair)	Cases (N = 35) vs. Controls (N = 105) Crude relative risk (95% CI) --Carbamazepine: 33.0 (4.3 to 255.6) --Phenytoin: 9.6 (2.0 to 46.6)	Cases (N = 35) vs. Controls (N = 105) Multivariate relative risk (95% CI) --Carbamazepine: 301.8 (13.6 to 6700.2) --Phenytoin: 290.8 (9.2 to 9239.3) Other drugs / categories not shown here.	Not reported

Evidence Table 7. Adverse Events, Observational Studies

Author, year	Comments
Lin (2005) {ID 2065} (Fair)	Using the dermatologist's review, the positive predictive value of discharge diagnosis for SJS / TEN was only 60% (35/58). Diagnosis relied on subjective clinical judgment; therefore, ascertainment of cases may be incomplete due to misdiagnosis or misses. Confidence intervals were wide due to the small number of cases.

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

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Yes	Yes	Yes	No	Yes	Yes
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Yes	Yes	Yes	No	Yes	Yes
Vasudev, 2000(29) India	Yes	Method not reported	Yes	Yes	Yes	No
Bahk (2005) {ID 2025} South Korea	Method not reported	Method not reported	Yes	Yes	No	No

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

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Yes	Yes-attrition, crossovers. No-adherence, contamination.	No	No	Yes	Fair
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Yes	Yes-attrition, crossovers. No-adherence, contamination.	No	No	Yes	Fair
Vasudev, 2000(29) India	No	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	No	Poor
Bahk (2005) {ID 2025} South Korea	No	Yes-attrition, adherence No-crossovers, contamination	No (unable to evaluate for differential)	Yes (modified)	Yes	Poor

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

	External Validity				
Author, year Country	**(1) Number screened/ eligible/ enrolled /randomized**	**(2) Exclusion criteria**	**(3) Run-in/ Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	--/38/38/38	Not reported	Washout (taper old/titrate new drug)	No	Yes
Obrocea, 2002(19) U.S. Extension of Frye, 2000	--/--/45/(?) 45	Not reported	Washout (taper old/titrate new drug)	No	Yes
Vasudev, 2000(29) India	--/--/30/30	Seizure disorder, cerebrovascular disease, neurologic disorder, overt hematologic, cardiac, hepatic, renal, or thyroid disorder; mental retardation; any drug taken for present mania episode; drug/alcohol dependence or abuse within past 12 mo; need for electroconvulsive therapy or neuroleptic at any time during study	Washout (medication-free for at least a period of 6 months)	Unable to determine	Yes
Bahk (2005) {ID 2025} South Korea	81/--/74/74	Organic brain diseases; history of substance abuse or dependence within 1 mo; axis I DSM-IV diagnoses; use of depot antipsychotics within one cycle before study entry	Washout	Unable to determine	Yes

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

Author, year Country	(6) Funding	(7) Relevance?
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Ted and Vada Stanley Foundation	Possible. Applicable to hopitalized patients with refractory bipolar disorder with rapid cycling. The dosage titration was probably faster than what would be used in an outpatient setting. Small sample size limits generalizability.
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Theodore and Vada Stanley Foundation	Results applicable to hospitalized patients with refractory bipolar disorder with rapid cycling. The dosage titration was probably faster than what would be used in an outpatient setting. Small sample size limits generalizability.
Vasudev, 2000(29) India	1) Novartis India Ltd and Novartix Pharma, Basel, Switzerland for CBZ. 2) Torrent Pharmaceutical Ltd.	As subjects were inpatients with acute mania, the dosage titration was probably done faster than what would be used in an outpatient setting. Small sample size limits generalizability.
Bahk (2005) {ID 2025} South Korea	Grant from Janssen Pharmaceuticals Korea	Generalizability may be limited to acute treatment of mania with risperidone as the antipsychotic.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Hartong, 2003(90) The Netherlands	Yes	Yes	Yes, but data not presented by treatment group.	Yes
Tohen, 2002(87) U.S.	Yes	Method not reported	Yes	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Hartong, 2003(90) The Netherlands	Yes	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination	Yes
Tohen, 2002(87) U.S.	Yes	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Hartong, 2003(90) The Netherlands	No	Yes	Fair	--/--/144/144	Deviant laboratory values; nonpsychiatric medications that could interfere
Tohen, 2002(87) U.S.	Yes (modified)	Unable to determine	Fair	330/--/--/251	Serious and unstable medical illness; DSM-IV substance dependence; intolerance to study drugs; treatment with lithium, AED, or an antipsychotic medication within 24 h of randomization

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Hartong, 2003(90) The Netherlands	Run-in for acutely randomized patients on double-blind treatment; entered actual prophylactice phase after recovery from acute episode	No	Yes	Supported partly by Ciba-Geigy (later Novartis Pharma) and the Dutch Fund for Mental Health
Tohen, 2002(87) U.S.	None	No	No (olanzapine is not established antimanic therapy)	Sponsored by Lilly Research Laboratories

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Hartong, 2003(90) The Netherlands	Results are applicable to prevention of bipolar II (DSM-IV) recurrence in patients not previously treated prophylactically.
Tohen, 2002(87) U.S.	Patients were hospitalized for at least the first week; therefore, results may not be generalizable to a solely outpatient population. Sham reporting of valproate concentrations may have limited the ability of investigators to fine-tune doses to maximize response and may not reflect clinical practice.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Tohen, 2003(21) U.S.	Yes	Method not reported	Yes	Yes
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Method not reported	Method not reported	No	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Tohen, 2003(21) U.S.	Yes	Not reported	Yes	Yes-attrition, adherence No-crossover, contamination	Yes
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Not reported	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Tohen, 2003(21) U.S.	No	Unable to determine	Fair	--/--/--/251	Same as for Tohen, 2002 with addition of treatment with clozapine within 4 wk of randomization and serious suicidal risk
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Yes (modified)	Yes	Fair	--/--/349/175	> 6 DSM-IV manic, hypomanic, mixed, or depressive episodes in previous year; DSM-IV diagnosis of or treated within prior year for panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; epilepsy; cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; actively suicidal; score >/= 3 on item 3 of 31-item Hamilton Rating Scale for Depression

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Tohen, 2003(21) U.S.	None	No	No (olanzapine is not established antimanic therapy)	Sponsored by Lilly Research Laboratories
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Run-in	No	Yes	Grant from Glaxo-SmithKline

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Tohen, 2003(21) U.S.	Patients were hospitalized for at least the first week; therefore, results may not be generalizable to a solely outpatient population. Sham reporting of valproate concentrations may have limited the ability of investigators to fine-tune doses to maximize response and may not reflect clinical practice.	
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Results may be applicable to less severely ill bipolar cases.	Effects of baseline differences between treatment groups on results were not explained.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Bowden, 2000(22) Canada, U.S.	Method not reported	Method not reported	Yes	Yes
Small, 1991(30) (--) U.S.	Method not reported	Method not reported	No--Carbamazepine was significantly youner (p = 0.02); nalysis of covariance for the effects of age did not change the significance of any of the rating scale data	Yes
Lusznat, 1988 (23) U.K.	Method not reported	Method not reported	No	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Bowden, 2000(22) Canada, U.S.	Not reported	Not reported	Not reported	Yes-attrition, adherence No-crossover, contamination	Yes
Small, 1991(30) (--) U.S.	Yes	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	Yes
Lusznat, 1988 (23) U.K.	Yes, but method not described	Yes	Yes	Yes-attrition, adherence. No-crossover contamination	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Bowden, 2000(22) Canada, U.S.	Yes (modified)	Yes	Fair	4758/--/571/372 (Number screened from Baldessarini, 2000)	Intolerance to divalproex or lithium; alcohol abuse in past 6 mo; current substance dependence or positive urine toxicology test; concomitant confounding drug treatment; central nervous system, neuromuscular, or uncontrolled systemic disorders; serious suicidal risk; ongoing individual psychotherapy; failure to adhere to open-phase protocol; pregnancy
Small, 1991(30) (--) U.S.	No	Yes	Poor	94/52/52/52	Axis I DSM-III-R diagnoses, significant medical problems, affective episodes associated with physical illness, current substance abuse, or any contraindiation to either lithium or carbamazepine
Lusznat, 1988 (23) U.K.	No	Yes	Poor	128/54/54/54	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Bowden, 2000(22) Canada, U.S.	Run-in, washout	No	Yes	Sponsored by Abbott Laboratories
Small, 1991(30) (--) U.S.	Yes-run-in and washout	No	Yes (lithium)	Grant from the National Institute of Mental Health
Lusznat, 1988 (23) U.K.	None	Unable to determine	Yes	Partially supported by grant from Ciba-Geigy

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Bowden, 2000(22) Canada, U.S.	Results may be applicable to mainly uncomplicated and less severely ill patients; trial sample may represent a minority of patients with bipolar disorder.	Unable to determine LTFU (30/187 (16%) Divalproex vs. 9/91 (10%) Lithium vs. 24/94 (25%) Placebo discontinued for "Other" reasons, which included lost to follow-up, intercurrent illness, administrative reasons, or other reasons; p = 0.01 for Lithium vs. Placebo) (see Bowden, 2000)
Small, 1991(30) (--) U.S.	Limited by high dropout rate and small sample size entering follow-up. Results mainly applicable to a difficult-to-treat cohort of patients.	External validity is compromised by a high dropout rate (partly due to noncompliance by patients in manic episodes). The study methods are mainly applicable to a difficult-to-treat cohort of patients referred to a tertiary care facility who were initially hospitalized (87% were ultimately discharged); long-term results are difficult to generalize because of small
Lusznat, 1988 (23) U.K.	Limited by small sample size. Results may not be applicable to a solely outpatient population.	

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Greil, 1997(24) (--) Germany	Yes	Yes	No (An apparently higher proportion of carbamazepine patients had no prior suicide attempts and 2 episodes of illness.)	Yes
Greil, 1999(89)(--"bipolar I") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes
Greil, 1999(89)(--"bipolar II/NOS") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes (in Greil, 1997)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Greil, 1997(24) (--) Germany	No	No	No	Yes-attrition, adherence No-crossover, contamination	Yes
Greil, 1999(89)(--"bipolar I") Germany	No	No	No	Yes-attrition, adherence, contamination No-crossover,	Yes
Greil, 1999(89)(--"bipolar II/NOS") Germany	No	No	No	Yes-attrition, adherence No-crossover, contamination	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Greil, 1997(24) (--) Germany	Yes	No	Poor	Not reported/375/175/144	Not reported
Greil, 1999(89)(--"bipolar I") Germany	Yes	No	Poor	Not reported/Not reported/Not reported/114	Prophylactic treatment immediately before onset of the index episodes; alcohol or drug abuse
Greil, 1999(89)(--"bipolar II/NOS") Germany	Yes	No	Poor	Not reported/Not reported/Not reported/57 (This population is a subset of the population described in Greil, 1997	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Greil, 1997(24) (--) Germany	None	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)
Greil, 1999(89)(--"bipolar I") Germany	None	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)
Greil, 1999(89)(--"bipolar II/NOS") Germany	None	Yes (no preventive treatment immediately before onset of the present bipolar episode; however, eligibility criteria did not state whether AEDs could be used as	Yes	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Greil, 1997(24) (--) Germany	Not applicable to rapid cyclers.	Results may be applicable to patients who are initially hospitalized, stabilized, in remission, and in need of maintenance treatment (excludes rapid cyclers). No major differences were observed between study patients and non-study patients and between completers and non-completers.
Greil, 1999(89)(--"bipolar I") Germany	Applicable to patients with bipolar I disorder (DSM-IV).	Applicable to a selective population of patients with bipolar I disorder (DSM-IV) who have been hospitalized at least once and require prophylaxis.
Greil, 1999(89)(--"bipolar II/NOS") Germany	Applicable to patients with bipolar II disorder or bipolar disorder NOS (DSM-IV).	Applicable to selective population of patients with bipolar II disorder or bipolar disorder NOS (DSM-IV) who have been hospitalized at least once and require prophylaxis.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Lerer, 1987(25) (--) U.S.	Method not reported	No (blinded physician reported directly to unblinded psychiatrist)	No (An apparently higher proportion of lithium patients had a moderate or good previous response to lithium.)	Yes
Coxhead, 1992(26) (--) U.K.	Method not reported	Method not reported	Yes	Yes
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes	Method not reported	No (apparently higher proportion of men in placebo group; NSD)	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Lerer, 1987(25) (--) U.S.	Yes	Yes	Yes	Yes-attrition No-crossover, adherence, contamination	Yes
Coxhead, 1992(26) (--) U.K.	Yes, but method not described	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination	Yes
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Not reported	Yes	Yes	Yes-attrition, adherence No-crossover, contamination	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Lerer, 1987(25) (--) U.S.	No	Yes	Poor	Not reported/Not reported/34/34	Not reported
Coxhead, 1992(26) (--) U.K.	Yes	No	Fair	145/Not reported/32/31	Not reported
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes (modified)	Yes	Fair	--/--/966 enrolled/463 randomized	> 6 DSM-IV manic, hypomanic, mixed, or depressive episodes in the year prior to enrollment; DSM-IV diagnosis of, or had received treatment within the year pior to enrollment for, panic disorder, obsessive-compulsive disorder, social phobia, or bulimia nervosa; history of or current epilepsy; clinically significant cardiac, renal, hepatic, neoplastic, or cerebrovascular disease; actively suicidal or Hamilton Rating Scale for Depression (HAM-D) score >/= 3 on item 3 (suicidality)

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Lerer, 1987(25) (--) U.S.	Washout	Not reported	Yes	Carbamazepine and placebo supplied by Ciba-Geigy, U.S.A.
Coxhead, 1992(26) (--) U.K.	Run-in	Yes	Yes	Ciba-Geigy provided support and financial assistance
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Run-in Washout of prior psychotropic medications	No	Yes	Supported by GlaxoSmithKline

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Lerer, 1987(25) (--) U.S.	Diagnostic classification has changed since DSM-III. Results may apply to a mixture of bipolar types under DSM-IV.	Applicable to bipolar disorder; however, the diagnostic classification has changed since DSM-III. Therefore, these data would apply to a mixture of bipolar types under DSM-IV.
Coxhead, 1992(26) (--) U.K.	Limited by small sample size.	
Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Probably generalizable bipolar I disorder with depressive episode.	Results generalizable to patients with bipolar I disorder who recently experienced a depressive episode and who were able to be stabilized on lamotrigine mono- or add-on therapy.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Kleindienst, 2002(31) (--) Germany, Switzerland	Yes	No (open-label)	No (higher extraversion score in carbamazepine group; extraversion was found to be unrelated to both inter-episodic morbidity and risk for drop-out)	Yes
Greil, 1998(32) (--) Germany, Switzerland	Yes	No (open-label)	Yes (although data not reported in this article)	Yes
Denicoff, 1997(27) (--) U.S.	Method not reported	No	Not reported	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Kleindienst, 2002(31) (--) Germany, Switzerland	No	No	No	Yes-attrition, adherence No-crossovers, contamination	Yes
Greil, 1998(32) (--) Germany, Switzerland	No	No	No	Yes-attrition No-crossover, adherence, contamination	Yes
Denicoff, 1997(27) (--) U.S.	No	No	Yes	Yes-attrition, crossovers, adherence No-contamination	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Kleindienst, 2002(31) (--) Germany, Switzerland	Yes	No	Poor	--/--/--/171	Not reported
Greil, 1998(32) (--) Germany, Switzerland	Yes	No	Poor	--/--/--/171	Affective and schizoaffective psychoses; bipolar disorder according to DSM-IV criteria; preventive treatment immediately before the onset of the index episode; alcohol or drug abuse; rapid cyclers
Denicoff, 1997(27) (--) U.S.	No	Yes	Poor	--/--/52/52	Other severe medical illness; another current Axis I disorder, usch as substance abuse

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Kleindienst, 2002(31) (--) Germany, Switzerland	None	Not reported	Yes	Grant from BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)
Greil, 1998(32) (--) Germany, Switzerland	None	Not reported	Yes	Grant from BMFT, Ministry of Research and Technology of the Federal Republic of Germany (abbreviations not defined)
Denicoff, 1997(27) (--) U.S.	Washout	No	Yes	Research assistant support from Ciba-Geigy; support of the Ted and Vada Stanley Foundation

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Kleindienst, 2002(31) (--) Germany, Switzerland	May apply to hospitalized patients, possibly more severe cases. Limited by threats to internal validity (open-label design).	Open-label design introduces possibility of bias. No major differences between study patients and non-study patients was found; therefore, results may be generalizable to hospitalized bipolar patients who need prophylactic treatment. However, the study was conducted in psychiatric university hospitals in Germany and may have included more severe cases.
Greil, 1998(32) (--) Germany, Switzerland	May apply to hospitalized patients, possibly more severe cases. Limited by threats to internal validity (open-label design). Some caution is warranted in generalizing the results because the study involved subgroup analyses.	Open-label design introduces possibility of bias. The study was conducted in psychiatric university hospitals in Germany and may have included more severe cases. Some caution is warranted in generalizing the results because the study involved subgroup analyses ("classical" vs. "nonclassical") (Note: The patient sample is the same one used in the study by Kleindienst (2000), which evaluated bipolar I and bipolar II/NOS subgroups.)
Denicoff, 1997(27) (--) U.S.	Nonselective study population; threats to internal validity weaken generalizability of results.	

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Zajecka, 2002(28) (--) U.S.	Method not reported	Method not reported	No	Yes
Gyulai, 2003(33) (--) U.S.	Method not reported	Method not reported	Yes	Yes
McIntyre, 2002(37) (--) Canada	Method not reported	Method not reported	Yes	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Zajecka, 2002(28) (--) U.S.	No	No	Yes	Yes-attrition, adherence No-crossovers, contamination	Yes
Gyulai, 2003(33) (--) U.S.	Not reported	Not reported	Not reported	Yes-attrition No-crossover, adherence, contamination	Yes
McIntyre, 2002(37) (--) Canada	Yes, but method not described	Unable to determine if careprovider was the assessor	No	Yes-attrition No-crossovers, adherence, contamination	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Zajecka, 2002(28) (--) U.S.	Yes (modified)	Yes	Fair	--/--/--/120	Axis I or II disorder that would interfere with compliance; unstable medical condition or interfereing medication; drug or alcohol withdrawal symptoms; platelet count < 100,000 mm^3; mood disorder secondary to a medical condition; previous divalproex or olanzapine failures (investigator's opinion)
Gyulai, 2003(33) (--) U.S.	Yes (modified)	Yes	Fair	4758/--/571/372 (Number screened from Baldessarini, 2000)	History of substance dependence; substance abuse within 6 mo; severe medical conditions (see Bowden, 2000 for other exclusion criteria not mentioned in this report)
McIntyre, 2002(37) (--) Canada	Yes	No	Poor	--/--/36/36	Prior bupropion SR or topiramate exposure; substance dependence diagnosed within past 30 d; electroconvulsive therapy within prior 4 wk; suicide risk; nephrolithiasis; seizures; active neurological or medical problems; psychotic

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Zajecka, 2002(28) (--) U.S.	Run-in Washout of prior psychotropic medications	No	No (olanzapine is not established antimanic therapy)	Supported by Abbott Laboratories
Gyulai, 2003(33) (--) U.S.	Run-in (open-label phase)	No	Yes	Sponsored by Abbott Laboratories
McIntyre, 2002(37) (--) Canada	None	No	Yes	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Zajecka, 2002(28) (--) U.S.	Limited by possible selection bias, as previous study drug failures were excluded.	
Gyulai, 2003(33) (--) U.S.	Results may be applicable to mainly uncomplicated and less severely ill patients; trial sample may represent a minority of patients with bipolar disorder.	
McIntyre, 2002(37) (--) Canada	Limited by small sample size. Results may be applicable to patients with mild-to-moderate bipolar depression who have an inadequate response to mood stabilizers.	Results may be applicable to patients with mild-to-moderate bipolar depression who have an inadequate response to mood stabilizers and have low suicide risk. Small sample size may limit generalizability of results.

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

	Internal Validity			
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**
Okuma, 1990(34) (--) Japan	No and method not reported; 2 patients received only placebo tablets of carbamazepine by mistake	No (blind was erroneously broken in 1 case)	No (Fewer patients aged and age of onset 20 to 29 y and more outpatients in lithium group; statistical analyses showed no significant deviation in the improvement rate in both treatment groups.)	Yes

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(5) Outcome assessors masked?	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?
Okuma, 1990(34) (--) Japan	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)	Yes	Yes-attrition, adherence, contamination No-crossovers	No

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating	*External Validity* (1) Number screened/eligible/ enrolled/ randomized	(2) Exclusion criteria
Okuma, 1990(34) (--) Japan	No	Yes	Poor	--/--/105/105	Carbamazepine or lithium treatment immediately prior to trial; renal, cardiovascular, liver, or hematologic disease

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Okuma, 1990(34) (--) Japan	None	Not reported	Yes	Not reported

Quality Table 2. Active-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Okuma, 1990(34) (--) Japan	May be a selective population of Asian patients; questionable quality of trial conduct.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Solomon, 1997(38) U.S.	Method not reported	Method not reported	No	Yes	Yes	No

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Solomon, 1997(38) U.S.	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Poor

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Solomon, 1997(38) U.S.	--/--/12/12	Treatment of acute (index) episode with valproate or carbamazepine; medical contraindication including significant renal, liver, or cardiovascular disease; encephalopathy, mental retardation, or terminal illness; focal neurologic deficits; seizure disorder or paroxysmal activity on electroencephalogram within past 2 y; structural brain damage from trauma, cerebrovascular disease, or demyelinating disease	Run-in	No (but yes for divalproex)	Yes	Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression; Grant from Abbott Laboratories

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Solomon, 1997(38) U.S.	Limited by pilot study results and small sample size.	Pilot study results prevent definitive conclusions. Small sample size limits generalizability of results.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Calabrese, 2000(35) U.S., Canada	Method not reported	Method not reported	No (an apparently higher proportion of patients had a prior suicide attempt in the lamotrigine group than the placebo group)	Yes	Yes, but masking not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Calabrese, 2000(35) U.S., Canada	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Calabrese, 2000(35) U.S., Canada	--/--/324/182	DSM-IV Axis II diagnosis suggestive of likely noncompliance or nonresponsiveness to pharmacotherapy; actively suicidal or score > / = 3 on item 3 of the 17-item Hamilton Rating Scale for Depression (HAM-D); panic disorder, obsessive-compulsive disorder, social phobia, or eating disorder within previous year; previous lamotrigine therapy if treatment duration was >/= 6 wk and was within 6 mo of study; allergic or idiosyncratic reaction to treatment, including rash; previous lamotrigine therapy in clinical study	Run-in	No	No (placebo)	Grant from Glaxo Wellcome, Inc.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Calabrese, 2000(35) U.S., Canada	Results may apply to patients with rapid cycling disorder (DSM-IV).	Results may be applicable to a selective population of patients with rapid cycling disorder (DSM-IV) who tolerated < 6 wk of lamotrigine or are lamotrigine-naïve.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Mishory, 2003 Israel	Method not reported	Method not reported	Not reported	Yes	Yes	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Mishory, 2003 Israel	Yes	Yes-attrition, crossovers No-adherence, contamination	No	No	Yes	Poor

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Mishory, 2003 Israel	--/--/--/23	Rapid cycling	Washout	No	No (placebo)	NARSAD Young Investigator Award and a grant from the Dreyfus Health Foundation

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?	
Mishory, 2003 Israel	Limited by small sample size. Results may reflect a selective population of compliant patients.	Small sample size limits generalizability of results. Results may reflect a selective population of compliant patients since any post-randomization dropout was excluded from analyses and

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Calabrese, 1999(94) Australia, France, U.K., U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Calabrese, 1999(94) Australia, France, U.K., U.S.	Yes	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	Yes	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Calabrese, 1999(94) Australia, France, U.K., U.S.	--/--/--/195	Rapid-cycling bipolar disorder; abnormal thyroid function tests; panic disorder; obsessive-compulsive disorder; social phobia; bulimina nervosa in previous 12 mo; history of substance dependence (previous year) or abuse (previous month); positive toxicologic screen; chronic cardiac, renal, or hepatic condition; unstable medical condition; epilepsy; active suicidal ideation	Washout	No	No (placebo monotherapy)	Grant from Glaxo Wellcome Research and Development

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Calabrese, 1999(94) Australia, France, U.K., U.S.	May be generalizable to patients with uncomplicated bipolar I depression.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Pande, 2000(41) U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported
Weisler, 2004 {ID 2094} U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Pande, 2000(41) U.S.	Not reported	Yes-attrition No-crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair
Weisler, 2004 {ID 2094} U.S.	Yes	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	No	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Pande, 2000(41) U.S.	--/--/117/117	Uncontrolled medical illnesses; DSM-IV Axis I disorders; medications other than lithium and/or valproate that could alter assessments of efficacy	Run-in	No	No (placebo add-on)	Parke-Davis Pharmaceutical Research
Weisler, 2004 {ID 2094} U.S.	--/--/--/204	Not reported, except concomitant therapy with antidepressants, cytochrome P450 inhibitors, or anxiolytic (with exception of lorazepam) and sedative-hypnotic drugs were prohibited	Yes	No (Reported in Ketter, 2004)	No (placebo)	Supported by a grant from Shire, Newport, KY

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Pande, 2000(41) U.S.	May be generalizable to patients with bipolar I disorder not responding to lithium, valproate, or combination of both
Weisler, 2004 {ID 2094} U.S.	Unclear because exclusion criteria were not reported; generalizability may be limited by high early dropout rate (53%), uncertain extent of lorazepam co-therapy, and a sample size too small to detect rare carbamazepine adverse events such as agranulocytosis and aplastic anemia.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Weisler, 2005 {ID 2098} U.S., India	Method not reported	Method not reported	Yes	Yes	Not reported	Yes
Salloum, 2005 {ID 2049} U.S.	Yes	Method not reported	Yes	Yes	Yes (No--dosing investigator)	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Weisler, 2005 {ID 2098} U.S., India	Yes	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	Yes	Fair
Salloum, 2005 {ID 2049} U.S.	Yes	Yes-attrition, adherence No-crossovers, contamination	No	Yes (modified)	No	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Weisler, 2005 {ID 2098} U.S., India	--/--/--/239	Electroconvulsive therapy or clozapine within past 3 mo; antidepressants within 4 wk. Concomitant electroconvulsive therapy, antidepressants, lithium, antipsychotics, grapefruit juice, anxiolytic or sedative-hypnotic drugs, and other psychotropic drugs, except lorazepam.	Run-in and washout	Not reported	No (placebo)	Grant from Shire, Wayne, PA
Salloum, 2005 {ID 2049} U.S.	Not reported / 72 / 72 / 59	Schizophrenia, schizoaffective disorder, any nonbipolar psychotic disorder, mental retardation, impaired cognitive function; current DSM-IV diagnoses of opioid or cocaine dependence or current use of intravenous drugs; epilepsy, history of brain injury, or organic brain syndrome; severe cardiac, liver, kidney, endocrine, hematologic, or other unstable medical condition; persistent elevation of liver function enzyme levels > 3-fold above reference range; inability to read or understand study forms	No	Not reported	Yes for bipolar disorder No for alcohol dependence (placebo added on to lithium)	Grants from the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and National Institute of Mental Health (NIMH)

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Weisler, 2005 {ID 2098} U.S., India	Results may apply to carbamazepine monotherapy of bipolar I disorder with recent mania/mixed episodes
Salloum, 2005 {ID 2049} U.S.	Limited by small sample size, high noncompletion rate (39 / 59, 66.1%), and to selected population of patients with concurrent diagnoses of alcohol use and bipolar disorders without certain co-psychiatric and substance use disorders (such as opioid and cocaine dependence; see *Exclusion criteria).* In addition, randomized patients were more likely to be employed, in a higher socioeconomic class, and unmarried than patients who were excluded.

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Internal Validity

Author, year Country	(1) Randomization adequate?	(2) Allocation concealment adequate?	(3) Groups similar at baseline?	(4) Eligibility criteria specified?	(5) Designated Outcome assessors masked?	(6) Care provider masked?
Davis, 2005 {ID 2045} U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Yes

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Davis, 2005 {ID 2045} U.S.	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Fair

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

	External Validity					
Author, year Country	**(1) Number screened/ eligible/ enrolled/ randomized**	**(2) Exclusion criteria**	**(3) Run-in /Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**
Davis, 2005 {ID 2045} U.S.	--/--/25/25	Active Axis I disorder other than bipolar I, borderline or antisocial personality disorder, previous history of intolerance to divalproex, significant suicidality, psychoactive substance use disorder in remission < 3 mo	Washout	Not reported	No (placebo)	Not reported

Quality Table 3. Placebo-Controlled Trials: Bipolar Disorder

Author, year Country	(7) Relevance?
Davis, 2005 {ID 2045} U.S.	Limited by use of one veterans mental health clinic, small study population, predominance of male patients, short-term therapy, and low completion rate (12 / 25, 48%). Findings need to be confirmed in a larger well-designed trial.

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

	Internal Validity						
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Outcome assessors masked?**	**(6) Care provider masked?**	**(7) Patient masked?**
Skelton, 1991(43) U.S.	Method not reported	Method not reported	Not reported	No	Not reported	Not reported	Not reported

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

Author, year Country	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/ high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality Rating
Skelton, 1991(43) U.S.	No	No	No	Yes	Poor

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

	External Validity						
Author, year Country	**(1) Number screened/eligible/ enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**	**(5) Control group standard of care?**	**(6) Funding**	**(7) Relevance?**
Skelton, 1991(43) U.S.	--/--/12/12	Not reported	None	Unable to determine	No (both study treatments were AEDs)	Not reported	Limited by small sample size, selective population, and threats to internal validity.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity				
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**
Morello, 1999(44) U.S.	Method not reported	Method not reported	Yes (crossover trial)	Yes	Yes
Gomez-Perez(45) Mexico	Method not reported	Method not reported	No	Yes	Not reported
Lindstrom, 1987(46) Sweden	Method not reported	Method not reported	Not reported	Yes	Not reported

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Morello, 1999(44) U.S.	Yes	Yes	Yes-attrition, crossovers, adherence No-contamination	No	No
Gomez-Perez(45) Mexico	Yes	Yes	Yes-attrition, crossovers, adherence No-contamination	No	No
Lindstrom, 1987(46) Sweden	Not reported	Not reported	Yes- attrition, crossover. No- adherence contamination.	Not reported	No

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

			External Validity	
Author, Year Country	**(11) Post-randomization exclusions?**	**(12) Quality Rating**	**(1) Number screened/eligible / enrolled/ randomized**	**(2) Exclusion criteria**
Morello, 1999(44) U.S.	No	Fair	--/28/25/25	Non-diabetic peripheral neuropathy (DPN) pain more severe than DPN pain; severe depression by diagnosis or Beck Inventory; receiving treatment for seizures; symptomatic postural hypotension; symptomatic coronary artery or peripheral vascular disease; creatinine clearance < 30 ml/min; prior treatment with gabapentin or amitriptyline only if doses exceeded the study's maximum dosage of either drug.
Gomez-Perez(45) Mexico	Yes	Poor	--/--/16/16	Mild diabetic peripheral neuropathy; normal nerve conduction velocity, cardiac disease, liver disease, renal failure, hematologic abnormalities, glaucoma, myasthenia gravis, monoamine oxidase inhibitor therapy within 15 d
Lindstrom, 1987(46) Sweden	No	Poor	--/--/12/12	Cardiovascular disease, liver and/or renal insufficiency

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Morello, 1999(44) U.S.	Washout	No	Yes	Not reported
Gomez-Perez(45) Mexico	Washout	Previous therapy not reported	No (control was nortriptyline-fluphenazine combination, first reported to be effective by the authors in 1985)	Ciba-Geigy Mexicana provided active drugs and placebos
Lindstrom, 1987(46) Sweden	None	No	No (tocainide)	Folksam Research Foundation and the Vivian L. Smith Foundation for Restorative Neurology

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Relevance?
Morello, 1999(44) U.S.	Limit on maximal dose of gabapentin may not reflect usual clinical practice. Small sample size limits generalizability of results.
Gomez-Perez(45) Mexico	Limited by small sample size.
Lindstrom, 1987(46) Sweden	Limited by small sample size and problems with internal validity.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity				
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**
Leijon, 1989(47) Sweden	No. One patient had a known allergy to carbamazepine and was therefore randomized only to amitriptyline and placebo. In this case, allocation of treatment was not random.	Yes (pharmacy carried out randomization and distribution of drugs)	Yes	Yes	Yes
Dallocchio, 2000(69) Italy	Method not reported	No (open-label)	No (Duration of pain was significantly longer in the gabapentin group than the amitriptyline group: mean (SD), 34 (11) vs. 22 (12) mo).	Yes	No
Lechin, 1989(42) Venezuela	Method not reported	Method not reported	Yes (according to authors; data not reported)	Yes	Yes

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Leijon, 1989(47) Sweden	Yes	Yes	Yes-attrition, crossovers No-adherence, contamination	No	No
Dallocchio, 2000(69) Italy	No	No	Yes-attrition No-crossovers, adherence, contamination	No	Yes
Lechin, 1989(42) Venezuela	Yes	Yes	Yes-attrition, adherence No, contamination	No	No

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

			External Validity	
Author, Year Country	**(11) Post-randomization exclusions?**	**(12) Quality Rating**	**(1) Number screened/eligible / enrolled/ randomized**	**(2) Exclusion criteria**
Leijon, 1989(47) Sweden	Yes	Poor	27/15/15/15	Contraindication to amitriptyline and carbamazepine; patients who could not be evaluated in a satisfactory way
Dallocchio, 2000(69) Italy	No	Poor	--/--/25/25	Renal, hepatic, or cardiovascular insufficiency; diabetic neuropathy not meeting entry criteria; neuropathy of different etiology; current or previous diagnosis of psychiatric disorder
Lechin, 1989(42) Venezuela	Yes	Poor	--/--/68/59	Severe physical illness, psychotic episodes, drug or alcohol addiction, epilepsy, mental retardation

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Leijon, 1989(47) Sweden	Washout	Yes	Yes (amitriptyline)	Grants from the County Council of Östergötland and the Swedish Association of the Neurologically Disabled
Dallocchio, 2000(69) Italy	Washout	No	Yes (amitriptyline)	Not reported
Lechin, 1989(42) Venezuela	Run-in, washout	No	No (pimozide)	Grant from the Foundation of the Institute of Experimental Medicine

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Relevance?
Leijon, 1989(47) Sweden	Limited by small sample size and problems with internal validity.
Dallocchio, 2000(69) Italy	Limited by small sample size and threat to internal validity (open-label design).
Lechin, 1989(42) Venezuela	Results pertain to patients with severe, refractory trigeminal neuralgia.

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

	Internal Validity				
Author, Year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**
Keczkes, 1980(98)	Method not reported	Method not reported	Not reported	Yes	No
Lockman, 1973(97) U.S.	Method not reported	Method not reported	Yes	No	Not reported
Gilron, 2005{ID 2001} Canada	Yes (?) (balanced Latin square)	Yes (centralized)	Yes	Yes	Yes

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(6) Care provider masked?	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?
Keczkes, 1980(98)	No	No	No for all	No	Yes
Lockman, 1973(97) U.S.	Yes	Yes	Yes-attrition, adherence, crossover No- contamination	No	Yes
Gilron, 2005{ID 2001} Canada	Yes	Yes	Yes-attrition No-crossovers, adherence, contamination	Yes	No

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

			External Validity	
Author, Year Country	**(11) Post-randomization exclusions?**	**(12) Quality Rating**	**(1) Number screened/eligible / enrolled/ randomized**	**(2) Exclusion criteria**
Keczkes, 1980(98)	No	Poor	--/--/40/40	Bacterial infection (other than those secondary to herpes zoster), tuberculosis, diabetes mellitus, peptic ulcer, hypertension, cardiovascular disease, lymphomas, leukemia
Lockman, 1973(97) U.S.	No	Poor	--/--/8/8	Not reported
Gilron, 2005{ID 2001} Canada	No	Fair	86/--/--/57	Another painful condition as severe as the diabetic neuropathy or postherpetic neuralgia; recent myocardial infarction, unstable angina, or congestive heart failure; central neurologic disorder; serious mood disorder; history of serious drug or alcohol abuse; lack of a primary care physician

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(3) Run-in/Washout	(4) Class naïve patients only?	(5) Control group standard of care?	(6) Funding
Keczkes, 1980(98)	None	Yes (prior AED therapy was not reported)	No (prednisolone)	Not reported
Lockman, 1973(97) U.S.	None	Yes (pain not relieved by either conventional or narcotic analgesics)	No (aspirin or multivitamin)	Supported in part by research grants from the National Institutes of Health, American Heart Association, National Foundation-March of Dimes, and U.S. Public Health Service
Gilron, 2005{ID 2001} Canada	None	No	Yes (morphine)	Supported by a grant from the Canadian Institutes of Health Research

Quality Table 5. Active-Controlled Trials: Neuropathic Pain

Author, Year Country	(7) Relevance?
Keczkes, 1980(98)	Limited by small sample size.
Lockman, 1973(97) U.S.	Limited to rare patients with Fabry's disease and very small sample size.
Gilron, 2005{ID 2001} Canada	Limited by small sample size.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Backonja, 1998 U.S.	Yes	Method not reported	Yes	Yes	Yes	Yes
Bone, 2002 U.K., Ireland.	Yes	Method not reported	Yes	Yes	Not reported	Yes
Tai, 2002 U.S.	Yes	Method not reported	Yes	Yes	Yes (for adverse events)	Yes
Serpell, 2002 U.K. and Republic of Ireland	Yes	Yes	No, lower ratio of men to women in gabapentin group (63:90) than placebo group (78:74)	Yes	Not reported	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Backonja, 1998 U.S.	Yes	Yes – attrition No - crossovers, adherence, contamination	No	Yes (modified)	Yes	Fair
Bone, 2002 U.K., Ireland.	Yes	Yes – attrition, adherence, crossovers No - contamination	No	Yes	No	Fair
Tai, 2002 U.S.	Yes	Yes – attrition, adherence, crossovers No - contamination	No	No	Yes	Poor
Serpell, 2002 U.K. and Republic of Ireland	Yes	Yes – attrition, adherence No – crossovers, contamination	No	Yes (modified)	Yes	Fair

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Backonja, 1998 U.S.	232/--/165/165	Presence of other severe pain that could confound assessments; investigational drug within 30 days of screening; amputations other than toes; creatinine clearance less than 60 ml/min	run in and washout	No
Bone, 2002 U.K., Ireland.	33/19/19/19	Coexisting epilepsy; allergy to gabapentin; significant hepatic or renal insufficiency; severe hematologic disease; history of illicit drug or alcohol abuse; serious psychiatric condition; other severe pain that could confound assessments	Non-treatment run-in. Washout.	No
Tai, 2002 U.S.	--/--/14/14	Severe cognitive impairment; pregnancy; seizure disorder; major depression or Beck Depression Inventory score > 16; hypersensitivity to gabapentin; renal insufficiency (creatinine clearance < 60 ml/min)	Washout	No
Serpell, 2002 U.K. and Republic of Ireland	351/351/307/307	Failure to respond to previous treatment with gabapentin >/= 900 mg/d or failure to respond to gabapentin at any dose level due to side effects; creatinine clearance </= 60 ml/min or renal impairment; clinically significant hepatic, respiratory, hematologic illnesses, or unstable cardiovascular disease; significant neurologic or psychiatric disorders unrelated to causes of neuropathic pain; other severe pain that might impair assessments; other serious or unstable condition; illicit drug or alcohol abuse within the past year	Washout (prior to screening). Non-treatment run-in.	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Backonja, 1998 U.S.	No (placebo control)	Sponsored and authored by Parke-Davis
Bone, 2002 U.K., Ireland.	No (placebo control)	Pfizer Pharmaceuticals supplied study drugs
Tai, 2002 U.S.	No (placebo control)	Year 2000 New Investigator Award; clinical SCI grant from the Eastern Paralyzed Veterans Association
Serpell, 2002 U.K. and Republic of Ireland	No (placebo control)	Sponsored by Parke-Davis

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Backonja, 1998 U.S.	Large sample size and 71% of screened patients were randomized, suggesting results are probably generalizable to most patients with painful diabetic neuropathy.
Bone, 2002 U.K., Ireland.	Small sample size limits generalizability of results
Tai, 2002 U.S.	Very small sample size limits generalizability of results
Serpell, 2002 U.K. and Republic of Ireland	About 88% of screened pain clinic patients were randomized and eligibility criteria did not limit selection of patients according to type of neuropathic pain, suggesting results are likely to be generalizable to most patients in a specialized pain treatment setting. Excluding patients who were nonresponsive or intolerant of gabapentin introduced a possibility of selection bias. According to the authors, in a response to comments on the article (McCleane, 2003), only a very few of the 24 excluded patients had a history of nonresponsiveness or intolerance to gabapentin.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Rowbotham, 1998 U.S.	Method not reported	Yes	Yes	Yes	Not reported	Yes
Rice, 2001 U.K., Republic of Ireland	Yes	Method not reported	Yes	Yes	Not reported	Yes
Harke, 2001 Germany	Yes	Method not reported	Not reported (data not presented by treatment groups)	No	Not reported	Yes, but method not reported
Campbell, 1966 U.K.	Yes	Method not reported	No (6% of the group that received carbamazepine first had been injected for pain vs. 29% of the group that received placebo first)	Yes (However, patients with trigeminal neuralgia were admitted to the trial without selection.)	Yes	Yes
Nicol, 1969 U.S.	Method not reported	Method not reported	Not reported (data not presented by treatment groups)	No	Not reported	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Rowbotham, 1998 U.S.	Yes	Yes-attrition, adherence. No-crossover, contamination	No	Yes (modified)	Yes	Fair
Rice, 2001 U.K., Republic of Ireland	Yes	Yes-attrition, adherence. No-crossover, contamination	No	Yes (modified)	No	Fair
Harke, 2001 Germany	Yes, but method not reported	Yes-attrition No-crossovers, adherence, contamination	No	No	No	Poor
Campbell, 1966 U.K.	Yes	Yes-attrition, crossovers, adherence, contamination	No	No	Yes	Poor
Nicol, 1969 U.S.	Not reported	Yes-crossovers No-attrition, adherence, contamination	No	No	No	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Rowbotham, 1998 U.S.	292/--/--/229	Prior treatment with gabapentin; hypersensitivity to drug or ingredients; neurolytic or neurosurgical therapy for postherpetic neuralgia; immunocompromised; significant hepatic or renal insufficiency; significant hematologic disease; other type of severe pain; experimental drug or study within 2 months of screening; history of illicit drug or alcohol abuse within past year; any serious or unstable medical or psychological condition	Run-in, washout of prior medications	No
Rice, 2001 U.K., Republic of Ireland	411/359/--/334	Failure to respond to previous treatment with gabapentin >/= 1200 mg/d; failure to respond to gabapentin at any dose level due to side effects; contraindications to gabapentin	Run-in, washout of prior medications	No
Harke, 2001 Germany	77/68/43/43	Strong psychological and affective components in Minnesota Multiphasic Personality Inventory and interview by psychiatrists; arrhythmia, angina, allergy, cardiopulmonary insufficiency, analgesic use	Run-in	No
Campbell, 1966 U.K.	--/--/77/77	Difficulty attending regularly due to age, infirmity, geography; pain due to disseminated sclerosis	None	No
Nicol, 1969 U.S.	--/--/64/44	Facial pain diagnosis other than trigeminal neuralgia	None	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Rowbotham, 1998 U.S.	No (placebo control)	Sponsored and authored by Parke-Davis
Rice, 2001 U.K., Republic of Ireland	No (placebo control)	Fully funded by Pfizer Ltd.
Harke, 2001 Germany	No (placebo with Spinal Cord Stimulation upon recurrence of pain)	Not reported
Campbell, 1966 U.K.	No (placebo control)	Geigy Pharmaceutical Company Limited supplied carbamazepine
Nicol, 1969 U.S.	No (placebo control)	Geigy Pharmaceuticals supplied carbamazepine and placebo

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Rowbotham, 1998 U.S.	Results mainly applicable to uncomplicated patients not previously treated with gabapentin for postherpetic neuralgia.
Rice, 2001 U.K., Republic of Ireland	Results applicable to patients who did not previously fail gabapentin >/= 1200 mg/d or were not previously treated with the drug. There may have been selection bias for previous responders to higher doses of gabapentin.
Harke, 2001 Germany	Results pertain to patients who already achieved pain relief with Spinal Cord Stimulation; small sample size limits generalizability of results.
Campbell, 1966 U.K.	Nonselective patient population with trigeminal neuralgia; however, small sample size limits generalizability of results.
Nicol, 1969 U.S.	Small sample size and unorthodox analyses of treatment effects limit the interpretation and generalizability of results

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Drewes, 1994 Denmark	Method not reported	Method not reported	Yes	Yes	Yes	Yes
Simpson, 2000 U.S.	Yes	Yes	No (CD4+ count was higher in the evaluated lamotrigine group vs. placebo group; 377 vs. 153 cells/mm3; p = 0.01) The effects of these differences on the trial results were not explained.	Yes	Not reported	Yes
Finnerup, 2002 Denmark	Yes	Yes	Yes	Yes	Not reported	Yes
McCleane, 1999 U.K.	Yes	Method not reported	No (mean duration of pain was 87 mo in the lamotrigine group vs. 61 mo in the placebo group; not statistically significant)	Yes	Not reported	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Drewes, 1994 Denmark	Yes	Yes-attirtion, crossovers, adherence No-contamination	No	No	No	Poor
Simpson, 2000 U.S.	Yes	Yes-adherence, crossover No-attrition, contamination	Yes	Yes	Yes	Fair
Finnerup, 2002 Denmark	Yes	Yes-attrition, crossovers, adherence No-contamination	Yes	No	Yes	Poor
McCleane, 1999 U.K.	Yes	Yes-attrition, crossover No-adherence, contamination	Yes (26%)	No	Yes	Fair

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Drewes, 1994 Denmark	--/--/20/20	Severe obesity, liver disease, anticoagulant therapy, phenobarbital, primidone, intolerance to valproate	Washout	No
Simpson, 2000 U.S.	--/--/42/42	Alternative causes of neuropathy; drugs that could be contributing to neuropathy (other than antiretroviral agents); acute, active opportunistic infections except oral thrush, orogenital or rectal herpes, and *Mycobacterium avium* - intracellular bacteremia within 2 wk; major, active psychiatric disorders; chemotherapeutic agents; systemic corticosteroids or immune modulators; addition of dideoxynucleosides to existing antiretroviral regimen; valproic acid therapy.	Washout	No
Finnerup, 2002 Denmark	436/100/30/30	Concomitant cerebral damage; dementia, serious hepatic or renal disease; other significant illness	Washout	No
McCleane, 1999 U.K.	--/--/--/100	AED therapy	None	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Drewes, 1994 Denmark	No (placebo control)	Sponsored by Rhône-Poulenc Rorer A/S
Simpson, 2000 U.S.	No (placebo control)	Research grant support and study drug provided by Glaxo Wellcome, Inc.
Finnerup, 2002 Denmark	No (placebo control)	Grants from several foundations and legacies. Glaxo Wellcome A/S Denmark provided lamotrigine and placebo. Pharma + Medico International Aps provided hCG tests.
McCleane, 1999 U.K.	No (placebo control)	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Drewes, 1994 Denmark	Small sample size limits generalizability of results
Simpson, 2000 U.S.	Results should be considered preliminary (see larger study by Simpson, 2003). Small sample size and high dropout rate (mainly due to lamotrigine-induced rash) compromise external validity.
Finnerup, 2002 Denmark	Small sample size limits generalizability of results
McCleane, 1999 U.K.	May apply to broad range of neuropathic pain types, as a particular type was not specified.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Zakrzewska, 1997 U.K.	Method not reported	Method not reported	Not reported but age clinically different	Yes	Not reported	Yes
Simpson, 2003 U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes
Vestergaard, 2001 Denmark	Yes	Yes	Yes	Yes	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Zakrzewska, 1997 U.K.	Yes	Yes-attrition, crossover, contamination No-adherence	No	No	Yes	Poor
Simpson, 2003 U.S.	Yes	Yes-attrition, adherence No-crossovers, contamination	Yes (24%)	No	No	Fair
Vestergaard, 2001 Denmark	Yes	Yes-attrition, crossovers, adherence No-contamination	No	No	Yes	Fair

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Zakrzewska, 1997 U.K.	--/--/14/14	Surgery for trigeminal neuralgia (including nerve injections but excluding local anesthetic injections) within 1 yr	Washout	No
Simpson, 2003 U.S.	--/--/227/227	Valproate therapy within 4 wk; any previous or current use of lamotrigine; other neurologic disorders that could confound the diagnosis of peripheral neuropathy (e.g., myelopathy)	Run-in and Washout	No
Vestergaard, 2001 Denmark	--/31/31/30	Dementia; other severe cognitive impairment; diabetic neuropathy; malignancy; recent myocardial infarction; severe heart insufficiency; liver or renal failure; history of alcohol or drug abuse	Washout of prior medications and before crossover	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Zakrzewska, 1997 U.K.	No (placebo added on to existing carbamazepine or phenytoin)	Glaxo-Wellcome R and D
Simpson, 2003 U.S.	No. Placebo control, added on to existing stable doses of analgesics, tricyclic antidepressants, class I antiarrhythmics, or AEDs, herbal remedies, alternative therapies (e.g., massage, acupuncture); or adjustable doses of as-needed opioids; or analgesics for new acute conditions (up to 10 d).	GlaxoSmithKline and individual grants
Vestergaard, 2001 Denmark	No (placebo control)	Grants from the Danish Medical Research Council and the Danish Pain Research Center. Glaxo Wellcome A/S Denmark provided lamotrigine and placebo tablets and covered transport expenses

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Zakrzewska, 1997 U.K.	Results may apply to lamotrigine add-on therapy for refractory trigeminal neuralgia; however, problems with internal validity and complex statistical analyses complicate the estimations of the treatment effect, and the small sample size limits the generalizability of results.
Simpson, 2003 U.S.	According to protocol, patients who developed serious rash or hypersensitivity were to be discontinued from the trial and would have been excluded from efficacy analyses. No cases of serious rash (associated with hospitalization and discontinuation of study drug) were reported in the study and the frequency of discontinuation due to adverse events was similar between LTG and placebo. The primary efficacy analysis was based on patients who completed the trial per protocol. Therefore, the generalizability of results may be limited.
Vestergaard, 2001 Denmark	Small sample size limits generalizability of results

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Gorson, 1999 U.S.	Method not reported; also unclear if baseline measurements were taken before randomization	Method not reported	Not reported	Yes	Yes	Yes
Kochar, 2004(57) India	Method not reported	Yes	Yes; however, duration of diabetic neuropathy not reported	Yes	Yes	Yes
Kochar, 2002 India	Method not reported	Method not reported; administration of study drugs by an apparently unblinded researcher might have compromised blinding.	No (under Results, a greater proportion of valproate patients had pain scores >/= 5 at baseline) Duration of diabetic neuropathy and concomitant analgesics not reported	No	Yes	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Gorson, 1999 U.S.	Yes	Yes-contamination No-attrition, crossovers, adherence	No	Yes	No	Fair
Kochar, 2004(57) India	Yes	Yes-attrition No-crossovers, adherence, contamination	No	No	Yes	Fair
Kochar, 2002 India	Not reported	Yes-attrition No-crossovers, adherence, contamination	Yes	No	Yes	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Gorson, 1999 U.S.	--/--/40/40	Diabetes and chronic renal insufficiency, painful diabetic plexopathy, or lumbosacral polyradiculopathy, peripheral vascular disease, another painful condition, or other cause for neuropathy	Washout--may have been inadequate, since improvement in pain scores on gabapentin seemed to carryover into the placebo treatment period	Unable to determine
Kochar, 2004(57) India	48 screened / 43 eligible / 43 enrolled / 43 randomized	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, steroid therapy	None	Not reported
Kochar, 2002 India	60 screened / Number eligible not reported / Number enrolled not reported / 57 randomized	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, steroid therapy. Patients who did not tolerate study drug were dropped from the study.	None	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Gorson, 1999 U.S.	No (placebo control added on to any existing stable doses of nonsteroidal antiinflammatory drugs or narcotics)	Warner Lambert (Parke-Davis Pharmaceuticals)
Kochar, 2004(57) India	No (placebo)	Not reported
Kochar, 2002 India	No (placebo)	Not reported

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Gorson, 1999 U.S.	Small sample size. Results may not be applicable to a substantial proportion of patients with diabetes who have coexistent peripheral vascular disease or renal insufficiency.
Kochar, 2004(57) India	Small sample size limits generalizability of results
Kochar, 2002 India	Results may reflect selection bias, as only patients who tolerated medication were continued in the study. Small sample size limits generalizability of results.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Saudek, 1977 (--) U.S.	Method not reported	Method not reported	Yes	Yes	Yes	Yes
Dalessio, 1966 (--), only RCT described here U.S.	Method not reported	Yes	Not reported	No	Not reported	Not reported
McCleane, 1999 U.K.	Yes	Method not reported	No	Yes	Not reported	Not reported
Gilron, 2001 (--) U.S.	Method not reported	Method not reported	Yes	No	Not reported	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Saudek, 1977 (--) U.S.	Yes	Yes-adherence, crossover No-attrition, contamination	Not reported	Unable to determine	Yes	Poor
Dalessio, 1966 (--), only RCT described here U.S.	Not reported (however, patients were able to identify active agent based on pain relief)	No for all	No	Unable to determine	Unable to determine	Poor
McCleane, 1999 U.K.	Not reported (however, there was potential for burning at infusion site with phenytoin and not with the saline placebo)	Yes-attrition No-crossovers, adherence, contamination	No	Yes	No	Fair
Gilron, 2001 (--) U.S.	Yes	Yes-attrition, crossovers No-adherence, contamination	No for main study Yes for confirmatory study	Yes?	Unable to determine	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Saudek, 1977 (--) U.S.	--/--/--/12?	Other diabetic neuropathies (radiculopathy, mononeuropathy, amyotrphy, or autonomic neuropathy); alcoholism; uremia; carcinoma; other possible etiologies of neuropathy	None	Not reported
Dalessio, 1966 (--), only RCT described here U.S.	--/--/10/10	Not reported	None	Not reported
McCleane, 1999 U.K.	--/--/20/20	Oral AEDs, membrane stabilizers	Washout	No
Gilron, 2001 (--) U.S.	--/--/3/3	Multiple sclerosis, continuous pain, dense sensory loss related to an invasive procedure (I.e., anesthesia dolorosa)	Washout	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Saudek, 1977 (--) U.S.	No (placebo)	Supported in part by the Cornell General Clinical Research Center Division of Research Resources, National Institutes of Health, and by the New York Diabetes Association
Dalessio, 1966 (--), only RCT described here U.S.	No (placebo)	Not reported
McCleane, 1999 U.K.	No (placebo)	Not reported
Gilron, 2001 (--) U.S.	No (placebo)	Supported by Intramural Project Grant from the National Institute of Dental and Craniofacial Research and by Ortho-McNeil Pharmaceuticals

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Saudek, 1977 (--) U.S.	Threats to internal validity and small sample size limit generalizability of results.
Dalessio, 1966 (--), only RCT described here U.S.	Small sample size and short duration of therapy (3 days) limit generalizability of results to long-term treatment of patients.
McCleane, 1999 U.K.	Limited to acute treatment of neuropathic pain using parenteral phenytoin. Small sample size limits generalizability of results.
Gilron, 2001 (--) U.S.	Multiple crossovers increased power of study, but extremely small sample size limits generalizability of results.

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	Internal Validity					
Author, year Country	**(1) Randomization adequate?**	**(2) Allocation concealment adequate?**	**(3) Groups similar at baseline?**	**(4) Eligibility criteria specified?**	**(5) Designated Outcome assessors masked?**	**(6) Care provider masked?**
Rockliff, 1966 (--) U.S.	Method not reported	Method not reported	Not reported	Yes	Not reported	Yes
Chadda, 1978 (--) India	Method not reported	Method not reported	Not reported	Yes	Yes	Yes, method not reported
Rull, 1969 (--) Mexico	Method not reported	Method not reported	Not reported	No	Yes	Yes
Simpson, 2001 U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Yes
Eisenberg, 2001 (--) Israel	Yes	No	No	Yes	Not reported	Yes

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Patient masked?	(8) Reporting of attrition, crossovers, adherence, and contamination?	(9) Loss to follow-up: differential/high?	(10) Intention-to-treat (ITT) analysis?	(11) Post-randomization exclusions?	(12) Quality rating
Rockliff, 1966 (--) U.S.	Yes	Yes-attrition, crossovers No-adherence, contamination	No	Yes	No	Fair
Chadda, 1978 (--) India	Yes	Yes-attrition No-crossovers, adherence, contamination	No	No	No	Poor
Rull, 1969 (--) Mexico	Yes	Yes-attrition, crossover No- adherence, contamination	No	No	Yes	Poor
Simpson, 2001 U.S.	Yes	Yes-attrition No-crossovers, adherence, contamination	No	Unable to determine	No	Poor
Eisenberg, 2001 (--) Israel	No	Yes-attrition, adherence No-crossovers, contamination	No	No	Yes	Poor

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

	External Validity			
Author, year Country	**(1) Number screened/eligible/enrolled/randomized**	**(2) Exclusion criteria**	**(3) Run-in/Washout**	**(4) Class naïve patients only?**
Rockliff, 1966 (--) U.S.	--/--/9/9	Atypical facial pain, posthperpetic neuralgia	None	Not reported
Chadda, 1978 (--) India	--/--/40/40	Other causes of neuropathy	Yes, washout.	Not reported
Rull, 1969 (--) Mexico	--/--/30/30	Not reported	None	Not reported
Simpson, 2001 U.S.	Part 1: --/--/60/60 Part 2: --/12/11/11 Part 3: --/42/42/Not applicable	Severe pain other than diabetic neuropathy pain; amputations other than toes; renal failure (creatinine clearance < 60 ml/min); treatment in last 30 d with tricyclic antidepressants, mexiletine, carbamazepine, phenytoin, valproate, dextromethorphan, opioids, capsaicin, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, benzodiazepines, or over-the-counter centrally acting agents	30-d washout of previous medications	No
Eisenberg, 2001 (--) Israel	160/--/--/59	Age < 18 or > 75 y; renal or liver dysfunction; epilepsy; other painful conditions; received antiepileptics, antidepressants, or membrane-stabilizing agents for reasons other than pain relief, or use of opioids	None	No

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(5) Control group standard of care?	(6) Funding
Rockliff, 1966 (--) U.S.	No (placebo)	Study performed by Geigy Pharmaceuticals
Chadda, 1978 (--) India	No (placebo)	M/S. Parke-Davis (India) Ltd. Kindly supplied the drug for the trial.
Rull, 1969 (--) Mexico	No (placebo)	JR Geigy Laboratories furnished the drug and placebo used in the study
Simpson, 2001 U.S.	No (placebo)	Not reported
Eisenberg, 2001 (--) Israel	No	Supported by Glaxo-Wellcome

Quality Table 6. Placebo-Controlled Trials: Neuropathic Pain

Author, year Country	(7) Relevance?
Rockliff, 1966 (--) U.S.	Small sample size limits generalizability of results.
Chadda, 1978 (--) India	Small sample size limits generalizability of results.
Rull, 1969 (--) Mexico	Patients represented a heterogeneous group of different types of peripheral diabetic neuropathy. Absence of eligiblity criteria and small sample size make it difficult to generalize results.
Simpson, 2001 U.S.	
Eisenberg, 2001 (--) Israel	May apply to patients not treated with other systemic agents for neuropathic pain; limited by small sample size

Quality Table 7. Quality Assessment: Observational Studies

Author, year	(1) Non-biased selection?	(2) Low overall loss to follow-up?	(3) Adverse events pre-specified and defined?	(4) Ascertainment techniques adequately described?	(5) Non-biased and adequate ascertainment methods?	(6) Statistical analysis of potential confounders?	(7) Adequate duration of follow-up?	(8) Overall adverse event assessment quality
Goodwin, 2003(79)	Yes	Not clear	Yes	Yes	No	Yes	Yes	Fair
Rzany, 1999(80)	Yes	Not clear	Yes	No	Unable to determine	Yes	Yes	Fair
Tohen, 1995(78)	Yes	Not clear	Yes	Yes	No	No	Yes	Poor
Ibáñez, 2005 {ID 2063}	Yes	Yes	Yes	Yes	Yes	Yes	Yes (each case followed up for 4 wk or to hospital discharge; surveillance system in place for 22 y)	Good
Vestergaard (2004) {ID 2066}	Yes	Yes	Yes (ICD10 codes)	Yes	Yes	Yes	Yes	Good
Lin (2005) {ID 2065}	Yes	Yes	Yes	No (ICD-9-CM codes not specified)	No(?) (ICD-CM codes used)	Yes	Yes	Fair