

# Lithium Trumps Valproate for Bipolar Disorder

Deborah Brauser | July 25, 2011

July 25, 2011 — Lithium is more effective in treating episodes of bipolar disorder (BD) than valproate. However, there is little difference between the 2 agents in reducing suicidality in this patient population, according to 2 new studies.

In the first study, which observed more than 4000 Danish patients with BD, those taking lithium had fewer hospital admissions and less need for switching and/or adding medications than did those taking valproate.

"The advantage for lithium is robust and most likely to be evident following treatment for a depressive episode," said Lars Vedel Kessing, MD, Psychiatric Center Copenhagen, University Hospital of Copenhagen, Rigshospitalet, Denmark, in a release.

The study [was published](#) in the July issue of the *British Journal of Psychiatry*.

Commenting on these findings for *Medscape Medical News*, Maria A. Oquendo, MD, professor of clinical psychiatry at Columbia University and the New York State Psychiatric Institute, New York City, said that it was also interesting to see how well lithium did in terms of addressing mixed states — "something that is not generally observed in clinical trials and is very encouraging.



**Dr. Maria A.  
Oquendo**

"I think the take-home message is that clinicians in the US need not be so gun shy about using lithium," added Dr. Oquendo, who was not involved in the study.

However, in a randomized controlled trial (RCT) of almost 100 patients with BD and previous suicide attempts, [published online July 18](#) in the *American Journal of Psychiatry*, Dr. Oquendo and colleagues found no significant differences between those treated with valproate or lithium in number of or time to suicide attempts or hospitalizations due to suicide plans.

"We were very surprised by this because we thought that lithium was going to better protect patients against these behaviors," said Dr. Oquendo.

"Still, I think that we can't say there isn't some smaller effect there, which would still be important in this patient population."

## Largest Study, Longest Follow-Up

In the first observational cohort study, investigators evaluated psychiatric hospital data on 4268 patients with BD (58% female; median age, 50 years) prescribed either valproate ( $n = 719$ ) or lithium ( $n = 3549$ ) between 1995 and 2006.

"Valproate is one of the most used mood stabilizers for BD, although the evidence for [its] effectiveness is sparse," write the researchers.

Results showed that, regardless of episode type that led to their hospital admission, those taking valproate had a higher admission rate than did those taking lithium (hazard ratio [HR], 1.33; 95% confidence interval, 1.18 – 1.48).

The overall admission rate was also significantly higher for patients in the valproate group vs those in the lithium group who experienced a depressive (HR, 1.87), manic (HR, 1.24), or mixed index episode (HR, 1.22).

In addition, the valproate-treated group had a higher rate of switching to or adding on the opposite treatment drug, antidepressants, antipsychotics, or anticonvulsants, than did the lithium group (HR, 1.86).

The largest effect favoring lithium was evident for index depression (HR, 2.52) for switching to/adding on, report the investigators.

"In daily clinical practice, treatment with lithium seems in general to be superior to treatment with valproate," they write.

"This population-based, nationwide register linkage study included up to 12 years follow-up and is by far the largest study, with the longest follow-up, of individuals with valproate or lithium ever described."

Dr. Oquendo noted that this study was also striking because it looked at response in the context of what the index episode was.

"So what's the likelihood that people will do better on lithium than on valproate if they start out in a mixed state or a depressed state? That kind of data is extremely useful and applicable to this country," she said.

### **Highest Suicide Rate**

The authors of the second study note that few double-blind RCTs have assessed mood stabilizers and suicidal behaviors in exclusively bipolar samples.

"This is the psychiatric condition with the highest suicide attempt and suicide death rate, and yet we have no treatments that are specifically approved for treating these behaviors," said Dr. Oquendo.

"There was a bunch of naturalistic data going back to the 1970s suggesting that lithium might have specific antisuicidal properties. We felt that the only way to really test that was with an RCT."

For Dr. Oquendo's study, 98 patients between the ages of 18 and 75 years with BD and at least 1 past suicide attempt were randomized to receive either lithium ( $n = 49$ ; 76% female; mean age, 33 years) or valproate ( $n = 49$ ; 69% female; mean age, 34 years) plus adjunctive medication.

Time to suicide attempt and time to suicide event, along with suicide completions, were all primary outcome measures.

A suicide event could include an attempt, hospitalization, or change in medication in response to suicidal ideation. Follow-up continued for up to 2.5 years.

Results showed that 45 suicide events occurred during the study period by 35 patients (16 from the lithium group, 19 from valproate group). Of these, 18 total suicide attempts were made by 6 of the patients treated with lithium and 8 of those treated with valproate. There were no suicide completions in either group.

In addition, there were no significant differences between the lithium and valproate groups in time to suicide attempt (507 vs 480 days) or time to suicide event (114 days vs 138 days).

"There were also no differences between treatment groups in proportion achieving remission from acute episode, time to hospitalization for any reason, or time on study medication," report the researchers.

The investigators attribute the lack of difference in the suicidal outcomes to the several possibilities, including the fact lithium had a more modest antisuicidal effect that was not detected, was due to other untested factors, or simply that both treatments have a comparable effect on suicidality.

"I think that the very large effects reported with lithium in the literature, in naturalistic studies, are probably overstated. However, smaller effects than 5-fold differences would still be extremely important because of the morbidity and mortality associated with these patients," said Dr. Oquendo.

The investigators note that large-scale trials of antisuicidal interventions in BD are desperately needed.

"A multisite study to demonstrate even modest differences that could change current prescribing practices in the United States may be lifesaving," they write.

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authors of both studies report several disclosures, which are listed in the original articles.

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