Efficacy and Safety of Oxcarbazepine in Bipolar Disorder

Dear Editor:

The recent review by Pratoomsri et al on the use of oxcarbazepine (OXC) in the treatment of bipolar disorder (BD) requires comment. The authors summarize case reports, retrospective chart reviews, open prospective studies, and double-blind studies reporting the efficacy and effectiveness of OXC in treating BD. Nevertheless, they fail to show the many biases in these reported studies. For example, they report the 2 double-blind, multicentre trials of 2 weeks’ duration comparing OXC with haloperidol and lithium, respectively, in patients with acute mania. Although OXC and the comparator drug were of equal efficacy in both studies, these studies were limited by relatively small sample sizes, lack of placebo control, and meager descriptions of study designs and outcomes.

Besides, in the study by Hummel et al, the individual courses and scores of the Young Mania Rating Scale suggest a certain antimanic property of OXC only in patients with low-to-moderate manic episodes. Thus the usefulness of OXC monotherapy in severe mania appears doubtful.

Other studies cited by Pratoomsri et al show many limitations: methodological bias, small samples, insufficient follow-up periods, and confounding factors (patients concomitantly treated with several psychoactive drugs, for example, or different clinical profiles of enrolled patients). In other words, results may not be generalizable and should be interpreted cautiously.

Patients showed a percentage of dropouts due to hyponatremia, also when very small samples were considered, suggesting that this is probably a very common side effect; further, few patients were able to handle any more than 1500 to 1800 mg daily, which is about three-quarters of the rated maximum dosage. We have data showing that patients with severe or psychotic mania do not respond to OXC at all. A very recent multicentre trial showed that OXC is not significantly superior to placebo for the treatment of BD in children and adolescents. OXC seems to benefit adults with clinically significant impulsive aggression and is effective and well-tolerated in refractory BD patients and schizoaffective disorder patients, but only as an add-on to concomitant therapies with mood stabilizers, antipsychotics, and antidepressives. Therefore, in 2006, there was still a lack of serious double-blind, placebo-controlled studies with sufficient samples of patients and adequate follow-up periods to confirm the efficacy and safety of OXC for the treatment of acute phases and maintenance of BD.

References


Marianna Mazza, MD, PhD
Pietro Bria, MD
Salvatore Mazza, MD
Rome, Italy

Reply: Oxcarbazepine in the Treatment of Bipolar Disorder: A Review

Dear Editor:

We appreciate the opportunity to respond to the comments made by Dr Mazza, Dr Bria and Dr Mazza regarding our review of oxcarbazepine (OXC) in the management of bipolar disorder (BD). We take issue with their assertion that we failed to address shortcomings in the studies we summarized.

To address their points individually: The sample sizes and durations of the double-blinded trials comparing OXC with haloperidol and lithium were clearly stated in our article. Lack of placebo control in these studies is also obvious from our summary. Contrary to Mazza et al’s assertion, we specified that the Hummel study was carried out in patients with “mild-to-moderate mania.” We did not feel that the limitations inherent in the design of case reports, retrospective chart reviews, and open-label studies—which are familiar to clinicians—required belabouring. The range of frequencies of hyponatremia reported across published reports (3% to 51%) is outlined in the relevant section of our report.

Regarding the dosing of OXC, not all patients will require or be able to tolerate the maximum recommended dose. We suggested a modest starting dosage of 150 mg twice daily, which “should increase every few days to a maximum of 2400 mg daily, depending on clinical response and side effects.”

Mazza et al rightly point out that OXC has not been demonstrated superior to placebo in children and adolescents with BD. The treatment of BD in this population is a neglected area of therapeutics and certainly requires further
study. Unfortunately, the report they cite was published after our review was completed. In a similar vein, given the dearth of studies of OXC in subtypes of mania, publication of Mazza et al’s data regarding the efficacy of OXC in severe and psychotic mania would be a valuable addition to the literature.

It is an unfortunate consequence of the current pharmacoeconomic climate—and the limited remaining duration of patent protection for OXC—that adequately powered clinical trials to definitively assess its safety and efficacy are unlikely to be carried out. We feel that patients with BD refractory to standard therapies will benefit from the availability of other treatment options. In this light, we believe that our clinical recommendations are appropriately cautious and justified by the available data:

We recommend using OXC as monotherapy or as add-on therapy in refractory mania, but recommend it be used predominantly as an add-on treatment for other phases of BPD in patients who have not improved using well-established treatments or in patients who have difficulty tolerating adequate dosages.1, p 540

References

Wetid Pratoomsri MD
David Bond, MD
Lakshmi Yatham, MBBS
Vancouver, Canada

Re: Community Treatment Orders for Psychiatric Patients: The Emperor With No Clothes

Dear Editor:

We appreciated reading the spirited debate between Dr O’Reilly, on the one hand, and Dr Kisely and Ms Campbell, on the other, about community treatment orders (CTOs)1–4 and were pleased to see that the results of our North Carolina study5 continue to animate discussion of this important and controversial topic. Clearly, the use of legal leverage in community-based mental health treatment poses challenging questions for research and policy; it is hardly surprising that experts disagree, in good faith, about both the intervention and the evidence for its effectiveness.

Several points underlying Kisely and Campbell’s critique of our study in North Carolina warrant further comment.

First, Kisely and Campbell write,

The 1-year follow-up is therefore of a highly selected and potentially unrepresentative population that was not dangerous and was sufficiently compliant to participate in baseline and follow-up assessments.1, p 684

The attrition problem that these authors highlight (18% in our study) was substantial but irrelevant to the hospital outcome data. We included admissions data for all study participants—even dropouts—in the “intent-to-treat” analysis of hospital recidivism.

Kisely and Campbell’s suggestion that our study excluded all patients who were dangerous requires a qualifier. The exclusion criterion applied to patients with a documented recent history of serious violent behaviour involving weapon use or causing physical injury. However, one-third of randomized participants had engaged in acts of simple battery, or had been involved in physical fights, during the 4 months preceding enrolment. An additional 20% had made verbal threats of harm to others. Suicidality was also not an exclusion criterion. We think our study generalizes to a broader clinical population than one might imagine from reading Kisely and Campbell’s critique.

Second, these authors write that the study failed to show “significant differences between intervention and control groups in terms of hospital or other outcomes . . . over the following 12 months.”1 In fact, using repeated-measures analysis, we found that “assignment to the outpatient commitment group was associated with a significantly lower odds of any readmission (odds ratio 0.64; 95% confidence interval, 0.46 to 0.88; P < 0.01).”5 This result was obtained from an intent-to-treat, monthly time-series analysis using the original randomized groups.

As Kisely and Campbell correctly observe, our analysis also revealed that the apparent effect of the intervention was concentrated heavily among participants who received extended court-ordered treatment. Still, the result was sufficiently strong to achieve statistical significance for the experimental group as a whole.

Finally, Kisely and Campbell state,

Analysis of subjects who have not been randomly assigned to CTO groups of less or more than 180 days may reflect a bias where a CTO was selectively extended when it seemed to be helping the patient.1, p 684

Our evidence suggests the opposite was true. Participating mental health centres agreed in advance to systematically review each expiring court order and file a petition to renew if the patient continued to meet legal criteria for outpatient commitment. Consequently, patients with a history of...
Dear Editor:

Drs Swanson and Swartz raise more questions than answers about their study. We will deal with these in turn. On the issue of attrition, we clearly stated that, of those who were randomized, there was an 82% completion rate in the North Carolina study. However, this does not take into account attrition prior to randomization. Of all eligible subjects, only 57% completed the North Carolina study.

They also say that the randomized controlled trial (RCT) samples were more typical than we suggest because only subjects with a documented recent history of violent behaviour involving weapons or causing physical injury were excluded, as opposed to less serious violence or verbal threats of harm. But what does that mean? Were the police involved? Were the patients arrested, charged, or convicted? These are crucial distinctions—our study of community treatment orders (CTOs) showed that it was only the presence of a conviction for injury against others that predicted the use of CTOs. It is not unreasonable to suggest that patients convicted of assault may more closely resemble those excluded from the North Carolina study than those who made verbal threats or were involved in physical fights, who might or might not have been arrested or convicted. Moreover, this discussion does not apply to the New York study, where any history of violence led to exclusion.

Our commentary on the New York and North Carolina studies is based on the metaanalyses of our Cochrane Review. There was no statistical difference on either fixed- or random-effects models between patients randomly assigned to intervention or control groups. Post hoc subanalyses of patients nonrandomly allocated to longer orders are inevitably subject to selection bias. We suggest that this might have led to cases with a good prognosis being differentially selected; Swanson and Swartz suggest the opposite. The only way of elucidating this is to repeat the study with random allocation to 3 groups: control subjects, orders of less than 180 days, and orders of greater than 180 days.

They also say that, when using repeated-measures analysis, they found the outpatient commitment group had a significantly lower chance of readmission with an intent-to-treat, monthly time-series analysis using the original randomized groups. Their paper actually states,

> Although the overall group assignment (outpatient commitment or control) was significant in this model, as demonstrated in Table 2, this effect was dependent on increasing days of outpatient commitment.

Further, the reader is referred to a table (Table 2 in their paper) where they present analyses of the effect of being on outpatient commitment for more than 180 days. What exactly does this mean? Is the effect in their logistic regression model? Is it only apparent after 180 days? We can only rely on the information as given in their paper. However, this does seem a strange method of presenting the results of an RCT, which is not consistent with the methodology of the Cochrane Collaboration. It also seems merely another way of saying that only nonrandom allocation to orders of longer duration leads to reduced admission.

References


Stephen Kisely, MD, MSc
Leslie Anne Campbell, BScN, MSc
Halifax, Nova Scotia

References


