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Abstract

Expert consensus emphasizes the need for better recognition and accurate diagnosis of bipolar disorder. Current research on lithium, divalproex, and lamotrigine provides new insight into the effective management of this illness. Advances in identifying the mechanism of action of mood stabilization has focused on signaling pathways within the cell that are associated with neurotrophic effects. Clinical research has led to confirmatory evidence of lithium's efficacy in all phases of bipolar disorder, with the greatest effects seen in the treatment and prevention of mania. Compared to divalproex, lithium has also been found to have greater efficacy in the prevention of suicide. Lamotrigine has emerged as a first line treatment for bipolar depression, an area of weakness for other mood stabilizers. Oral loading of divalproex leads to rapid stabilization of mania without imposing a greater adverse effect burden than conventional dosing. Because no single agent is universally effective in all phases of the illness, combination therapy with two or more agents is often the best option.

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Introduction

A growing appreciation for the importance of recognizing and treating bipolar disorder has highlighted the significance of achieving a better understanding of the mood stabilizers [1]. Clinical identification of symptoms of depression may often lead to the precipitate use of an antidepressant, when a more deliberate exploration of the patient's

history might have resulted in a diagnosis of bipolar disorder [2]. As the prevalence of antidepressant use rises dramatically, particularly by primary care physicians [3], the serious problems associated with antidepressant monotherapy in bipolar patients is becoming more apparent. At the same time our knowledge of mood stabilizers is increasing, and new options are becoming available. This commentary reviews the recent literature that has been published during the last year on three of the most frequently prescribed mood stabilizers: lamotrigine, lithium, and divalproex.

A fundamental questions is: What constitutes a "mood stabilizer"? No consensus definition is accepted among investigators, nor is the term officially recognized by the Food and Drug Administration (FDA). To begin to address this question, it is worth noting that comprehensive management of bipolar disorder requires treatment of acute mania and depression, as well as prevention of mania and depression during the maintenance phase. The most stringent definition of a mood stabilizer would require efficacy in all phases, while the most inclusive definition would allow agents that were effective in any one of the phases without increasing instability with regard to the other phases [4].

A review undertaken by Bauer and colleagues designed to evaluate how well specific agents met the various definitions of mood stabilizer found that lithium and divalproex had unequivocal evidence for efficacy in acute mania, lithium for acute depressive episodes and in the prophylaxis of mania and depression, and lamotrigine for prophylaxis of mood episodes, principally depressive episodes. They concluded that only lithium, which has some degree of efficacy in all phases, is a true mood stabilizer based on the most restrictive definition [5]. It should be noted that lithium's efficacy in acute depression is less robust than it is for mania.

New Insights Into Mechanisms of Action

The mechanism of action of the mood stabilizers is unknown, but likely involves multiple signaling pathways within the cell. Because the clinical effects of mood stabilizers

demonstrate similarities, common mechanisms or biochemical targets may underlie their activity, and the identification of a common mechanism would have the potential to shed light on the molecular origins of bipolar disorder itself [6]. Although our current understanding has not yet reached this level, a number of intriguing observations have been made.

Much of the work that has been published recently on the biochemical effects of chronic lithium administration has focused on lithium's effect on cellular resilience and structural plasticity. Lithium has been found to increase the concentration of N-acetyl-aspartate (NAA), for example, in bipolar patients and controls. NAA concentrations may be a marker for neuronal viability and functioning, suggesting that lithium, shown to bring about an increase in this marker, exerts neurotrophic effects in the brain. Additionally, lithium has been found to enhance dendritic branching, the development of new synapses, and even neurogenesis [7, 8]. A comparison of the effects lithium and divalproex on NAA concentrations using magnetic resonance spectroscopy demonstrated significant increases in lithium treated patients, but not divalproex treated patients [9]. These results suggest that lithium and valproate may not share a common mechanism of action, at least in this respect.

An important candidate for the mechanism by which lithium exerts its neuroprotective effects is via the inhibition of glycogen synthase kinase-3 (GSK-3) [10]. GSK-3 plays a role in the regulation of the function of diverse proteins including transcription factors and cytoskeletal elements that are putatively involved in the maintenance and development of neurons. In vitro, lithium inhibition of GSK-3 occurs with a K(i) of 1-2 mM (equivalent to serum concentrations of 1-2 mEq/l), but may be lower in vivo. Gould and colleagues evaluated in vivo activity of lithium on GSK-3 at typical therapeutic levels by measuring a transcription factor that is a marker of GSK-3 inactivation. Their results indicated significant inhibition of GSK-3 at lithium levels of 0.77 and 0.80 mEq/l. The evidence of a role for GSK-3 inhibition in the treatment of bipolar disorder is compelling, and may provide a theoretical framework for the development of new compounds with tolerability or efficacy advantages over existing mood stabilizers.

A neurotrophic mechanism of effective treatment of bipolar disorder is also supported by the finding that glutamatergic damage and damage due to high glucocorticoid levels that inhibit adult neurogenesis likely contribute to the cell loss in cortical and limbic brain regions found in patients with bipolar disorder. Bauer and colleagues reviewed the preclinical evidence that some of the neurotrophic effects of lithium may be mediated by reducing glutamatergic excitotoxicity, and increasing glutamate reuptake by glial cells [11]. They suggest that one of the implications of this finding is that lithium may have the potential to reverse long-term neurocognitive impairment associated with bipolar disorder, however they note that further studies will be required to empirically test this hypothesis.

Divalproex has some effects in common with lithium, however not all the indications of enhanced cellular resilience and neuroplasticity are seen. As noted, divalproex was not found to increase levels of NAA, however divalproex may indirectly inhibit GSK-3 [6], and promote the expression of genes for cytoprotective factors such as bcl-2 [12]. Unlike lithium, divalproex increases regional concentrations of gamma aminobutyric acid (GABA) by increasing synthesis and inhibiting its metabolism [13]. The GABA-ergic properties of divalproex are probably central to its anticonvulsant efficacy, and may also account for its robust efficacy in bipolar mania. Valproate also demonstrates some degree of efficacy in anxiety, and sedation is a common adverse effect, both consistent with a GABA-ergic mechanism.

Lamotrigine is an anticonvulsant like divalproex, but it has a substantially different mechanism of action. Unlike divalproex, lamotrigine does not enhance plasma GABA levels [14], but appears to exert antiglutamatergic activity that may underlie its efficacy in mood disorders, as well as serve a neuroprotective role by preventing excitotoxicity in hyperglutamatergic states [15]. Lamotrigine inhibits use-dependent sodium channels that are recruited during repeated firing of action potentials, a mechanism that is possibly central to its anticonvulsant efficacy. It also inhibits calcium channels that regulate calcium influx required for the release of neurotransmitter in response to membrane

depolarization. Finally it has weak antagonist affinity for the postsynaptic N-methyl-D-aspartate (NMDA) receptor [15]. Unlike GABA-ergic anticonvulsants, the antiglutamatergic properties of lamotrigine make it more activating than sedating. Insomnia is a typical adverse effect.

Efficacy in the Treatment of Acute Mania

Much of the research published in the past year on the treatment of acute mania has focused on achieving rapid antimanic effects with a divalproex loading strategy. Lamotrigine has not demonstrated efficacy in the treatment of acute mania [16] and lithium has been established as an effective treatment for many years.

Divalproex loading has been found to be safe and effective. In some ways, however, the term "loading" is a misnomer. In other contexts, such as the initiation of phenytoin, loading refers to administering doses that are higher than the expected maintenance dose, in order to reach the desired serum level in fewer than four half-lives. Loading of divalproex generally refers to starting 20 mg/kg, thereby omitting the titration phase, and starting a patient on a full maintenance dose on day one. The less common strategy of using 30 mg/kg initially, then decreasing to 20 mg/kg for maintenance is more representative of true loading.

Pooled analysis of oral loading of divalproex for acute mania, found earlier efficacy compared to standard divalproex titration, as well as improved efficacy over lithium on days 7/8. No efficacy differences were found compared to olanzapine. Orally loaded divalproex was tolerated as well or better than other active treatments [17]. No additional advantage was found with intravenous loading of valproate, which was comparable to oral loading in both efficacy and adverse effects [18]. A test of the immediate effects of a single intravenous dose of valproate found no therapeutic benefit over a period of 120 minutes [19].

Efficacy in the Treatment of Acute Depression

Lamotrigine is emerging as a first line treatment for bipolar depression because of the robustness of its effect; however because there are nine positive controlled trials of lithium and, as yet, far fewer involving lamotrigine, the weight of evidence continues to favor lithium for this indication. This conclusion was reached by a review of controlled studies of bipolar depression, which further determined that patients who have failed lithium should be considered refractory [20]. Appropriate second line treatments include lamotrigine, a second mood stabilizer, a newer generation antidepressant, or the atypical antipsychotic olanzapine. The authors note however, that there is a paucity of research that can be used for rational clinical decision making in the treatment of refractory bipolar depression.

An inadequate research base for clinical decision making remains a challenge. The tenets of evidence based medicine require that treatment decisions be based on the most rigorous and up-to-date information available. Prospective, double-blind, placebo-controlled studies are the gold standard in terms of quality of evidence, but the expense associated with these types of studies limits their number. Given the complexity of bipolar disorder, and the many different clinical presentations that are seen in practice, the clinician must frequently go beyond this type of evidence, as well as evidence from less rigorous studies such as open-label or case-control designs. The problem of evidence is exacerbated by stringent inclusion and exclusion criteria used in controlled trials that often exclude the kind of patients that are most likely to be encountered in clinical practice, such as those with substance abuse and other co-morbidities.

In order to address this evidence gap, expert consensus guidelines have been developed which provide guidance for clinicians based on clinical experience, and interpretation of the literature by leaders in the field of bipolar disorder. The International Consensus Group on Bipolar I Depression Treatment Guidelines reviewed the evidence from clinical trials of numerous agents being studied for bipolar depression [21]. A primary finding of the group was that one of the most pressing impediments to good care is that the diagnosis of bipolar depression is often overlooked, and that there is a widespread

misconception that antidepressant monotherapy should be a first-line treatment for bipolar I depression. They concluded that lithium, lamotrigine, and the olanzapine/fluoxetine combination are appropriate first-line treatments.

Maintenance Treatment

Because bipolar disorder is a chronic illness characterized by cyclic recurrence of mood episodes and sub-syndromal symptoms during much of the interepisode periods, maintenance therapy in which periods of symptom free functioning are lengthened, represents a higher level of effective treatment that simple acute stabilization. With the recognition that symptoms of depression account for the preponderance of long-term morbidity [22], the focus has recently been placed primarily on the prevention of bipolar depression. This interest has been reinforced by two long term studies comparing the efficacy of lamotrigine to lithium and placebo in the maintenance of euthymic mood in bipolar disorder, which found a robust effect of lamotrigine in the prevention of bipolar depression [23-25].

McElroy and colleagues found that patients who received continuation therapy with lamotrigine after successful treatment of acute bipolar depression experienced sustained improvement, as well as fewer episodes of mania compared to the previous year. This supports the finding that lamotrigine, having greatest utility in bipolar depression, also has some smaller degree of efficacy in the prevention of mania [26].

The two FDA registrational studies for lamotrigine's indication for the treatment of bipolar I disorder utilized a partially enriched design. Patients were treated for acute mania or depression, gradually switched to lamotrigine monotherapy, and those who remained stable for at least a week on lamotrigine alone were randomized to continued lamotrigine, lithium monotherapy, or placebo. They were then followed for 18 months for recurrence of symptoms as assessed by a decision to intervene on the part of the blinded clinician responsible for the patient's care. Patients in the lithium and the lamotrigine treatment groups did not require any additional intervention for a period that

was substantially (and significantly) longer than placebo; lamotrigine was found to have a particularly robust effect in the prevention of depression. A combined analysis found modest, but significant efficacy in the prevention of mania. Notably, this very recent study was the largest that has been undertaken evaluating the efficacy of lithium in the maintenance phase of bipolar disorder. As expected, this study confirmed that lithium's efficacy in the prevention of mania that is greater than its efficacy in the prevention of depression [23, 24].

In addition to maintenance, lamotrigine has also been studied in acute bipolar depression. One randomized placebo controlled trial noted efficacy at 50 mg with a more robust effect at 200 mg [27].

Only one recently published controlled trial has examined the efficacy of divalproex in the prevention of depressive episodes. The duration of treatment was 52 weeks, and patients were allowed to receive adjunctive paroxetine or sertraline for breakthrough depression [28]. Six outcome measures were evaluated. Among the subgroup of patients who were given an antidepressant, fewer patients taking divalproex discontinued the study compared to placebo. Selecting out an enriched subgroup, the authors found that patients who responded to divalproex during the open label stabilization phase relapsed later on divalproex than lithium. This finding supports the theory that patients who have a good initial response to a medication are likely to continue to do well on it, and that patients who respond well to divalproex may represent a distinct population – separate from patients who do well on lithium.

Further exploration of the data found that patients previously hospitalized for a mood episode also relapsed later on divalproex compared to lithium. Because of the large number of outcome measures and extensive subgroup analysis, this study must be viewed as exploratory, and the results provisional.

Although the long-term efficacy of lithium maintenance therapy is well-established, the question of duration of treatment requires further attention. A physician, primarily

interested in long-term stabilization of mood, and minimization of morbidity associated with the illness, may be at odds with a patient who may view continued treatment with ambivalence. In particular, patients who have been stable for a number of years may request a trial of medication discontinuation. Abrupt discontinuation of lithium has been associated with acute relapse. [29], and a recent case-control study adds evidence to the observation that rapid withdrawal of lithium places patients at high risk for immediate decompensation [30]. Following abrupt lithium withdrawal, patients were found to have an increased rate of affective relapse, particularly into an episode of depression.

As opposed to rapid discontinuation of lithium, gradual discontinuation has been shown to markedly reduced early recurrences of mania or depression [31]. Equally important, however, are the longer-term effects on affective stability. A prospective study followed 32 patients for 9 years after undergoing a controlled lithium discontinuation protocol [32]. Each of the patients had experienced a good response to lithium maintenance for a minimum of 5 years. The total rate of recurrence following gradual taper and discontinuation was 7% in the first week, 32% in the first month, 62% in the first year, and 81% at the end of the 9 year follow-up period. Despite long-term stability on lithium maintenance, even controlled discontinuation is associated with a high relapse rate.

Rapid cycling bipolar disorder is more difficult to stabilize, and tends to lead to higher rates of treatment refractoriness. Some studies have found lithium to be less effective than anticonvulsants in the treatment of rapid cycling bipolar disorder [33], however a definitive determination remains to be made due to methodological issues with these studies. A meta-analysis was undertaken by Tondo and colleagues of studies involving the long-term treatment of rapid cycling with lithium, carbamazepine, lamotrigine, divalproex, and topiramate. Studies with a total of 1,856 patients met the inclusion criteria. Despite the large number of patients, and the resultant power to detect differences between treatment groups, no clear advantage for any treatment was found. All of the medications were less effective in rapid cycling (especially the depressive phase) compared to non-rapid cycling bipolar disorder [34].

Predicting Response to Treatment

Lithium, lamotrigine and divalproex have all demonstrated efficacy in the treatment of bipolar disorder, however, patients who respond well to one medication have often completely failed on others. It can be very difficult to predict in advance which medication will be most effective in a specific patient. Frequently, when faced with a choice of potentially effective treatment options, the initial trial is chosen based simply on side effect profile [35]. Identifying phenotypic characteristics predictive of a favorable response would be a preferable strategy. New data show that unequivocal responders to long-term monotherapies each have a very different clinical profile, including clinical presentation and course, comorbidity, and in particular, family history [36].

A comparison of lithium and lamotrigine involved 164 subjects from 21 families of bipolar probands [37]. The lithium responders were more likely to have an episodic clinical course, and less comorbidity. Lamotrigine responders were more likely to experience rapid cycling along with panic attacks and substance abuse comorbidity. The relatives of lithium responders had a significantly higher risk of bipolar disorder, while the relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major depression, and panic attacks.

A greater number of pretreatment episodes of abnormal mood has been proposed as a predictor of poor lithium response, however a study by Bratti and colleagues found little support for this relationship [38]. A review of available research on this topic found that 68% of studies failed to find any differences in lithium response related to number of pretreatment episodes.

Combination Therapy

Frequently, patients will not have an adequate response to a single mood stabilizer, or they will not be able to tolerate the full therapeutic doses required for effective monotherapy treatment. Furthermore, no single agent is effective in all patients at

controlling all phases of the illness. Combination therapy is often the best option. By targeting more than one cellular process putatively involved in the pathophysiology of bipolar disorder, the use of combined therapy can produce an additive, or even a synergistic effect. This type of strategy may also result in a therapeutic response at lower doses of each agent, potentially avoiding some of the dose-dependent adverse effects. Because lithium has more evidence of efficacy than any other agent, it is a good candidate for use in combination with other mood stabilizers. Furthermore, many of the adverse effects of lithium are dose-dependent, and there can be substantial benefit associated with attaining clinical response at lower serum levels. The combination of lithium with lamotrigine may be a particularly good strategy. Lithium has robust efficacy in the treatment and prevention of mania, while lamotrigine has an opposite and complimentary profile [39].

A review of the available literature by Zarate and colleagues identified data that demonstrated gains in efficacy over monotherapy when two mood stabilizers were used together [40]. Specifically the combination of a mood stabilizer plus an antipsychotic is most effective for acute mania. Somewhat counterintuitively, for depression, the use of an antidepressant with or without a concomitant mood stabilizer has not shown superiority to two mood stabilizers or a single mood stabilizer by itself. Large controlled trials with antidepressants are not available; however given the risks associated with antidepressant use in bipolar disorder, optimization of a single mood stabilizer, or augmentation with a second mood stabilizer, should be considered prior to antidepressant use.

Suicide Prevention

Because the underlying etiology of bipolar disorder is unknown, the focus of treatment remains optimization of functioning, and minimization of symptoms and adverse outcomes such as job loss, financial difficulties, legal problems, and relationship disruption. The most serious adverse outcome of bipolar disorder is suicide. Eight to ten

percent of the deaths of patients with bipolar disorder are due to suicide, however the type of treatment that they receive may influence this type of mortality.

A retrospective study of 20,638 health plan members found that patients treated with lithium had significantly fewer suicides and suicide attempts compared with patients treated with divalproex [41]. Although a sample of this size could not be randomized the major predictor of whether a patient was placed on lithium or divalproex was simply the year that treatment was initiated. After adjustment for age, sex, health plan, diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs, the risk of suicide death was 2.7 times higher during treatment with divalproex than during treatment with lithium. The mechanism by which lithium exerts its anti-suicide effects is not known, but it appears to be distinct, to some degree, from its mood stabilizing and antidepressant effects.

Adverse Effects

Much of the work done in the past year to increase our understanding of adverse effects has focused on the treatment of bipolar disorder in women of child-bearing potential. The association of polycystic ovarian syndrome (PCOS) with divalproex has long been a source of concern, but establishing a causal relationship has been difficult due to the higher incidence of PCOS among patients with epilepsy. A review of the literature funded by the manufacturer of divalproex notes that several theories have been put forward for the higher prevalence of PCOS among patients treated with divalproex, which has been hypothesized to trigger the disease directly, or via weight gain that triggers elevated testosterone and other reproductive abnormalities [42]. The author concludes, however, that the current evidence to link divalproex with PCOS is inadequate, and prospective longitudinal studies are needed to clarify this issue.

Providing preliminary support for an association between divalproex and PCOS, is a pilot, open-label study which included 38 women taking either divalproex or lithium, and evaluated them for menstrual abnormalities and biochemical evidence of both

hyperandrogenism and adverse metabolic parameters. Fifty percent of divalproex-treated females had menstrual abnormalities compared to 15 percent of those treated with lithium. Women receiving divalproex also had findings associated with metabolic syndrome.

The treatment of bipolar disorder is substantially complicated when the patient is pregnant. The use of effective medication carries some level of risk to the fetus, however this risk must be balanced against the risk of the disease itself in an untreated state. Pregnant women who are manic characteristically engage in impulsive, high-risk behaviors, and suicide is a serious risk most often associated with depressive episodes. Additionally, the fetal programming hypothesis theorizes that biological correlates of maternal mood states can lead to enhanced susceptibility of the child to the later development of psychiatric disorders. For example, Van den Bergh and Marcoen found that maternal anxiety during pregnancy predicted externalizing behaviors and anxiety at age 8 and 9 [43]. Importantly, the effect of anxiety affected the fetus more than any other factor, including smoking during pregnancy, low birth weight, or anxiety of the mother when the child is 8 or 9. Although this study involved mothers with anxiety rather than bipolar disorder, it suggests that the importance of effective treatment during pregnancy may extend beyond reducing the potential for dangerous behavior.

An expert panel review of the literature on mood stabilization during pregnancy noted that divalproex and carbamazepine are known teratogens [44]. Lithium also has teratogenic properties – it is specifically associated with Epstein's anomaly – however the panel concluded that the risk of developing this heart defect may have been overestimated in the past. Lamotrigine appears to be associated with a lower rate of malformations overall, and among some neurologists it has emerged as a first-line treatment for women with epilepsy during their reproductive years [45]. The panel emphasized that treatment can be managed most effectively if pregnancy is planned; however it is important to keep in mind that mania can be associated with hypersexuality, impulsively, and poor judgement. Therefore the possibility of an unplanned pregnancy must be taken into account.

A recent prospective study of 147 pregnancies that focused on the safety of lamotrigine confirmed that it may be relatively safe during pregnancy [45]. The risk of malformations in this small study was 2.0% in women treated with lamotrigine, similar to that reported in infants of women with epilepsy who received no treatment during pregnancy.

The most significant adverse effect associated with the use of lamotrigine is the risk of serious rash. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), which have mortality rates of less than 5 percent and 30 percent respectively [46], have been reported with lamotrigine use. In clinical trials of bipolar disorder and other mood disorders, the rate of serious rash was 0.08 percent in adult patients receiving lamotrigine as monotherapy, and 0.13% for those receiving lamotrigine as adjunctive therapy. The definition of serious rash used in these trials was somewhat broad, including any skin reaction associated with patient hospitalization and discontinuation of treatment with lamotrigine or any case reported as possible SJS or TEN [47]. This definition of serious rash may have led to an overestimation of the true risk. Indeed among the 2,642 patients from the various clinical trials sponsored by the company there was only one hospitalized for rash, and that patient had been rapidly titrated to 100 mg by the end of the second week [data from GSK].

An alternative source of epidemiological data on the risk of rash with lamotrigine comes from the German registry for serious cutaneous reactions, which is an academically-based organization that ascertains hospitalized cases of SJS and TEN in Germany. The registry is structured as an intensive reporting system, regularly contacting more than 1,500 departments in hospitals and intensive care facilities, and is estimated to have a 95% rate of ascertainment for SJS or TEN in Germany [48]. Cases are confirmed by a registry physician and reviewed by a dermatology expert committee. Based on data from the registry, the incidence of SJS/TEN among adults taking lamotrigine for any indication was 0.02 percent [49]. Since 1994, when the recommended rate of dose titration was changed, the rate has been approximately 0.01 percent.(one in 10,000).

Conclusions

As our knowledge of the mood stabilizers becomes more sophisticated, a better understanding of the strengths and weaknesses of each individual agent is emerging. Identifying phases of bipolar disorder most responsive to a particular agent, as well as developing clinical profiles that assist in predicting in advance which medication will be effective in a specific patient, moves clinical care away from trial and error toward more rational decision making. Currently, lithium appears to be the best option for long-term stabilization of all phases of the illness. Divalproex appears to be particularly effective in the rapid stabilization of acute mania, especially when an oral loading strategy is utilized. Lamotrigine is unique in its ability to manage the depressed phase of the illness. While a few existing studies of drug combinations do suggest possible synergisms, the literature on combined treatments markedly lags behind the dominant monotherapy literature. It is hoped that future studies of combinations will employ less that full doses of each drug in order to evaluate potential synergisms.

Looking forward, multiple trials are currently underway to evaluate the efficacy of the newer generation antipsychotics in the manic, depressed, and maintenance phases of bipolar disorder, and the options for treatment continue to expand. Nevertheless, despite decades of research into the illness, our understanding of bipolar disorder, and our ability to treat it effectively remains limited. Among psychiatric disorders the disability caused by bipolar disorder worldwide ranks behind only unipolar depression and alcohol abuse [50], and the current level of interest in this disease reflects a need for better treatment options. The mood stabilizing effects of divalproex and lamotrigine were discovered serendipitously after the medications had begun to be used for other indications. Although each one represents an important advance in the field, many patients continue to experience incomplete response, relapse, and significant adverse effects. Continuing research into the mechanism of action of mood stabilizers, and the biochemical basis of the disease has the potential to lead to more effective treatments that more directly target the underlying etiology.

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Chronic treatment with lithium has been shown to increase NAA concentrations, which may be a good marker for neuronal viability and/or functioning. Using H magnetic resonance spectroscopy the authors quantified NAA concentrations in patients treated with lithium, divalproex, and healthy controls.

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