

UPDATE OF AED-BIPOLAR DISORDER LITERATURE SEARCH

January 2007

METHODS

Literature Search

To identify articles relevant to each key question, a librarian searched the Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects (DARE), Medline/PubMed (1966–2005), and Embase (1974–2005). We also checked reference lists of included review articles. In electronic searches for efficacy trials, we combined terms for AEDs, bipolar or mood disorder, neuropathic pain, fibromyalgia, randomized clinical trials (RCTs), systematic reviews, and meta-analyses. For adverse event studies, we combined terms for AEDs, adverse effects, and various types of observational studies. All searches were limited to English language and human studies. (See Appendix A for complete search strategy.) Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 9.0).

When the search was rerun there were 74 RCTs, 5 meta-analyses and 96 reviews. The total unduplicated was 153. When matched with the original database from the DERP, 66 were already in, so there were 87 new records for review.

Study Selection

Population. We included studies that involved adult outpatients with one of the following indications:

- a. Bipolar Disorder as diagnosed by validated DSM (*Diagnostic and Statistical Manual of Mental Disorders*) criteria. We excluded trials that included heterogeneous patient populations unless data was presented separately for patients with bipolar disorder or manic episodes.

Drugs. At least one of the treatment groups had to consist of one or more of the following interventions alone or in combination, and the efficacy and safety outcomes had to be distinguished for the individual AED: carbamazepine, ethotoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, tiagabine, topiramate, valproate/valproic acid/ divalproex, and zonisamide. We excluded studies in which an AED was compared to itself (e.g., dose or formulation comparisons). When a study evaluated sodium valproate or valproic acid, we referred to the agent as *valproate*, but we used *divalproex* if it was the agent studied.

Outcomes. For assessing effectiveness of the AEDs, we included studies that reported one or more of the following as primary, secondary, or tertiary outcome measures:

Bipolar Disorder: These we designated as scores on symptom rating scales, responder rates, remission, relapse or recurrence, speed and duration of response and remission, use of other medications for acute episodes, functional capacity (quality of life, work productivity) danger to self (suicide attempts and completions), and hospitalization. A number of rating scales were used to measure improvement in symptoms. The abbreviations of the rating scales are defined for each trial in their individual tabulated summary in Evidence Tables 1-3. The abbreviations to the rating scales as they appeared in fair-quality reports are shown in Table 2.

Table 1. Psychiatric Rating Scales

Abbreviation*	Rating Scale
BPRS	Brief Psychiatric Rating Scale
B-R MRS	Bech-Rafaelsen Mania Rating Scale
CARS-M	Clinician Administered Rating Scale for Mania
CGI-BP	Clinical Global Impression for Bipolar Disorder
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
DSS	Depressive Syndrome Scale
GAS	Global Assessment Scale
HAM-D	Hamilton Depression Rating Scale, 17-item or not specified
HDRS	Hamilton Depression Rating Scale, 21-item
HRSA	Hamilton Rating Scale for Anxiety
HRSD	Hamilton Rating Scale for Depression
ISS	Internal state scale
Life Chart	Life Chart for Recurrent Affective Illness
MADRS	Montgomery-Asberg Depression Rating Scale
MRS	Mania Rating Scale
PNSS	Positive and Negative Syndrome Scale
PSR	Psychiatric Status Rating
YMRS	Young Mania Rating Scale

* Actual abbreviation used in reports; note that there were several abbreviations used for the Hamilton Depression Rating Scale (HAM-D, HDRS, and HRSD) and an alternate abbreviation for the Bech-Rafaelsen Mania Rating Scale (BRMS).

We used the author's definition of response, remission, recurrence, or relapse. Where these terms were not defined, we used an outcome measure that most closely approximated the outcome, such as Kaplan-Meier estimates of survival for assessing remission, and "breakthrough depression" for relapse. DSM-IV-TR criteria specify that a *recurrence* is indicated by either a shift in the polarity of the mood episode or an interval between episodes of at least 2 months without manic symptoms. The term *relapse* is not mentioned.

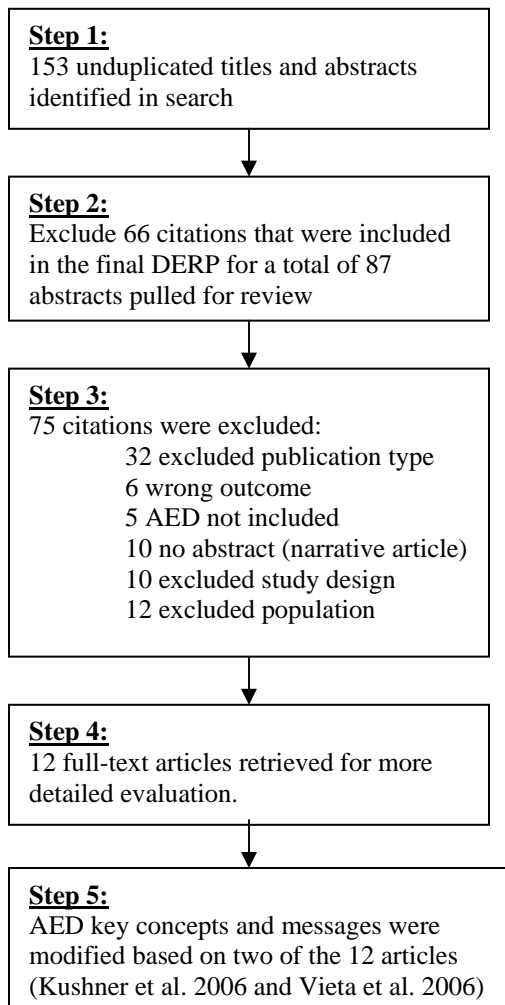
The Global Assessment Scale (GAS) was used as a measure of functional capacity in bipolar trials. The GAS evaluates the patient's global functioning, taking into account behavioral disturbances, distress levels, impulsivity, reality testing, self-care, and social functioning.

For hospitalization, we looked for rates of hospitalization due to events relevant to efficacy or safety of treatment, such as psychiatric episodes or adverse events.

Safety Outcomes: These were designated as overall adverse event reports; withdrawals due to adverse events; serious adverse events (including overdoses); and specific adverse events or adverse events that resulted in withdrawal (e.g., dizziness, drowsiness/sedation, rash, hepatotoxicity, thrombocytopenia, and hyperammonemia).

Design. For effectiveness, we included RCTs and good-quality systematic reviews or meta-analyses that involved human subjects and whose titles, abstracts, and full texts were published in English. We excluded articles that did not report original research data (e.g., editorials, certain letters, duplicate publications) as well as studies that were reported only as abstracts. For safety, we included RCTs involving the target diagnoses, good-quality systematic reviews of adverse events in patients with any diagnosis, as well as long-term (at least 1-year) retrospective or prospective observational cohort studies that included at least two AEDs in patients with any diagnosis. We included case-control studies only if two or more drugs were compared individually and a specific adverse event of interest was evaluated. We included studies that used large administrative or prescription databases as long as they met the inclusion criteria for cohort or case-control studies.

In the first stage of study selection, titles and abstracts were identified for full-text retrieval if they met the inclusion criteria. In the second stage, the same inclusion criteria were applied to the full-text articles. Studies that were not published or available in full reports were excluded. In the final stage, two reviewers independently evaluated full-text articles.



Science Panel Review of Evidence

Twelve articles were sent to Science Panel members for review. Five of the 12 articles used data from studies included and reviewed in the DERP, so their information was already included in the review. Other articles did represent original research, but the findings did not result in any changes to the science panel's key concepts or key messages. Several articles did focus on weight change on medications for bipolar disorder. These findings reinforced the panel's previous findings that adverse events were different depending on the medication used for bipolar disorder.

The panel agreed that two articles, one on gabapentin and the other on topiramate, warranted minor modifications of the key concepts and messages. Kushner et al combined 4 randomized trials of topiramate monotherapy for acute mania for inpatients. All 4 trials were negative. Our previous key concept emphasized that there was little, if any, evidence regarding the use of the antiepileptic topiramate for bipolar disorder. We have now modified our key concepts to reflect this stronger, negative evidence regarding use of this agent.

The study by Vieta and colleagues was conducted in Europe. The authors examined the addition of gabapentin to other AED or lithium therapy in an RCT study of 25 patients, half of whom dropped during the study. The authors found that the gabapentin group performed somewhat better on a global outcome measure, but there was no difference in mania-specific measures, hospitalizations, or rates of recurrence. Given the mixed findings, very small sample size and high dropout rate, the science panel unanimously judged that the Vieta article finding did not change our previous key concepts or messages. We did add the work "acceptable" before "evidence" in the message describing the status of the gabapentin literature. This change in the modifier acknowledges that evidence regarding the use of gabapentin does exist, but it is not acceptable to change the key concepts.

Tim Carey reviewed suggestions from the Science Panel members and made the minor modifications. Revised AED key concepts and messages were sent back to the panel members for review. All science panel members reviewed the final key concepts and messages and approved the changes. They will be incorporated into the RTI testing and dissemination products. We will next update the literature in late 2007- early 2008.

Kushner SF, Kahn A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind, placebo controlled trials. *Bipolar Disord.* 2006; 8: 15-27.

Vieta E, Manuel-Goikolea J, Martinez-Aran A et al. A double-blind, randomized controlled prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry* 2006; 67: 473-7.

UPDATE ON AED'S IN BIPOLAR DISORDER

Twelve full text articles were reviewed. Five of the 12 articles used data from studies included and reviewed in the DERP.

1. Sachs, Bowden, Calabrese et al., (2006). Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder
2. Bowden, Calabrese, Ketter et al., (2006). Impact of Lamotrigine and Lithium on Weight in Obese and Nonobese Patients with Bipolar I Disorder
3. Calabrese, Goldberg, Ketter, et al., (2006). Recurrence in Bipolar I Disorder: A Post Hoc Analysis Excluding Relapses in Two Double-blind Maintenance Studies.
4. Suppes, Brown, Schuh, et. al., (2005). Rapid versus non rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: Post hoc analyses of 47-week data.
5. Weisler, Hirschfeld, Cutler, et al., (2006). Extended-Release Carbamazepine Capsules as Monotherapy in Bipolar Disorder.

After reviewing the 12 studies, our recommendation is that no changes in key concepts or messages seem warranted. A brief summary is provided for the studies below.

1. Calabrese, Shelton, Rapport, et al., (2005). A 20-Month, Double-blind, Maintenance Trial of Lithium Versus Divalproex in Rapid-Cycling Bipolar Disorder.

Lithium vs divalproex. Small double blind RCT among rapid cycling patients. No difference in relapse rates at 20 months (56 and 50%). No change in key concepts.

2. Kushner, Khan, Lane, et al., (2006). Topiramate Monotherapy in the Management of Acute Mania: Results of Four Double-blind Placebo-controlled Trials

Topiramate monotherapy for acute mania- combined secondary analysis of 4 double blind RCT's. Patients all hospitalized, followed for up to 12 weeks. Not effect when compared with placebo, less effective than lithium. NOTE: This might strengthen our key concept regarding the lack of efficacy of topirimate, previously we had emphasized lack of evidence of benefit, now we have some evidence of lack of benefit.

3. Ketter, Greist, Graham, et al., (2006). The Effect of Dermatologic Precautions on the incidence of Rash With Addition of Lamotrigine in the Treatment of Bipolar I Disorder: A Randomized Trial.

Safety study. Multi-site study of 1175 pts randomly assigned to 'usual care' vs 'dermatologic precautions' when started on lamotrigine. Dermatologic precautions is special instructions in skin care to try to reduce both rates of dermatologic reaction and

premature discontinuation of lamotrigine due to rash false alarms. No Stevens-Johnson syndrome. Rates of non-serious rash similar between groups. No change in key concept.

4. Nierenberg, Ostacher, Calabrese, et al., (2006). Treatment-Resistant Bipolar Depression: A Step-BD Equipoise Randomized Effectiveness Trial of Antidepressant Augmentation with Lamotrigine, Inositol, or Risperidone.

Complex study of treatment-refractory depression in bipolar disorder. Patients were randomly assigned to receive one of 3 meds (lamotrigine vs inositol vs risperidone) as add-on therapy. Complex design, with some elements of patient choice. Trend toward more improvement with lamotrigine. Small study (56pts), no difference in outcomes, but very under-powered. No change in key concepts.

5. Brown, McElroy, Keck, et al., (2006). A 7-week, Double-blind Trial of Olanzapine/Fluoxetine Combination Versus Lamotrigine in the Treatment of Bipolar I Depression.

RCT comparing olanzapine/fluoxetine combination pill vs lamotrigine in acute bipolar I depression. Olanzapine/fluoxetine group did somewhat better over 7 week course. No change in key concepts.

6. Vieta, Goikolea, Martinez-Aran, et al., (2006). A Double-blind, Randomized, Placebo-Controlled, Prophylaxis Study of Adjunctive Gabapentin for Bipolar Disorder.

A double-blind, randomized, placebo controlled prophylaxis study adjunctive gabapentin in bipolar disorder. Pfizer sponsored, conducted in Europe. Testing adding gabapentin rx to pts in remission on mood stabilizer such as lithium, lamotrigine, divalproate etc. Started with 25 patients prior to randomization, with 50% drop out, so only 13 patients available for analysis. Global clinical impression scale showed benefit to gabapentin group ($p=0.0046$), but no difference in time to relapse, YMRS, HAM-D, etc. Given the small sample size, high drop out and conflicting results, we don't think this study can change key messages. However, worth a careful read since its gabapentin.

7. Young, Geddes, MacRitchie, et al., (2006). Tiagabine in the Maintenance Treatment of Bipolar Disorder.

Review of tiagabine in bipolar disorder. No RCT's only case series. No evidence. No change in key messages.