Drug Class Review

Antiepileptic Drugs for indications other than Epilepsy

Final Report Update 2 Evidence Tables

October 2008

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

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

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

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Head-to-Head Controlled Trials

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
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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

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
Bahk (2005) South Korea (Poor)	Oral lorazepam < / = 4 mg/d; injectable lorazepam except within 24 h before completing rating scales; antiparkinsonian drugs	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

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
Bahk (2005) South Korea (Poor)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(13) Method of adverse effects assessment?
Bahk (2005) South Korea (Poor)	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)	Monitoring

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

Author, year Country Trial name (Quality score)	(14) Adverse effects reported
Bahk (2005) South Korea (Poor)	**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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

Author, year Country Trial name (Quality score)	(15) Total withdrawals; withdrawals due to adverse events	(16) Comments
Bahk (2005) South Korea (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Head-to-Head Controlled Trials

Author, year Country Trial name (Quality score)
Bahk (2005) South Korea (Poor)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000 U.S. (Fair)	Levothyroxine; diuretic; triiodothyronine, clonazepam	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000 U.S. (Fair)	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)	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000 U.S. (Fair)	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).	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000 U.S. (Fair)	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%	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000 U.S. (Fair)	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. Randomized-controlled trials in patients with bipolar disorders

Frye, 2000
U.S.
(Fair)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002 U.S. (Fair) Same trial as Frye 2000	Levothyroxine; diuretic; triiodothyronine, clonazepam	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002 U.S. (Fair) Same trial as Frye 2000	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002 U.S. (Fair) Same trial as Frye 2000	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.	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002 U.S. (Fair) Same trial as Frye 2000	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002 U.S. (Fair) Same trial as Frye 2000	Not reported	A post hoc test was used for specific paired comparisons.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Obrocea, 2002
U.S.
(Fair)
Same trial as Frye 2000

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S	SB RCT, open-label, outpatient	DSM-IV diagnosis of bipolar I, II or not otherwise specified; no medications or a stable medication regimen for at least 1m prior to study entry; aged 18-65y; sodium serum levels between 134-146 mEq/L; currently experiencing hypomania (YMRS ≥ 12), confirmed on at least 2 occausions prior to randomization; no substance abuse/dependence within the past month; non-pregnant and not nursing; no hypersensitivity to oxcarbazepine or carbamazepine; no severe liver disease or dysfunction; no hyponatremia; no suspecion of chronic infectious disease	Oxcarbazepine 300 mg/d (increased to maximum 2400 mg/d, target dose 1200 mg/d, mean 1350 mg/d) vs Divalproex 500 mg/d (increased to minimum blood level of 50 mg/mL, mean 1167 mg/d) for 8w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S	Lorazepam 10 mg allowed for acute agitation; no other changes in ongoing medications were permitted Oxcarbazepine vs. Divaproex Lithium: 1(6.7%) vs. 1(6.7%) Anticonvulsants: 0(0%) vs. 2(13.3%) Antidepressants: 6(40.0%) vs. 3(20.0%) Antipsychotics: 1(6.7%) vs. 2(13.3%) Psychostimulants: 0(0%) vs. 1(6.7%) Anti-anxiety drugs: 1(6.7%) vs. 3(20.0%) Number of types of concomitant medications across groups found to be non-significant (p=0.56)	Clinical symptoms rated using YMRS, the IDS-C, and the Clinical Global Impressions scale for use in bipolar disorder	Oxcarbazepine vs. Divaproex Age: 30.1(8.0) vs. 36.9(9.9); p<0.05 Male (%): 6(40%) vs. 6(40%) Ethnicity: White: 14(93.3%) vs. 10(66.7%) Hispanic: 1(6.7%) vs. 4(26.7%) Other: 0(0%) vs. 1(6.7%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S	Oxcarbazepine vs. Divaproex Bipolar I: 4(26.7%) vs. 8(53.3%) Bipolar II: 7(46.7%) vs. 4(26.7%) Bipolar NOS: 4(26.7%) vs. 3(20.0%) Weight (lbs): 84.99(26.2) vs. 84.09(26.5); p=0.91 YMRS: 22.07(5.86) vs. 20.53(6.02) CGI1c: 4.08(0.86) vs. 4.00(0.68)	Number screened not reported / 30 eligible / 30 enrolled / 30 randomized	13 withdrawn / 6 lost to follow-up / 17 analyzed	Oxcarbazepine vs. Divaproex YMRS, mean change: -63.8% vs. -79.0%; p<0.001 vs baseline; between-group, p=0.95 IDS-C, mean change: -48.7% vs. -19.7%; p=0.82 CGI1c: 2.00(1.63) vs. 2.75(1.75); between-group, p=0.37

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S								AEs reported and assessed at every visit	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S	Oxcarbazepine vs. Divaproex Side effects, median: 2.0 vs. 3.0; between-group, p=0.29 Most common side effects were drowsiness or sedation in both groups; other common side effects were dizziness or lightheadedness, blurred vision, increased thirst and headaches in the oxcarbazepine group; tiredness, decreased appetite, and weight gain in the divaproex grop No patients developed hyponatremia	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007 U.S	Oxcarbazepine vs. Divaproex Total withdrawals: 13(53.3%) Withdrawals due to AEs: 1(3.3%) Other reasons for withdrawal inlcude worsening mood symptoms, lack of improvement, and personal reasons	Clinical symptoms were evaluated weekly for 4w, then biweekly for 4w for a total of 8w 16 patients used monotherapy, 14 as add-on treatment; detailed concomitant medical treatment described in text Results from a tw-wave ANOVA with one between-subjects factor (group) and one within-subjects factor showed non-signficant effects for groups (p=0.81), visits (p=0.25) and group/visit interaction (p=0.31) Rater blind to treatment assignments completed all ratings

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2007
U.S

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000 India (Poor)	Diazepam, promethazine	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000 India (Poor)	Not reported	Numbers screened and eligible not reported / 30 enrolled / 30 randomized	6 (20.0%) withdrew / lost to follow-up NR 30 analyzed	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000 India (Poor)	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	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000 India (Poor)	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%	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000 India (Poor)	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. Randomized-controlled trials in patients with bipolar disorders

Vasudev, 2000
India
(Poor)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(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
Bowden, 1994 U.S.	Multicenter, randomized, double-blind, parallel-group, placebo-controlled study Inpatient setting	Men and women 18-65y who met Research Diagnostic Criteria for manic disorder based on the structured interview and rating scale of the Schedule for Affective Disorders and Schizophrenia; YMRS ≥ 14	Divalprox sodium 750 mg/d tid (increased to 1000 mg/d at 3d) vs. Lithium 900 mg/d tid (increased to 1200 mg/d at 3d) vs. Placebo	3 to 21 day washout period based on half-life of the psychoactive drug taken on admission

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(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
Bowden, 1994 U.S.	Patients terminated from study if they required psychoactive medication; protocol allowed use of adjunctive chloral hydrate (maximum 4 g/d) or lorazepam (maximum 2 mg/d) as need for control of agitation, irritability, restlessness, insomnia and hostile behaviors; medications not permitting within 8h of assessment; neuroleptic drugs not allowed NSD observed among groups for antimania medication use	SADS, Research Diagnostic criteria, SADS-C, GAS on the first and last day of study; Affective Disorder Rating Scale (ADRS) given on days 3, 5, 7, 9, 12, 18, and 20; SADS-C and GAS administered on days 5, 10, 15, and 21; YMRS	Divalproex vs. Lithium vs. Placebo Age: 40.4(12.8) vs. 39.1(11.2) vs. 39.0(10.0) Male (%): 36(52%) vs. 26(72%) vs. 42(57%) Ethnicity: White: 50(73%) vs. 24(66%) vs. 53(74%) Black: 12(17%) vs. 6(17%) vs. 14(19%) Other: 7(10%) vs. 6(17%) vs. 7(9%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(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
Bowden, 1994 U.S.	Divalproex vs. Lithium vs. Placebo Duration of illness (y)_: 18.0(12.4) vs. 16.1(11.0) vs. 18.0(10.4) Any major mood episodes: 11(19%) vs. 1(4%) vs. 6(10%) Mania episode: 8(14%) vs. 0(0%) vs. 0(0%); p<0.05 Groups comparable except 8 patients with > 4 episodes were in the divalproex group Prior lithium treatment: 54(78%) vs. 31(86%) vs. 61(82%) Effective, tolerated: 22(41%) vs. 16(52%) vs. 19(31%) Effective, not tolerated: 7(13%) vs. 0(0%) vs. 6(10%) Ineffective, tolerated: 19(35%) vs. 11(35%) vs. 31(51%) Ineffective, not tolerated: 6(11%) vs. 4(13%) vs. 5(8%)	Number screened not reported / number eligible not reported / 179 enrollled / 179 randomized	82 withdrew / lost to follow-up not reported / 176 analyzed (ITT population)	Divalproex vs. Lithium vs. Placebo GAS, mean change: 7.6 vs. NR vs. 3.8; p=0.06 ADRS, mean change: Mania: -4.9 vs. -5.9 vs. -0.2 Elation/grandosity: -2.6 vs. NR vs. -0.7 Psychosis: -2.7 vs. NR vs. 0.6 > 50% improvement, Manic Syndrome subscore: 48% vs. 49% vs. 25%; p=0.004, divalproex vs. placebo; p=0.025, lithium vs. placebo

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Bowden, 1994 U.S.	Divalproex patients had greater improvement on Manic Syndrome subscale (day 5), MRS (day 10) and the Behavior and Ideation subscale score than placebo Divalproex had greater improvement in elevated modd, less need for sleep, excessive activity and motor hyperactivity than placebo; greater improvement in excessive activity and motor hyperactivity than lithium group	Divalproex vs. Lithium vs. Placebo Of 142 patients with known lithium responsiveness prior to the study: Responders: MRS, mean change: -7.4 vs. -15.3 vs. -4.0 Non-responders: MRS, mean change: -10.8 vs. -1.0 vs. -3.2	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?
Bowden, 1994 U.S.	Monitored

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Bowden, 1994 U.S.	Divalproex vs. Lithium vs. Placebo AEs: 58(84%) vs. 33(92%) vs. 58(78%) Asthenia: 9(13%) vs. 7(19%) vs. 7(9%) Constipation: 7(10%) vs. 6(17%) vs. 5(7%) Diarrhea: 8(12%) vs. 5(14%) vs. 13(18%) Dizziness: 11(16%) vs. 3(8%) vs. 4(5%) Fever: 1(1%) vs. 5(14%) vs. 3(4%); p<0.05, lithium vs. divalproex Headache: 15(22%) vs. 14(39%) vs. 24(32%) Nausea: 16(23%) vs. 11(31%) vs. 11(15%) Pain: 13(19%) vs. 1(3%) vs. 15(20%); p<0.05, lithium/divalproex vs. placebo Somnolence: 13(16%) vs. 7(19%) vs. 11(15%) Twitching: 2(3%) vs. 3(8%) vs. 0(0%); p<0.05, lithium vs. placebo Vomiting: 10(14%) vs. 9(25%) vs. 3(4%); p<0.05, divalproex vs. lithium/placebo No AEs related to bleeding or bruising occurred in any patient with reduction in platelet count (platelet count, mean change: 77x10^9/L divalproex only); hepatic function did not change or improve with divalproex Lithium patients had increased platelet, WBC, and neutrophil counts No other clinically significant changes observed in any group	Divalproex vs. Lithium vs. Placebo Total withdrawals: 33/69(48%) vs. 22/36(61%) vs. 47/74(64%) Withdrawals due to AEs: Not reported (rate of intolerance to treatment higher in lithium group)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Active-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(16) Comments
Bowden, 1994 U.S.	Medication adjustments made by an unblinded physician throughout the study Patients terminated from study if they had a reducation > 50% from baseline in SADS-C Mania Rating score; no SADS-C Mania rating score > 2; and GAS score > 70

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	RCT, open-label, add-on therapy, single-center (Mood and Anxiety Disorders Unit of the University of Turin)	Patients with a diagnosis of bipolar disorder, manic or hypomanic episodel YMRS ≥ 16; Hamitlton Depression Rating Scale ≤ 7; > 1y lithium treatment Patients excluded if administered other concurrent drugs (except benzodiazepines) during index manic or hypomanic episode	Valproate 500-1500 mg/d (mean dose 972 mg/d) vs. Olanzapine 7.5-15.0 mg/d (mean dose 11.25) add-on to lithium for 8w	Not reported
Ichim, 2000 South Africa	DB, RCT, pilot study, inpatient	Male and female inpatients, aged 18-65y; admitted with an acute manic episode. All must meet DSM-IV criteria for manic phase of BPD Patients excluded if they had abnormal liver function, thyroid function, or hematological findings; other acute medical disorder or medical disorder requiring frequent changes in medication; received treatment with neuroleptic deport preparation within the last month or fluoxetine within past 5w; or had drug or alcohol abuse	Lamotrigine (titrated from 25 mg/d at 1w to 50 mg/d at 2w and finally, 100 mg/d at 3w) vs. Lithium 400mg bid	1d; a longer wash-out period not practical due to difficulty of withholding treatment from disturbed patients

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	Benzodiazepines; lithium dosages maintained unchanged throughout study; no other concmitant medications allowed during study	YMRS, CGI-S and CGI-I administered weekly throughout study	Valproate vs. Olanzapine Age: 48.6(12.8) vs. 45(12.4); p=0.528 Male (%): 5(56.6%) vs. 7(58.3%); p=0.899 Ethnicity: Not reported
Ichim, 2000 South Africa	Lorazepam 4-12 mg/d as rescue medication allowed to control aggression; any exisiting psychotropic medication discontinued for > 1d before entering study	Psychiatric condition measured using MRS, Brief Psychiatric Rating Scale (BPRS), CGI, and the Global Assessment Functioning scale every week for 4w	Lamotrigine vs. Lithium Age: 33.6 vs. 31.9 Male (%): 8(53.3%) vs. 8(53.3%) Ethnicity: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	Valproate vs. Olanzapine Bipolar I: 4(44.4%) vs. 5(41.7%); p=0.899 Duration of illness (y): 18.0(7.45) vs. 16.4(10.7); p=0.236 Lithium blood levels (mmol/L): 0.78(0.13) vs. 0.76(0.12); p=0.679	Number screened not reported / number eligible not reported / 21 enrolled / 21 randomized	0 withdrawn / 0 lost to follow-up / 21 anaylzed	Valproate vs. Olanzapine Mean change, YMRS: -17.67(6.89) vs. -20.08(5.64); p=0.367 Mean change, CGI-S: -2.56(0.88) vs. -3.08(0.66); p=0.100 CGI-I: 1.44(0.52) vs. 1.33(0.49); p=0.625 Both groups showed significant reduction (p<0.001) YMRS scores associated with type of drug (p=0.014); type of BPD (p=0.389) and duration of illness (p=0.836) had not effect on predicting YMRS reduction
Ichim, 2000 South Africa	Lamotrigine vs. Lithium Duration of episode (d): 13.3 vs. 19.3; p=0.048; p=0.076 with outlier removed Depressive episodes: 0.7 vs. 0.7 Previous admissions: 1.8 vs. 2.9 BPRS: 52.8 vs. 46.8 MRS: 34.4 vs. 31.6 CGI-S: 4.93 vs. 4.67; NSD GAF: 44.7 vs. 45.5	Number screened not reported / number eligible not reported / 30 enrolled / 30 randomized	5 withdrawn / lost to follow-up not reported / 20 analyzed	Lamotrigine vs. Lithium BPRS: 30.2 (p=0.0002) vs. 28.2(0.0005); NSD between groups MRS: 14.3 (p=0.0002) vs. 13.2(p=0.0005); NSD between groups CGI-S: 2.77(p=0.0002) vs. 2.83(p=0.0005); NSD between groups CGI-I: Both groups showed improvement, NSD between groups GAF: 55.7 (p=0.001) vs. 56.2 (p=0.002); NSD between groups

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	Valproate vs. Olanzapine Responders: 6(66.7%) vs. 10(83.3%); p=0.375 Response at week 4 significant between-group, p=0.030 in favor of Olanzapine Remission: 5(55.6%) vs. 7(58.3%); p=0.899	
Ichim, 2000 South Africa	Lamotrigine vs. Lithium Response rate (≥ 50% reduction in MRS): 8(53.3%) vs. 9(60.0%) Response rate (≥50% reduction in BPRS): 7(46.7%) vs. 4(26.7%) Response rate (CGI-S=1-2): 7(46.7%) vs. 4(26.7%)	Lamotrigine vs. Lithium Rescue medication, mean dose (mg/d): 2.65 vs. 2.66; NSD between groups

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	AEs reported at every time pont by direct interview with patinent; no administration of specific scale
Ichim, 2000 South Africa	BP measured at each visit

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	Valproate vs. Olanzapine Somnolence: 1(11.1%) vs. 3(25.0%) Tremor: 2(22.2%) vs. 2(16.7%) Weight gain: 1(11.1%) vs. 1(8.3%) Headache: 1(11.1%) vs. 1(8.3%)	Total withdrawals: 0(0%) Withdrawals due to AEs: 0(0%)
Ichim, 2000 South Africa	No significant AEs noted in either group; no rashes reported in Lamotrigine group	Lamotrigine vs. Lithium Total withdrawals: 2/15(13.3) vs. 3/15(20%) Withdrawals due to AEs: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Maina, 2006 Italy	MMRM showed difference between groups disappeared over time for the CGI-S outcome
Ichim, 2000 South Africa	Selection bias; absence of placebo group; low dosages to minimize AEs

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	DB, RCT, multi-center Inpatient and outpaient setting	Untreated patients diagnosed as endogenous manics (i.e., manic-depressive psychosis, manic-type or manic, depressive psychosis, circular-type but currently manic according to the International Classification of Diseases, 9th edition); aged 14-65y	Carbamazepine 100 mg tid (maximum dose, 900 mg/d; range 300-900 mg/d) vs. Chloropromazine 50 mg tid (maximum dose, 450 mg/d; range 150-450 mg/d) for 3-5w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	Psychotropic drugs prohibited; hypnotics allowed at bedtime	Physician assessment of degree of illness (0-normal, 4-extremely severe) and improvement (0-6) weekly; Clinical Psychopharmacology Research Group (CPRG) scale assessed mania weekly	Age: 35.5 Male (%): 32(53.3%) Ethnicity: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	Monopolar mania: 11(18.3%) Bipolar mania: 41(68.3%) Mixed mania: 1(1.7%) First mania attack: 7(11.7%) NSD between groups in regards to background characteristics (data NR) Carbamazepine vs. Chloropromazine Moderate severity: 16(50%) vs. 12(43%) Severe severity: 14(44%) vs. 12(43%) Symtom rating scale: 74.5 vs. 71.6	Number screened not reported / number eligible not reported / 63 enrolled / 63 randomized	8 withdrawn / lost to follow-up not reported / 55 analyzed	Carbamazepine vs. Chloropromazine Marked improvement: 12(40%) vs. 5(20%) Moderate marked improvement: 21(70%) vs. 15(60%) Improvement slight higher in carbamazepine group though not significant Rate of improvement: 1w: 20% vs. 13% 2w: 45% vs. 43% 3w: 65% vs. 52% 4w: 76% vs. 60% 5w: 77% vs. 54% 6w: 71% vs. 56%

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	Carbamazepine vs. Chloropromazine Onset of improvement: 3d: 4(12.5%) vs. 2(7.1%) 4-7d: 15(46.9%) vs. 11(39.3%) 8-10d: 2(6.3%) vs. 1(3.6%) 11-14d: 1(3.1%) vs. 2(7.1%) 15d: 10(31.3%) vs. 12(42.9%) NSD between groups in regard to onset of improvement	No correlation between overall therapeutic response and any patient characteristics (e.g., age); nor between overall therapeutic response and treatment group	Carbamazepine vs. Chloropromazine Symptom rating scale: 44.3 vs. 47.8 Difference in scores: 30.2 vs. 23.8 Trend toward greater decrease in rating score observed in carbamazepine group, NSD between groups in overall changes in rating scale

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	Side effects evaluated weekly using scale (0-none, 3-severe); laboratory measures taken weekly to determine if drug should be discontinued in the event of serious AEs	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979 Japan	Carbamazepine vs. Chloropromazine AEs: 59% vs. 86%; p<0.05 Drowsiness: 29% vs. 59%; p<0.05 Headache: 26% vs. 31% Cutaneous symptoms: 16% vs. Dry mouth: 15% vs. 24% Lassitude: 15% vs. 21% Dizziness: 12% vs. 28% Orthostatic hypotension: 0% vs. 17% Weakness: 0% vs. 17% Hypersalivation: 0% vs. 17% Nasal stuffiness: 0% vs. 17%; p<0.05 Abnormal changes in serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and leukocyte count in both groups; none disclosed any serious AE suggestive of kidney, liver or heart damage	Total withdrawals: 8/63(12.7%) Withdrawals due to AEs: 4/63(9.5%) (due to blurred vision, fever, exanthenia and leg numbness)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Okuma, 1979
Japan

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	DB, single-center Inpatient setting	Bipolar Manic by the Research Diagnostic Criteria and by the DSM-III criteria	Carbamazepine 200-400 mg/d (titrated against side effects, maximum dosage of 1600-2000 mg/d; mean dose 1242 mg/d) vs. Neuroleptics (chloropromazine, thioridazine, pimozide) vs. Lithium for 21d	2d placebo-controlled phase before administration of medication

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	None	Consensus ratings twice daily by nurse-observers using the Bunney-Hamburg scale for depression, mania, anxiety, anger and psychosis	Age: Not reported Male (%): Not reported Ethnicity: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	Responders (n=12) vs. Nonresponders (n=9) MRS: 8.0(1.4) vs. 3.4(2.2); p<0.001 Age on onset: 20.3(4.9) vs. 17.9(4.7); p=0.30 Duration of illness: 18.3(11.4) vs. 15.3(12.1); p=0.59 Total episodes: 42.5(50.3) vs. 18.2(17.3); p=0.15 Prior illness (w): 288.8(258.9) vs. 269.1(275.0); p=0.88 Prior hospitalization (w): 156.5(297.9) vs. 61.7(56.6); p=0.31 Prior manic episodes: 23.5(29.0); vs. 10.3(8.6); p=0.17 Prior depressive episodes: 19.0(21.7) vs. 7.8(8.9); p=0.25 Episodes/year: 4.4(6.0) vs. 1.2(0.8); p=0.098 Episodes in prior year: 7.0(5.6) vs. 2.7(2.4); p=0.03 Dysphoric: 6.2(1.9) vs. 4.5(2.1); p<0.10	Number screened not reported / number eligible not reported / 19 enrolled / 19 randomized	0 withdrawn / 0 lost to follow-up / 19 analyzed	Degree of improvement with carbamazepine similar to those treated with neuroleptics and lithium in previous studies Response (≥ 2 ponts in mania ratings): 12(63%) Responders were signficantly more manic during placebo phase than nonresponders; more dysphroic and more rapid cyclers than nonresponders; even though there was marked to moderate response, they were as symptomatic as non-responders Response correlated with degree of psychosis (r=0.41, p<0.09) and anxiety (r=0.46, p<0.05) No relationship between carbamazepne blood levels to degree of clinical antimanic response

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	8/9 patients with placebo discontinuation trials led to relapse of manic or psychotic symptomalogy; a second carbamazepine trial lead to improvement again Robust response in 6/7 patients receiving lithium in addition to carbamazepine at end of trial	Responders (n=12) vs. Nonresponders (n=9) MRS < 2.5: 7(58.3%) vs. 2(22.2%); NSD Sleep improvement significantly improvement in responders (p<0.001) than non-responders (between-group, p<0.01)	Negative history for affective illness in first degree relatives with responders; positive history equally distributed between groups (p=0.04)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	No AEs reported No patients had EEG abnormalities	Total withdrawals: 0(0%) Withdrawals due to AEs: 0(0%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Post, 1987 Canada	Improvement on carbamazepine was not always complete within this time frame

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	RCT, multicenter, open-label, parallel-group study Inpatient and outpatient setting	Patients ≥ 18y with DSM-IV diagnosis of bipolar disorder and hospitalized for treatment of acute manic or mixed episode; female patients of childbearing age must be using effective birth control	Divalproex sodium 15-20 mg/kg/d (titrated up to optimize clinical response; average dose 1504 mg/d) vs. Lithium (1800 mg/d for acute mania, between 900-1200 mg/d for maintenance; average dose 1213 mg/d) for 12m Divalproex vs. Lithium Average follow-up (d): 306(119) vs. 339(85); p=0.025	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	Anticoagulants were prohibited; lithium and divalproex allowed in combination with other study drug; during initial hospital stay most patients received an antipsychotic combined with study medication; some patients continued with antipsychotics or antidepressants	Mania Rating Scale and the Depressive Syndrome Scale at baseline and at discharge; QoL and clinical outcomes assessed every 3m; interviews conducted by investigators using the World Health Organization Composite Internation Diagnostic Interview (CIDI); Medical Outcomes Stuy 36-item short-form Health Survey, the Mental Health Index to report additional QoL and other patient ouc	Divalproex vs. Lithium Age: 33.8(13.8) vs. 37.4(11.7) Male (%): 50(48.1%) vs. 48(49.5%) Ethnicity: White: 62(59.6%) vs. 56(57.7%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	Divalproex vs. Lithium Rapid cycling: 11(11.1%) vs. 13(13.4%) Mixed mania: 50(48.1%) vs. 54(55.2%) Alcohol abuse: 46(44.2%) vs. 47(48.2%) Drug abuse: 45(43.3%) vs. 48(49.5%) Hospitalization during acute phase (d): 11.0(9.4) vs. 11.7(9.6) MRS: 22.0(8.9) vs. 23.2(8.5) DSS: 24.0(7.3) vs. 25.2(8.0) SF-36, physical component: 484.3(9.6) vs. 49.4(9.8) SF-36, mental component: 40.4(14.2) vs. 39.3(14.0) Previous lithium: 68(65%) vs. 61(63%) Previous divalproex: 45(43%) vs. 31(32%)	Number screened not reported / number eligible not reported / 221 enrolled / 221 randomized	142 withdrawn / 47 lost to follow-up / 172 analyzed Only 201/221 entered maintenance phase (between-group, p=0.051 for available follow-up data) --	Divalproex vs. Lithium Monotherapy: 3m: 26% vs. 22% >3m: 69% vs. 63% Use of combination with lithium or divalproex: 3m: 14% vsl 18% >3m: 3% vs. 6% Use of antidepressants or antipsychotics: 3m: 47% vs. 50% >3m: 29% vs. 30%

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	Divalproex vs. Lithium No mania and depression (m): 5.3(4.6) vs. 5.4(4.4); p=0.814 Physical component: 1m: 48.2(11.2) vs. 50.4(9.8) 3m: 49.0(10.7) vs. 50.7(11.1) 6m: 49.8(11.2) vs. 49.9(10.1) 9m: 48.8(11.4) vs. 49.1(10.1) 12m: 49.1(10.9) vs. 50.4(9.8) Mental component: 1m: 42.0(14.4) vs. 42.2(12.9) 3m: 41.8(13.4) vs. 40.4(14.1) 6m: 43.5(13.8) vs. 42.6(12.5) 9m: 44.7(12.9) vs. 43.2(13.7) 12m: 44.1(12.6) vs. 43.1(12.2) NSD between groups based on the MCS; or base on the PCS or measures of disability days (data NR)	Divalproex vs. Lithium Mental health: 1m: 64.5(19.0) vs. 65.8(17.1) 3m: 66.0(18.1) vs. 63.1(19.5) 6m: 66.3(18.2) vs. 64.5(17.1) 9m: 67.6(17.3) vs. 65.1(19.0) 12m: 66.8(18.8) vs. 65.7(17.1) Time to first hospitalization not significant between groups (p=0.616) Hospital stay (d): 11.3(21.4) vs. 14.1(27.7); p=0.417 Mean hospital stay was lower in patients continuing therapy than those who discontinued (p=0.016)	Use of mood stabilizers (n=129) vs no-use of mood stablizers (n=72): MCS scores: 6m: 43.7 vs. 40.7; p=0.194 9m: 44.9 vs. 40.7; p=0.057 12m: 44.0 vs. 41.9; p=0.280 Restricted activity (d): 12.8(2.4) vs. 23.6(4.8); p=0.048

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	AEs recorded during acute phase; during 12m maintenance phase, AEs monitored

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	No AEs reported	Divalproex vs. Lithium Total withdrawals: 142/221 Withdrawals due to AEs: 7/104(7%) vs. 14/97(14%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Revicki, 2005 U.S.	Medical resource use and costs were collected; study medication costs higher in divalproex group, but medical and inpatient costs were low (p=0.693) NSD between early dropouts (n=17) and those who continued based on gender, race, age, hospitalization; only significant in education (p=0.049), nocompliance (p<0.0001), suicidality (p=0.005) and discharge setting (p=0.046)	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1997 Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	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)	Carbamazepine vs. Lithium Age, mean (SD), y: 42 (14) vs. 45 (14) Male / Female: 46% / 54% vs. 50% / 50% Ethnicity not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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) 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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1997 Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1997 Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1997 Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1997 Germany MAP Study (Multicenter study of long-term treatment of affective and schizoaffective psychoses study) (Poor)	Open-label design.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1998 Germany, Switzerland MAP Study (Poor)	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	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1998 Germany, Switzerland MAP Study (Poor)	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)	*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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1998 Germany, Switzerland MAP Study (Poor)	*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 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1998 Germany, Switzerland MAP Study (Poor)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1998 Germany, Switzerland MAP Study (Poor)	Not reported	Total withdrawals: 28/85 (32.9%) vs. 12/86 (14.0%) (before suffering recurrence; p = 0.004)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 "bipolar II/NOS" Germany MAP Study (Poor)	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.	Age, mean, y: 41 Female: 60% Ethnicity not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 "bipolar II/NOS" Germany MAP Study (Poor)	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	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)	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 "bipolar II/NOS" Germany MAP Study (Poor)	NSD in survival times by Kaplan-Meier estimates (ITT, p = 0.17 to 0.94)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 "bipolar II/NOS" Germany MAP Study (Poor)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 "bipolar II/NOS" Germany MAP Study (Poor)	Not reported	Carbamazepine vs. Lithium Total withdrawals: 11/29 (38%) vs. 7/28 (25%) Withdrawals due to adverse events: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	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)	Age, mean, y: 40 Male / Female: 50% / 50% Ethnicity not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Greil, 1999 (-- "bipolar I") Germany MAP Study (Poor)	Not reported	Total withdrawals: 17/56 (30%) vs. 5/58 (8%) Withdrawals due to adverse events: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Kleindienst, 2002 Germany, Switzerland MAP Study (Poor)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Kleindienst, 2002 Germany, Switzerland MAP Study (Poor)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Kleindienst, 2002 Germany, Switzerland MAP Study (Poor)	% 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 1. Randomized-controlled trials in patients with bipolar disorders

Kleindienst, 2002 Germany, Switzerland MAP Study (Poor)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Kleindienst, 2002 Germany, Switzerland MAP Study (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	Run-in acutely randomized patients on double-blind treatment; entered actual prophylactile phase after recovery from acute episode.
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	7- to 14-d washout of psychotropic medications other than chloral hydrate or barbiturates for sedation

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Hartong, 2003 The Netherlands (Fair)	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.	Mean age (SD) 41.9 (13.9) 45.7% male, 54.3% female Ethnicity not reported
Lerer, 1987 U.S. (Poor)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Hartong, 2003 The Netherlands (Fair)	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	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)
Lerer, 1987 U.S. (Poor)	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	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 ($p < 0.01$)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Hartong, 2003 The Netherlands (Fair)	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)
Lerer, 1987 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Hartong, 2003 The Netherlands (Fair)	Monitored	
Lerer, 1987 U.S. (Poor)	Monitoring	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Hartong, 2003 The Netherlands (Fair)	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%)
Lerer, 1987 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

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.
Lerer, 1987 U.S. (Poor)	Cannot exclude the possibility of a type II error.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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	None
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	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.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Lusznat, 1988 U.K. (Poor)	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.	Not reported
Coxhead, 1992 U.K. (Fair)	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.	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Lusznat, 1988 U.K. (Poor)	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	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)
Coxhead, 1992 U.K. (Fair)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Lusznat, 1988 U.K. (Poor)	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%)	
Coxhead, 1992 U.K. (Fair)	*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 1. Randomized-controlled trials in patients with bipolar disorders

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.	
Coxhead, 1992 U.K. (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Lusznat, 1988 U.K. (Poor)	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
Coxhead, 1992 U.K. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Lusznat, 1988 U.K. (Poor)	High rate of drop-outs, which appeared to occur at random.
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 1. Randomized-controlled trials in patients with bipolar disorders

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.	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Small, 1991 U.S. (Poor)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Small, 1991 U.S. (Poor)	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	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.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Small, 1991 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Small, 1991 U.S. (Poor)	Monitored with the general inquiry part of the Systematic Assessment of the treatment of Emergent Events (SAFTEE)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Small, 1991 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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)	Washout - previous carbamazepine or lithium was tapered over 1 mo if patient had been randomized to the other treatment

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Denicoff, 1997 U.S. (Poor)	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	Age, mean (SD), y: 41.3 (11.4) Male / Female: 25 / 27 Ethnicity not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Denicoff, 1997 U.S. (Poor)	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.	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Denicoff, 1997 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

Denicoff, 1997 U.S. (Poor)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Denicoff, 1997 U.S. (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2000 Canada, U.S. (Fair)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2000 Canada, U.S. (Fair)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2000 Canada, U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2000 Canada, U.S. (Fair)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2000 Canada, U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	Same as Bowden, 2000

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Gyulai, 2003 U.S. (Fair)	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.	Age, mean (SD), y: 39.2 (11.8) Male / Female: Data not reported Ethnicity not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Gyulai, 2003 U.S. (Fair)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Gyulai, 2003 U.S. (Fair)	*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 1. Randomized-controlled trials in patients with bipolar disorders

Gyulai, 2003 U.S. (Fair)	Not reported (see Bowden, 2000)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Gyulai, 2003 U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	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	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	Nonpsychotic 54.6% Mixed Episode 43.0% Manic Episode 57.0% Rapid Cycling 57.4%	330/--/--/251	79/ Not reported /248	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 ($p < 0.03$)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2002 U.S. (Fair)	3 Divalproex patients excluded from primary efficacy analysis because of no postbaseline assessment.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2003 U.S. (Fair)	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):	Olanzapine vs. Divalproex Mean (SD) age: 40.0 (12.1) vs. 41.1 (12.3) 42.6% male, 57.4% female 80.9% Caucasian

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2003 U.S. (Fair)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2003 U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2003 U.S. (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Tohen, 2003 U.S. (Fair)	*Treatment-emergent AEs*	Olanzapine vs. Divalproex
	Significantly more common on olanzapine: somnolence, dry mouth , increased appetite, weight gain, akathisia, increased alanine aminotransferase	Total withdrawals: 106/125 (84.8%) vs. 106/126 (84.1%) (p = 1.00)
	Significantly more common on divalproex: nausea, nervousness, rectal disorder, low albumin, low platelets	Withdrawals due to adverse events: 31/125 (24.8%) vs. 25/126 (19.8%) (p = 0.37)
	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)	Withdrawals due to weight gain: 4/125 (3.2%) vs. 0/126 (0.0%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	1- to 3-day non-drug run-in 1- to 3-day washout of previous psychoactive medications

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Zajecka, 2002 U.S. (Fair)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Zajecka, 2002 U.S. (Fair)	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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Zajecka, 2002 U.S. (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Zajecka, 2002 U.S. (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Zajecka, 2002 U.S. (Fair)	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 Total cholesterol, mg/dl: -1.69 vs. 13.29 (p = 0.019) LDL, mg/dl: -4.43 vs. 8.78 (p = 0.022) Platelet count (x 109/l): -52.19 vs. 0.78 (p < 0.001)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	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.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	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.	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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) 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	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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Bowden, 2003 Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia Lamictal 606 Study (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2003 U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	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).	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2003 U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2003 U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2003 U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2003 U.S., Canada, Denmark, Finland, U.K. Lamictal 605 Study (Fair)	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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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	None
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	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

McIntyre, 2002 Canada (Poor)	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.	Topiramate (N = 18) vs. Bupropion SR (N = 18) Age, mean, y: 39 vs. 43 Male / Female: 11 / 7 vs. 10 / 8
Okuma, 1990 Japan (Poor)	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	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

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

McIntyre, 2002 Canada (Poor)	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	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
Okuma, 1990 Japan (Poor)	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	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%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

McIntyre, 2002 Canada (Poor)	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)
Okuma, 1990 Japan (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

McIntyre, 2002 Canada (Poor)	Monitored	
Okuma, 1990 Japan (Poor)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

McIntyre, 2002 Canada (Poor)	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%)
Okuma, 1990 Japan (Poor)	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 1. Randomized-controlled trials in patients with bipolar disorders

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.	
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 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	RCT, multicenter, inpatient and outpatient	Inclusion- Total score 20 or greater on MADRS and 4 on CGI-S; at least 1 episode of mania or mixed to require treatment w/mood stabilizer or antipsychotic Exclusion- Serious suicide risk; substance abuse in last 30 days; YMRS 14 or more; currently taking or previously failed on olanzapine or lamotrigine	olanzapine/fluoxetine combination (OFC) 6/25, 6/50, 12/25, or 12/50 mg/day vs. lamotrigine 200 mg/day 7 weeks	2 day screening and all patients were tapered off all meds24 hours prior to randomization/

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	Anticholinergic meds allowed for EPS and benzodiaepines or other hypnotics	Overall bipolar status as measured by CGI-S, MADRS, YMRS, BPRS, CGI-I, PGI, GAF (Global Assessment of Functioning Scale), MOS, BSI (Brief Symptom Inventory) Patients evaluated at randomization, 3 days, 4 days, then weekly	37.0 years 60.0% female 81.7 white

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	Age of onset 19.0 years Outpatients 99%	NR/NR/NR/410	139/ 47/410	Change from baseline at 7 weeks-mixed effects model repeated measures (SE) OFC vs. lamotrigine CGI-S -1.43(0.06) vs. -1.18(0.06) P = 0.002 MADRS -14.91(0.49) vs. -12.92(0.50) P = 0.002 YMRS -1.68(0.18) vs. -0.94(0.18) P= 0.001 GAF 11.00((0.52) vs. 9.22(0.52) P = 0.010 BSI -0.8 (0.05) vs. -0.67(0.05) P= 0.028 CGI-I 2.41(0.06) vs. 2.63(0.06) P = 0.003 PGI 2.59(0.06) vs. 2.84(0.06) P = 0.002 BPRS -11.62(0.55) vs. -10.80(0.57) P = 0.253

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	OFC vs. lamotrigine Responders (> 50 reduction in MADRS) 68.8% vs. 59.7% P = 0.073 Time to response median (95% CI) 17(14 to 22) vs. 23 (21 to 34) P = 0.010

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	Evaluation of TEAEs, discontinuation due to Aes, vital sign measurements and lab tests, all via MedDRA

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006 USA bipolar I depression	Treatment-emergent AEs OFC vs. lamotrigine % Smnolence 18.5 vs. 8.3 P = 0.003 Inceased appetite 17.6 vs. 8.3 P = 0.008 Dry mouth 15.6 vs. 5.9 P = 0.002 Increased weight 14.1 vs. 2.0 P < 0.001 Dizziness 13.7 vs. 7.8 P = 0.078 Sedation 13.7 vs. 2.5 P < 0.001 Headache 11.7 vs. 9.3 P = 0.52 Tremor 10.7 vs. 1.5 P < 0.001 Fatigue 8.3 vs. 5.4 P = 0.328 Nausea 7.8 vs. 7.8 P = 0.99 Insomnia 4.4 vs. 8.8 P 0.076 Rash 2.9 vs. 6.9 P = 0.071 Suicidal or self-injurious behavior 0.5 vs. 3.4 P = 0.037	139 withdrawals 32 due to AEs

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Brown, 2006
USA

bipolar I depression

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006 USA STEP-BD Bi-polar depression	RCT open-label	Inclusion - 1) were at least 18 years old, 2) met criteria for bipolar disorder type I or II with a current DSM-IV major depressive episode of at least 8 weeks before pathway entry, and 3) had not responded to treatment in first 12 weeks of standard or randomized care pathways for bipolar depression, or had a well-documented failure (e.g., a medical chart was available) to respond to at least two trials of antidepressants or an antidepressant and mood stabilizer regimen. Patients were required to be taking a mood stabilizer or agree to begin treatment with a mood stabilizer. Only patients who refused ECT at this stage were eligible for randomization to the open-label treatment conditions Exclusion- history of nonresponse to, intolerance of, or any medical contraindications to at least two of the study medications; if they met criteria for mixed episode or hypomania or if they met criteria for current substance abuse or dependence diagnosis	Lamotrigine doses started at 50 mg/day for 2 weeks, followed by 50 mg b.i.d. for 2 weeks, then increases in daily dose every week until the target dose of between 150 and 250 mg/day was reached. Inositol doses started at 2.5 to 5 g with a target dose of between 10 and 25 g. Risperidone doses started at between 0.5 and 1.0 mg with titration up to 6 mg as tolerated. up to 16 weeks	None at this point

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006 USA STEP-BD Bi-polar depression	Yes- Subjects were managed with an optimized mood stabilizer regimen (lithium, valproate, combined lithium and valproate, or carbamazepine) plus either one or two antidepressants.	recovery rate within equipoise randomization strata. Recovery was defined as 1) no more than two symptoms meeting DSM-IV threshold criteria for a major depressive, manic, or hypomanic episode, as determined with the clinician-administered Clinical Monitoring Form, and 2) no significant symptoms present for 8 weeks, consistent with the DSM-IV definition of full remission. Secondary outcome measures included Clinical Global Impression (CGI) severity ratings, Clinical Monitoring Form SUM-D and SUM-M scores, and Global Assessment of Functioning scores	33.0 - 53.8 years median age range 55% female 86% white

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006 USA STEP-BD Bi-polar depression		67/NR/NR/66	NR/NR/69 (Three subjects were willing to accept random assignment to any of the three treatments and therefore are included in two strata and are counted twice in the pairwise comparisons)	Recovery rate lamotrigine 23.8% vs. inositol 17.4% vs. risperidone 4.6%, SUM-D score base/end lamotrigine 7.0/3.9 vs. inositol 7.7/6.6 vs. risperidone 6.3/7.6 a significant difference in score between those assigned to lamotrigine and those assigned to risperidone (normal approximation z=2.85, p=0.004) or inositol (normal approximation z=-2.14, p=0.03). CGI rating base/end lamotrigine 4.6/2.9 vs. inositol 4.2/3.9 vs. risperidone 4.4/4.1 a significant difference in score between those assigned to lamotrigine and those assigned to risperidone (normal approximation z=2.85, p=0.004) or inositol (normal approximation z=-2.29, p=0.02).

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006	Duration of treatment (weeks)
USA	lamotrigine 12.2 vs. inositol 8.6%
STEP-BD	vs. risperidone 5.8
Bi-polar depression	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006 USA STEP-BD Bi-polar depression	NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006 USA STEP-BD Bi-polar depression	NR	NR NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nierenberg, 2006
USA
STEP-BD
Bi-polar depression

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	RCT open-label	Inclusion - at least 18 years; met criteria for DSM-IV bipolar I or II disorder, current major depressive episode Patients had to be currently on treatment with a mood stabilizer at adequate plasma level, all patients had previously been treated with a conventional antidepressant (SSRI, TCA, venlafaxine or bupropion) in an adequate dose and during at least 6 weeks without sufficient response or tolerance (including switch into mania or hypomania) in the current or in a prior episode. Exclusion- current alcohol or substance abuse or dependence; a severe neurological or other somatic illness; (risk of) pregnancy; current or recent (1 week) use of another antidepressant, an antipsychotic, or a benzodiazepine other than lorazepam >4 mg/day.	tranylcypromine 100 mg/day vs. lamotrigine 400 mg/day 10 weeks	NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	currently on treatment with a mood stabilizer at adequate plasma level	Clinical Global Impressions Scale for Bipolar Illness (CGI-BP) the IDS-C and the Young Mania Rating Scale (YMRS) Assessments at baseline, week 1, week 2 and from then biweekly until week 10	46.2 years 47.4% female Ethnicity NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	Duration of illness 23.6 years	1242/NR/NR/20/20 8/0/19	response of depression tranylcypromine (5/8, 62.5%) lamotrigine (4/11, 36.4%) (P = NS).

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	Tranylcypromine vs. Lamotrigine, mean (SD) change from baseline CGI-BP-Severity of depression 1.0 (2.8) vs. 0.6 (1.8) YMRS scores +1.25 (3.3) vs. +2.2 (7.9) CGI-BP-Severity of mania 0.0 (0.0) vs. 0.2 (1.0) Switch into mania (n, %) 0 (0) vs. 2 (18.2)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	10 patients who received tranylcypromine, side effects occurred in eight patients, including ataxia (n = 2), dizziness (n = 3), weakness, trembling (n = 2), high blood pressure, headaches, dry mouth, cold/hot flushes and impotence. In the 13 patients who received lamotrigine, nine patients reported side effects, including pain in attachment of muscles, transpiration, itching and irritated eyes, tremor (n = 2), diarrhoea, tiredness, obsessions and itchy rash over body	8 withdrawals in 1st 10 weeks 5 due to Aes

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Nolen, 2007 USA and Holland Refractory Bi Polar depression	Very small, no AE assessment reported and then Aes reported in way that cannot be compared.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	RCT, double blind	Inclusion- met DSM-IV criteria for bipolar disorder (BD) type I or II, with a current major depressive episode; outpatients, age 18–65, who spoke fluent English, and had a baseline 17-item Hamilton Depression Rating Scale (HAM-D) score of ≥16. Patients must have been treated with a mood stabilizer for at least the past 4 weeks Exclusion - a current hypomanic, manic, or mixed episode, score of ≥12, current psychotic symptoms, substance abuse/dependence during the past 3 months, current antidepressant use, discontinuation of any mood stabilizer, antidepressant, or antipsychotic medication within less than 5 half-lives, past treatment with lamotrigine or citalopram in combination with current mood stabilizer(s), unstable medical condition, history of Stevens– Johnson syndrome, lamotrigine-induced rash, or pregnancy.	lamotrigine 81.3-100 mg/day citalopram 21 mg/day as add-on treatment 12 weeks	None

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	treated with a mood stabilizer for at least the past 4 weeks (confirmed by clinical recordswhen available), including one or more of lithium (baseline serum level ≥0.6 mmol/L), divalproex sodium (baseline serum level ≥50 µg/mL), or carbamazepine (baseline serum level ≥4.0 µg/mL).	HAM-D, MADRS, YMRS, CGI Assessed at baseline, and weeks 1, 2, 4, 6, 8, 10 and 12	41 years 85% female Ethnicity NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	65% single, 40% living alone 70% completed at least some post-secondary education 60% unemployed, and 65% on disability	NR/NR/NR/20	8/0/19	Change in total MADRS score (citalopram -14.2, vs. Lamotrigine - 13.3 P = NS

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	Respose and remission shown in graphs but There were numerical, but no significant differences between treatment groups in favor of citalopram.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	NR except for withdrawal due to.	8 withdrawals 4 due to AEs

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Schaffer, 2006 Canada	small n

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	RCT, open label	Inclusion - Outpatients between the ages of 18–65; clear history of BDII confirmed by SCID-research version interview and met criteria for DSM-IV bipolar II disorder (hypomanic episode duration of 4 or more days), current episode depressed, and currently had a score of 18 or greater on the Hamilton Rating Scale for Depression-17 item (Ham-D17) or ontgomery–Asberg Depression Rating Scale (MADRS). Exclusion - history of clinically relevant intolerance or nonresponse to lithium (Li) or lamotrigine (LTG), an unstable medical illness, psychotic symptoms, active suicidal ideation or intent, or substance abuse or dependency within the last month. Women who were pregnant, planning to conceive, or breastfeeding	Lamotrigine (LTG) 900 mg/day Lithium (Li) 200 mg/day	Tapered off of former meds but no set time.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	Short-term use of limited benzodiazepines/hypnotics for a maximum of 5 consecutive days, on no more than one occasion over the course	HAM-D, MADRS, YMRS, CGI-BP, GAF	36 years 63% female 77% white

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	NR/NR/NR/102	50/18/90	LTG avs. Li Mean Ham-D 17 (SE) 8.00±1.28 vs. 6.97±1.33

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	Met response criteria (50% or greater reduction on Ham-D-17) LTG 67.5% vs. Li 55.1% remission rates without switch; LTG 75.6% vs. Li 59.2%	Mean baseline YMRS scores (SD) LTG 6.84±4.34 and Li 6.71±3.82 (p=0.63) mean endpoint scores (SE) LTG 2.92±0.93 and Li 3.00±0.97 P=0.68 Mean baseline CGI-BP severity scores LTG 4.5±0.7 and Li 4.6±0.6 mean endpoint scores(SE) LTG 1.9±0.31 and Li 2.2±0.32 p=0.61

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	NR- vital signs (weight, blood pressure, and pulse) were measured and a side effect assessment completed (but method not reported)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008 USA (Texas)	Lamotrigine vs. Lithium Cognitive slowing 7.3% vs. 26.5% Decreased sexual interest 2.4% vs. 16.3% Dizziness/lightheadedness 7.3% vs. 30.6% Drowsiness/panic 9.8% vs. 30.6% Dry mouth 19.5% vs. 53.1% Feeling dull 2.4% vs. 18.4% Impaired memory .0% vs. 20.4% Increase thirst 7.3% vs. 49.0% Increased appetite 4.9% vs. 28.6% Increased urinary frequency 2.4% vs. 32.7% Increased weight 4.9% vs. 22.5% Nausea/vomiting 24.4% vs. 46.9% Ringing in ears .0% vs. 12.2% Tremor 9.8% vs. 40.8% Upset stomach 19.5% vs. 42.9% Word finding 4.9% vs. 24.5%	50 withdrawals 18 due to Aes

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Suppes, 2008
USA (Texas)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(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
Bowden, 2006 U.S	DB, RCT, muticenter Inpatient setting	Male and female patients, aged 18-65y; hospitalized for acute excaberation; current DSM-IV-TR primary diagnosis of bipolar I disorder, manic or mixed type, confirmed by the Structured Clincial Interview; MRS ≥ 18 with > 4 item scores over 1	Divalproex ER qd (initial 25 mg/kg rounded to nearest 500 mg, increased by additional 500 mg on day 3; dose adjustments on days 7, 12, and 17 for emerging AEs, mean dose at end of study 3057 mg/d) vs. Placebo qd for 21d	3d minimum screening/wash-out period

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(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
Bowden, 2006 U.S	No adjunctive psychotropic medciations allowed; only lorazepam allowed during washout and treatment periods (maximum dose was 2 mg, during screening 6 mg/d, 1-7d was 4 mg/d, and 8-10d was 2 mg/d); lorazepam not allowed within 8h before efficacy assessment	SADS-C (including the MRS and Depressive Syndrome Scale) and the GAS assessed on days 1, 5, 10, 15 and 21; the DSS only on the first and last day	Divalproex vs. Placebo Age: 37.0(10.71) vs. 38.1(10.28); p=0.322 Male (%): 113(60%) vs. 96(54%); p=0.245 Ethnicity: White: 135(72%) vs. 135(76%); p=0.403

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(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
Bowden, 2006 U.S	Divalproex vs. Placebo Weight (kg): 87.4(22.23) vs. 87.1(21.39); p=0.888 Manic episdoe: 107(57%) vs 88(50%) Mixed episode: 80(43%) vs. 79(45%); p=0.752 Psychotic features: 36(19%) vs. 39(22%); p=0.520 < 6 manic episodes: 68(37%) vs. 79(45%); p=0.032 < 6 mixed episodes: 112(61%) vs. 105(60%); p=0.593 < 6 depressive episodes: 114(62%) vs. 104(60%); p=0.820 Rapid cycling: 9(5%) vs. 13(7%); p=0.381 Age, first manic episode (y): 22.6(9.8) vs. 23.8(10.8) p=0.564 Age, first mixed episode (y): 25.4(9.7) vs. 25.7(10.8); p=0.912 Age, first depressive episode (y): 20.9(9.1) vs. 22.2(9.7); p=0.381 < 6 bipolar hospitalizations: 109(58%) vs. 117(66%);; p=0.553 Age, first hospitalization (y): 26.6(10.2) vs. 28.3(11.7); p=0.284 Suicide attempts: 105(56%) vs. 95(54%); p=0.603	Number screened not reported / number eligible not reported / 377 enrolled / 377 randomized	13 withdrawn / lost to follow-up not reported / 364 analyzed (ITT population)	Divalproex vs. Placebo MRS, mean change: -11.5(10.9) vs. -9.0(10.9); p=0.013; p=0.007 for treatment differences MSS, mean change: -6.7(6.0) vs. -5.3(6.0); p=0.009 BIS, mean change: -4.5(5.1) vs. -3.4(5.1); p=0.019 Items of MRS, mean change: More energetic: -1.3 vs. -1.0; p<0.05 Elevated mood: -1.2 vs. 1.0 Less need for sleep: -1.7 vs. -1.2; p<0.01 Increased activity: -1.3 vs. -1.0; p<0.05 Generalized motor hyperactivity: -1.2 vs. -0.9; p<0.05 Pressured speech: -1.1 vs. -0.9 Grandiosity: -0.9 vs. -0.8 Overt anger: -0.6 vs. -0.5 Poor judgement: -0.8 vs. -0.5 Racing thoughts: -0.8 vs. -0.5; p<0.001 Lack of insight: -0.2 vs. -0.3

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(12) Results	(12) Results	(12) Results
Bowden, 2006 U.S	Divalproex vs. Placebo Resonders (≥ 50% improvement MRS): 48% vs. 34%; p=0.012 Remission: 48% vs. 35%; p=0.015 Effectiveness: 38% vs. 26%; p=0.032 Discharged from hospital: 17% vs. 20%	MRS, mean change, treatment interaction signficant (p=0.006) Divalproex vs. Placebo Higher baseline MSS scores (>13): -15.0 vs. -9.6 Lower baseline MSS scores (< 13): -7.5 vs. -7.7 Treatment difference not a function of age, gnder, race, episode type, presence of psychotic features, rapid cycling, previous episodes, drug abuse or baseline DSS	Divalproex vs. Placebo Rescue medicaton: 74% vs. 79% Dose of rescue medication higher in placebo group than divalproex group on day 1; similar on all other days

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(13) Method of adverse effects assessment?
Bowden, 2006 U.S	AEs monitored throughout study; hematological, blood chemistry, vital signs, physical examination and urinalysis performed periodically

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(14) Adverse effects reported	(15) Total withdrawals; withdrawals due to adverse events
Bowden, 2006 U.S	Divalproex vs. Placebo AEs: 162(84%) vs. 134(72%); p=0.006 Somnolence: 64(33%) vs. 26(14%); p<0.001 Nausea: 53(28%) vs. 28(15%); p=0.004 Dyspepsia: 49(26%) vs. 18(10%); p<0.001 Headache: 40(21%) vs. 40(22%); p=0.9 Dizziness: 39(19%) vs. 15(8%); p=0.003 Vomiting: 35(18%) vs. 12(6%); p=0.001 Diarrhea: 28(15%) vs. 18(10%); p=0.16 Pain: 23(12%) vs. 16(9%); p=0.314 Abdominal pain: 19(10%) vs. 8(4%); p=0.045 Pharyngitis: 19(10%) vs. 8(4%); p=0.045 Mean changes in laboratory parameters (p<0.05): RBC: -0.01(0.28) vs. 0.05(0.28) Platelets: -58.8(59.9) vs. -1.2(49.6) Moncytes: 1.88(3.03) vs. 0.29(2.37) Basophils: -0.05(0.23) vs. 0.02(0.25) Protein (g/dL): -0.27(0.51) vs. 0.03(0.52) Albumim (g/dL): -0.19(0.31) vs. 0.02(0.28) Bilirubin (mg/dL): -0.09(0.21) vs. 0.01(0.26) Alkaline phosphatase (IU/L): -12.15(13.07) vs. -1.58(14.91) Aspartate aminotransferase (IU/L): -3.93(11.42) vs. -0.19(10.32) Alanine aminotransferase (IU/L): -6.41(18.13) vs. 1.92(17.76) Sodium (mEq/L): 0.64(2.63) vs. 0.03(2.85) Calcium (mEq/L): -0.2(0.43) vs. 0.07(0.43) Weight gain (kg): 1.8(3.43) vs. 0.5(2.89); p<0.001 BMI (kg/m2): 0.61(1.14) vs. 0.14(1.06); p<0.001 Fasting glucose (mg/dL): -1.24(35.49) vs. 1.71(26.1); p=0.371 Cholesterol (mg/dL): -13.47(30.93) vs. -2.46(32.76); p=0.001 HDL (mg/dL): -6(9.84) vs. -2.79(10.56); p=0.001	Divalproex vs. Placebo Total withdrawals: 80/192(42%) vs. 89/185(48%) Withdrawals due to AEs: 19/192(10%) vs. 6/185(3%); p=0.003

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Placebo-Controlled Trials

(1) Author, year Country Trial name (Quality score)	(16) Comments
Bowden, 2006 U.S	Those discontinued due to AEs had hgihe mean serum valproate concentrations than patients who did not (p=0.012); those who discontinued due to GI AEs also had higher mean serum valproate concentrations (p=0.002) Two cases of pancreatitis reported (one during study, one after); one death in divalproex group (not related to study drug)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study Outpatient setting	Adults aged 18-70y; bipolar I disorder (defined by the DSM-IV carier and supported by the Structured Clinical Interview for the DSM-IV Axis I Disorders and the YMRS score ≥ 18); received either lithium or valproate for > 6w; erm level of mood stabilizers between 0.5-1.2 mEq/L for lithium and 45-100 mg/L for valproate	Topiramate 25 mg/d (titrated weekly - 50, 75, 100, 150, 200, 300, and 400 mg/d; adjusted for any emerging AEs; mean dose 254.7 mg/d) vs. Placebo for 12w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Lithium or divalproex sodium; permitted to continue taking a stable dose of an oral antipsychotic agent; use of short-acting benzodiazepine (lorazepam) for sleep or agitation permitted only during first 4w of titration period Topiramate vs. Placebo Valportate: 91(66.9%) vs. 78(54.9%) Lithium: 45(33.1%) vs. 64(43.0%) Lorazepam: 15(11.0%) vs. 23(16.2%) Alprazolam: 2(1.5%) vs. 2(1.4%) Clonazepam: 2(1.5%) vs. 0(0%) Escitalopram: 2(1.5%) vs. 0(0%) Sertraline: 2(1.5%) vs. 1(0.7%) Bupropion: 1(0.7%) vs. 3(2.1%) Paroxetine: 1(0.7%) vs. 2(1.4%)	YMRS, Clinical Global Impressions-Severity of Illness scale (CGI-S), Brief Psychiatric Rating Scale (BPRS), Montgomery-Asberg Depression Rating Scale (MADRS) and the Global Assessment scale assessed at each visit	Topiramate vs. Placebo Age: 41.0(12.2) vs. 39.0(11.9) Male (%): 58(40.6%) vs. 67(46.5%) Ethnicity: White: 119(83.2%) vs. 122(84.7%) Black: 14(9.8%) vs. 14(9.7%) Hispanic: 5(3.5%) vs. 6(4.2%) Asian: 2(1.4%) vs. 1(0.7%) Other: 3(2.1%) vs. 1(0.7%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Topiramate vs. Placebo BMI (kg/m2): 31.0(7.8) vs. 30.4(7.3) Rapid cycling: 39(27.3%) vs. 43(29.9%) Mania: 105(73.4%) vs. 102(70.8%) Mixed: 30(21.0%) vs. 35(24.3%) Missing: 0(0%) vs. 7(4.9%) Hospitalizations: 2.7(5.8) vs. 3.3(13.1) Psychotic episodes: 42(29.4%) vs. 36(25.0%) Number of psychotic episodes: 7.3(20.0) vs. 7.8(17.1)	424 screened / number eligible not reported / 287 enrolled / 287 randomized	110 withdrew / 31 lost to follow-up / 278 analyzed (ITT population)	Topiramate vs. Placebo YMRS, mean change: -10.1(8.7) vs. -9.6(8.2); p=0.797 CGI-S, mean change: -0.9(1.1) vs. -0.9(1.1); p=0.698 BPRS, mean change: -3.3(9.6) vs. -4.8(9.0); p=0.052 MADRS, mean change: 0.6(8.8) vs. -1.1(9.0); p=0.057 GAS, mean change: 7.2(9.9) vs. 7.1(11.5); p=0.838

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Topiramate vs. Placebo Response rate, > 50% reduction in YMRS: 39.0% vs. 38.0%; p=0.914	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Reports of AEs and vital signs at every visit; clinical laboratory tests and serum pregnancy tests every 4w and at the end of treatment; serum levels of lithium, valproate and topiramate at baseline, end of dose titration and end of study

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

	HDL (mg/dL): -6(9.84) vs. -2.79(10.56); p=0.001 LDL (mg/dL): -7.89(28.92) vs. -0.07(29.9); p=0.003 Triglycerides (mg/dL): 1.53(90.73) vs. -4.34(98.66); p=0.556	
Chengappa, 2006 U.S.	Topiramate vs. Placebo AEs: 122(85.3%) vs. 120(83.9%) Headache: 34(23.8%) vs. 37(25.9%) Paresthesia: 33(23.1%) vs. 5(3.5%); p<0.05 Upper respiratory tract infection: 25(17.5%) vs. 16(11.2%) Diarrhea: 24(16.8%) vs. 12(8.4%); p<0.05 Nausea: 22(15.4%) vs. 17(11.9%) Somnolence: 22(15.4%) vs. 23(16.1%) Anorexia: 19(13.3%) vs. 8(5.6%); p<0.05 Insomnia: 17(11.9%) vs. 16(11.2%) Memory difficulty: 16(11.2%) vs. 10(7.0%) Dizziness: 15(10.5%) vs. 15(10.5%) Abnormal vision: 12(8.4%) vs. 7(4.9%); NSD between groups Suicidality: 1(0.7%) vs. 2(1.4%) Death: 0(0%) vs. 0(0%) Clinical laboratory visits and vital signs were within normal range Body weight, mean change (kg): -2.5(3.4) vs. 0.2(3.0); p<0.001 BMI, mean change (kg/m2): -0.84(1.2) vs. 0.07(1.1); p<0.001	Topiramate vs. Placebo Total withdrawals: 57/143(39.9%) vs. 53/144(36.8%) Withdrawals due to AEs: 20/143(13.9%) vs. 10/144(6.9%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Chengappa, 2006 U.S.	Topiramate vs. Placebo Follow-up (d): 70.8(31.6) vs. 74.7(30.0) out of total 91 possible days Adjunctive treatment with topiramate not associated with worsening of symptoms; similar poritons of patients in each group experienced worsening symptoms; NSD between groups	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	Placebo-controlled, double-blind study Outpatient setting	Women aged 18-40y; distubred by mood changes, distrustfulness, impulsivity and stormy relationships; DSM-IV criteria for borderline personality disorder using the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders; Structured Clinical Interview for DSM-IV Axis I Disorder and Revised Diagnostic Interview for Borderlines and DSM-IV bipolar I disorder criteria (not curretnly in depressive or hypomanic episodes) With no previous treatments with divalproex sodium, medical illness, alcohol and drug abuse; not pregnant, breastfeeding, planning to become pregnant or having unprotected sex	Divalproex sodium 250 mg bid (mean dose, 850 mg/d) vs. Placebo for 6m	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	No other psychotropic drug allowed during the study	Two self report measures: Symptom Checklist 90 (SCL-90) and the McLean version of the modified Overt Aggression Scale (MOAS) Checklist measured at each visit	Divalproex vs. Placebo Age: 27.3(7.4) vs. 26.4(7.3); NSD Male (%): 0(0%) vs. 0(0%) Ethnicity: White: 15(75%) vs. 5(50%); NSD Black: 3(10%) Hispanic: 4(13.3%) Biracial: 2(6.7%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	Divalproex vs. Placebo GAF score: 51.6(6.5) vs. 50.2(7.0); NSD Individual therapy: 12(60%) vs. 7(70%); NSD Medication: 9(45%) vs. 3(30%); NSD Hospitalized: 1(5%) vs. 2(20%); NSD	Number screened not reported / number eligible not reported / 30 enrolled / 30 randomized	19 withdrew / 12 lost to followup / 13 analyzed (20 analyzed at 8w)	Divalproex vs. Placebo SCL-90 interpersonal: -31.7% vs. -14.8%; p=0.0408 SCL-90 anger/hostility: -29.6% vs. -11.0; p=0.0117 SCL-90 depression: -21.3% vs. -25.4%; NSD MOAS total: -42.1% vs. -13.4%; p=0.0278

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	Weight gain, mean change (lbs): 2.6(5.6) vs. 0.3(4.0); p=0.1175 Weight gain (%): 1.9(3.9) vs. 0.12(3.1); p=0.1185	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	Divalproex vs. Placebo Major depressive episode: 0(0%) vs. 2(20%) Menstrual changes: 1(5%) vs. 1(10%); NSD Tremors/diarrhea: 1(5%) vs. 0(0%) Hair loss: 0(0%) vs. 1(10%) Increase hepatic transaminases: 1(5%) vs. 0(0%) Thrombocytopenia: 0(0%) vs. 0(0%)	Divalproex vs. Placebo Total withdrawals: 13/20(65%) vs. 6/10(60%) Withdrawals due to AEs: 1/20(5%) vs. 3/10(30%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Frankenburg, 2002 U.S.	12h trough levels were done at 1w, 1m and then every 2m for dose adjusting Due to high level of attrition at 6m, analyses repeated using only data collected up to 8w	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Single center, placebo-controlled, double-blind Inpatient setting	Aged 18-65y, meeting DSM-III-R criteria for bipolar disorder, manic phase; failure to respond adequately to a trial of lithium or intolerance of lithium side effects; females must be postmenopausal or surgically sterilized	Divalproex sodium 250mg tid vs. Placebo for 7-21 days	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Treatment with all psychotropic medication discontinued; only lorazepam 1 mg qid allowed to treat agitation or insomina up to day 9	YMRS, Global Assessment Scale (GAS), Brief Psychiatric Rating Scale, Augmented (BPRS-A) on days 7, 14, 21	Valproate vs. Placebo Age: 39.7(11.8) vs. 34.6(14.7) Male (%): 13(76.5%) vs. 13(68.4%) Ethnicity: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Valproate vs. Placebo Duration of illness (y): 12.2(10.9) vs. 11.2(9.7) MRS: 28.2(5.8) vs. 28.6(6.9) GAS: 30.0(5.9) vs. 31.6(5.5)	Number screened not reported / number eligible not reported / 43 enrolled / 43 randomized	35 withdrew / 0 lost to follow-up / 36 analyzed (ITT efficacy analysis of all 43 patients)	Valproate vs. Placebo YMRS, median improvement: 54% vs. 5.0%; p=0.003 GAS, improvement (points): 20 vs 0; p=0.002 BPRS-A, median improvement: 17 vs 3; p=0.001 Response rate, > 50% improvement: 9(53%) vs. NR

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	On four of the 18 standard BPRS subscales (conceptual disorganization, tension, hostility, excitement), valproate improved significantly more than placebo (p<0.005); as well as increased motor activity (p=0.006); no subscale showed significant change in favor of placebo	Analysis of covariance of patients score at termination, valproate patients improved significantly more than placebo on the YMRS (p=0.005), GAS (p=0.001) and the BPRS-A (p=0.001)	ITT analysis showed that valproate patients improved more significantly on the YMRS (p=0.013), GAS (p=0.004) and total BPRS-A (p=0.002) than the placebo patients Subgroup analysis of patients receiving lorazepam on valproate (n=13) showed a significantly greater improvement on the YMRS (p=0.016), GAS (p=0.008) and the BPRS-A (p=0.002) than placebo patients (n=12)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Blood chemistry studies, hematologic studies and urinalyses repeated at days 7, 14 and 21

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Valproate (n=20) vs. Placebo (n=23) GI discomfort with vomiting: 5(25%) vs. 5(22%) GI discomfort without vomiting: 1(5%) vs. 2(8.7%) Headache: 4(20%) vs. 6(26%) Sedation/fatigue: 4(20%) vs. 1(4.3%) Constipation: 0(0%) vs. 3(13%) Swelling/pain: 1(5%) vs. 2(8.7%) Ataxia: 2(10%) vs. 0(0%) Dysuria: 0(0%) vs. 2(8.7%) Palpitations: 1(5%) vs. 1(4.3%) Diplopia: 1(5%) vs. 1(4.3%) Tightness in chest: 1(5%) vs. 0(0%) Dry eyes: 1(5%) vs. 0(0%) Sinus pressure: 1(5%) vs. 0(0%) Dysarthria: 1(5%) vs. 0(0%) Depression: 1(5%) vs. 0(0%) Diarrhea: 1(5%) vs. 0(0%) Anorexia: 1(5%) vs. 0(0%) Agitation: 1(5%) vs. 0(0%) Bruising: 0(0%) vs. 1(4.3%) Lump in throat: 0(0%) vs. 1(4.3%) Panic attacks: 0(0%) vs. 1(4.3%)	Valproate vs. Placebo Total withdrawals: 13/17(76.5%) vs. 15/19(78.9%) Withdrawals due to AEs: 2/17(12%) vs. 1/19(5.3%); [5/43(11.6%) included patients who withdrew before 7d) Withdrawals defined as those who did not complete 21 days

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Pope, 1991 U.S	Presence of unblinded investigator adjusted dosage to achieve desired serum concentrations; also performed sham adjustments; he was informed if any patient complained of an AE; this investigator broke the blinding by informing ward physician and staff of allocation when a patient withdrew; investigator performing rating remained blinded Valproate vs. Placebo Follow-up (d): 13.6(4.9) vs. 12.4(5.0) -- 36/43 patients completed at least 7 days, only those analyzed Individual patients characteristics listed in table 1; figures 1 and 2 describe change in the YMRS and GAS; valproate showed greatest improvement

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Multicenter, double-blnd, randomized, placebo-controlled, parallel-group study	Aged 18-75y with diagnosis of bipolar I or II disorder (according to the DSM-IV criteria) treated with any standard mood stabilizer; > 2 bipolar episodes during last year; CGI scale for Bipolar Illness, Modified score ≥ 4 with last episode occurring within past 6m; euthymic at randomization (Hamilton Rating Scale for Depression ≤ 8 and YMRS ≤ 4)	Gabapentin 1200 mg/d (with emerging symptoms, increased to 2400 mg/d; with AEs, reduced to 900 mg/d) vs. Placebo for 12m	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Lithium, valproate, carbamazepine or any combination; no treatment with antipsychotics or antidepressants allowed	Clinical Global Impressions scale for Bipolar Illness, Modified (CGI-BP-M); 7-point ranging scale (1-not ill, 7-extremely ill); other assessments included the YMRS, Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A), Pittsburgh Sleep Quality Index (PSQI) at each visit	Gabapentin vs. Placebo Age: 46.2(14.3) vs. 47.6(15.8) Male (%): 3(23.1%) vs. 4(33.3%) Ethnicity: Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Gabapentin vs. Placebo Weight (kg): 74.6(13.8) vs. 63.8(12.1) Seasonal pattern: 3(25.0%) vs. 2(16.7%) Rapid cycling: 5(38.5%) vs. 6(50.0%) Bipolar II: 1(7.7%) vs. 5(41.7%) Diagnosis (y): 20.9(11.5) vs. 16.5(10.5) Episodes, total: 33.8(25.1) vs. 17.8(18.7) Manic: 6.8(8.3) vs. 4.1(6.3) Hypomanic: 6.(7.9) vs. 5.1(7.6) Depressive: 19.3(19.0) vs. 8.3(7.9) Mixed: 0.8(1.6) vs. 0.4(0.9) Hospitalizations: 4.1(5.4) vs. 2.4(2.3)	Number screened not reported / number eligible not reported / 25 enrolled / 25 randomized	12 withdrew / 0 lost to follow-up / 25 analyzed	Gabapentin vs. Placebo CGI-BP-M, mean change: -2.1 vs. -0.6; p=0.0046 YMRS, mean change: 3.1 vs. -0.6; p=0.2038 HAM-D, mean change: 1.3 vs. 2.5; p=0.6753 HAM-A: -0.3 vs. -0.9; p=0.8443

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Gabapentin vs. Placebo PSQI, mean change: -1.3 vs. 0.2; p=0.3362 PSQI-1, mean change: -0.1 vs. 0; p=0.7649 PSQI-2, mean change: 0 vs. 0.4; p=0.3117 PSQI-3, mean change: 0.3 vs. 0.2; p=0.7888 PSQI-4, mean change: 0.2 vs. 0.3; p=0.5518 PSQI-5, mean change: 0 vs. 0; p=0.9521 PSQI-6: -1.1 vs. -0.6; p=0.0267 PSQI-7: -0.3 vs. -0.2; p=0.7842	Gabapentin vs. Placebo Time from randonmization to first new episode showed NSD between groups (p=0.6658); HR 1.344

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Side effects were systematically collected

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Gabapentin vs. Placebo AEs reported: 10(77%) vs. 7(58%) Constipation: 4(31%) vs. NR Headache: 3(23%) vs. NR Nausea: 3(23%) vs. NR Dizziness: 2(15%) vs. NR Insomnia: 2(15%) vs. NR Tremor: 2(15%) vs. NR	Gabapentin vs. Placebo Total withdrawals: 7/13(54%) vs. 6/12(50%) Withdrawals due to AEs: 1/13(7.7%) vs. 1/12(8.3%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Vieta, 2006 Spain	Prophylactic study

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Double-blind, multicenter, placebo-controlled, fixed-dose, parallel study Outpatient setting	Male or non-pregnant females > 18 years with a diagnosis of bipolar II disorder who were currently experiencing a major depressive episode of at least 8w duration; HAMD-17 > 18; HAMD-item1 or HADM-item7 > 3; no suicidal activity	Lamotrigine 200 mg/d vs. Placebo for 8w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Not reported	Montogomery-Asberg Depression Rating Scale (MADRS); Clinical Global Impressions of Improvement (CGI-I); Hamilton Depression Rating Scales; Beck Melancholia Scale; Clinical Global Impressions of Severity (CGI-S) and Mania Rating Scale from the Schedule of Affective Disorders and Schizophrenia (MRS) and the Treatment Satisfaction Question at 8w	Lamotrigine vs. Placebo Age: 38.1(11.5) vs. 36.5(1.9) Male (%): 39(35.8%) vs. 40(36.7%) Ethnicity: White: 70(64%) vs. 82(75%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.		Number screened not reported / number eligible not reported / 221 enrolled / 221 randomized	66 withdrew / lost to follow-up not reported / 214 analyzed	Lamotrigine vs. Placebo MADRS, mean change: -13.4(1.0) vs. -12.0(1.0) HAMD-17, mean change: -11.1(0.8) vs. -9.4(0.8) HAMD-31, mean change: -16.0(1.1) vs. -13.8(1.2) HAMD-item 1, mean change: -1.4(0.1) vs. -1.3(0.1)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Lamotrigine vs. Placebo BMS, mean change: -6.8(0.5) vs. -5.4(0.5) CGI-S, mean change: -1.4(0.1) vs. -1.3(0.1) CGI-I, mean change: 2.5(0.1) vs. 2.8(0.1) MRS-16, mean change: -0.4(0.3) vs. 0.1(0.3)	Lamotrigine vs. Placebo Responders, MADRS: 59(54.1%) vs. 48(45.7%) Responders, HAMD-17: 56(51.4%) vs. 42(40%) Responders, BMS: 62(56.9%) vs. 47(44.8%) Responders: CGI-I: 66(60.6%) vs. 47(44.8%)	Lamotrigine vs. Placebo Remission, MADRS: 45(41.3%) vs. 36(34.3%) Remission, HAMD-17: 28(25.7%) vs. 29(27.6%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Treatment emergent AES reported at each study treatment visit and at follow-up visit

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Lamotrigine vs. Placebo Any AEs: 88(81%) vs. 85(78%) Headache: 30(28%) vs. 39(36%) Dry mouth: 10(9%) vs. 7(6%) Insomnia: 9(8%) vs. 7(6%) Diarrhea: 8(7%) vs. 18(17%) Nasopharyngitis: 8(7%) vs. 9(8%) Nausea: 8(7%) vs. 15(14%) Dizziness: 7(6%) vs. 8(7%) Rash: 7(6%) vs. 7(6%) Cough: 6(6%) vs. 5(5%) Sedation: 6(6%) vs. 2(2%) Somnolence: 6(6%) vs. 5(5%) Fatigue: 3(3%) vs. 7(6%) Vomiting: 2(2%) vs. 6(6%) Non-factal serious AEs: 0(0%) vs. 5(5%) Pneumonia: 0(0%) vs. 1(1%) Suicidal ideation: 0(0%) vs. 2(2%) Suicide attempt: 0(0%) vs. 1(1%) Agitation: 0(0%) vs. 1(1%) Cellulitis: 0(0%) vs. 1(1%) Fatal AEs: 0(0%) vs. 0(0%)	Lamotrigine vs. Placebo Total withdrawals: 30/111(27%) vs. 36/110(33%) Withdrawals due to AEs: 4/111(4%) vs. 5/110(5%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA100223) U.S.	Serious AES not related to study drug

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Double-blind, multicenter, placebo-controlled, fixed-dose, parallel study Outpatient setting	Male or non-pregnant females > 18 years with a diagnosis of bipolar II disorder who were currently experiencing a major depressive episode of at least 8w duration; HAMD-17 > 18; HAMD-item1 or HADM-item7 > 3; no suicidal activity	Lamotrigine 200 mg/d vs. Placebo for 8w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Not reported	Montogomery-Asberg Depression Rating Scale (MADRS); Clinical Global Impressions of Improvement (CGI-I); Hamilton Depression Rating Scales; Beck Melancholia Scale; Clinical Global Impressions of Severity (CGI-S) and Mania Rating Scale from the Schedule of Affective Disorders and Schizophrenia (MRS) and the Treatment Satisfaction Question at 8w	Lamotrigine vs. Placebo Age: 40.5(12.5) vs. 38.2(12.1) Male (%): 58(45.7%) vs. 56(45.9%) Ethnicity: White: 94(74%) vs. 84(69%) Black: 18(14%) vs. 26(21%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.		Number screeneed not reported / number eligible not reported / 259 enrolled / 259 randomized	107 withdrew / lost to follow-up not reported / 243 analyzed	Lamotrigine vs. Placebo MADRS, mean change: -12.6(1.0) vs. -11.7(1.0) HAMD-17, mean change: -9.8(0.7) vs. -9.3(0.7) HAMD-31, mean change: -15.0(1.1) vs. -13.7(1.1) HAMD-item1, mean change: -1.3(0.1) vs. -1.2(0.1)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Lamotrigine vs. Placebo BMS, mean change: 13.3(2.0) vs. 13.4(2.2) CGI-S, mean change: -5.5(0.4) vs. -5.2(0.4) CGI-I, mean change: 2.8(0.1) vs. 2.8(0.1) MRS-16, mean change: -0.1(0.3) vs. -0.1(0.3)	Lamotrigine vs. Placebo Responders, MADRS: 56(45.5%) vs. 48(40.0%) Responders, HAMD-17: 51(41.5%) vs. 39(32.5%) Responders, BMS: 52(42.3%) vs. 48(40.0%) Resonders, CGI-I: 59(48.0%) vs. 47(39.2%)	Lamotrigine vs. Placebo Remission, MADRS: 33(26.8%) vs. 36(30.0%) Remission, HAMD-17: 18(14.6%) vs. 29(24.2%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Treatment emergent AEs were reported at each study treatment visit

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Lamotrigine vs. Placebo Any AEs: 95(75%) vs. 87(71%) Headache: 26(20%) vs. 26(21%) Diarrhea: 17(13%) vs. 7(6%) Nausea: 14(11%) vs. 12(10%) Dry mouth: 13(10%) vs. 8(7%) Somnolence: 10(8%) vs. 4(3%) Back pain: 7(6%) vs. 7(6%) Dizziness: 8(6%) vs. 2(2%) Rash: 8(6%) vs. 2(2%) Insomnia: 6(5%) vs. 9(7%) Nasopharyngitis: 4(3%) vs. 10(8%) Non-fatal serious AEs: 4(3%) vs. 6(5%) Mania episode: 1(1%) vs. 1(1%) Mixed manic depressive episode: 0(0%) vs. 1(1%) Suicidal ideation: 1(1%) vs. 2(2%) Agitation: 1(1%) vs. 1(1%) Acute stress disorder: 0(0%) vs. 1(1%) Depression: 0(0%) vs. 1(1%) Limb injury: 0(0%) vs. 1(1%) Muscle injury: 0(0%) vs. 1(1%) Vomiting: 0(0%) vs. 1(1%) Abdominal pain: 1(1%) vs. 0(0%) Hepatic encephalopathy: 1(1%) vs. 0(0%) Depressive symptom: 1(1%) vs. 0(0%) Fatal AEs: 0(0%) vs. 0(0%)	Lamotrigine vs. Placebo Total withdrawals: 52/131(40%) vs. 55/128(43%) Withdrawals due to AEs: 13/131(10%) vs. 9/128(7%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA30924) U.S.	Serious AES not related to study drug

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.	Multicenter, double-blind, placebo-controlled, flexible dose trial Outpatient setting	Subjects > 18 years; diagnosis of bipolar I or II disorder; current episode depressed (defined by the DSM-IV, based on modified Structured Clinical Interview for DSM-IV); currently experiencing a major depressive episode; one major depressive, manic or mixed episode in past 10y; or two hypomanic episodes (for bipolar II) in past 10y; duration of current episode 2-52w; HAMD-17 > 18	Lamotrigine flexible dose (100-400 mg/d, target dose 360 mg/d) vs. Placebo for 10w	Not reported

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.	Not reported	17-item Hamilton Depression Rating Scale (HAMD-17); HAMD-31; HAMD-item1; Montgomery-Asberg Depression Rating Scale (MADRS); Mania Rating Scale (MRS); Schedue for Affective Disorders and Schizophrenia-Change Version (SADS-C); and the Clinical Global Improvession of Improvement (CGI-I) and Severity (CGI-S) at all visits	Lamotrigine vs. Placebo Age: 40.5(11.3) vs/ 40.9(11.2) Male (%): 37(35.9%) vs. 42(40.8%) Ethnicity: White: 90(87%) vs. 89(86%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.		Number screened not reported / number eligible not reported / 206 enrolled / 206 randomized	69 withdrew / lost to follow-up not reported / 202 analyzed (204 for safety)	Lamotrigine vs. Placebo HAMD-17, mean change: 4d: -2.6(4.4) vs. -2.7(4.4); p=0.674 8d: -4.3(5.7) vs. -4.1(5.4); p=0.805 15d: -5.7(5.6) vs. -6.1(5.8); p=0.607 22d: -7.5(5.6) vs. -7.5(6.7); p=0.775 29d: -8.3(6.6) vs. -8.4(7.8); p=0.804 36d: -8.8(7.3) vs. -9.0(7.4); p=0.717 43d: -9.4(7.4) vs. -10.0(7.9); p=0.388 50d: -10.0(7.9) vs. -10.1(7.9); p=0.661 57d: -9.5(8.0) vs. -10.1(7.6); p=0.414 64d: -10.4(8.1) vs. -10.2(7.9); p=0.932 71d: -10.2(8.3) vs. -10.6(8.1); p=0.710 HAMD-31, mean change: 4d: -4.0(6.8) vs. -4.0(6.3) 8d: -6.5(8.8) vs. -6.1(8.2) 15d: -7.7(8.7) vs. -8.6(9.0) 22d: -10.8(9.0) vs. -11.0(10.1) 29d: -11.8(10.1) vs. -12.4(11.4) 36d: -12.7(11.1) vs. -13.2(10.8) 43d: -13.7(11.4) vs. -15.1(11.9)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.	Lamotrigine vs. Placebo HAMD-item1, mean change: 4d: -0.2(0.7) vs. -0.2(0.8) 8d: -0.4(0.9) vs. -0.4(0.8) 15d: -0.7(1.1) vs. -0.5(0.9) 22d: -0.8(1.1) vs. -0.7(1.0) 29d: -0.9(1.1) vs. -0.9(1.0) 36d: -0.9(1.1) vs. -0.9(1.0) 43d: -1.1(1.2) vs. -1.0(1.1) 50d: -1.1(1.2) vs. -1.0(1.1) 57d: -1.1(1.3) vs. -1.0(1.1) 64d: -1.2(1.2) vs. -1.0(1.2) 71d: -1.2(1.2) vs. -1.1(1.2) SAD-C, 16 item, mean change: 4d: 0.4(3.5) vs. -0.3(3.5) 8d: -0.4(4.3) vs. -0.7(3.5) 15d: -0.2(4.5) vs. -0.6(2.9) 22d: -0.7(4.7) vs. -0.8(3.7) 29d: -0.9(4.7) vs. -1.0(4.0) 36d: -0.5(5.3) vs. -1.3(4.1) 43d: -0.3(5.8) vs. -1.3(4.2) 50d: -1.0(5.2) vs. -0.9(5.6) 57d: -0.8(5.6) vs. -1.3(4.5) 64d: -0.9(5.6) vs. -1.3(5.1) 71d: -0.8(5.9) vs. -1.6(4.9)	Lamotrigine vs. Placebo MADRS, mean change: 4d: -2.8(5.4) vs. -2.6(6.5) 8d: -4.7(7.2) vs. -4.1(7.4) 15d: -6.1(8.4) vs. -6.4(7.9) 22d: -8.1(7.9) vs. -8.3(9.3) 29d: -9.4(8.9) vs. -10.0(9.3) 36d: -9.7(9.4) vs. -10.5(9.0) 43d: -10.4(9.5) vs. -11.5(9.7) 50d: -11.7(10.8) vs. -11.5(9.9) 57d: -10.9(11.2) vs. -11.6(9.9) 64d: -12.4(11.4) vs. -11.4(9.9) 71d: -12.1(11.2) vs. -12.3(12.3) CGI-S, mean change: 4d: -0.2(0.4) vs. -0.1(0.5) 8d: -0.3(0.7) vs. -0.2(0.6) 15d: -0.4(0.7) vs. -0.4(0.8) 22d: -0.6(0.9) vs. -0.6(0.9) 29d: -0.8(1.0) vs.	Lamotrigine vs. Placebo CGI-I, mean total score: 4d: 3.7(0.6) vs. 3.8(0.7) 8d: 3.6(1.0) vs. 3.6(0.8) 15d: 3.4(1.0) vs. 3.4(0.8) 22d: 3.2(1.1) vs. 3.3(0.9) 29d: 3.1(1.2) vs. 3.1(1.0) 36d: 3.1(1.2) vs. 3.0(1.0) 43d: 2.9(1.3) vs. 2.8(1.1) 50d: 2.9(1.3) vs. 2.9(1.1) 57d: 3.0(1.4) vs. 2.8(1.1) 64d: 2.8(1.4) vs. 2.8(1.2) 71d: 2.9(1.4) vs. 2.8(1.2) SAD-C, 11 item, mean change: 4d: 0.6(3.2) vs. -0.3(3.1) 8d: 0.1(3.7) vs. -0.5(3.0)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.	Subjects who received at least one dose of study drug evaluated for safety

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010) U.S.	Lamotrigine vs. Placebo Any AEs: 97(94%) vs. 89(88%) Headache: 42(41%) vs. 37(37%) Nausea: 21(20%) vs. 31(31%) Somnolence: 18(17%) vs. 10(10%) Dizziness: 18(17%) vs. 8(8%) Rash: 17(17%) vs. 12(12%) Infection: 17(17%) vs. 11(11%) Insomnia: 14(14%) vs. 10(10%) Pain: 12(12%) vs. 9(9%) Xerostomia: 12(12%) vs. 6(6%) Influenza: 11(11%) vs. 15(15%) Diarrhea: 9(9%) vs. 13(13%) Accidental injury: 8(8%) vs. 9(9%) Serious AEs: 4(4%) vs. 4(4%) Attempted suicide: 1(1%) vs. 0(0%) Cancer: 1(1%) vs. 0(0%) Mania: 1(1%) vs. 1(1%) Suicide: 1(1%) vs. 0(0%) Chest pain: 0(0%) vs. 1(1%) Emotional liability: 0(0%) vs. 1(1%) Visual field defect: 0(0%) vs. 1(1%) Fatal AEs: 1(1%) vs. 0(0%)	Lamotrigine vs. Placebo Total withdrawals: 35/103(34%) vs. 34/103(33%) Withdrawals due to AEs: 14/103(14%) vs. 8/103(8%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCAA2010)
U.S.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	Multicenter, double-blind, placebo-controlled, randomized, fixed-dose trial; followed by an open-label continuation phase Outpatient setting	Males and females > 18 years in generally good physical health; diagnosis of bipolar I disorder, current depressed episode, as defined by DSM-IV and the Structured Clinical Interview for DSM-IV; currnly experiencing a major depressive episode, > 2 mood episodes in past 5y and > 1 manic or mixed episode; duration of current depressive episode 2-52w; HAMD-17 > 18	Lamotrigine 200 mg/d vs. Placebo (during continuatin phase, placebo patients titrated to 200 mg/d) for 8w (21w of a continuation phase)	Not reported; after double-blind phase, 5w blinded transition to open-label medication

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	Not reported	17-item Hamilton Depression Rating Scale (HAMD-17); HAMD-31; HAMD-item1; Montgomery-Asberg Depression Rating Scale (MADRS); Mania Rating Scale (MRS); Schedue for Affective Disorders and Schizophrenia-Change Version (SADS-C); and the Clinical Global Improvession of Improvement (CGI-I) and Severity (CGI-S) and the Personal Global Impression of Improvement (PGI-I) and the Quality of Life in Depression Scale (QLDS)	Lamotrigine vs. Placebo *Double-blind phase:* Age: 37.6(12.6) vs. 37.3(11.5) Male (%): 55(42.6%) vs. 56(47.5%) Ethnicity: White: 37.6(12.6%) vs. 23.7(11.5%) *Continuation phase:* Age: 38.585(12.3) Male (%): 73(47.1%) Ethnicity: White: 134(86%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	*Double-blind phase:* Number screened not reported / number eligible not reported / 257 enrolled / 257 randomized *Continuation phase:* Number screened not reported / number eligible not reported / 161 enrolled	*Double-blind phase:* 85 withdrew / lost to follow-up not reported / 243 analyzed *Continuation phase:* 56 withdrew / lost to follow-up not reported / 153 analyzed	*Double-blind phase* Lamotrigine vs. Placebo MADRS, mean change: -12.2 vs. -11.2; p=0.523 HAMD-17, mean change: -9.3 vs. -8.7 HAMD-31, mean change: -14.4(12.7) vs. -13.0(12.1) HAMD-item1, mean change: -1.2 vs. -1.0 CGI-S, mean change: -1.2(1.4) vs. -1.1(1.3) CGI-I: 2.9 vs. 2.9 MRS-16, mean change: 0.6(6.2) vs. -0.7(5.4) MRS-11, mean change: 1.0(5.4) vs. 0.0(4.7)	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	*Double-blind phase* Lamotrigine vs. Placebo QLDS, mean change: -10.8(10.4) vs. -7.0(10.7) PGI-I: 3.1(1.7) vs. 3.0(1.4)	*Continuation phase* Lamotrigine vs. Placebo CGI-S, mean change from baseline: -2.2(1.3) vs. -2.2(1.3) CGI-I: 1.8(1.0) vs. 1.8(0.9) MADRS, mean change from baseline: -20.9(10.1) vs. -21.6(9.0)	*Continuation phase* Lamotrigine vs. Placebo QLDS, mean change from baseline: -15.6(9.0) vs. -15.2(10.7) PGI-I: 1.9(1.2) vs. 1.9(0.9)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	Monitored

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910) U.S.	*Double-blind phase; [Continuation phase]* Lamotrigine vs. Placebo AEs: 97(75%) vs. 84(71%); [115(74%)] Headache: 32(25%) vs. 26(22%); [17(11%)] Infection: 14(11%) vs. 25(21%); [20(13%)] Nausea: 11(9%) vs. 18(15%); [8(5%)] Rash: 12(9%) vs. 7(6%); [12(8%)] Xerostomia: 12(9%) vs. 5(4%); [0(0%)] Back pain: 7(5%) vs. 6(5%); [5(3%)] Insomnia: 7(5%) vs. 5(4%); [9(6%)] Influenza: 6(5%) vs. 6(5%); [0(0%)] Abdominal pain: 6(5%) vs. 2(2%) Diarrhea: 6(5%) vs. 4(3%); [5(3%)] Pain: 6(5%) vs. 4(3%); [6(4%)] Accidental injury: 5(4%) vs. 6(5%); [13(8%)] Dizziness: 4(3%) vs. 8(7%); [5(3%)] Vomiting: 2(2%) vs. 7(6%); [0(0%)] Pharyngitis: 0(0%) vs. 0(0%); [7(5%)] Fatigue: 0(0%) vs. 0(0%); [5(3%)] Somnolence: 0(0%) vs. 0(0%); [5(3%)] Serious AEs: 5(4%) vs. 6(5%); [9(6%)] Suicidal: 2(2%) vs. 2(2%); [0(0%)] Suicidal ideation: 0(0%) vs. 0(0%); [3(2%)] Attempted suicide: 1(1%) vs. 1(1%); [0(0%)] Mania: 1(1%) vs. 0(0%); [5(3%)] Dystonic movement: 0(0%) vs. 1(1%); [0(0%)] Meningitis: 0(0%) vs. 1(1%); [0(0%)] Motor dysfunction: 0(0%) vs. 1(1%); [0(0%)]	*Double-blind phase* Lamotrigine vs. Placebo Total withdrawals: 52/133(39%) vs. 33/124(27%) Withdrawals due to AEs: 16/133(31%) vs. 9/124(27%) *Continuation phase* Total withdrawals: 56/161(35%) Withdrawals due to AEs: 13/161(23%)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

GSK (SCA40910)
U.S.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

Solomon, 1997
U.S.
(Poor)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Solomon, 1997 U.S. (Poor)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

Solomon, 1997 U.S. (Poor)	Results are inconclusive (pilot study). Small sample size, confounding co-medications, nonblinded research psychiatrist.

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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. placebo at week 5 (p < 0.05).

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 1999 Australia, France, U.K., U.S. (Fair)	Elicited by investigator

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Calabrese, 2000 U.S., Canada (Fair)	Monitored	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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
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 1. Randomized-controlled trials in patients with bipolar disorders

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
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 1. Randomized-controlled trials in patients with bipolar disorders

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.
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 1. Randomized-controlled trials in patients with bipolar disorders

Mishory, 2003 Israel (Poor)		
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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Mishory, 2003 Israel (Poor)	Not reported
Pande, 2000 U.S. (Fair)	Monitoring

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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)
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 1. Randomized-controlled trials in patients with bipolar disorders

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.
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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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%

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Weisler, 2004, Shire Dossier, 2005 U.S. SPD417 Study (Fair)	Monitoring										

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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/ul: 1.151 vs. 0.053 (p

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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%

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Weisler, 2005 U.S., India SPD417 Study (Fair)	Monitoring

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Salloum, 2005 U.S. (Fair)	Monitoring										

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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)

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

Davis, 2005 U.S. (Fair)	Monitoring	

Evidence Table 1. Randomized-controlled trials in patients with bipolar disorders

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 1. Randomized-controlled trials in patients with bipolar disorders

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 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Head-to-Head Trials

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Frye, 2000(20) U.S. (extension of this trial by Obrocea, 2002(19))	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes-attrition, crossovers. No-adherence, contamination.
Obrocea, 2002(19) U.S. Extension of Frye, 2000	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes-attrition, crossovers. No-adherence, contamination.
Vasudev, 2000(29) India	Yes	Method not reported	Yes	Yes	Yes	No	No	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Quality rating	Funding
No	No	Fair	Ted and Vada Stanley Foundation
No	No	Fair	Theodore and Vada Stanley Foundation
No	Yes (modified)	Poor	1) Novartis India Ltd and Novartix Pharma, Basel, Switzerland for CBZ. 2) Torrent Pharmaceutical Ltd.

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Bahk (2005) {ID 2025} South Korea	Method not reported	Method not reported	Yes	Yes	No	No	No	Yes-attrition, adherence No-crossovers, contamination
Suppes (2007) U.S.	Method not reported	Method not reported	No Oxcarbazepine younger (3.1 ± 8 vs. 36.9 ± 9.9 years, p=0.05); 53% of oxcarbazepin group Bipolar 1 vs. 27%	Yes	Yes	Not reported	No	Yes-attrition No-adherence, crossovers, contamination

Active-Controlled Trials

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination?
Bowden, 1994 U.S.	No	No	No All 8 patients who averaged 4 or more manic episodes/year for past 2 years in divalproex group. Efficacy results unchanged when these patients removed from analysis.	Yes	Yes	Not clear. Unblinded physician adjusted dose on day 5	Yes	Yes - attrition, adherence No - crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No (unable to evaluate for differential)	Yes (modified)	Poor	Grant from Janssen Pharmaceuticals Korea
No	No	Poor	Novartis

Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Quality rating	Funding
Yes - high loss and differential loss	Yes (modified)	Poor	Funded in part by a grant from Abbott Laboratories, North Chicago, Il

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Bowden, 2000(22) Canada, U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported	Yes-attrition, adherence No-crossover, contamination
Bowden, 2003(39) Australia, Canada, Greece, New Zealand, U.K., U.S., Yugoslavia	Method not reported	Method not reported	No	Yes	Not reported	Yes	Yes	Yes-attrition, adherence No-crossover, contamination
Brown 2006	NR	NR	yes	Yes	yes	yes	yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes (modified)	Fair	Sponsored by Abbott Laboratories
No	Yes (modified)	Fair	Grant from Glaxo-SmithKline
no/no	Only as a secondary analysis - primary was MMRM	fair	

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Calabrese, 2003(40) (--) U.S., Canada, Denmark, Finland, U.K.	Yes	Method not reported	No (apparently higher proportion of men in placebo group; NSD)	Yes	Not reported	Yes	Yes	Yes-attrition, adherence No-crossover, contamination
Coxhead, 1992(26) (--) U.K.	Method not reported	Method not reported	Yes	Yes	Yes, but method not described	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination
Denicoff, 1997(27) (--) U.S.	Method not reported	No	Not reported	Yes	No	No	Yes	Yes-attrition, crossovers, adherence No-contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes (modified)	Fair	Supported by GlaxoSmithKline
Yes	Yes	Fair	Ciba-Geigy provided support and financial assistance
Yes	No	Poor	Research assistant support from Ciba-Geigy; support of the Ted and Vada Stanley Foundation

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Greil, 1997(24) (--) Germany	Yes	Yes	No (An apparently higher proportion of carbamazepine patients had no prior suicide attempts and 2 episodes of illness.)	Yes	No	No	No	Yes-attrition, adherence No-crossover, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes	Poor	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Greil, 1998(32) (--) Germany, Switzerland	Yes	No (open-label)	Yes (although data not reported in this article)	Yes	No	No	No	Yes-attrition No-crossover, adherence, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes	Poor	Grant from BMFT, Ministry of Research and Technology of the Federal Republic of Germany (abbreviations not defined)

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Greil, 1999(89)(-- "bipolar I") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes	No	No	No	Yes-attrition, adherence, contamination No-crossover,

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes	Poor	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Greil, 1999(89)(-- "bipolar II/NOS") Germany	Yes	No (open-label)	Yes (but by-treatment data not reported)	Yes (in Greil, 1997)	No	No	No	Yes-attrition, adherence No-crossover, contamination
Gyulai, 2003(33) (--) U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported	Yes-attrition No-crossover, adherence, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes	Poor	Grant from the BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)
Yes	Yes (modified)	Fair	Sponsored by Abbott Laboratories

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Hartong, 2003(90) The Netherlands	Yes	Yes	Yes, but data not presented by treatment group.	Yes	Yes	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination
Ichim, 2000 South Africa	Method not reported	Method not reported	No Mean duration of index episode before hospitalization statistically longer in lithium group (p=.048). Analysis wth outlier removed showed no significant difference in groups.	Yes	Not reported	Yes	Yes	Yes - attrition No - adherence, crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	No	Fair	Supported partly by Ciba-Geigy (later Novartis Pharma) and the Dutch Fund for Mental Health
No	Yes	Poor	Lamotrigine samples provided by GlaxoWellcome

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Kleindienst, 2002(31) (--) Germany, Switzerland	Yes	No (open-label)	No (higher extraversion score in carbamazepine group; extraversion was found to be unrelated to both inter-episodic morbidity and risk for drop-out)	Yes	No	No	No	Yes-attrition, adherence No-crossovers, contamination
Lerer, 1987(25) (--) U.S.	Method not reported	No (blinded physician reported directly to unblinded psychiatrist)	No (An apparently higher proportion of lithium patients had a moderate or good previous response to lithium.)	Yes	Yes	Yes	Yes	Yes-attrition No-crossover, adherence, contamination
Lusznat, 1988 (23) U.K.	Method not reported	Method not reported	No	Yes	Yes, but method not described	Yes	Yes	Yes-attrition, adherence. No-crossover contamination
Maina, 2007 Italy	Method not reported	Method not reported	Yes	Yes	Not reported	No	No	Yes - attrition No - adherence, crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	Yes	Poor	Grant from BMFT, Ministry of Research and Technology of the FRG (abbreviations not defined)
Yes	No	Poor	Carbamazepine and placebo supplied by Ciba-Geigy, U.S.A.
Yes	No	Poor	Partially supported by grant from Ciba-Geigy
No	Yes	Fair	Not reported

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

McIntyre, 2002(37) (--) Canada	Method not reported	Method not reported	Yes	Yes	Yes, but method not described	Unable to determine if careprovider was the assessor	No	Yes-attrition No-crossovers, adherence, contamination
Nierenberg 2006	Equipoise randomization - method NR	NR	Some differences - more women and more BPI in Lam group vs R group; l grp higher CGI No differenecs in lam vs inositol grps	Yes	n	No	No	No
Nolen 2007	NR	Yes	No, important differences due to small sample size.	Yes	n	No	No	Yes
Okuma, 1979 Japan	No	No	Yes Stated, but data not shown	Yes Very broad criteria	Not reported	Yes	Yes	Yes - attrition, adherence No - crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes	Poor	Not reported
Unclear - NR	Unclear	Fair to poor	
Yes/Yes (75% tranycypramine vs 45% lamotrigine)	Yes	Fair to poor	
No	No	Poor	Drug samples provided by Fujisawa Pharmaceutical Co. Ltd.

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Okuma, 1990(34) (--) Japan	No and method not reported; 2 patients received only placebo tablets of carbamazepine by mistake	No (blind was erroneously broken in 1 case)	No (Fewer patients aged and age of onset 20 to 29 y and more outpatients in lithium group; statistical analyses showed no significant deviation in the improvement rate in both treatment groups.)	Yes	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)	No (physician assessor was masked but treatment allocation was erroneously revealed in 1 case)	Yes	Yes-attrition, adherence, contamination No-crossovers
Post, 1987 U.S.	Not reported	Not reported	Not reported	Yes Very broad criteria	Yes	Not reported	Yes	Not reported
Revicki, 2005	Not reported	Not reported	Yes	Yes	No	No	No	Yes - attrition, adherence No - crossovers, contamination
Schaffer 2006	NR	NR	Unclear	Yes	yes	yes	yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	No	Poor	Not reported
Not reported	Not reported	Poor	Not reported
Yes - differential and high (at 12 months)	Yes	Fair	Abbott Laboratories, Abbott Park, IL
no/no	no, 1 patient missing (5%)	Fair	

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Small, 1991(30) (--) U.S.	Method not reported	Method not reported	No--Carbamazepine was significantly youner (p = 0.02); nalysis of covariance for the effects of age did not change the significance of any of the rating scale data	Yes	Yes	Yes	Yes	Yes-attrition, adherence No-crossover, contamination
Suppes, 2008 U.S.	Method not reported	Method not reported	Yes	Yes	Yes	No	No	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Yes	No	Poor	Grant from the National Institute of Mental Health
Yes High loss to follow-up and differential: 49% (20/41) lamotrigine 61%(30/49) lithium	Yes (modified)	Fair	NIMH Grant; Stanley Medical Research Institiute Grant; GlaxoSmithKline provided study medication

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Tohen, 2002(87) U.S.	Yes	Method not reported	Yes	Yes	Yes	Not reported	Yes	Yes-attrition No-crossover, adherence, contamination
Tohen, 2003(21) U.S.	Yes	Method not reported	Yes	Yes	Yes	Not reported	Yes	Yes-attrition, adherence No-crossover, contamination
Zajecka, 2002(28) (--) U.S.	Method not reported	Method not reported	No	Yes	No	No	Yes	Yes-attrition, adherence No-crossovers, contamination

Placebo-Controlled Trials

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes (modified)	Fair	Sponsored by Lilly Research Laboratories
Yes	No	Fair	Sponsored by Lilly Research Laboratories
Yes	Yes (modified)	Fair	Supported by Abbott Laboratories

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

	Internal Validity							
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Designated Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination?**
Bowden, 2006 U.S.	Not reported	Not reported	Yes	Yes	No reported	Yes	Yes	Yes - attrition, No - crossover, adherence, contamination
Calabrese, 1999(94) Australia, France, U.K., U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Loss to follow-up: differential/ high?	Intention-to-treat (ITT) analysis?	Quality rating	Funding
No	Yes	Fair	Abbott Laboratories, Abbott Park, Ill
No	Yes (modified)	Fair	Grant from Glaxo Wellcome Research and Development

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

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	Yes	Yes-attrition No-crossovers, adherence, contamination
Chengappa, 2006 U.S.	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes - attrition, adherence No - crossover, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes (modified)	Fair	Grant from Glaxo Wellcome, Inc.
Yes - high loss 40% topiramate and 37% placebo discontinued early	Yes	Fair	Ortho-McNeil Neurologics, Inc., Titusville, N.J.

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Davis, 2005 {ID 2045} U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Yes	Yes	Yes-attrition No-crossovers, adherence, contamination
Frankenburg, 2002 U.S.	Method not reported	No	Not reported for relevant bipolar prognostic factors	Yes	Yes	Yes	Yes	Yes-attrition No-adherence, crossovers, contamination
Mishory, 2003 Israel	Method not reported	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes-attrition, crossovers No-adherence, contamination
Pande, 2000(41) U.S.	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported	Yes-attrition No-crossovers, adherence, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes	Fair	Not reported
No differential Yes - high loss	Yes (modified)	Poor	Grant from Abbott Laboratories
No	No	Poor	NARSAD Young Investigator Award and a grant from the Dreyfus Health Foundation
No	Yes (modified)	Fair	Parke-Davis Pharmaceutical Research

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Pope, 1991 U.S.	No	Yes	Yes	Yes	Yes	No (one unblinded investigator monitored and adjusted doses and did not reveal assignment.)	Yes	Yes - attrition, contamination No - crossover, adherence
Salloum, 2005 {ID 2049} U.S.	Yes	Method not reported	Yes	Yes	Yes (No--dosing investigator)	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	No	Fair	National Institutes of Mental Health, Bethesda; Philip S Weld Memeorial Fund, McLean Hospital; Abbott Laboratories, Chicago
No	Yes (modified)	Fair	Grants from the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and National Institute of Mental Health (NIMH)

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Solomon, 1997(38) U.S.	Method not reported	Method not reported	No	Yes	Yes	No	Yes	Yes-attrition No-crossovers, adherence, contamination
Study #SCA100223	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Study #SCA30924	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Study #SCA40910	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes	Poor	Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression; Grant from Abbott Laboratories
N/N	Described as LOCF, but excluded 6/221 (2.7%) for unknown reasons	Fair	Glaxosmithkline
Slightly higher: 40% vs 43%	Described as LOCF, but 16/259 (6.2%) excluded for unknown reasons	Fair	Glaxosmithkline
High: No Differential: 39% vs 27%	Described as LOCF, but 14/257 (5.4%) excluded for unknown reasons	Fair	Glaxosmithkline

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Study #SCAA2010	NR	NR	Yes for demographics and scale scores, but proportion of patients with bipolar I and II subtypes, respectively, NR	Yes	Yes	Yes	Yes	Yes
Vieta, 2006 Spain	No	No	Probable important differences. Total number of episodes 33.8 in gabapentin vs. 17.8 in placebo; 19.3 depressive episodes in gabapentin vs. 8.3 in placebo group. Mean time from diagnosis 20.9 years in gabapentin vs.16.5 year placebo group.	Yes	Not clear	Yes	Yes	Yes-attrition No-crossovers, adherence, contamination
Weisler, 2004 {ID 2094} U.S.	Method not reported	Method not reported	No	Yes	Not reported	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

N/N	Described as LOCF, but excluded 4/206 (1.9%) for unknown reasons	Fair	Glaxosmithkline
Yes High loss to follow-up: 54% (7/13) gabapentn 50% (6/12) placebo	Yes (last obseration carried forward)	Poor	Pfizer S.A., Madrid, Spain
No	Yes (modified)	Fair	Supported by a grant from Shire, Newport, KY

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

Weisler, 2005 {ID 2098} U.S., India	Method not reported	Method not reported	Yes	Yes	Not reported	Yes	Yes	Yes-attrition, adherence No-crossovers, contamination

Evidence Table 2. Quality assessment of randomized controlled trials in patients with bipolar disorders

No	Yes (modified)	Fair	Grant from Shire, Wayne, PA

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Anthony 1972 Australia	Comparison between 3 treatments Setting NR	Inclusion- 2 or more migraines a month	Prindolol Clonidine Carbamazepine	NR

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Anthony 1972 Australia	NR	Responses were classified 'as: (a.) headache-free: (b) more than half improved (half or less than half the previous frequency of headache); and (c) unimproved. Assessed monthly	Age 18-65 % female 79 Ethnicity NR	NR	NA	NR/NR/153

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Anthony 1972 Australia	% improved Prindolol 52% Clonidine 40% Carbamazepine 29% The response to prindolol was found to be better than that to carbamazepine at the 1% to 2% probability level (0.01 < P < 0.025), and the response to clonidine was not significantly better than that to carbamazepine (0.1 < P < 0.2).	NR	Prindolol vs. clonidine vs. carbamazepine Drowsiness, tiredness, weakness 2 vs.15 vs. 7 Dryness of mouth, sore tongue: bad taste . . .. .. 0 vs. 10 vs. 0 Giddiness, ataxia .. .. 1 vs. 0 vs. 10 Faintness, dizziness .. 3 vs. 5 vs. 3 Nausea 2 vs. 5 vs. 6 Vomiting :: :: :: 1 vs. 0 vs. 0 Increased appetite .. 0 vs. 0 vs. 1 Epigastric discomfort 0 vs. 1 vs. 1 cramps, limb pains .. .. 6 vs. 1 vs. 0 Irrltability, agitation 4 vs. 2 vs. 2 Insomnia, nlghtmares 0 vs. 1 vs. 1 Bruising, prominent veins 0 vs. 1 vs. 0	Total withdrawals NR 28 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Anthony 1972 Australia	Follow-up ranged from 1 to 18 months, none of the carbamazepine for more than 4 months, no randomization or controls of any type reported. Study design and reporting sure have come a long way since 1972!

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Bartolini 2005 Italy	open-label, randomized, controlled study	Inclusion- Forty-nine consecutive patients with chronic migraine and a history consistent with a diagnosis of episodic migraine without aura. Exclusion- analgesic drug overuse	Topiramate 75 mg Valproate 750 mg	None
Diener 2007 Multinational	Open label for 6 months followed by Double-blind RCT	Inclusion- 18–80 years of age and fulfilled International Headache Society criteria for migraine with or without aura; a history of migraine for at least 1 year, with a mean of at least four migraine days per month during the 3 months before Exclusion- used migraine prophylactic medication in the month before trial entry; flunarizine in the 3 months before; had experienced poor or no efficacy with more than two regimens of migraine prophylactic medication; overused acute medication (defined as ≥10 days in every 4 weeks for opioids, ergots, triptans,or combination analgesics, and ≥15 days in every 4 weeks for other analgesics), or had	Topiramate 50-200 mg/day Placebo	None

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bartolini 2005 Italy	NR	Patient diary and MIDAS	Mean age 41.8 years % female 70 Ethnicity NR	NR	49 enrolled	5/0/44
Diener 2007 Multinational	B-blockers and tricyclic antidepressants allowed for indications other than migraine prevention and acute pain meds triptans, ergots, opiates, and other analgesics	Patient diaries and migraine disability assessment test (MIDAS) and the short-form 12 (SF-12) general health status questionnaire were completed at the start and end of the open-label phase and at the end of the double-blind phase; the six-item headache impact test (HIT-6) was completed during weeks 0, 8, and 26 of the open-label phase, and weeks 8 and 26 of the	Mean age 39.8 years % female 87 Ethnicity NR	NR	954 sreened 818 open label 514 double blind phase	Open label portion 118/25(other)/818 Double blind portion 95/27/512

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Bartolini 2005 Italy	Toprimate vs.. Valproate Thirty-day Headache Frequency (mean (SD)) Baseline 26.1 (2.3) vs.. 27.0 (1.3) After 1 Month 10.4 (9.3) vs.. 6.1 (4.5) 3 Months 2.76 (3.9) vs.. 3.2 (2.9) MIDAS scores (mean (SD)) Baseline 27.8(12.1) vs.. 25.2(3.6) 3 months 7.1(10.3) vs. 5.7 (6.4) Reduction of at least 50% in	NR	NR	5 withdrawals 5 due to Aes
Diener 2007 Multinational	In double-blind phase- The mean increase in number of migraine days was greater in the placebo (1.19 days in 4 weeks, 95% CI 0·71 to 1·66; p<0·0001 vs. topiramate (0·10, –0·36 to 0·56; p=0·5756; mean difference between groups –1·09, –1·75 to –0·43). Patients in the placebo group had a greater number of days on acute medication than did those in the topiramate group (mean diff erence between groups	Monitoring of adverse events at each visit, by physical examination and laboratory measurements when the investigator felt this to be necessary (and in weeks 8 and 26 of the open-label phase for measurements of sodium, potassium, chloride, and bicarbonate), and by assessment of vital	Open label, double-blind toprimate vs. placebo Paraesthesia 411 (50%), 77 (30%) vs.55 (21%) Fatigue 102 (12%), 18 (7%) vs. 10 (4%) Disturbance in attention 100 (12%) 11 (4%) vs.12 (5%) Anorexia or decreased appetite 92 (11%), 13 (5%) 9 (3%) Weight decreased 74 (9%) 23 (9%) vs. 18 (7%) Nausea 71 (9%), 11 (4%) vs. 10 (4%) Dysgeusia 48 (6%)	Open label portion 118 withdrawals 56 due to Aes Double blind portion 95 withdrawals 3 due to AEs

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Bartolini 2005 Italy	Completers analysis
Diener 2007 Multinational	

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Dodick 2007 USA	RCT Double-blind Multicenter (46)	Inclusion- 18 years of age or older, diagnosis of chronic migraine as defined by Silberstein–Lipton criteria, and have a MIDAS score of at least 11 at visit 1 Women were required to be postmenopausal, surgically unable to become pregnant, or using an adequate method of birth control; no clinically significant abnormalities on neurological examination at visit 1. Exclusion- previous failure on more than 2 previous trials of migraine-preventive medication; failure on a prior trial of topiramate therapy; history of cluster headache, basilar, ophthalmoplegic, or hemiplegic migraines; onset of migraine after the	Topiramate 100 mg/day Placebo	Washout 56 days
Gupta 2006 India	RCT Double-blind crossover Single center	Inclusion- Diagnosis of migraine; Duration of disease: at least 1 year; 4 to 10 migraine headache attacks per month; Each attack separated by pain free interval of at least 48 hours; Age at onset less than 50 years; Age at entry 18 to 65 years; Females of childbearing age group that are neither pregnant nor lactating and are ready to use reliable methods of contraception during the study; Concomitant migraine prophylactics withdrawn 1 month prior to entry ; Patient being able to fill a headache diary Exclusion- Experienced headaches other than migraine; Overused acute migraine treatments	Topiramate 50 mg Lamotrigine 50 mg Placebo	1 month washout before randomization

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Dodick 2007 USA	acetaminophen, aspirin, NSAIDs, opioids, triptans, prescribed NSAIDs, and ergot derivatives, were allowed but could not be used for more than 4 days per week during the maintenance period	MIDAS, Migraine Disability Assessment- baseline and end; MSQ, Migraine-Specific Quality of Life Questionnaire; every 28 days starting at screening and washout PGIC, Physician's Global Impression of Change; at end SGIC, Subject's Global Impression of Change at end	Mean age 38.2 years % female 85.3 Ethnicity NR	NR	NR/NR/328	306
Gupta 2006 India	Rescue medications (diclofenac potassium and paracetamol combination tablets)	Head ache diary - primary outcomes were responder rate for frequency of migraine headache attacks per month and mean headache intensity for the migraine headaches individually (more than 50% reduction in baseline migraine headache frequency or intensity).	Mean age 29.41 years % female 78.33 Ethnicity NR	NR	129/NR/60	4/0/57

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Dodick 2007 USA	Topiramate vs.. Placebo MIDAS, >50% improvement 56% vs placebo 45%; P = .074 MSQ, results NR PGIC, improvement 72% vs 59% P = .037 SGIC improvement, 75% vs 61%, P = .025)	treatment-emergent adverse events, vital signs, physical and neurological evaluations, and clinical laboratory parameters (eg, blood chemistry, hematological tests, and urinalysis). And spontaneously reported adverse events were recorded at each visit	NR	NR
Gupta 2006 India	responder rate for frequency (≥50% reduction in monthly migraine frequency) topiramate versus placebo (63% vs 30%, P < .001), and versus lamotrigine (63% vs 46 %, P = .02). Responder rate for headache intensity for the topiramate versus placebo (50% vs 10%, P < .001), and versus lamotrigine (50% vs 41%, P = .01)	reports of adverse events communicated historically during visits, as transcribed on headache diaries, physical and neurological examination, and clinical laboratory tests	Lamotrigine vs.. Placebo vs.. Topiramate # Sleepiness and concentration difficulty 2 vs. 0 vs. 3 Paresthesias 2 vs. 1 vs. 3 Gastrointestinal intolerance 2 vs. 3 vs. 3 Anorexia 1 vs. 4 vs. 1 Giddiness 2 vs. 2 vs. 2 Rash 2 1 0 0 Palpitations 0 vs. 2 vs. 0 Menorrhagia 0 vs. 1 vs. 0 Hair loss 0 vs. 1 vs. 0 Pain in lower limbs 0 vs. 1 vs. 0	4 withdrawals 0 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Dodick 2007 USA	goes with Silberstein S, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A 4-month, randomized, doubleblind, placebo-controlled trial. Headache. 2007;47: 170-180.
Gupta 2006 India	Croos over study

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Mei 2006 Italy	RCT Double-blind NR (probably single center)	Inclusion- Patients affected by chronic migraine with medication overuse aged between 18 and 65 years Exclusion- (1) arterial hypertension; (2) history or symptoms suggestive of ischemic heart disease or other vasculopathies such as Prinzmetal angina, Wolff-Parkinson-White syndrome, or other conduction anomalies or arrhythmias; (3) use of MAOIs or methysergide or other ergots in 2 weeks preceding ; (4)recent alcohol abuse; (5) lactation, pregnancy, fertile women not using adequate contraceptive methods; (6) use of carbonic anhydrase inhibitors; (7) renal stone diathesis;	Topiramate 50-100 mg/day Placebo	Washout phase of other preventive treatments of 2 weeks and a prospective baseline phase of 4 weeks

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Mei 2006 Italy	Acute medication: sumatriptan 100-mg , zolmitriptan 2.5-mg, rizatriptan 10-mg , almotriptan 12.5-mg, eletriptan 40-mg, frovatriptan 2.5-mg was randomized vs.. Placebo in the TPM group. And paracetamol 1000 mg in the 1st placebo group	Patient diaries reducing the monthly number of days with at least 4 hours of headache and in reducing the amount of acute medication taken Responders = a reduction of at least 50%, in the number of days in which they presented with headache and the same reduction in	Mean age 46 years % female 69 Ethnicity NR	NR	NR/54/50	15/NR/35

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Mei 2006 Italy	Days w/ headache (SD) TPM 24.38 (3.93) at baseline to 3.14 (0.91) vs. Placebo 23.50 (3.70) days at baseline to 15.36 (4.38) (P < 0.0001 vs placebo). Acute trmts. mean amout of doses per 28 days(SD) 30.81 (3.56) to 3.19 (1.04) vs. placebo group, base 29.14 (4.19) to 15.43(4.43) (P < 0.0001 vs placebo).	Patient reported Aes	TPM vs. placebo # of events Paresthesias 18 vs. 2 Fatigue 8 vs. 1 Anorexia 9 vs. 0 Weight loss 7 vs. 0 Alteration of taste 10 vs. 0 Memory impairment 5 vs. 2 Difficulty concentrating 4 vs. 2 Somnolence 2 vs. 0 Speech difficulties 6 vs. 0 Insomnia 1 vs. 2 Sensation of nuchal constriction 0 vs. 1 Dizziness 0 vs. 3	15 withdrawals 15 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Mei 2006 Italy	This study is really a completers analysis and is mucked up additionally by the 2nd randomization of the active arm between triptans and placebo for acute treatment

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Millan-Guerro 2007 Mexico	RCT Double-blind Single center- hospital	Inclusion- diagnosed with recurrent migraine unresponsive to available abortive and/or prophylactic agents Exclusion- Pregnant women, patients suffering daily headaches, as well as patients whose radiological tests, including CAT, revealed any pathology	Histamine 1-10 ng 2x a week Sodium valproate 500 mg daily	1 month washout at beginning

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Millan-Guerro 2007 Mexico	500 mg acetaminophen tablets if they had moderate or severe headache	(i) headache frequency, measured by numbers of attacks per month, (ii) intensity of pain (scale from 1 to 3), (iii) duration of pain, measured by hours of headache per attack, (iv) intake of rescue analgesics, measured by the number of acetaminophen tablets (500 mg) taken per month, and (v) Migraine Disability Assessment (MIDAS) every 30 days for 3 months	Mean age 32 years % female 86.3 Ethnicity NR	Headache duration 15 years 3.8 headaches per month	NR/NR/92	11/NR/92

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Millan-Guerro 2007 Mexico	Histamine vs. sodium valproate Intensity- Eighty-seven percent reported a 53% reduction P < 0.001 , vs. 58% reported a 33% reduction. Duration- Eighty-four percent reported an 82% reduction P < 0.001 vs. 54% of patients reported a 17% reduction Rescue med- 83% of patients reported a 53% reduction in the number of tablets ingested P < 0.001 vs. 77% patients reported a 25% reduction No difference was observed between frequency and MIDAS	Safety assessments	NR	11 withdrawals 6 due to Aes (all valproate)

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Millan-Guerro 2007 Mexico	

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Silberstein 2006 USA	RCT Double-blind Multicenter (27)	Inclusion- 18 and 65 years required to have a history of migraine with or without aura, as assessed by International Headache Society criteria, > 12 months; an average of 3 to 8 migraine episodes per month (defined as 28 days) for 3 months (84 days) Exclusion- previously failed to respond to TPM therapy or had taken preventive medication within 2 weeks of the start of the prospective baseline period; >15 headache days per month during the 3 months before; diagnosis of cluster headache; basilar, ophthalmoplegic, hemiplegic, or transformed migraine; or migraine aura exclusively (without headache); previously failed to respond to >2 adequately dosed migraine preventive medications, had migraine onset after the age of 50 years, or overused acute migraine treatment	Toprimate - 200 mg/day or maximum tolerated dose Placebo	1 month washout at beginning

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silberstein 2006 USA	acute headache pain medications and other concomitant meds that were not specified	change in mean monthly (28-day) migraine frequency during the entire double-blind phase compared with the prospective baseline period; median percent reduction in monthly migraine frequency and the proportion of responders (those with ≥50%, ≥75%, or 100% reduction in monthly migraine frequency). Assessed every 2 to 3 weeks during the trial	Mean age 40.5 years % female 85.8 Ethnicity 88.6% white, 9.0% blabk, and 2.4% other	35.5% migraine with aura	Screened NR 213 enrolled	56 withdrawn 7 LTF 211 analyzed

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Silberstein 2006 USA	Toprimate vs. placebo Reduction in mean monthly migraine frequency -1.43 vs. -1.04, P=NS ≥50% reduction in monthly migraine frequency 39.9% [n = 55] vs 34.2% [n = 25]; P=NS ≥75% reduction in monthly migraine frequency 19.6% [n = 27] vs 8.2% [n = 6]; P = 0.03	measurement of vital signs, physical examinations, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), and evaluation of adverse events	Toprimate vs. placebo n(%) Subject w/ 1 or more AE 126 (90.0) vs. 51 (69.9) Paresthesia (mostly in the extremities) 63 (45.0) vs.4 (5.5) Dizziness 22 (15.7) vs. 8 (11.0) Fatigue 22 (15.7) vs. 6 (8.2) Nausea 20 (14.3) vs. 3 (4.1) Weight loss 19 (13.6) vs. 1 (1.4) Anorexia 19 (13.6) vs. 5 (6.8) Somnolence 16 (11.4) vs.4 (5.5) Difficulty with memory 15 (10.7) vs.1 (1.4) Upper respiratory tract infection 18 (12.9) vs. 7 (9.6)	56 withdrawals 25 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Silberstein 2006 USA	

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Silberstein 2007 USA	RCT Double-blind Multicenter (46)	Inclusion- Adult subjects with a diagnosis of chronic migraine, defined according to Silberstein/ Lipton criteria for transformed migraine; required to have at least 15 headache days per 28 days; On at least half of these days, subjects were required to have experienced migraine with or without aura or migrainous headache. Migrainous headache was defined as moderate to severe headache with 1 or more of the following migraine features: unilateral pain or pain worse on 1 side of the head, pulsatile pain, photophobia and/or phonophobia, nausea and/or vomiting, or pain made worse by physical activity; Migraine Disability Assessment (MIDAS) score of at least 11 at visit 1. Exclusion- Previously failed more than 2 adequate trials of migraine preventive medications (adequate was defined as a trial of at least 3 months' duration at the recommended dose); Previously failed an adequate trial of topiramate therapy due to lack of efficacy or adverse events; History of cluster headache or basilar, ophthalmoplegic, or hemiplegic migraines; Migraine onset after age 50; Overuse of acute migraine medication; H	Toprimate - 100 mg/day Placebo	14 to 28 Washout of preventative migaine meds and then up to 2 weeks tapering period at end

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silberstein 2007 USA	acute headache pain medications such as analgesics, NSAIDs n, triptans, opioids, and ergot derivatives was permitted for symptomatic relief of headache but could not exceed 4 days per week during the maintenance period	Change from baseline in the mean monthly (28 day) number of migraine/migrainous days, MIDAS, Physician's Global Impression of Change, Subject's Global Impression of Change, and the Migraine-Specific Quality-of-Life Questionnaire Assessed every 28 days	Mean age 38.2 years % female 85.3 Ethnicity 80.4% white, 14.7% blabk, 1.0% Asian and 3.9% other		686 screened/328 enrolled and randomized	146 withdrew 31 LTF 306 analyzed

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Silberstein 2007 USA	Mean (±SD) reduction from baseline of toprimate 6.4 (±5.8) migraine/migrainous days per month compared with 4.7 (±6.1) for the placebo group (P = .010) Mean reduction of migraine/migrainous headache days (topiramate −6.4 vs placebo −4.7, P = .010) migraine headache days relative to baseline (topiramate −5.6 vs placebo −4.1, P = .032).	Measurement of vital signs, serial physical and brief neurologic examinations, and clinical laboratory parameters and spontaneously reported adverse events were collected and recorded at each visit.	Toprimate vs. placebo % Subjects w/ any adverse event, 82.5 vs. 70.2 Paresthesia 28.8 vs. 7.5 Upper respiratory tract infection 13.8 vs. 12.4 Fatigue 11.9 vs. 9.9 Hypoesthesia 9.4 vs. 0 Dry mouth 9.4 vs. 3.1 Difficulty with concentration/attention 9.4 vs. 2.5 Taste perversion 9.4 vs. 2.5 Nausea 8.8 vs. 8.1 Difficulty with memory, not otherwise specified 6.9 vs. 6.2 Somnolence 5.6 vs. 4.3 Injury 5.0 vs. 1.2 Anorexia 5.0 vs. 5.6 Sinusitis 4.4 vs. 5.0 Dizziness 3.8 vs. 7.5	146 withdrawals 28 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Silberstein 2007 USA	

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Silberstein 2008 USA	RCT Double-blind Multicenter (23) 15-week double-blind phase consisting of a 6-week titration period, an 8-week maintenance period,	Inclusion- male and female, 16 to 65 years, clinical diagnosis of migraine headache at least 1 year , defined as at least five headache attacks lasting 4 to 72 hours with or without aura; experienced three to nine migraine attacks during the 4-week single-blind baseline phase and onset of migraine headaches before 50 years of age Exclusion- experienced a total of 14 headache days with each headache lasting 4 hours (of either migraine or non-migraine type) during the last 28 days of the single-blind baseline phase, required symptomatic (acute) therapy more than 3 days per 7 consecutive day period for a non-migraine headache during the last 28 days of the single-blind baseline phase, missed more than 20% of their expected doses of placebo during the last 28 days of the single-blind baseline phase, or missed three or more consecutive migraine diary entries during the last 28 days of the single-blind baseline phase; previously failed more than three standard courses of a commonly effective preventive migraine treatment or had taken antidepressants (except ssris,), beta-blockers, ver	Oxcarbazepine 1200 mg/day Placebo	1 month run-in

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silberstein 2008 USA	Yes- analgesics for acute relief and other ie. Vitamins, estrogen	Change from baseline in # of migraine attacks during the last 28-day period of the double-blind phase; change from baseline in # of migraine attacks during the entire double-blind phase; proportion of patients who responded to treatment with at least a 50% reduction in migraine attacks; change from baseline in # of migraine days; change from baseline in peak severity of migraine attacks; change from baseline in acute therapy consumption; and change from baseline in # of non-migraine headache days during the last 28 days of the double-blind phase and the entire double blind phase; patient functional status (Migraine Disability Assessment Test [MIDAS]), Assessed daily through interactive phone	Mean age 32 years % female 86.3 Ethnicity NR	82% took at least one concomitant medication during study	324 screened/ 170 enrolled and randomized	47 withdrew LTF NR 170 analyzed

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Silberstein 2008 USA	No. of migraine attacks, LS mean (SE) 1.10 (0.209) vs. 1.16 (0.209) P=0.8220 Patients with 50% reduction in no. of migraines, n (%) 23 (27.1) vs. 20 (23.5) P= 0.5573 No. of migraine days (change) -1.65 (0.330) vs. -2.02 (0.331) P= 0.3876 Acute migraine therapy administered, LS mean (SE) 0.98 (0.306) vs. 1.53 (0.306) P=0.1670 Change in MIDAS grade, LS mean (SE) 1.16 (0.173) vs. 0.64 (0.165) P=0.0055	reports of adverse events, physical and neurologic evaluations, and clinical laboratory tests	Oxcarbazine vs. placebo n (%) any AE, 68 (80.0) vs. 55 (64.7) Fatigue 17 (20.0) vs. 6 (7.1) Dizziness 15 (17.6) vs. 6 (7.1) Nausea 14 (16.5) vs. 4 (4.7) Somnolence 7 (8.2) vs. 6 (7.1) Balance disorder 5 (5.9) vs. 2 (2.4) Insomnia 5 (5.9) vs. 6 (7.1) Migraine 5 (5.9) vs. 2 (2.4) Paraesthesia 5 (5.9) vs. 1 (1.2) Sinusitis 2 (2.4) vs. 5 (5.9	47 withdrawals 13 due to Aes

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Silberstein 2008 USA	

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Silvestrini 2003 Italy	RCT Double-blind Single center	Inclusion- 28 consecutive patients referred Headache Centre who were diagnosed as affected by CDH; suffering from chronic migraine with acute medication overuse; a history of migraine without aura attacks before the occurrence of chronic migraine for at least 10 years; previously had failed to respond to at least four preventive adequate doses of medication for an adequate duration. Exclusion- use of carbonic anhydrase inhibitors, history of renal calculi, pregnancy or lactation; neurological diseases or taking any prophylactic treatment for headache at the moment of our observation	Topiramate 50 mg/day Placebo	28 day baseline assessment

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silvestrini 2003 Italy	Yes- analgesics for acute relief	Reduction in the 28-day headache frequency from the baseline phase to the first and second 4-week period of the maintenance phase. Interim history, review of the headache diary and a report of any adverse event was performed every two weeks	Mean age 43.5 years % female 64.3 Ethnicity NR		NR/NR/28	1 withdrawn 28 analyzed

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Results	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Silvestrini 2003 Italy	50% responder rate was 71% (10 patients) in the topiramate group and 7% (1 patient) in the placebo group (odds ratio: 32.5, 95% c.l. 3.1–337). Patients reporting more than 75% reduction in headache frequency were 6 (42%) in the topiramate group and 0 in the placebo group (odds ratio 36, 95% c.l. 1.76–733), whereas those referring a greater than 90% benefit were 4 (28%) in the topiramate group and 0 in the placebo group (odds ratio 10.8, 95% c.l. 0.5–228).	Patient reported Aes	Topiramate vs. placebo Gastric intolerance 7% vs. 0 Paresthesias 14% vs 7% Sleepiness 14% vs. 0	1 withdrawal 1 due to AE

Evidence Table 3. Randomized-controlled trials in patients with migraine

Author Year Country Trial Name	Comments
Silvestrini 2003 Italy	

Evidence Table 4. Quality assessment of randomized-controlled trials in patients with migraine

Author, Year	*Internal Validity* Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Anthony, 1972	No	No	Not reported	Yes	Not reported	Not reported
Bartolini, 2005	Not reported	Not reported	Yes	Yes	No, open-label	No, open-label
Diener, 2007	Yes	Yes	Yes	Yes	Not reported	Yes
Dodick, 2007	Yes	Unclear	Yes	Yes	Not reported	Assumed - stated double-blind design
Gutpa 2007	Yes	Yes	Yes	Yes	Yes	Yes
Mei, 2006	Not reported	Not reported	Yes	Yes	Not reported	Assumed - stated double-blind design

Evidence Table 4. Quality assessment of randomized-controlled trials in patients with migraine

Author, Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Anthony, 1972	Not reported	Yes - attrition, adherence No - crossovers, contamination	Yes - differential. Non-completers: 10% (8/79) prindolol 11% (8/73) clonidine 24% (12/51) carbamazepine	Yes	Poor	Boehringer Ingelheim Pty Ltd and Gelgy Ltd (Australia)
Bartolini, 2005	No, open-label	Yes - attrition, adherence No - crossovers, contamination	No Non-completers: 12% (6/49) total, with 3 drop-outs in each drug group	Unclear (49 randomized, 6 drop-outs, results on 44--89.9% analyzed)	Poor	Not reported
Diener, 2007	Yes	Yes - attrition, adherence No - crossovers, contamination	No Non-completers (double-blind phase): 20% (52/259) placebo 18% (45/255) topiramate	Yes	Good	Janssen-Cilag EMEA
Dodick, 2007	Assumed - stated double-blind design	Not reported	Not reported	No	Poor	Ortho-McNeil Jansson Scientific Affairs, LLC
Gutpa 2007	Yes	Yes - attrition, adherence No - crossovers, contamination	No Non-competers: 7% (4/60) for each condition	Yes	Good	Not reported
Mei, 2006	Assumed - stated double-blind design	Yes - attrition, adherence No - crossovers, contamination	No Non-completers: 30% (9/30) drug 30% (9/30) placebo	Reported as ITT but 70% were analyzed	Fair	Not reported

Evidence Table 4. Quality assessment of randomized-controlled trials in patients with migraine

Author, Year	*Internal Validity* Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Millan-Guerrero, 2007	Not reported	Not reported	Yes	Yes	Not reported	Yes
Silberstein, 2006	Not reported	Not reported	Yes	Yes	Yes	Yes
Silberstein, 2007	Does not clearly meet standard	Does not clearly meet standard	Yes	Yes	Not reported	Assumed - stated double-blind design
Silberstein, 2008	Does not clearly meet standard	Does not clearly meet standard	Yes	Yes	Yes	Yes
Silvestrini, 2003	Not reported	Not reported	Yes	Yes	Not reported	Not reported

Evidence Table 4. Quality assessment of randomized-controlled trials in patients with migraine

Author, Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Millan-Guerrero, 2007	Yes	Yes - attrition No - adherence, crossovers, contamination	No Non-completers: 13% (6/46) sodium valproate 11% (5/46) histamine	No	Fair	Not reported
Silberstein, 2006	Assumed - stated double-blind design	Yes - attrition, adherence No - crossovers, contamination	Yes - differential Non-completers: 31% (43/140) topiramate 18% (13/73) placebo	Yes with LOCF	Fair	Ortho-McNeil Neurologics, Inc, NJ
Silberstein, 2007	Assumed - stated double-blind design	Yes - attrition, adherence No - crossovers, contamination	Yes - high loss Non-completers: 44% (73/165) topiramate 45% (73/163) placebo	Yes	Fair	Ortho-McNeil Neurologics, Inc, NJ
Silberstein, 2008	Yes	Yes - attrition, adherence No - crossovers, contamination	Yes - differential Non-completers: 38% (32/85) oxcarbazepine 21% (18/85) placebo	Yes	Fair	Novartis Pharmaceuticals Corporation
Silvestrini, 2003	Yes	Yes - attrition No - adherence, crossovers, contamination	No Non-completers: 7% (1/14) topriamate 50 mg/d 0% (0/14) placebo	Yes	Fair	Not reported

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Arnold 2007 USA	Double-blind PCT 3 outpatient research centers	Age ≥18 years; met the ACR criteria for fibromyalgia; score of 4 on the average pain severity item of the Brief Pain Inventory (BPI) (26) at screening and randomization	Gabapentin Placebo Dosing schedule- Week 1: 300 mg qd Week 2: 300 mg bid Weeks 3 & 4: 300 mg bid + 600 mg qd Weeks 5 & 6: 600 mg tid Week 7+ (for at least 4 consecutive weeks): 600 mg bid + 1200mg qd Tapering phase: dose steadily decreased by 300mg qd	7- to 60-day screening phase Antidepressants: 14-day washout, except for fluoxetine, which required a 30-day washout

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Arnold 2007 USA	Episodic use of sedating antihistamines; acetaminophen or over-the-counter NSAIDs	Primary outcome: self-reported pain severity Method: BPI (short form) average pain severity score Secondary outcomes: interference of pain with general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life Other outcomes: Response to treatment; overall impact of fibromyalgia Timing: weekly - weeks 1 & 2); biweekly - weeks 3-12	Mean age 48.2 yrs (SD 11.2) 90% female 97% white 1% African-American <1% Asian	Mean baseline BPI pain severity score: 5.9 (SD 1.5) Mean baseline BPI pain interference score*: 5.0 (SD 2.0) *Statistically significant between-group difference: gabapentin 4.7 (SD 2.0) vs placebo 5.3 (SD 1.9); p<0.05	252/NR/150

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Arnold 2007 USA	31/5/119 for efficacy outcomes, 150 for safety outcomes	12 wk timepoint for all outcomes BPI average pain severity score (primary outcome): gabapentin 3.2 (SD 2.0) vs placebo 4.6 (SD 2.6); mean between group difference 1.4 (SD 0.6); mean change from baseline: gabapentin -2.5 vs placebo -1.4 BPI average pain interference score: gabapentin 2.2 (SD 2.2) vs placebo 3.6 (SD 2.8); mean between group difference 1.4 (SD 0.6); mean change from baseline: gabapentin -2.5 vs placebo -1.7 FIQ total score: gabapentin 26.2 (SD 15.1) vs placebo 37.3 (18.1); mean between group difference 11.1 (SD 3.0); mean change from baseline: gabapetin -20.1 vs placebo -10.4 CGI severity score: gabapentin 3.1 (SD 1.0) vs placebo 3.8 (SD 1.3); mean between group difference 0.7 (SD 0.3); mean change from baseline: gabapentin -1.3 vs placebo -0.7 Mean tender point pain threshold: gabapentin 2.0 (SD 0.9) vs placebo 1.8 (SD 1.0); mean between group difference 0.2 (SD 0.1); mean change from baseline: gabapentin 0.2 vs placebo 0.1 Medical Outcomes Study Sleep Problems Index: gabapentin 33.4 (SD 19.5) vs placebo 47.8 (20.9); mean between group difference 14.4 (SD 1.4); mean change from baseline: gabapentin -22.6 vs place Montgomery Asberg Depression Rating Scale: gabapentin 9.1 (SD 9.	Patient self-report and physician-determined during regular assessments

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Arnold 2007 USA	Gabapentin (n=75) vs placebo (n=75): Headache: 20 (26.7%) vs 16 (21.3%) Dizziness: 19 (25.3%) vs 7 (9.3%); p<0.05 Sedation: 18 (24.0%) vs 3 (4.0%); p<0.001 Nausea: 16 (21.3%) vs 16 (21.3%) Somnolence: 14 (18.7%) vs 6 (8.0%) Edema: 12 (16.0%) vs 6 (8.0%) Lightheadedness: 11 (14.7%) vs 1 (1.3%); p<0.01 Insomnia: 9 (12.0%) vs 6 (8.0%) Diarrhea: 8 (10.7%) vs 5 (6.7%) Pharyngitis: 7 (9.3%) vs 11 (14.7%) Asthenia: 6 (8.0%) vs 5 (6.7%) Depression: 6 (8.0%) vs 3 (4.0%) Flatulence: 6 (8.0%) vs 4 (5.3%) Nervousness: 6 (8.0%) vs 1 (1.3%) Weight gain: 6 (8.0%) vs 0; p<0.05 Amblyopia: 5 (6.7%) vs 1 (1.3%) Anxiety: 5 (6.7%) 2 (2.7%) Cold virus: 5 (6.7%) vs 11 (14.7%) Dry mouth: 5 (6.7%) vs 3 (4.0%)	31 withdrawals; 19 due to AEs	

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Crofford 2005 USA	Double-blind PCT 40 study centers	Age ≥18 years; met the ACR criteria for the diagnosis of FMS; score of ≥40mm on the 100mm VAS of the SF-MPQ; mean score of ≥4 on 0-10 pain rating scale based on at least 4 daily pain diary entries	Pregabalin 150-450mg qd placebo	7-day (SMRs, antidepressants, antiepileptics corticosteroids, benzodiazepines, opioid analgesics, tramadol, mexiletine, anti-Parkinsons medications) to 30-day (tenderpoint site injections and fluoxetine) washout

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Crofford 2005 USA	acetaminophen, aspirin, symptomatic migraine medication	Primary outcome: daily patient assessment of FMS pain SF-MPQ measurements at baseline, weeks 1, 3, 5 and 8 MAF, HADS and SF-36 at baseline and 8 wks PGIC and CGIC at 8 wks	Mean age 48.6 yrs 92% female 94% white	Mean baseline pain score 7.0	825/594/529

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Crofford 2005 USA	119/NR/varied for efficacy, 529 for safety	Least squares mean at 8 wks pregabalin 150mg vs pregabalin 300mg vs pregabalin 450mg vs placebo Pain score: 5.74 vs 5.47 vs 4.94 vs placebo 5.88 Total SF-MPQ score: 17.38 vs 16.98 vs 14.05 vs 18.50 FMS intensity score: 5.05 vs 4.65 vs 4.65 vs 5.17 Sleep quality diary: 4.91 vs 4.68 vs 3.99 vs 5.30 MOS-Sleep problems index: 45.66 vs 45.26 vs 40.44 vs 54.16 MAF global fatigue index: 30.67 vs 29.37 vs 29.14 vs 32.85 HADS anxiety: 8.35 vs 8.36 vs 7.56 vs 8.41 HADS depression: 6.82 vs 7.23 vs 6.65 vs 7.41 SF-36 general health score: 53.89 vs 55.28 vs 54.38 vs 49.34	Spontaneous report and observed at clinic visits

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Crofford 2005 USA	Placebo (n=131) vs Pregabalin 150mg (n=132) vs 300mg (n=134) vs 450mg (n=132) Any AE: 101 (77%) vs 102 (78%) vs 118 (88%) vs 121 (92%) Dizziness: 14 (10.7%) vs 30 (22.7%)vs 42 (31.3%) vs 65 (49.2%) Somnolence: 6 (4.6%) vs 21 (15.9%) vs 37 (27.6%) vs 37 (28.0%) Headache: 25 (19.1%) vs 16 (12.1%) vs 20 (14.9%) vs 17 (12.9%) Dry mouth: 2 (1.5%) vs 9 (6.8%) vs 8 (6.0%) vs 17 (12.9%) Peripheral edema: 1 (0.8%) vs 7 (5.3%) vs 9 (6.7%) vs 14 (10.6%) Infection: 22 (16.8%) vs 11 (8.3%) vs 13 (9.7%) vs 13 (9.8%) Asthenia: 8 (6.1%) vs 7 (5.3%) vs 12 (9.0%) vs 11 (8.3%) Euphoria: 1 (0.8%) vs 2 (1.5%) vs 11 (8.2%) vs 10 (7.6%) Thinking abnormal: 4 (3.1%) vs 7 (5.3%) vs 5 (3.7%) vs 10 (7.6%) Weight gain: 2 (1.5%) vs 10 (7.6%) vs 13 (9.7%) vs 9 (6.8%) Sinusitis: 3 (2.3%) vs 6 (4.5%) vs 5 (3.7%) vs 9 (6.8%) Pharyngitis: 3 (2.3%) vs 3 (2.3%) vs 2 (1.5%) vs 8 (6.1%) Accidental injury: 4 (3.1%) vs 3 (2.3%) vs 7 (5.2%) vs 7 (5.3%) Confusion: 0 (0.0%)vs 1 (0.8%) vs 5 (3.7%) vs 7 (5.3%)	119/48	

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Crofford 2008 USA FREEDOM	6 wk open label followed by 26 wk double blind , multicenter placebo controlled, largely institutional center	Adult patients meeting ACR criteria for fibromyalgia and must have scored their pain over the previous week as ≥40 mm on the 0-100 mm pain VAS at screening and baseline visits. Inclusion in DB phase: ≥50% reduction in pain VAS score from open label baseline and self rating of overall improvement on the PGIC scale of "much improved" or "very much improved".	Open label phase 1-3 wks: escalating doses of pregabalin 150 mg-600 mg, 4-6 weeks: optimal fixed doses of 300, 450 and 600 mg/day DB phase: placebo, 300, 450 600 mg/day	washout-1-7 days depending on drug class, Fluoxetine required 30 day washout

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Crofford 2008 USA FREEDOM	upto 4g/d acetaminophen	Primary outcomes: 1)<30% reduction in VAS score relative to open label baseline at 2 consecutive visits of DB phase, 2) Worsening in the judgment of the investigator of FM symptoms necessitating alternate treatment. Secondary outcomes: Patients' impression of overall health status measured by PGIC Aspects of pain, symptoms of disturbed modd and functioning measured by FIQ Sleep profile and overall sleep problems measured by MOS-Sleep scale Fatigue measured by MAF Physical and mental health measured by SF-36 health survey Variable timepoints and end of study	Open label: Pregabalin 49.5 (SD 11.6) 93% female white: 88%, black: 5%, Other: 7% DB-Pregabalin vs. Placebo 48.8(SD 11.9) vs 49(SD 10.5) female: 93% vs 94% White: 91% vs 88% Black: 3% vs 4% Other: 6% vs 8%	Open label phase Duration of FM, months Mean (SD) : 123.3(100.5) No. of painful tender poitns: Mean (SD) 17.1 (1.7) DB phase: Pregabalin vs Placebo Duration of FM, months: 128.7 (110.2) vs 114.0(90.2) no. of painful tender points: 17.0(1.8) vs. 17.2(1.6) Comorbidities: hypertension 29%, insomnia 28%, depression 26%	1777 NR enrolled to open label treatment: 1051 enrolled to DB: 566

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Crofford 2008 USA FREEDOM	Number withdrawn: Open label: 37% : DB phase: 71.3% (Prgabalin and Placebo) Loss to follow-up: not reoprted specifically. Reported as Defaulted which could either mean withdrawl of consent or lost to follow-up. Analyzed: Placebo=287, Pregabalin= 279	Primary outcome: Patients with LTR by wk 26 N (%) placebo: 174 (61) Pregabalin: 90 (32) Time to LTR for 1st quartile of patients : Placebo 7(95% CI, 5-9), Pregabalin: 34(95% CI, 21-48) , Median : Placebo 19(95% CI, 14-36), Pregabalin: N/A , p value between groups <0.0001 <u>Secondary outcomes (p-value vs placebo for all secondary outcomes<0.0001)</u> PGIC: time to LTR (days): Median (95% CI): Placebo 20(15-35), Pregabalin: 126 (7-NUL) FIQ : time to LTR (days): Median (95% CI): Placebo 14(NA), Pregabalin: 19(15-41) MOS: time to LTR (days): Median (95% CI): Placebo 14(NA), Pregabalin 42(41-43) MAF: time to LTR(days): Median (95% CI) Placebo 27(16-42); Pregabalin 119(69-155) SF-36 Physical component: time to LTR (days): Median (95% CI): Placebo 15(14-19); 49(42-71) SF-36 mental component: time to LTR (days): Median(95% CI): Placebo 14 (14-15), Pregabalin 42(41-43)	AE assessed via non specific questioning and sponteneous reporting, vital signs, physical exam, abbreviated neurologic exam, and clinical laboratory evaluation.

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Crofford 2008 USA FREEDOM	DB phase: Placebo vs. Pregabalin Insomnia: 6% vs 6% Nausea: 5% vs 5% Anxiety: 2% vs 5% Arthralgia: 2% vs 5% Sinusitis: 3% vs 5% Influenza 1% vs 5% URTI: 3% vs 4% Weight increased:<1 vs 4% During open label phase: serious AE :0.8% DB phase serious AE: Placebo 1%, Pregabalin 2.9% 2 patients died. None of the serious AE or deaths were considered treatment related	Open label phase: 37% ; 19% DB phase placebo 81%; 7% , pregabalin: 61.6%; 16.8%	

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Arnold 2008 Article in Press The journal of Pain	Double blind, PCT 84 research centers	Adult patients meeting ACR criteria for fibromyalgia and had a pain score of at least 40 mm on a 100 mm VAS. Completion of 4 out of 7 daily entries in the pain diaries during single blind period.	1 week placebo run-in followe dy 2 weeks of dose escalation period with 300-600mg/day DB phase-300=600mg/day	7 day placebo run-in

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Arnold 2008 Article in Press The journal of Pain	analgesic medications acetaminophen ≤4gm/day and aspirin ≤325mg/day for cardiac prophylaxis.	Primary outcome: comparison of endpoint mean scores measured on awakening Method: 11-NRS ranging from 0-10. Provisional priamry outcomes method of assessment PGIC, FIQ Secondary outcomes: self reoprted sleep by MOS scale and other subscales Depressive, anxiety symptoms measured by HADS Fatigue using MAF. Health related quality of life using ShortForm -36 health survey Timing of assessment: Patient pain and sleep scores collected at 1 week placebo run-in and randomization, visit 3,4,5, 6 and7 PGIC, SF-36, FIQ, MAF, HADS at week 7	50.1(11.4) 94.5% female White: 91.0% Black: 4.4% Other:4.6%	Mean (SD) Weight; 83.1 (20.1) Duration of FM: 10.0 (8.0) Baseline mean pain score: 6.7(1.3) Number of painful tender points N=723 mean(SD): 16.9(1.8)	1195/NR/750

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Arnold 2008 Article in Press The journal of Pain	259/69 (includes those who withdrew consent and were lost to follow-up)/745	LS mean (SE) at 14 weeks for placebo, 300mg, 450mg,600mg Mean pain score: 5.64(0.15), 4.93(0.16), 4.66(0.15), 4.64(0.15) FIQ total score: 51.99(1.34), 49.03(1.34), 46.75(1.31), 46.65 (1.33) Mean sleep quality: 5.07(0.16), 4.33(0.16), 3.96 (0.15), 3.73 (0.15) MOS overall sleep problem index: 51.63(1.40), 46.89(1.39), 45.43(1.37), 43.19(1.38) MAF: 32.42(0.71), 31.51(0.71), 31.02(0.70), 30.92 (0.70) HADS Anxiety total: 8.33(0.24), 7.71(0.23), 7.82(0.23), 7.54(0.23) HADS Depression Total: 6.51(0.24), 6.65(0.24), 6.19(0.24), 6.23(0.24)	Observed and sponteneously reported AE ranked by the investigator, physical exam, 12-lead ECG, and clinical laboratory evaluation.

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Arnold 2008 Article in Press The journal of Pain	Pregabalin 300mg (n=183), 450mg (n=190), 600mg (n=188), placebo(n=184) Patients reporting AE: 81%, 88%, 88%, 72% Dizziness (%): 27.9, 37.4, 42.0, 7.6 Somnolence (%): 12.6, 19.5, 21.8, 3.8 Weight increased (%):12.0, 12.6, 13.8, 2.2 Headache: 7.7, 12.2, 7.4, 10.3 Peripheral edema: 6.6, 6.3, 12.2, 2.7 Fatigue: 8.2, 5.9, 9.0, 4.3 Blurred vision: 3.8, 6.8, 11.7, 0.5 Nausea: 6.0, 8.4, 8.0, 8.7 Constipation: 2.7, 7.4, 10.1, 3.8 Disturbance in attention: 4.9, 6.3, 7.4, 1.1 Balance disorder: 1.6, 9.5, 6.9, 0.5 Euphoric mood: 4.4, 5.8, 7.4, 0.0 Sinusitis: 4.9, 6.9, 4.3, 4.3 Back pain: 4.4, 7.9, 3.2, 2.7 Dry mouth: 3.8, 4.2, 6.9, 0.5 Increased appetite: 3.3, 3.7, 6.4, 0.5 Memory impairment: 4.4, 5.3, 3.2, 0.5 Diarrhea: 4.4, 2.6, 4.3, 6.3 Upper UTI: 2.2, 4.7, 3.2, 6.5	Total withdrawals 259; withdrawals due to AE 144	

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Mease, 2008 USA	Double blind, PCT 79 research centers	Adults meeting ACR criteria for fibromyalgia had an average pain score of ≥ 4 on an 11 point numeric rating scale during baseline assessment and reported a score of ≥40 on the 100mm VAS of the SF-MPQ at both screenig and randomization visits. Discontinuation of SMR, antidepressants, Antiepileptic drugs, corticosterioids, benzodiazepines, opioid narcotics,mexiletene, and anti-parkinson's disease medications ≥ 7 days before screening visit, tender point injections and fluoxetine ≥30 days before, tramodol, dextromethorphan and NSAID ≥2 days before and zolpidem and diphenhydramine ≥1 day before	pregabalin patients began with 150 mg/day and dosage escalated to fixed dose of 300mg, 450mg and 600mg/day within first week of treatment administered twice daily	NR

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Mease, 2008 USA	aspirin for cardiac prophylaxis ≤325/day and acetaminophen and ≤4g/day and rescue medication.	Primary outcomes: 1) mean pain score as measured by 11 point NRS, 2) management of fibromyalgia -as measured by PGIC and FIQ secondary outcome: Sleep quality measured by 11 point NRS, Functioning assessed by SF-36 health survey, Sheehan Disability Scale and The Fibromyalgia Health Assessment Questionnaire, additional pain assessment by SF- MPQ, Fatigue measured by MAF, and Anxiety and Depression measured by HADS. Mean pain score assessed at weekly visits, PGIC and	49 (18-82) Female: 94% Caucasian:90.2% Black:4.6% Hispanic: 4.4% Other: 0.8%	Placebo, 300mg, 450 mg, 600mg Postmenopausal women (%): 58.5, 62.1, 52.7, 59.4 BMI (mean): 30.0, 31.4, 30.2, 30.5 Duration of FM prior to baseline mean (SD): 105.7(82.8), 115.4(103.5), 114.7(101.5), 111.0(91.4) No. of painful tender points mean (SD): 17.0(1.9), 17.1 (1.6), 17.3(1.3), 17.0(1.6)	1328/NR/751

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment
Mease, 2008 USA	263/25/748	**Mean pain score** Placebo: 5.70, change from baseline: -1.40 Pregabalin 300mg: 5.26, change from baseline-1.84 tx difference vs placebo-0.43, p=0.0449 450 mg: 5.23, change from baseline: -1.87 difference vs pplacebo: -0.47 p=0.449, 600mg: mean 5.04, change from baseline: -2.06, difference vs placebo -0.66, p=0.0070 **PGIC (%) : Any improvement:** Placebo 56.1, Pregabalin 300mg 70.8, 450 mg: 72.2 , 600mg :68.6, p value vs placebo : ≤0.05 FIQ total score: (mean) placebo 50.66 change from baseline: -13.66, pregabalin 300 mg 48.18, change from baseline -16.15, difference vs placebo -2.48, 450 mg 48.62, change from baseline: -15.71, , difference vs placebo -2.05, 600 mg 49.45, change from baseline: -14.88, difference vs placebo -1.21. p value vs placebo for all treatment arms=NS **Mean Sleep quality score:** Placebo5.41, change -1.32, pregabalin 300mg: 4.54, change -2.19, difference from placebo -0.86 p value=0.0001, Pregabalin 450mg 4.44, change -2.29, difference between placebo -0.97, p<0.0001, 600mg: 4.20, change -2.53, difference between placebo-1.21, p<0.0001	volunteered by patients or observed by clinicians, clinical, laboratory assessments, physical exam, neurologic exam, 12-lead ECG.

Evidence Table 5. Randomized-controlled trials in patients with fibromyalgia

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Mease, 2008 USA	Placebo (n=190) Pregabalin 300mg (n=185), 450mg (n=183), 600mg (n=190), Patients reporting AE:76%, 89%, 92%, 94% Dizziness (%): 8.4, 32.4, 43.7, 46.3 Somnolence (%): 5.3, 21.1, 24.0, 27.9 Weight gain: 2.6, 8.1, 8.7, 13.7 Dry mouth (%): 2.1, 7.6, 10.4, 10.5 Nausea (%): 5.8, 4.9, 4.4, 10.5 Amblyopia(%): 1.6, 6.5, 6.6, 8.9 Thinking abnormal(%): 1.1, 8.1, 6.6, 8.9 Constipation(%): 0.5, 4.9, 6.6, 8.4 Headache (%): 6.3, 8.1, 9.3, 7.9 Increased appetite(%): 1.6, 2.2, 8.2, 7.9 Amnesia(%): 2.1, 2.7, 3.8, 7.4 Euphoria(%): 2.6, 3.2, 6.0, 7.4 Ataxia(%): 0.5, 1.6, 4.4, 6.8 Asthenia(%): 2.6, 7.0, 5.5, 5.8 Incoordination(%): 0.0, 2.7, 3.8, 5.3 Nervousness(%): 1.1, 1.1, 0.0, 5.3 Peripheral edema(%): 1.1, 2.7, 2.2, 5.3	Total withdrawals 263 Withdrawals due to AE 157	

Evidence Table 6. Quality assessment of randomized-controlled trials in patients with fibromyalgia

	Internal validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Arnold, 2007	Not reported	Not reported	No Drug group had significantly lower average pain interference score & higher SF-36 Bodily pain score	Yes	Not reported	Implied - double-blind, placebo controlled design	Implied - double-blind, placebo-controlled design
Crofford, 2005	Yes	Not reported	Yes	Yes	Not reported	Implied - double blind, placebo-controlled design	Implied - double blind, placebo-controlled design
Crofford, 2008	Unclear, described as telerandomization	Not reported	Yes	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes (implied double blind)

Evidence Table 6. Quality assessment of randomized-controlled trials in patients with fibromyalgia

Author, Year	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Arnold, 2007	Yes - attrition No - crossovers, adherence, contamination	No Non-completers: 24% (18/75) drug 17% (13/75) placebo	Yes	Fair	NIH grant from National Institute of Arthritis and Musculoskeletal and Skin Diseases
Crofford, 2005	Yes - attrition, adherence No - crossovers, contamination	No Non-completers: 22% (29/132) PGB 150 mg/d 17% (23/134) PGB 300 mg/d 25% (33/132) PGB 450 mg/d 26% (34/131) placebo	Yes	Fair	Pfizer Global Research & Development
Crofford, 2008	Attrition-Yes, Crossover-Yes Adherence- NR Contamination-NR	Yes/No (Double blind phase) Noncompleters: Pregabalin 300mg/day:52%, 450mg/day: 67%, 600mg/day: 63%, placebo: 81% difference between 300mg and	Yes	Fair	Pfizer Global Research & Development

Evidence Table 6. Quality assessment of randomized-controlled trials in patients with fibromyalgia

Author, Year	*Internal validity* Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Mease,2008	Unclear	Not reported	Yes	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes ((implied double blind)
Arnold, 2008 (study in Press)	Yes	Not reported	Yes	Yes	Yes (implied double blind)	Yes (implied double blind)	Yes

Evidence Table 6. Quality assessment of randomized-controlled trials in patients with fibromyalgia

Author, Year	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Mease,2008	Attrition Yes, Crossover- No, Adherence- No Contamination- No	Yes, No % non-completers: pregabalin 600 mg/day: 41.6%,450mg/day: 33.9%, 300mg/day: 33.5%, placebo 31.6%, difference between groups (600mg/day and placebo): 10%, p value between groups p=0.044	Yes, LOCF 3/751 excluded from analysis =0.4%	Fair	Pfizer Global Research & Development
Arnold, 2008 (study in Press)	Attrition-yes, crossover-No, Adherence-No, Contamination-No	No, No Noncompleters: Pregabalin 600mg/day: 39.9%, 450mg/day: 34.2%, 300mg/day: 32.8%, placebo: 32.1%	Yes, LOCF 5/750 excluded from analysis =0.6%	Fair	Pfizer Global Research & Development

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Kimos, 2007 Canada	DB RCT, multicenter	Females 18-45y were recruited; diagnosis of masticatory muscle pain based on the diagnostic classification of Dworkin and LeResche for at least 6m that is not attributable to recent acute trauma or previous infection or active inflammatory cause; moderate to severe baseline score of > 50mm using a 100m VAS; pain upon palpation in > 3 points (anterior, medial and posterior temporalis; or deep, inferior ro anterior portion of the masseter); patients seeking treatment for TMD/Orofacial pain clinic considered for participation as well Patients were excluded if there was clinical evidence of inflammatory TMD; were pregnant or nursing; had epilepsy, cardiac, renal or hepatic disorders; were intolerant to gabapentin; had dental or periodontal disease, oral pathology lesions, oral infection or neuropathic facial pain; any patients wearing occlusal splint appliance < 6m	Gabapentin 300 mg/d, increased 300 mg every 3d, maximum dose 4200 mg; if medication discontinued for any reason, a decrease of 300 mg every 3d occurred; study medication for 12w	In cases where patient required analgesic medication, patients reported on second visit after 1w washout period

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Kimos, 2007 Canada	Subjects asked to discontinue any pain medications (relaxants, anti-inflammatories, or combination drugs - e.g. narcotics and acetaminophen) and other medications that could influence pain (e.g., hypnotics) Other drugs allowed (TCA, benzodiazepines, specific serotonin re-uptake inhibitors) as long as there were no changes to dosage regimen Acetaminophen 500 mg used for breakthrough pain; instructed to take it every 6 h with maximum of 4000 mg/d Gabapentin vs. placebo TCAs: 0(0%) vs. 2(10%) SSRIs: 8(33%) vs. 5(25%)	CMM pain intensity and daily function measured on a 10cm VAS; the number of tender sites using the palpation index (positive and negative responses)	Age: 33.58 Male: 0(0%) Ethnicity: NR	Gabapentin vs placebo Tension headache: 14(56%) vs. 10(40%) Poor sleep quality: 12(48%) vs. 5(20%) Recurrent headaches: 11(44%) vs. 7(28%) Neck pain: 4(16%) vs. 3(12%) Migraines: 2(8%) vs. 4(16%) Fibromyalgia: 1(4%) vs. 0(0%)	79 screened / 50 eligible / 50 enrolled / 50 randomized

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment	Adverse events
Kimos, 2007 Canada	14 withdrawn / lost to follow-up not reported / 44 analyzed	Gabapentin vs. placebo VAS-pain, reduction (%): 51.04(38.89) vs. 24.30(43.54); between-group, p=0.037 Palpation index, reduction: 6.46(4.11) vs. 1.90(5.02); between-group, p=0.002 VAS-function, reduction (%): 52.61(42.42) vs. 18.63(55.22); between-group, p=0.026	Method of AE assessment not reported	Gabapentin vs. placebo Dizziness: 7(28%) vs. 2(8%); p=0.69 Drowsiness: 7(28%) vs. 5(20%); p=0.37 Memory/cognitive impairment: 4(16%) vs. 1(4%); p=0.17 Dry mouth: 3(12%) vs. 1(4%); p=0.30 Fatigue: 3(12%) vs. 2(8%); p=0.50 Ataxia: 1(4%) vs. NR Diarrhea: 1(4%) vs. 1(4%); p=0.75 Constipation: 1(4%) vs. NR Weight gain: 1(4%) vs. NR Chest tightness: 1(4%) vs. NR Numbness: NR vs. 1(4%) Accelerated HR: NR vs. 1(4%)

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Kimos, 2007 Canada	Gabapentin vs placebo Total withdrawals: 6/25(24%) vs. 8/25(32%) Withdrawals due to AEs: 4/50(8%)	ITT population: Gabapentin 24(48%) vs. placebo 20(40%); 6(12%) did not provide any follow-up visit A number of patinets were not compliant in completing their escape medication calendar; a further analysis of use of escape medication not feasible Positive correlation (r=0.70) in VAS-pain and palpation index Gabapentin showed statistically significant decresed in VAS-pain score (p=0.026), palpation index (p<0.001) and VAS-function (p=0.013) Main effects of time were significant in all three measures (p<0.001) No statistically significant interactions between time and study groups for VAS-pain (p=0.425) and -function (p=0.076) except PI (p=0.004) Number needed to treat to reduced pain in one: 4

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Muehlbacher M, 2006 Austria	DB RCT	Patients with chronic lower back pain > 6m with no neurological deficits; aged 18 or older. Patients were excluded if they were in acute psychotic or manic episodes; using opioids or topiramate; had cancer, systemic or cardiopulmonary disease; acute suicidality; alcohol or drug abuse; pregnant	Topiramate 50 mg/d (titrated 50 mg/wk to dose of 300 mg/d or placebo for 10w	Not reported

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Muehlbacher M, 2006 Austria	Patients asked to refrain from analgetic or anti-inflammatory drugs 1w before participation (novalgine, paracetamol, diclofenac, ketoprofen, ibuprofen) Antidepressant medications allowed (mirtazapine, paroxetine, venlafaxine, fluoxetine, amitriptyline, maprotiline, and doxepine	Structured Clinical Interview; German versions of the MPQ, State-Trait Anger Expression Inventory (STAXI), Oswestry Low Back Pain Disability Questionnaire (OLBPQ) and the SF-36 Health Survey to measure pain, anger, QoL and HRQoL	Topiramate vs. placebo Age: 48.8(5.4) vs. 48.7(5.0) Male: 29(60%) vs. 31(65%) Ethnicity: Not reported	Topiramate vs. placebo Weight (kg): 92.7(10.6) vs. 91.2(10.1) Partnership: 31(65%) vs. 31(65%) Depressive disorders: 13(27.1%) vs. 12(25.0%) Anxiety disorders: 4(8.3%) vs. 3(6.25%) Pain duration (y): 2.5 vs. 2.0 Leg pain: 6(12.5%) vs. 4(8.3%)	134 screened / 111 eligible / 111 enrolled / 96 randomized

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment	Adverse events
Muehlbacher M, 2006 Austria	7 lost to follow-up / 96 analyzed	Topiramate vs. placebo Mean changes: State-anger: -2.4 vs. -0.4 Trait-anger: -2.6 vs. -0.4 Anger-in: -2.1 vs. 0.1 Anger-out: -3.7 vs. -0.1 Anger-control: 1.0 vs. 0.0 Body weight (kg): -6.5 vs. -0.2 Pain rating index: -12.9 vs. -1.5 Physical functioning: 8.7 vs. -0.4 Role-physical: 8.7 vs. 0.4 Bodily pain: 4.1 vs. 0.9 General health: 5.4 vs. 0.9 Vitality: 6.7 vs. 0.6 Social functioning: 4.1 vs. 0.6 Role-emotional: 1.2 vs. 0.6 Mental health: 4.8 vs. 0.5 Between-group, p<0.001 for all outcomes measured except role-emotional (p=0.096)	Side-effects measured using a nonstructured questionnaire	Topiramate vs. placebo Somnolence: 2(4.2%) vs. 0(0%) Vision problems: 2(4.2%) vs. 1(2.1%) Psychomotor slowing: 2(4.2%) vs. 1(2.1%) Memory problems: 2(4.2%) vs. 1(2.1%) Dizziness: 5(10.4%) vs. 3(6.25%) Headache: 4(8.3%) vs. 3(6.25%) Paresthesia/tremor: 3(6.25%) vs. 1(2.1%)

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Muehlbacher M, 2006 Austria	Topiramate vs. placebo Total withdrawals: 2/48(4.2%) vs. 5/48(10.4%) Withdrawals due to AEs: Not reported	Male and female demographic data reported in table 1 Rapid changes occurred in the topiramate group between 3 and 5w of treatment (figures 2-5)

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/Washout Period
Todorov, 2005 U.S.	Open-label Single-center, general neurology practice	Candidates for treatment with gabapentin: diagnosed with chronic pain (e.g., musculoskeletal headaches, failed back syndrome, posttraumatic cervical strain, fibromyalgia); stabilized on current medications and still symptomatic; not been previously treated with tiagabine or gabapentin	Tiagabine 4 mg/d (2 mg bid, when needed the dose increased by 4 mg until optimum response, maximum dose 24 mg/d, mean 15 mg/d) vs. Gabapentin 200 mg/d (100mg bid, increased by 300 mg every week until optimum respose, maximum dose 2400 mg/d, mean 915 mg/d) for 3m	Not reported

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Todorov, 2005 U.S.	Patients allowed to continue analgesic or antidepressant therapy that were stabilized prior to study entry Tiagabine vs. Gabapetin NSAIDs: 10(22%) vs. 8(17%) Analgesics: 12(26%) vs. 11(24%) Antidepressants: 17(37%) vs. 11(24%) Anxiolytics: 7(15%) vs. 11(24%) Hypnotics: 4(9%) vs. 1(2%) Antimigrane: 6(20%) vs. 2(4%) Muscle relaxants: 6(20%) vs. 1(2%) Others: 25(54%) vs. 22(49%)	Patients rated pain intensity and sleep quality using 11-point scales, 0 (no pain) to 10 (excruciating pain) at baseline and 3m	Tiagabine vs. Gabapetin Age: 46.0(13.7) vs. 42.0(12.0) Male (%): 12(26%) vs. 8(18%) Ethnicity: Not reported	Tiagabine vs. Gabapentin Musculoskeletal headache: 21(46%) vs. 23(51%) Cervical pain: 12(26%) vs. 11(24%) Neuropathic pain: 8(17%) vs. 2(4%) Lumbar pain: 3(7%) vs. 5(11%) Multiple pain syndrome: 2(4%) vs. 4(9%) Pain intensity: 7.78(0.32) vs. 6.91(0.30) Sleep quality: 6.88(0.44) vs. 6.96(0.33)	Number screened not reported / 91 eligible / 91 enrolled / 91 randomized

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results	Method of adverse effects assessment	Adverse events
Todorov, 2005 U.S.	17 withdrawn / 9 lost to follow-up / 91 analyzed	Tiagabine vs. Gabapentin Mean change, pain intensity: -2.3 (p<0.001) vs. -1.2 (p=0.008); NSD between-groups Mean change, sleep quality: -3.0 (p=0.001) vs. -1.54 (p=0.019); between-group, p=0.04	AEs reported throughout study	Gastric upset most common AEs in Tiagabine, lead to 4 withdrawals Dizziness/drowsiness most common AEs in Gabapetin, lead to 4 withdrawals

Evidence Table 7. Randomized-controlled trials in patients with chronic pain

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Todorov, 2005 U.S.	Tiagabine vs. Gabapentin Total withdrawal: 10/46(22%) vs. 7/45(16%) Withdrawals due to AEs: 4/46(8.7%) vs. 4/45(11.1%)	

Evidence Table 8. Quality assessment of randomized-controlled trials in patients with chronic pain

Author, Year	*Internal Validity* Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kimos, 2007	Yes	Yes	Not reported	Yes	Not clear- main investigator masked	Not reported	Yes
Muehlbacher, 2006	No	Not reported	Yes	Yes	Not reported	Yes	Yes
Todorov, 2005	Not reported	No	Yes	Yes	No	No	No

Evidence Table 8. Quality assessment of randomized-controlled trials in patients with chronic pain

Author, Year	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Quality Rating	Funding
Kimos, 2007	Yes	No. Non-completers: 24% (6/25) gabapentin 32% (8/25) placebo	88% of randomized subjects in ITT (48% drug, 40% placebo). Of these, 12% attended only 1st visit - no meds, no follow-up data.	Fair	University of Alberta Fund for Dentistry. Pharmascience donated gabapentin.
Muehlbacher, 2006	Yes	No. Non-completers: 4% (2/48) topiramate 10% (5/48) placebo	Yes	Fair	"The study was conducted independent of any institutional influence and was not funded"
Todorov, 2005	Yes: attrition, aherence No: crossover, contamination	No Non-completers: 22% (10/46) tiagabine 16% (7/45) gabapentin	No	Poor	Not reported

Evidence Table 9. Observational studies of adverse events

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.

Evidence Table 9. Observational studies of adverse events

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

Evidence Table 9. Observational studies of adverse events

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)

Evidence Table 9. Observational studies of adverse events

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

Evidence Table 9. Observational studies of adverse events

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.

Evidence Table 9. Observational studies of adverse events

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
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 hospital 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	Control subjects with drug-related E-codes (e.g., accidental poisoning, therapeutic use, suicide attempt, assault, undetermined)

Evidence Table 9. Observational studies of adverse events

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
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 9. Observational studies of adverse events

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)
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%)	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 9. Observational studies of adverse events

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
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 9. Observational studies of adverse events

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.
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.

Evidence Table 9. Observational studies of adverse events

Author, year	Setting	Study design	Eligibility criteria	Exclusion criteria
Rzany, 1999(80) (Fair)	Inpatient hospital setting; rash developed in outpatient setting Participating countries: France, Germany, Italy, Portugal	Multinational, multicenter matched case-control study with comparison of AEDs Study period: Started February 1989 (in Italy) to March 1992 (in Germany); ended January 1993 (in France) to July 1995 (other countries)	Developed skin reaction when not hospital inpatients; reactions validated and classified as Stevens-Johnson syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) by an expert committee. Controls were patients admitted to the same hospital for an acute illness	Not reported

Evidence Table 9. Observational studies of adverse events

Author, year	Interventions	Number screened/ eligible/ enrolled	Number withdrawn/lost to follow-up/analyzed	Age Gender Ethnicity
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 9. Observational studies of adverse events

Author, year	Other population characteristics (diagnosis, etc)	How adverse events assessed	Adverse events reported
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 9. Observational studies of adverse events

Author, year	Adverse events reported	Adverse events reported	Withdrawals due to adverse events
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 9. Observational studies of adverse events

Author, year	Comments
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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 9. Observational studies of adverse events

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 showr 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 9. Observational studies of adverse events

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 10. Quality assessment of 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?
Goodwin, 2003(79)	Yes	Not clear	Yes	Yes	No	Yes	Yes
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)
Lin (2005) {ID 2065}	Yes	Yes	Yes	No (ICD-9-CM codes not specified)	No(?) (ICD-CM codes used)	Yes	Yes
Rzany, 1999(80)	Yes	Not clear	Yes	No	Unable to determine	Yes	Yes
Tohen, 1995(78)	Yes	Not clear	Yes	Yes	No	No	Yes
Vestergaard (2004) {ID 2066}	Yes	Yes	Yes (ICD10 codes)	Yes	Yes	Yes	Yes

Evidence Table 10. Quality assessment of observational studies

Author, year	(8) Overall adverse event assessment quality
Goodwin, 2003(79)	Fair
Ibáñez, 2005 {ID 2063}	Good
Lin (2005) {ID 2065}	Fair
Rzany, 1999(80)	Fair
Tohen, 1995(78)	Poor
Vestergaard (2004) {ID 2066}	Good