Oxcarbazepine Treatment of Bipolar Disorder

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Objective: To assess the effectiveness and safety of oxcarbazepine in bipolar disorder.

Method: A chart review of naturalistic treatment with oxcarbazepine in 42 outpatients with DSM-IV bipolar disorder (10 males, 32 females; mean ± SD age = 33.3 ± 12.4 years; 25 with bipolar disorder type I, 4 with bipolar disorder type II, and 13 with bipolar disorder not otherwise specified) was conducted. Patients had received oxcarbazepine monotherapy or adjunctive therapy between April 2000 and April 2002. Treatment response was defined as a Clinical Global Impressions-Improvement scale score of 1 (marked improvement) or 2 (moderate improvement).

Results: Oxcarbazepine was moderately to markedly effective in 24 subjects (57%). Mixed symptoms were the most common indication (52% [22/42]). The mean oxcarbazepine dose was 1056.6 mg/day, and mean treatment duration was 16.2 weeks. Sedation (17/42, 40%) was the most common side effect, but 16 patients (38%) had no side effects. Twenty-two patients (52%) stopped treatment, mostly due to side effects (12/22). Males were more likely to respond than females (10/10 vs. 14/32, p = .006). Dose, bipolar subtype, indication, past nonresponse to mood stabilizers, concurrent mood stabilizer use, and monotherapy use of oxcarbazepine did not differentially predict response.

Conclusion: Oxcarbazepine appeared effective in about one half of patients with bipolar disorder and was well tolerated.

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The use of anticonvulsants as mood stabilizers in the treatment of bipolar disorder is becoming more common.[1] Several studies indicate that both carbamazepine and valproate have mood-stabilizing abilities, either as adjunctive therapy with lithium or even as monotherapy.[2] Oxcarbazepine is a keto-congener of carbamazepine with fewer side effects and drug interactions than carbamazepine.[3] The efficacy of oxcarbazepine in treating bipolar disorder, however, is not as well established as that of carbamazepine.[3–12] A review of 3 early double-blind studies suggests that oxcarbazepine has antimanic properties compared with placebo, is as effective as haloperidol with fewer side effects, and is as effective as lithium with similar tolerability.[6] A recent small (N = 13), uncontrolled study of oxcarbazepine treatment of refractory bipolar patients, mostly with depressive symptoms, reported that 69% of patients exhibited a mild improvement but only 16% of patients exhibited a moderate/marked improvement.[12]

In this study, we report our clinical experience with this agent in outpatient treatment of bipolar disorder. We wished to assess efficacy primarily in adjunctive therapy and secondarily in monotherapy, if available.

METHOD

Charts of all patients treated by D.A.B. and J.K. in a private practice community setting were reviewed to identify patients treated with either adjunctive or monotherapy oxcarbazepine between April 2000 and April 2002. Forty-two outpatients were included who met DSM-IV criteria for bipolar disorder. The Cambridge Hospital Institutional Review Board approved the chart review proposal as minimal risk, and all charts were reviewed only by the treating clinicians. Data analyses were conducted on data extraction forms in which identifying features of patients were removed. Clinical response was then established based on a consensus of all authors. Diagnoses were as follows: 25 bipolar type I, 4 bipolar type II, and 13 bipolar not otherwise specified. Most patients were refractory and experiencing severe mood episodes with their current mood-stabilizing regimen and received either open adjunctive oxcarbazepine treatment added to their mood-stabilizing medications (lithium and/or valproate) or oxcarbazepine monotherapy.

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Clinical response was based on chart review using the Clinical Global Impressions-Improvement scale (CGI-I),[13] which rates improvement as follows: 1 = marked improvement, 2 = moderate improvement, 3 = mild improvement, 4 = no change, 5 = mild worsening, 6 = moderate worsening, and 7 = marked worsening. Responders were defined as those with moderate or marked improvement. Clinical response was rated retrospectively at the date of chart review, based on comparison of clinical state before introduction of oxcarbazepine with clinical state at the time of chart review if use was continued or at the time of oxcarbazepine discontinuation.

Chart review was conducted to assess duration of the affective episode before treatment with oxcarbazepine, use of concurrent medications, and history of failure to respond to mood-stabilizing agents. Relevant treatment information harvested included whether or not oxcarbazepine treatment induced any symptoms of mania or hypomania, incidence of adverse events, maximum and maintenance oxcarbazepine doses and durations of treatment, indications for treatment with oxcarbazepine, and reasons for discontinuation of oxcarbazepine treatment.

Statistical analysis included descriptive statistics, such as chi-square and Fisher exact tests, using the Statview statistical program (SAS Institute, Cary, N.C.). Proportional response rates are provided with 95% confidence intervals.

RESULTS

Clinical and demographic characteristics of the sample are provided in Table 1.

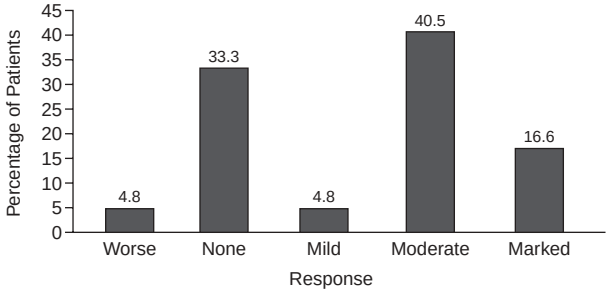
Oxcarbazepine, given in divided doses, was moderately to markedly effective in 24 subjects (57%) in the total sample (95% CI = 0.37 to 0.77) (Figure 1). The response rate is somewhat higher if restricted to those who received at least a 4-week trial of treatment, 23/34 (68% [95% CI = 0.49 to 0.87]). The only difference in demographic or clinical characteristics that was noted was that all males in the sample (10/10, 100%) responded compared with 14/32 females (44%) ($\chi^2 = 7.68$, $p = .006$; risk ratio = 2.29 [95% CI = 1.54 to 3.39]).

Most patients were being treated for refractory bipolar disorder: 33 (79%) had failed or not tolerated treatment with lithium, valproate, or carbamazepine. Sixty-nine percent (29/42) of patients had failed valproate, 45% (19/42) due to nonresponse and 24% (10/42) due to intolerance. Seventeen (40%) of 42 patients had previously failed lithium treatment, 31% (13/42) due to nonresponse and 10% (4/42) due to intolerance. Four (10%) of 42 patients had previously failed treatment with carbamazepine, 7% (3/42) due to nonresponse and 2% (1/42) due to intolerance. Fourteen percent (6/42) of patients had previously failed a combination of mood stabilizers due to nonresponse, 12% (5/42) while taking lithium and valproate and 2% (1/42) while taking lithium, valproate, and carbamazepine. The most common indication for treatment with oxcarbazepine was mixed mood symptoms (22/42, 52%). Oxcarbazepine was used as monotherapy in 11 patients (26%) and as a sole mood stabilizer in 26 (62%). Of the 11 monotherapy patients, 36% (4/11) experienced no effect or a worsening of their condition, and 64% (7/11) experienced mild-to-marked improvement, with 3 experiencing marked improvement. Of the 26 patients in whom oxcarbazepine was used as the sole mood stabilizer, 38% (10/26) experienced a worsening or no effect, and 62% (16/26) experienced a mild-to-marked improvement, with 6 experiencing a marked improvement. In patients taking concurrent medications (N = 31), the most common drugs were lithium (32% [10/31]), gabapentin (29% [9/31]), valproate (26% [8/31]), and clonazepam (23% [7/31]). Of these patients (N = 31), 39% (12/31) experienced a worsening to no effect, and 61% (19/31) had a mild-to-marked improvement, with 13% (4/31) having a marked improvement.

Table 1. Clinical, Demographic, and Treatment Characteristics of Patients With Bipolar Disorder (N = 42)

Characteristic	Value
Gender, N (%), male/female	10 (24)/32 (76)
Age, mean ± SD (range), y	33.3 ± 12.4 (13–59)
Oxcarbazepine dose, mean ± SD (range), mg/d	1056.6 ± 576.8 (150–2400)
Duration of treatment, mean ± SD (range), wk	16.2 ± 15.8 (1–71)
Indication for treatment, N (%)	
Mixed symptoms	22 (52)
Mania	12 (29)
Depression	3 (7)
Other	3 (7)
Rapid cycling	2 (5)
Bipolar diagnosis, N (%)	
Type I	25 (60)
Type II	4 (9)
Not otherwise specified	13 (31)

Figure 1. Clinical Response With Oxcarbazepine According to CGI-I Score in 42 Patients With Bipolar Disorder



Abbreviation: CGI-I = Clinical Global Impressions-Improvement scale.

A total of 52% (22/42) of patients discontinued treatment, 29% (12/42) due to side effects and 24% (10/42) due to lack of efficacy. The most commonly reported side effect was sedation (17/42, 40%). Other side effects reported included dizziness (3/42, 7%), headache and cognitive difficulty (2/42 each, 5%), and paresthesia, twitching, tactile impairment, diplopia, rash, nausea, weight gain, and leg pain/edema (1/42 each, 2%). Sixteen patients (38%) had no side effects.

DISCUSSION

Oxcarbazepine appeared useful as a mood stabilizer in the naturalistic treatment of bipolar disorder. It seemed equally effective as monotherapy or adjunctive therapy in this mostly treatment-refractory sample. An unexpected finding was the suggestion of a gender effect, with better response in males than females, but this was an unpredicted response that needs to be evaluated prospectively in other samples.

These results are consistent with and extend previous reports of possible benefit for oxcarbazepine.[3–12] Previous, randomized controlled studies have tended to be small and lacked placebo controls, along with being limited to acute mania in hospitalized patients. Our data suggest possible benefit in mostly refractory outpatients with predominantly mixed symptoms, which has not been the focus of previous studies.

The findings of this report should be interpreted in the context of the research design. Although 23% of patients discontinued oxcarbazepine treatment due to lack of efficacy, this rate is not very high for real-world clinical treatment because in that setting, as opposed to clinical trials, clinicians will often rapidly change treatments if sufficient efficacy is not observed. As with any nonrandomized study, this naturalistic evaluation did not control for possible confounding variables or effect modifiers, or selection bias. Further, since these results were not collected in the setting of a research protocol, outcome scale scores were not collected prospectively, thus introducing the risk of information bias. However, given the limited database of studies of oxcarbazepine, these results can serve as pilot data for prospectively designed studies, as well as provide information regarding the safety and clinical utility of these agents in the nonresearch setting.

CONCLUSION

Our review of naturalistic treatment with oxcarbazepine for bipolar disorder outpatients suggests that this agent may have potential mood-stabilizing benefits, with efficacy in 57% of the total sample. These pilot data need to be followed up by prospective, controlled studies in similar samples, preferably outpatients with depressive or mixed symptoms followed for 4 to 6 months or longer.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin and others), gabapentin (Neurontin), haloperidol (Haldol and others), oxcarbazepine (Trileptal).

REFERENCES

1. Ghaemi SN, Gaughan S. Novel anticonvulsants: a new generation of mood stabilizers? Harv Rev Psychiatry 2000;8:1–7
2. Post R, Denicoff K, Frye M, et al. Long-term outcome of anticonvulsants in affective disorders. In: Goldberg J, Harrow M, eds. Bipolar Disorders: Clinical Course and Outcome. Washington, DC: American Psychiatric Press; 1999:85–114
3. Ghaemi SN, Ko JY. Oxcarbazepine treatment of bipolar disorder: a review of the literature. Primary Psychiatry 2002;9:55–59
4. Muller AA, Stoll KD. Carbamazepine and oxcarbazepine in the treatment of manic syndromes: studies in Germany. In: Emrich HM, Okuma T, Muller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, the Netherlands: Excerpta Medica; 1984:139–147
5. Velinkoja M, Heinrich K. Effect of oxcarbazepine on affective and schizoaffective symptoms: a preliminary report. In: Emrich HM, Okuma T, Mueller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, the Netherlands: Excerpta Medica; 1984:208–210
6. Emrich H. Studies with oxcarbazepine (Trileptal) in acute mania. Int Clin Psychopharmacol 1990;5(suppl 1):83–88
7. Cabrera J, Muehlbauer H, Schley J, et al. Long-term randomized clinical trial on oxcarbazepine vs lithium in bipolar and schizoaffective disorders: preliminary results. Pharmacopsychiatry 1986;19:282–283
8. Greil W, Krueger R, Rossnagl G, et al. Prophylactic treatment of affective disorders with carbamazepine and oxcarbazepine: an open clinical trial. In: Pichot P, Berner P, Wolf R, et al, eds. Psychiatry: The State of the Art. New York, NY: Plenum Press; 1985:491–494
9. Tavormina G. Oxcarbazepine as a mood regulator: its efficacy, safety and tolerability vs carbamazepine [abstract]. Presented at the 22nd Collegium Internationale Neuro-Psychopharmacologicum; July 9–13, 2000; Brussels, Belgium
10. Hummel B, Stampfer R, Grunze H, et al. Acute antimanic efficacy and safety of oxcarbazepine in an open trial with an on-off-on design [abstract]. Presented at the 4th International Conference on Bipolar Disorder; June 14–16, 2001; Pittsburgh, Pa
11. Reinstein M, Sonnenberg J, Chasanov M. Oxcarbazepine and divalproex sodium in mania [abstract]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
12. Ghaemi SN, Ko JY, Katzow JJ. Oxcarbazepine treatment of refractory bipolar disorder: a retrospective chart review. Bipolar Disord 2002;4: 70–74
13. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222