Anticonvulsant Therapy and Suicide Risk in Affective Disorders

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Patients with major affective disorders are more likely to complete suicide than patients in any other medical group. Established risk factors for completed suicide in affective disorders include acute depression (with turmoil, hopelessness, global insomnia, anhedonia, anxiety and/or panic), mixed episodes, rapid cycling, substance abuse, aggression and/or impulsivity, low serotonergic activity, and hypothalamic-pituitary-adrenal axis activation. Although anticonvulsants have mood-stabilizing and antidepressant properties, few data are available on the antisuicide effects of anticonvulsant treatment in manic-depressive patients. On the other hand, as reviewed elsewhere in this issue, massive data have been accumulated on the antisuicide effect of lithium. This article discusses lithium versus anticonvulsants in the prevention of suicide associated with affective disorders and future treatment strategies to reduce this most serious complication of manic-depressive illness.

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Several psychological postmortem studies of completed suicides[1] indicate that 60% to 80% of suicides are associated with a diagnosis of a major affective disorder. Primarily because of suicide, the mortality rate for untreated manic-depressive patients is higher than it is for many types of heart disease and even some types of cancer. Patients with depressive and manic-depressive illnesses are more likely to attempt or complete suicide than patients in any other medical group.[2] In a review of 31 studies of 9389 manic-depressive patients—in which bipolar and recurrent unipolar patient data were combined—the lifetime prevalence of suicide ranged from 9% to 60%, with a weighted mean of 18.9%. Thus, it is critical to determine if long-term psychopharmacologic treatment exerts a positive influence on suicidal behavior. This article will discuss lithium and anticonvulsants, the differential effects of lithium and anticonvulsants on suicide and on risk factors for suicide, and treatment strategies to reduce this most serious complication of manic-depressive illness.

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LITHIUM VERSUS ANTICONVULSANTS

Controlled data on maintenance lithium treatment of patients with bipolar and recurrent unipolar depression date back to 1970,[3] and massive data have accumulated on the antisuicide effect of lithium.[2] Tondo and associates[4] recently conducted an impressive review of the possible antisuicide effect of lithium maintenance treatment in affective disorders, and they found that the risk of attempted and completed suicides averaged 3.2 (without lithium) versus 0.37 (with lithium) per 100 patient-years, an 8.6-fold difference.

On the other hand, although anticonvulsants have mood-stabilizing and antidepressant properties, few data are available on the antisuicide effects of anticonvulsant treatment in manic-depressive patients. In spite of this, we are witnessing a striking recent trend toward increased use of anticonvulsants in bipolar disorders. Indeed, today more than half of the bipolar patients being treated are on an anticonvulsant, primarily valproate.

Based on open studies, the types of affective disorders that correlate with a better response to anticonvulsants than to lithium are rapid cycling, mixed episodes, a previous poor response to lithium, secondary mania, and concurrent substance abuse. Indeed, there is little controversy associated with the use of anticonvulsants as first-line treatment in these conditions, although some would maintain that, in many cases, they should be combined with modest doses of lithium. This substantial shift away from lithium and toward anticonvulsants (particularly valproate) for maintenance treatment of bipolar disorder is particularly striking given the fact that to date only the anticonvulsant carbamazepine has been shown to have pro-

Table 1. Medications of Individual Patients (N = 9) at the Time of Suicide*

Patient	Diagnosis/ Disorder	Randomization Medication	Medication at Suicide[b]
1	Bipolar	Lithium	None
2[a]	Bipolar	Carbamazepine	Carbamazepine, amitriptyline
3[a]	Bipolar	Carbamazepine	Carbamazepine, clozapine
4[a]	Bipolar	Carbamazepine	Carbamazepine, amitriptyline
5	Bipolar	Carbamazepine	Carbamazepine
6	Bipolar	Carbamazepine	Imipramine, pipamperone
7[a]	Schizoaffective	Lithium	Perazine
8[a]	Schizoaffective	Carbamazepine	Trimipramine, clozapine
9	Unipolar	Amitriptyline	Tranylcypromine, trifluoperazine

*Adapted from reference 15.
[a]Committed suicide during initial acute major depressive episode and before the start of actual study phase.
[b]Estimated.

phylactic efficacy in bipolar disorders in randomized placebo-controlled trials. Still, all 5 of the randomized head-to-head comparisons of lithium versus carbamazepine maintenance[5–9] show superior prophylaxis with lithium. With regard to valproate,[10–14] while its acute antimanic effects have been demonstrated in a placebo-controlled trial,[10] it did poorly among those patients who had previously responded to lithium, suggesting 2 separate drug response patterns. In the only placebo-controlled study of valproate versus lithium in the prevention of bipolar relapses, neither acute drug could be distinguished from placebo on the major outcome variables. This illustrates the problem in placebo-controlled trials that exclude seriously ill patients who may be at increased risk for manic breakthroughs or suicide. Moreover, this particular trial used lithium in doses to provide blood levels (1.0 to 1.2 mEq/L) that are closer to those usually associated with acute rather than maintenance treatment; thus, dose-related side effects and patient dropouts occurred.

Returning to the question of suicide prevention, there is only 1 head-to-head comparison of lithium versus an anticonvulsant (in this case, carbamazepine) in the prevention of suicide, the study of Thies-Flechtner et al.,[15] a randomized prospective open-label study designed to evaluate attempted and completed suicides in relation to particular drug treatments. Outcomes were analyzed in 378 hospitalized patients with acute major depression and ICD-9 diagnoses of bipolar disorder (N = 175), schizoaffective disorder (N = 110), and recurrent unipolar disorder (N = 93). At discharge, patients were randomly assigned to lithium, carbamazepine, or amitriptyline and followed prospectively for 2.5 years; lithium or carbamazepine was administered to bipolar and schizoaffective patients, and lithium or amitriptyline was administered to recurrent unipolar patients. Follow-up visits were conducted at least every 3 months. Patients' medications at the time of suicide were estimated on the basis of family interviews, case records, and serum drug levels at the last follow-up visit; the time period between the last follow-up visit and the suicide was not reported. There were 9 serious suicide events in the 2.5 year period (5 suicides and 4 serious attempts) and 6 of the 9 events were in the bipolar group (Table 1).[15] Six of the events occurred in the first 6 months of treatment, a fact that underscores the importance of rigorous treatment during this especially high-risk period. Most of the suicide events occurred in the carbamazepine-treated group, and none of the 9 patients were taking lithium at the time of the event. This difference between lithium and carbamazepine was significant ($p < .01$). This was in spite of the fact that prior attempts were more frequent in the lithium-treated patients (43% vs. 34%). Methodological issues inherent in this study include whether the use of antidepressants was equal in the lithium and carbamazepine treatment groups and whether the antidepressants may have contributed to mixed episodes or rapid cycling—either of which can be associated with suicide. Moreover, two thirds of the suicides occurred in the first 6 months, suggesting that some of these events may reflect an inadequate acute antidepressant response, not just prophylactic failure. Finally, since patients with substance abuse usually respond less favorably to lithium than to anticonvulsants, exclusion of such patients may have biased the sample toward lithium responders and anticonvulsant nonresponders.

SUICIDE RISK FACTORS IN AFFECTIVE DISORDERS AND DIFFERENTIAL EFFECTS OF TREATMENT

Let us now examine what is known about the differential effects of lithium versus the anticonvulsants on those clinical symptoms that increase the risk of suicide. These include acute depression (with turmoil, hopelessness, global insomnia, anhedonia, anxiety, and/or panic), mixed episodes, rapid cycling, substance abuse, aggression, and/or impulsivity, low serotonergic activity, and hypothalamic-pituitary-adrenal (HPA) axis activation. Many of these factors are drawn from the National Institute of Mental Health (NIMH) collaborative studies reported by Fawcett and colleagues[16,17] in which all completed suicides (N = 32) in 954 patients with major affective disorder were assessed with regard to clinical features associated with subsequent suicide. A total of 13 (41%) suicides occurred during year 1 of assessment—8 within the first 6 months—and 19 (59%) suicides occurred during follow-up years 2 through 10. Six of the 9 clinical features in this study—panic attacks, severe psychic anxiety, diminished concentration, global insomnia,

moderate alcohol abuse, and severe loss of interest or pleasure (anhedonia)—were particularly associated with suicide within the first year. Three additional features—severe hopelessness, suicide ideation, and history of previous suicide attempts—were particularly associated with suicide between years 1 and 5. Unfortunately, direct head-to-head comparisons between lithium, valproate, or carbamazepine treatment are lacking for many of the established suicide risk factors, but data are available in some areas.

Anxiety or Panic

Valproate has demonstrated a moderate GABAergic effect in animal studies,[18,19] and long-term administration of lithium and carbamazepine elevate GABA levels in the rat hippocampus[20]; both findings suggest possible anxiolytic, antipanic effects. Valproate may reduce agitation in depressed patients, but whether that state of anxiety is similar to the anxiety or panic described in the NIMH study is unknown. In high doses, clonazepam is an anticonvulsant; in typical clinical doses, clonazepam has been shown to reduce symptoms in acutely manic patients.[21]

Mixed Episodes

Comparisons of carbamazepine versus lithium in mixed-episode patients are lacking. However, in the Bowden et al. study,[10] patients with mixed episodes demonstrated a better response to valproate (70%) than to lithium (40%). Freeman and colleagues[22] compared the efficacy of lithium with that of valproate in 27 patients with acute mania and found that both drugs were effective in improving manic symptoms. A favorable response to valproate was also associated with elevated pretreatment depression scores, and the authors concluded that treatment with valproate alone might be particularly effective in manic patients with mixed affective states.

Rapid Cycling

Patients with 4 or more episodes per year (the operative definition of a rapid cycler) show a relatively poor response to lithium alone,[23,24] although among rapid-cycling patients with no prior exposure to tricyclic antidepressants Kukopulos et al. [25] noted a robust prophylactic response to lithium alone. A more recent 5-year retrospective study[26] of clinical outcome of rapid-cycling bipolar patients given lithium alone or lithium combined with carbamazepine suggested that, although both groups improved, improvement was observed earlier in the patients who received the anticonvulsant along with lithium. All of the 8 rapid-cycling patients in the Bowden et al. acute mania study[10] were in the valproate group; of those patients, half responded to this anticonvulsant. In a larger sample (N = 101) of rapid-cycling bipolar patients,[27] valproate showed marked prophylactic effects against mania and mixed episodes, with poor-to-moderate antidepressant effects.

Substance Abuse

In another section of this supplement,[28] Dr. Nilsson presents data that show a 2.8-fold increase in suicide risk in patients with affective disorders and comorbid alcohol or drug abuse. Substance abuse has a particularly strong correlation with lethality in suicide, especially in men.[2] Patients who have affective disorders often use alcohol and illicit drugs to lessen the severe anxiety and pain associated with suicidal depression, but the combination of agents can actually diminish impulse control, impair judgment, and worsen the course of their illness. Generally, bipolar patients with concurrent substance abuse have shown a poor response to lithium treatment. It is not clear whether the poor response to lithium is due to the substance abuse per se or the rapid cycling of the mixed states frequently associated with it. In a small (N = 9) open-label study by Brady and colleagues,[29] patients with bipolar disorder and comorbid substance abuse showed significant improvement on valproate, reflected in a substantial decline in the Young Mania Rating Scale score and in the Hamilton Rating Scale for Depression (HAM-D). To my knowledge, prophylactic efficacy of valproate in bipolar patients with concurrent substance abuse has not been reported.

Aggression, Impulsivity, and Serotonergic Activity

Altered serotonin function has been postulated as part of the pathophysiology of affective disorders, and interference with serotonin synthesis or storage may induce depression in vulnerable individuals. Decreased levels of its principal metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF), decreased levels of its precursor (tryptophan) in the blood, low tryptophan to neutral amino acid ratios, and abnormalities in serotonergic function indicated by neuroendocrine challenge tests and platelet measures have all been reported in depressed patients.[30] As reviewed by Mann et al. in this supplement,[31] low CSF 5-HIAA, increased postmortem postsynaptic 5-HT receptors, and fewer presynaptic autoreceptors have also been noted in suicide victims.[32] A recent study[33] demonstrated a bimodal seasonal pattern in the availability of plasma L-tryptophan that matched seasonal patterns in the prevalence of violent suicide in a local population in Belgium.

Since the most violent suicide attempts are the ones that usually succeed, much has been written about aggressive and/or impulsive behavior associated with low serotonergic activity.[34,35] The action of lithium on serotonin systems may help to explain its possible antisuicide effect. Long-term lithium administration enhances serotonin turnover reflected by increased release and down-regulation of serotonin receptor sites in rat hippocampus.[36] Data on valproate-treated manic patients[37] compared with those treated with placebo show increased central serotonergic activity and a 5-hydroxytryptophan-induced cortisol response, which is a neuroendocrine indicator of the density of serotonergic cells. Although lithium has long been asso-

ciated with anti-aggressive properties, the drug has not been considered useful in severe agitation because of the time to response. However, a pilot study by Lee and associates[38] evaluated the clinical efficacy of lithium citrate for the rapid control of severe agitation in a small group of psychiatric inpatients and reported a 69% decline in Brief Psychiatric Rating Scale scores within 60 to 90 minutes after administration.

What about the impact of anticonvulsants on aggression and impulsivity? In a study of borderline personality disorder and behavioral dyscontrol,[39] carbamazepine was compared with placebo under double-blind conditions; those on carbamazepine were rated as substantially improved. In addition, less aggression and self-injury was noted in mentally retarded patients treated with valproate over a 2-year period.[40] Valproate has also demonstrated efficacy against aggression in patients with dementia.[41,42] Thus, lithium, valproate, and carbamazepine all show anti-aggressive effects that may be consistent with prevention of suicide.

The studies we have just reviewed are difficult to summarize since very few involved a direct comparison of lithium and an anticonvulsant in the same experimental paradigm and clinical group. However, it seems reasonable to conclude from this disparate data that both lithium and the anticonvulsants have effects on several of the suicide risk factors that could contribute to an antisuicidal effect clinically. Anticonvulsants appear to have the edge in treating mixed states, rapid cycling, and perhaps comorbid substance abuse, while lithium may have the edge in reducing aggression and impulsivity and enhancing serotonergic function. Finally, both classes of drugs have been reported to have beneficial effects against the depressive phase of the illness.

FUTURE TREATMENT STRATEGIES TO REDUCE SUICIDE RISK

Gabapentin and lamotrigine are new anticonvulsants that have each been recently approved as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.[43] Like valproate and carbamazepine—which are also used to treat patients with partial seizures—these 2 new anticonvulsants may prove to have mood-stabilizing and antidepressant properties that will benefit patients with affective disorders. Gabapentin has demonstrated anxiolytic-like effects in rat conflict tests,[44] and patients refractory to standard mood-stabilizing agents have shown a positive response to the drug, as judged by both physician and patient reports.[45] In an open-label study[46] of 15 bipolar outpatients refractory to standard mood stabilizers, 53% (N = 8) showed a positive response (measured by a reduction in HAM-D score) to gabapentin when it was administered either alone or in combination with existing treatment. In a retrospective study[47] of 73 patients with affective disorders, 67 had a positive response to gabapentin, and beneficial results were seen across the entire spectrum of bipolar disorder. To investigate the efficacy, tolerability, and safety of gabapentin in mania, McElroy and colleagues[48] treated 9 consecutive bipolar outpatients with open-label adjunctive gabapentin. Of the 9 patients, 7 displayed a moderate or marked reduction in manic symptoms within 1 month after addition of gabapentin, and another patient displayed moderate improvement after 3 months. The authors concluded that adjunctive gabapentin is generally well-tolerated and may have antimanic and mood-stabilizing effects in some patients with bipolar disorder.

Lamotrigine has been effective in treatment-resistant bipolar patients as reported in 2 case series and case reports.[49,50] An open-label, naturalistic, prospective study[51] of 5 rapid-cycling bipolar patients (DSM-IV) demonstrated a significant ($t = -5.26$, $p < .006$) reduction in mean Beck Depression Inventory total score in patients treated with either lamotrigine monotherapy or a combination of lamotrigine and other psychotropic agents. In a large (N = 75) open-label study in which Corn et al.[52] evaluated the efficacy of lamotrigine in treatment-refractory patients, a moderate-to-marked response to bipolar depression and rapid cycling was demonstrated by a decline in HAM-D score and a mania rating scale score.

A combination of lithium with an anticonvulsant may prove to be advantageous in patients who are in high-risk suicide groups. While this particular combination has the advantage of no complex drug interactions, the doses of each may need to be kept moderate to avoid additive side effects. Furthermore, medications administered in combination should generally be given with slow upward titration to individual patients' side effect thresholds, accompanied by monitoring of blood drug levels and pertinent laboratory parameters, and careful mapping of the patient's course of treatment and response.[53,54]

Data on lithium treatment of patients with affective disorders go back 30 years, and the antisuicide effect of lithium has been explored for the last 10 years. Data on valproate, carbamazepine, gabapentin, and lamotrigine treatment in patients with affective disorders at high risk for suicide are still relatively new. Thus, it is unwise to substitute anticonvulsants for lithium in patients with "typical" bipolar illness (absence of rapid cycles, mixed states, or comorbid substance abuse). Indeed, the practice of substituting an anticonvulsant for lithium in a patient who has responded to lithium and is tolerating it well is beyond unwise; it is irresponsible. It may turn out that the best course to follow for those patients who may need an anticonvulsant is to combine it with modest doses of lithium.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clonazepam (Klonopin), clozapine (Clozaril), gabapentin (Neurontin), imipramine (Tofranil and others), lamotrigine (Lamictal), tranylcypromine (Parnate), trifluoperazine (Stelazine), trimipramine (Surmontil).

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