

Effectiveness of Antiepileptic Drugs

for the Treatment of Bipolar

Disorder: Findings from a

Systematic Review

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Bipolar disorder is characterized by chronic and recurrent symptoms including mania, hypomania, and depressive and mixed episodes, with approximately 5.7 million Americans over age 18, or 2.6% of the U.S. population, suffering from the illness. The prevalence of the disorder may be higher due to its chronic and recurrent nature. Individuals with bipolar disorder often first present in general medical settings with depressive symptomatology. Long-term management typically occurs in mental health settings by psychiatrists or other mental health specialists. While there have been major advances in pharmacotherapy for bipolar disorder, evidence-based information on drug effectiveness is not always easily accessible to prescribers in daily practice. Available information has sometimes led to inappropriate use of various classes of drugs, specifically antiepileptic drugs (AEDs), for bipolar disorder. Originally approved in 1993 by the U.S. Food and Drug Administration (FDA) only for adjunctive treatment of partial complex seizures, the manufacturer of gabapentin (Neurontin), an AED, promoted its off-label use for treatment of psychiatric disorders, including bipolar disorder. The efficacy of the drug for this indication had not been demonstrated, nor had the manufacturer sought FDA approval for the indication. In 2004, 50 Attorneys General settled consumer protection claims regarding alleged deceptive off-label marketing practices of Pfizer subsidiary Warner-Lambert. At about the same time, a consortium of State Medicaid agencies funded a drug class review to compare effectiveness and adverse event profiles of AEDs in the treatment of bipolar mood disorder, neuropathic pain, and fibromyalgia. This article presents a summary of the findings from the drug class review related to prescription of the AEDs in bipolar disorder. (*Journal of Psychiatric Practice* 2007;14(suppl 1):9-14)

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Bipolar disorder is characterized by chronic and recurrent manic, hypomanic, depressive, and mixed symptomatic episodes, with approximately 5.7 million Americans over the age of 18 suffering from the illness.¹ The actual prevalence rate may also be higher because these estimates do not include institutionalized patients who are in prisons or jails, certain ethnic populations (e.g., African-Americans) in which the illness may be underdiagnosed, or persons with milder forms of the disorder.^{2,3} Onset of the illness can occur at any age; however, it is typically identified in late adolescence or early adulthood, with the peak period of onset between 15 and 19 years of age.¹

Individuals with bipolar disorder may first present in general medical settings with physical symptoms or with depressive symptomatology. However, long-term management typically occurs in a mental health setting by a psychiatrist or other mental health specialist. Studies have reported that this transition from general practice to a definitive diagnosis and treatment in a

psychiatric care setting can take years, including visits to more than four clinicians between the onset of the first symptoms and the diagnosis of bipolar disorder.² Individuals with bipolar disorder represent a population with serious psychiatric illness, in whom screening

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Table 1. Antiepileptic drugs included in clinical practice guidelines⁶

Practice Guideline	Indication	Recommendations				
		CBZ	GBP	LTG	OXC	VPA
American Psychiatric Association	Acute mania/mixed	Yes	—	—	Yes	Yes
	Acute bipolar depression	—	—	Yes	—	—
	Acute rapid cycling	—	—	Yes	—	Yes
	Maintenance	Yes	—	Yes	Yes	Yes
British Association of Psychopharmacology	Acute mania/mixed	Yes	—	—	—	Yes
	Acute bipolar depression	—	—	Yes	—	Yes
	Rapid cycling	—	—	Yes	—	Yes
	Maintenance	Yes	—	Yes	Yes	Yes
Australian and New Zealand	Acute mania/mixed	Yes	No	—	—	Yes
	Acute bipolar depression	Yes	No	Yes	—	Yes
	Maintenance, rapid cycling	Yes	No	Yes	—	Yes
	Maintenance	—	No	Yes	—	Yes

CBZ: carbamazepine; GBP: gabapentin; LTG: lamotrigine; OXC: oxcarbazepine; VPA: valproic acid / valproate
No = not recommended; Yes = recommended, — = not mentioned in guidelines

and appropriate treatment can be assisted by use of evidence-based practice, which can facilitate delivery of better psychiatric care.

While efficacious treatments are available for bipolar disorder, symptom recurrence or relapse and underresponse or nonresponse to treatment remain problems. Medication cannot cure the disease, although, with appropriate management and adherence to an appropriate treatment regimen, patients may maintain remission for months to years. The lack of long-term remission that is frequently seen may be largely due to the chronic, episodic, and phasic patterns of the illness, which can require very complex treatment strategies. Without appropriate treatment, patients with bipolar disorder experience functional impairment and have an increased risk of morbidity and mortality.

The approach to treatment is multifaceted and must address both acute mania and depression, as well as maintenance once remission has been achieved. In an effort both to treat acute symptoms and to reduce their recurrence, many clinicians use multiple agents in combination therapy as opposed to a single anti-manic agent. Many of the evidence-based treatment guidelines include polypharmacy in their recommendations and suggest the use of antipsychotics, antidepressants, and antiepileptic drugs (AEDs).^{1,4,5} Not all of the drugs within these classes are included in published treatment algorithms. Table 1 summarizes indications for AEDs recommended in selected guidelines for bipolar disorder.

The appropriate use of medications can reduce both acute symptoms and recurrence and facilitate the use of other treatments (e.g., psychotherapy) in combination with pharmacotherapy. Ultimately, appropriate medication therapy, when combined with other treatment modalities, can result in improved quality of life and a reduced risk of acute hospitalization.

Several studies published within the past few years outline pharmacotherapy patterns in the treatment of bipolar disorder. In 2000, Levine et al. studied ambulatory patients with bipolar I disorder and found that 50% of the patients received lithium, 40% received valproate, and 11% received carbamazepine. Only about 18% of the patients received monotherapy, while 40%–50% of the patients were also receiving antidepressants and benzodiazepines.⁷ In 2004, Craig et al. studied patterns of medication use in patients with bipolar disorder with psychotic features and reported that 80% were receiving antipsychotics and 52.3% were receiving antimanic agents at baseline. At the 2-year follow-up of these same patients, only 19.4% and 38.8% remained on their antipsychotics and antimanic medications, respectively, while nearly 45% were on no medication at all for the treatment of bipolar disorder. There is an apparent shift in use of drugs over the course of the disorder depending on the pattern of the illness. Patient adherence in the setting of long-term use of medications with known side effects can also be a concern.⁸

More recently, Ghaemi et al. published data on the medications prescribed for patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Lithium was the most commonly prescribed drug or drug class, with 38.4% of the patients receiving this agent.⁹ However, they also found a high rate of use of AEDs, including both the standard anticonvulsants, valproate (36.8%) and carbamazepine (5.8%), and the novel anticonvulsants, lamotrigine (15.4%), gabapentin (14.0%), and topiramate (5.2%). Selective serotonin reuptake inhibitors (SSRIs) were used in 21.6% of the patients, non-SRIs (i.e., bupropion, trazodone, nefazodone, mirtazapine) in 24.0%, atypical antipsychotics in 27.2%, typical antipsychotics in 3.8%, and benzodiazepines in 25.0%. It is important to understand these clinical patterns of care, since they can be helpful to prescribers in areas where there is a lack of evidence to support a given clinical practice.

While there have been major advances in pharmacotherapy for bipolar disorder, information about evidence-based findings and drug effectiveness is not always easily accessible to psychiatrists and other prescribers in their daily practices. Prescribers typically rely on sources of information that include personal experience, peer-reviewed and other publications, participation in continuing medical education, computer-based clinical decision support systems, clinical practice guidelines, pharmaceutical marketing and advertising, and peer consultation (see p. 35).¹⁰ Unfortunately, certain information available to prescribers through these mechanisms has led to inappropriate use of drugs in certain classes, including the AEDs.

Several AEDs (e.g., carbamazepine, valproate, lamotrigine) have been approved by the U.S. Food and Drug Administration (FDA) for use in specific bipolar disorder presentations (e.g., acute mania, mixed episodes, depression, and hypomania), with their efficacy compared with placebo supported by multiple randomized trials. Originally approved in 1993 by the FDA only for adjunctive treatment of partial complex seizures, gabapentin, an AED, was promoted by its manufacturer for off-label use in the treatment of psychiatric disorders, including bipolar disorder, although its efficacy for that indication had not been demonstrated.

Since 2003, a consortium of state Medicaid agencies has funded a series of drug class reviews coordinated by the Oregon Evidence-based Practice Center's Drug Effectiveness Review Project (DERP) to compare the effectiveness and adverse event profiles of multiple medications. These reviews were used by the states in an effort to utilize the best available evidence to inform

formulary and payment decisions. One of these state Medicaid reviews involving AEDs in the treatment of bipolar mood disorder, neuropathic pain, and fibromyalgia specifically addressed on- and off-label information on the use of AEDs in the treatment of bipolar disorder.⁶

This Medicaid document included a full systematic review concerning the use of AEDs in neuropathic pain and fibromyalgia as well as in bipolar disorder. In this article, we focus only on the drug class review findings related to use of these agents in bipolar disorder. The draft drug class review was posted in December 2005, and the final report was issued in May 2006. The report addressed the following key questions regarding the treatment of bipolar disorder:

1. Do AEDs differ in effectiveness for adult outpatients with bipolar disorder?
2. Do AEDs differ in safety or adverse events in adult outpatients with bipolar disorder?
3. Are there subgroups of patients with bipolar disorder for whom one specific AED is more effective or associated with fewer adverse events based on demographics (e.g., age, race, gender), other medications being taken, or comorbid conditions?

A detailed description of the methodology used in the AED drug class review (AED Review) is published elsewhere.⁶ While we globally reference the AED Review in this article, readers interested in individual articles or the full findings of the Review should access the full report, which is available online.⁶ The purpose of this paper is to summarize the findings of the AED Review.

KEY FINDINGS

Findings from the drug class review related to the use of AEDs in bipolar disorder were extracted and organized by a multidisciplinary panel of physicians and researchers, who were known to be key opinion leaders in the interpretation and dissemination of evidence-based findings on drug effectiveness. The multidisciplinary panel used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. The GRADE system addresses the strength of the evidence and provides a global qualitative assessment.¹¹ The outcomes of interest were remission, recurrence, and adverse events (including serious adverse events and suicide).

Remission/Recurrence

An evaluation of the efficacy of any psychiatric medication in maintaining remission is generally based on the

percentage of patients who do not experience symptomatic recurrence or prematurely discontinue study treatment because of symptoms. However, methods used to measure symptoms and functional status in populations of patients with bipolar disorder vary greatly across studies. Thus, evidence concerning the amount of improvement in manic or depressive symptoms is much less clear given difficulties comparing different symptom scores and functional status measures in these populations. Most available evidence does, however, demonstrate improvement in symptom scores compared with placebo when one of the medications that has been found efficacious is used.

Recurrence is a significant problem for patients with bipolar disorder even with treatment with AEDs. The incidence of recurrence in the studies examined in the AED Review ranged from 16% to 70% with placebo and from 6% to 65% with medication treatment. These broad ranges of percentages reflect the variable definitions of recurrence that were used, the different populations studied in the various trials, and the variable duration of follow-up. The level of absolute improvement in reducing recurrence ranged from 1%–23%, with a relative risk reduction ranging from 0.63–0.96.*

The evidence supports three AEDs (carbamazepine, valproic acid/valproate, and lamotrigine) as being efficacious in maintaining remission for adult outpatients with primary diagnoses of bipolar I disorder with recent mania or mixed episodes. The overall magnitude of benefit obtained with AEDs in patients with bipolar I disorder with recent manic or mixed episodes was an absolute improvement of the probability of attaining remission ranging from 7%–28%; the relative risk of attaining remission was between 1.17 and 2.87 compared with placebo. There was no acceptable evidence that supported choosing one agent over another based on speed of onset in attaining remission. Acceptable evidence is usually defined as published results of high quality head-to-head trials (i.e., direct evidence) or indirect comparisons between placebo-controlled trials of different medications.¹²

The evidence provides only modest support for the efficacy of the same three AEDs (carbamazepine, valproic acid/valproate and lamotrigine) in achieving and

maintaining remission in adult outpatients with bipolar I disorder with a recent depressive episode or in patients with bipolar II disorder. Less evidence is available concerning efficacy of treatment for these two subtypes of bipolar disorder than for bipolar I disorder with a recent manic or mixed episode. The overall magnitude of benefit obtained with AEDs relative to placebo in patients with bipolar I disorder with a recent depressive episode was an absolute improvement in attaining remission of 11%, with a relative rate of attaining remission of 1.44, compared with placebo. The overall magnitude of benefit in patients with bipolar II disorder of attaining remission compared with placebo was an absolute difference of 15%, with a relative rate of 1.58.

Carbamazepine, valproic acid/valproate and lamotrigine appear to have similar magnitudes of benefit in inducing remission, although the risk of recurrence is substantial for all agents. While the three drugs have similar magnitudes of benefit based on indirect comparisons, few studies have directly compared these medications with each other; therefore, these conclusions should be considered tentative since the risks of bias and low statistical power are more likely in studies reporting indirect comparisons.¹²

These three AEDs have rates of achieving and maintaining remission during treatment for bipolar I disorder similar to those obtained with lithium. Carbamazepine and valproate also demonstrated similar response rates to lithium in outpatient adults with acute mania.

Safety and Adverse Events

The overall risk of adverse events resulting in medication discontinuation is similar among carbamazepine, valproic acid/valproate, and lamotrigine, and the overall risk of adverse events with AEDs is similar to the risk with lithium across all clinical subtypes of bipolar disorder (Table 2).¹³ However, the types of adverse events encountered differ among the three AEDs and lithium. Serious adverse events, although uncommon, may occur with each agent; meaningful comparisons of the rates of these serious events among agents could not be performed. Overall evidence regarding comparative adverse event rates is based on a small number of studies. Between 5% and 24% of patients discontinue an AED due to adverse events. The broad range of estimates reflects the use of these medications in differing populations as well the differing vigilance with which adverse events were sought and documented in the component studies. Rates of serious adverse events with the AEDs ranged from 0% to 10.3%.

**Absolute improvement*: A comparison of numerical values over time (e.g., difference between post-test and pre-test scores). *Risk reduction*: The extent to which a treatment reduces a risk, in comparison with patients not receiving the treatment of interest (i.e., the percent reduction in events in treated individuals compared with controls).

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Table 2. Side effect profiles of lithium and certain AEDs used for the treatment of bipolar disorder^{a,13}

<i>Side Effect</i>	<i>Lithium</i>	<i>Carbamazepine</i>	<i>Valproate</i>	<i>Lamotrigine</i>
Hypothyroidism	++	—	—	—
Polyuria and diabetes insipidus	++	—	—	—
Weight gain	++	—	++	—
Weight loss	—	+	—	—
Tremor	++	—	++	—
Hair loss and thinning	+	—	++	—
Allergic rash and serious cutaneous syndromes	—	++	—	++
Worsening of psoriasis/myasthenia gravis	++	—	—	—
Leukocytosis	++	—	—	—
Thrombocytopenia	—	+	++	—
Leukopenia/aplastic anemia	—	++	+	—
Teratogenicity	++	++	++	?
Pregnancy rating ^b	D	D	D	C
Polycystic ovaries	—	—	+ ^c	—
Cognitive side effects	+ / ++	+	+	—

— Rarely attributed to drug; + uncommonly attributed to drug; + / ++ less commonly attributed to drug; ++ commonly attributed to drug.

^aThese are based on clinical impressions, discussions among colleagues, and data available in the literature. In some patients, mild side effects may lead to interventions and/or non-adherence, while in others, moderate side effects may be tolerated in the face of therapeutic efficacy.

^bU.S. FDA Use-in-Pregnancy Ratings: C = Risk cannot be ruled out (Human studies are lacking, and animal studies are either positive for risk or are lacking as well. However, potential benefits may outweigh the potential risk.); D = Positive evidence of risk (Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.)

^cEither definitive data are unavailable or it is controversial whether or not there is an association with valproate use in bipolar subjects.

Patients with bipolar disorder are at risk for suicide or suicide attempts. Evidence regarding protection against the risk of suicide attempts is limited and does not support a difference between valproate and carbamazepine. Both of these agents, particularly valproate, have been associated with lower protective effect against suicide attempts than lithium in observational studies. There are insufficient data to evaluate the risk of suicide attempts in patients taking other AEDs.

Evidence-Based Findings

Evidence from the AED Review shows that gabapentin is no more, and perhaps less, efficacious than placebo in the treatment of bipolar I disorder with recent mania and rapid cycling bipolar disorder. No acceptable evidence was found to support the use of gabapentin in achieving remission or preventing relapse in bipolar disorder. The evidence regarding efficacy of topiramate for

bipolar I disorder with recent manic, hypomanic, or mixed episodes and bipolar II disorder is sparse.¹⁴

Available evidence from the AED Review regarding potential differential efficacy among the AEDs in the treatment of patients with rapid cycling and other patient subgroups is extremely limited. Available evidence does not allow predictions to be made concerning which patient subpopulations will respond to any given AED. Nor does available evidence allow prediction of response to a subsequent AED based on response to an initial trial of therapy. Little evidence is available regarding differential efficacy of the three AEDs in subpopulations based on factors related to gender, age, ethnicity, or comorbidity.

CONCLUSION

While a systematic review of a drug class can provide evidence to inform prescribers about appropriate and

effective treatments, clinicians often do not use these complex and sometimes lengthy reviews. The evidence in the AED review and recent updates^{14,15} can be condensed into three clinical findings:

1. No clinical trial evidence supports the use of either gabapentin or topiramate as either a primary or adjunctive treatment in bipolar disorder.
2. Current evidence supports the use of three AEDs—carbamazepine, valproic acid/valproate, and lamotrigine—in maintaining remission in outpatient adults with a primary diagnosis of bipolar I disorder.
3. AEDs have been shown to be no better than lithium, which is an established and efficacious treatment for bipolar disorder.

Before translating these findings into actionable key messages for psychiatrists and other prescribers of AEDs, additional information is needed not only on the quality of the evidence reported in the AED Review but also on the perceptions of psychiatrists and others about the clinical significance of these findings. Materials and processes can then be developed to increase the likelihood that findings from the AED Review can be widely disseminated and used by psychiatrists and others as they consider pharmaceutical options for treating their patients with bipolar disorder.

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