Lithium Carbonate: Maintenance Studies and Consequences of Withdrawal

David L. Dunner, M.D.

The treatment of mood disorders with lithium carbonate has made a significant impact on the health of patients who have these disorders and on the nature of psychiatry itself. Perhaps the single, most important finding about the efficacy of lithium that has influenced American psychiatry is the fact that lithium, given over long periods of time, reduces the frequency and severity of subsequent affective episodes in manic depressive patients. This paper discusses the selection of patients for maintenance treatment, the dose of lithium, the maintenance treatment of patients who have breakthrough episodes, those with hypomanic breakthrough episodes, and rapid cycling. The use of lithium in unipolar depression and the elderly and the consequences of lithium discontinuation are also reviewed.

(J Clin Psychiatry 1998;59[suppl 6]:48–55)

Lithium treatment has made an important and significant impact on American psychiatry. In the early 1950s, in the United States, lithium was banished from the American pharmacoarena because of its toxicity when used as a salt substitute. Mania was rarely diagnosed in the United States, and patients with psychoses were invariably diagnosed as having schizophrenia. In contrast, lithium usage in Europe became widespread, and the diagnosis of bipolar disorder was much better accepted in Europe than in the United States.

A patient with an acute psychotic episode was likely to be called *manic* in Europe and *schizophrenic* in the United States.[1] Perhaps the most important single finding about the efficacy of lithium that influenced American psychiatry was the fact that lithium salts, given over long periods of time, reduced the frequency and severity of subsequent affective episodes in manic depressive patients.[2] Many treatments are available for successful outcome of acute mania or acute onset psychosis. However, lithium provided a maintenance effect; indeed, it was the maintenance effect that resulted in the acceptance of lithium as a treatment in the United States. That acceptance created the need for a diagnostic system to encourage the diagnosis of mania and discourage the diagnosis of schizophrenia in patients who had acute onset psychosis, and that led to what has been called the "third revolution in psychiatry" and a change in psychiatric practice away from only psychotherapy toward a psychopharmacologically oriented clinical practice.

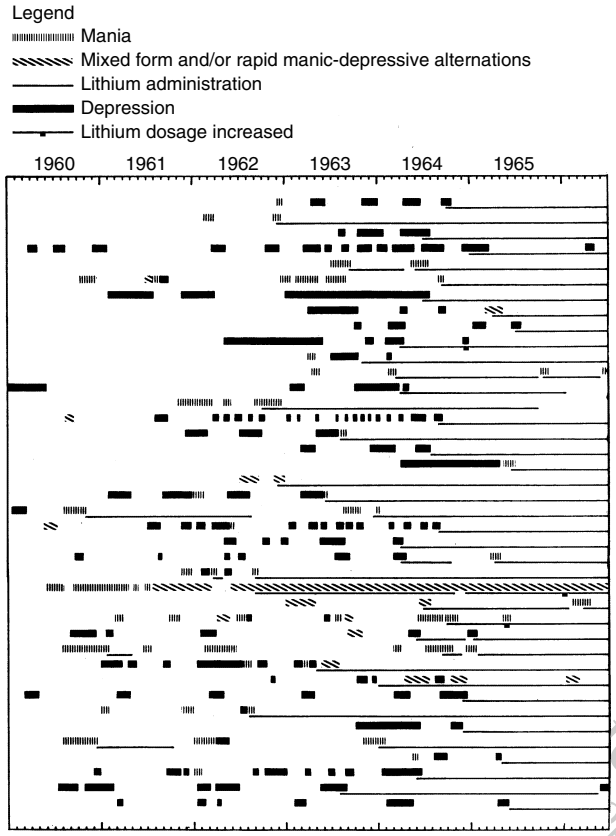
The early evidence of the maintenance effects of lithium was noted in studies by Baastrup and Schou (Figure 1) and reported in a landmark paper[2] which suggested that lithium reduced future episodes of bipolar disorder in most patients who had what we now term *bipolar I* and *bipolar II disorder*. These findings were not accepted by all clinical research groups. Methodological critiques suggested that patients who had dense and frequent episodes were likely to have fewer episodes in the next interval, and, therefore, the demonstration of decreased episode frequency after lithium treatment was merely a reflection of the natural history of bipolar disorder.[3] In order to assess the maintenance effect of lithium, double-blind placebo-controlled studies were undertaken in patients who had recurrent histories of bipolar disorder and were treated with lithium or placebo in what later became lithium clinics. Methodologically, lithium was administered in either a discontinuation design or a randomized double-blind design. The monitoring of such patients was by trained raters, not necessarily trained professionals. All studies showed a higher rate of manic episodes while patients were taking placebo than lithium. Because of these studies, lithium became an important drug in the early 1970s. The importance of lithium maintenance treatment also necessitated and resulted in the change in the nomenclature of mood disorders in the DSM in 1980. Furthermore, the treatment outcome studies necessitated the development

From the Department of Psychiatry & Behavioral Sciences, Center for Anxiety and Depression, University of Washington, Seattle.

Presented at the symposium "Lithium in the Treatment of Manic-Depressive Illness: An Update" held May 30–31, 1997, Sea Island, Ga., and supported by an educational grant from Solvay Pharmaceuticals, Inc.

Reprint requests to: David L. Dunner, M.D., Department of Psychiatry & Behavioral Sciences, University of Washington, 4225 Roosevelt Way Northeast, Suite 306, Seattle, WA 98105.

Figure 1. Course of Illness in Affectively Disordered Patients Prior to and After Lithium Treatment*



*From reference 2, with permission. A clear reduction in frequency of attacks during lithium administration is demonstrated.

Table 1. Double-Blind Placebo-Controlled Studies of Lithium Maintenance in Bipolar Disorders*

		Lithium		Placebo	
Study	Design	N	Patients Relapsing (%)	N	Patients Relapsing (%)
Baastrup et al[5] 1970	Discontinuation	28	0	22	55
Melia[6] 1970	Discontinuation	7	57	8	78
Coppen et al[7,8] 1971, 1973	Prospective randomization	17	18	21	95
Cundall et al[9] 1972	Crossover	12	33	12	83
Stallone et al[10] 1973	Prospective randomization	25	44	27	93
Prien et al[11] 1973	Prospective randomization	101	43	104	80
Prien et al[12] 1973	Prospective randomization	18	28	13	77
Fieve et al[13] 1976[a]	Prospective randomization	24	57	29	73
Dunner et al[14] 1976[b]	Prospective randomization	16	…	24	…
Quitkin et al[15] 1978[b]	Prospective randomization	3	0	3	67
Total		251	34	263	81

*Adapted from reference 16.
[a]Includes 28 bipolar II patients; relapse data are for bipolar II.
[b]Bipolar II patients.

of "lithium clinics," i.e., outpatient facilities with a focus on diagnosis and psychopharmacologic treatment of mood disorders.[4] These specialized facilities led to the emphasis on psychopharmacology in clinical training programs. The large number of patients attending these clinics also provided an opportunity for other research studies, including family and linkage studies of affective disorder patients.

MAINTENANCE STUDIES

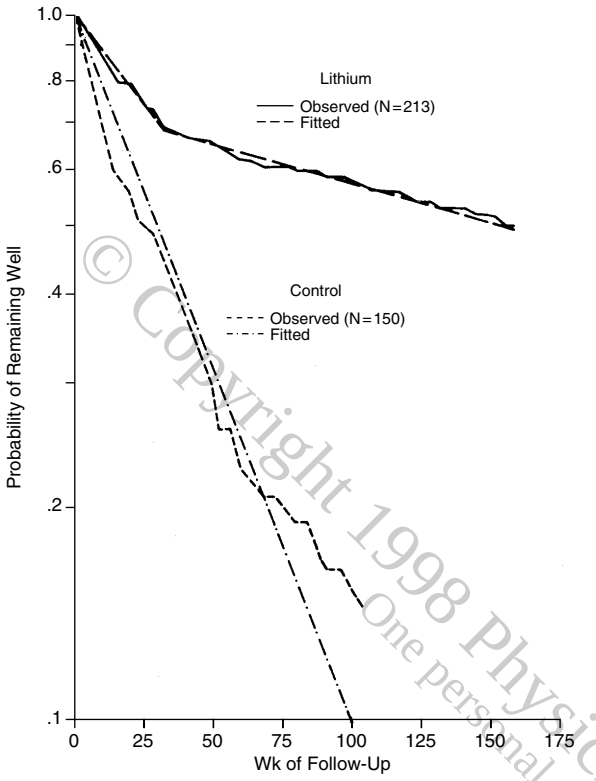
The efficacy of lithium salts in the prevention of manic episodes was supported by a number of studies[5–15] (Table 1) and these studies are summarized by Goodwin and Jamison.[16] A total of 251 bipolar patients treated with lithium and 263 bipolar patients treated with placebo revealed a relapse rate of 34% for lithium and 81% for placebo. Studies of bipolar I patients clearly showed a reduction in frequency and severity of mania. The effect of lithium against depression was more difficult to assess since bipolar I patients on placebo tended to show manic relapses that were so severe that they dropped out of treatment. The demonstration of an effect of lithium against recurrent depression was easier to show in bipolar II patients who, over time, demonstrated adequate maintenance effects against recurrence of depression.[14,15,17]

In assessing the other side of the coin, or those who failed lithium treatment, it was determined that a group of patients with high episode frequency prior to beginning lithium treatment constituted the largest group of lithium failures.[18] Through these studies, rapid cycling was identified.

Selection of Patients for Maintenance Treatment

How long should the patient with a first manic episode be treated? This question is perhaps best answered by reviewing data in regard to the course of bipolar disorder. It is evident that bipolar disorder is usually recurrent, and the mean episode frequency is about four episodes in 10 years.[19,20] However, there is often considerable variability regarding episode frequency. I recommend that patients be treated through the postmanic depressive phase, through an ensuing 6-month period of euthymia, and through the interval when they are most likely to experience recurrence of manic symptoms—namely, at 6 months after the initial episode and at the anniversary date of the initial episode. The best available data indicate that there is a higher relapse rate in the first 6 months after attaining euthymia than at other time intervals and that the relapse rate with lithium treatment is lower but insidious after the initial 6 months of treatment[21] (Figure 2). Once patients have become euthymic through the anniversary date of their initial episode, I would suggest tapering lithium and educating the patient about the possi-

Figure 2. Course of Remaining Well After Beginning Lithium Treatment*



*From reference 21, with permission. The control group could have had placebo treatment after lithium or could have been studied prior to lithium treatment. The lithium group is comprised of patients during their initial exposure to lithium. There is a biphasic distribution to the lithium treatment phase with a high relapse rate in the first 6 months.

bility of recurrence and the need to enter treatment quickly should signs of another cycle emerge.

Some investigators suggest that long-term maintenance therapy be given to patients who have had only one manic episode. Tohen et al.[22] reported on first-episode manic patients who were studied for up to 4 years. A total of 21 patients were taking lithium at discharge from the index episode; by 4 years, 11 patients were taking no medication. Outcome measures at follow-up, including evidence of relapse, current symptoms, and social adjustment were not found to correlate with treatment. If patients have a very acute onset, are very psychotic, or have disruptive mania, certainly consideration should be given to providing maintenance therapy after the first episode.

Some patients who have an interim cyclothymic disorder report that they feel calmer taking lithium, in which case it may be useful to continue lithium on an indefinite basis even if the patient has only had one episode. However, if patients have had two episodes, the benefits of maintenance treatment in reducing the morbidity of future episodes outweigh the risks of side effects from long-term treatment.

Dose of Lithium

The dose of lithium for maintenance treatment should provide a blood level of at least 0.5 mEq/L. Blood levels higher than 0.8 mEq/L in maintenance treatment may result in an increased incidence of renal function abnormalities and other side effects. Blood levels below 0.5 mEq/L may be less protective against recurrent episodes.[23,24]

Compliance

Compliance with lithium maintenance treatment can be a problem, and I recommend starting with low doses and increasing the dosage in a gradual manner so that side effects are minimized. Lithium can be given in a single bedtime dose. This single daily dosing technique may reduce the renal effects of lithium and enhance compliance. If patients have side effects with this regimen, switching to a sustained-release form of lithium may also reduce side effects and enhance compliance. Most patients experience few side effects during maintenance therapy. Side effects are most frequently encountered during acute treatment and are often associated with increasing the dose too quickly. Troublesome side effects during maintenance lithium therapy include tremor, polyuria, weight gain, complaints of memory loss, and complaints of "not being high."

Educational efforts directed toward the patient and family are important. Several publications are written for patients and families. The National Depressive and Manic Depressive Association and other support groups may also be helpful.

MAINTENANCE THERAPY

Treatment of Breakthrough Episodes

Maintenance treatment with lithium generally does not result in complete termination of episodes. Patients may and often do have mild breakthrough episodes, usually hypomanic episodes rather than full-blown mania and depressive episodes that occur in spite of maintenance treatment. The initial manic episode is often treated with a number of medications, including an antipsychotic, lithium, and a benzodiazepine. As the patient recovers from this episode, depression, sluggishness, fatigue, and hypersomnia may be experienced. It is possible that contributing factors to the fatigue may be excessive use of sedating antipsychotics, benzodiazepines, or lithium-induced hypothyroidism. Thus, these factors should be taken into account.

One consideration in treating of the depressed phase of a bipolar patient is the prevention of cycling to mania and rapid cycling. In the treatment of depressed bipolar patients, some studies[12,25–27] suggest avoiding tricyclic antidepressants, particularly because of the greater likelihood of their induction of rapid cycling compared with nontricyclic antidepressants. Any of the other classes of anti-

depressants seem to be satisfactory for treatment of the depressed bipolar patient, although less sedating medications might be preferable to more sedating medications.[28]

Because the suicide attempt rate in bipolar disorder is considerable, the depressed phase of bipolar disorder should be taken very seriously. Ameliorating factors such as regular exercise and bright light therapy may be of use for the more anergic hypersomnic depression. Psychotherapy may also be of importance for the treatment of bipolar depression, although its efficacy has not been determined through controlled studies.[29] In general, the clinician should review other medical causes of depression, continue the maintenance medication, add a less sedating antidepressant medication, and observe for the possibility of an induction into mania or switch into a hypomanic episode.

Treatment of Hypomanic Breakthrough Episodes

Treatment of hypomanic breakthroughs can be complicated and may involve the use of increased doses of mood-stabilizing medication and the possible addition of sedatives. More frequent visits with the patient and consultation with family members regarding the gravity of a hypomanic breakthrough may be necessary. The clinician must also make sure that the breakthrough episode does not result in full-blown mania and recognize that the hypomanic episode is likely to be followed by a depressive episode. Some patients cycle at particular times of the year, and anticipation of their cycle may be of assistance in treatment planning.

Frequency of Lithium Monitoring and Medical Tests

Guidelines for the initiation of lithium treatment suggest a physical examination, electrocardiogram for those over 40 years, and laboratory analysis including a complete blood count and thyroid and renal function tests. Lithium levels should be monitored frequently until the dose results in a satisfactory blood level. Once the patient is stabilized, renal and thyroid function tests and measurement of lithium level should be repeated every 2 to 3 months for the first 6 months of treatment and at least every 6 to 12 months thereafter.[30–32] Patients who are less stable should have more frequent visits with the clinician and blood level monitoring. If anticonvulsant mood stabilizers are used, blood drug levels, liver function tests, white blood cell counts, and platelet counts should also be monitored.

Rapid Cycling

Rapid-cycling bipolar disorder refers to an episode frequency of four or more manic, depressive, or mixed episodes within a 1-year period. The condition of rapid cycling was identified by Dunner and Fieve[18] in reviewing patients who showed a poor response to lithium maintenance therapy. A higher proportion of rapid-cycling bipolar patients, compared with non-rapid-cycling bipolar patients, are women.[33] Rapid cycling is a complication of bipolar rather than unipolar mood disorder. Frequently recurrent unipolar depressive episodes are rarely seen, and, when they occur, suggest the possibility of hypomanic episodes associated with the major depressive episodes, i.e., diagnosis of bipolar II disorder.

Some but not all studies suggest that rapid cycling may be associated with an underlying thyroid abnormality.[27,34–37] Interestingly, family studies of rapid-cycling patients show no difference in family loading for bipolar disorder as compared with non-rapid-cycling patients, nor does rapid cycling cluster in families of rapid cyclers.[38] The condition may be present at the onset of the illness, may occur during the course of illness, and may remit with return of the patient to regular cycling. Thus, the course of rapid cycling can be irregular. Some studies suggest that rapid cycling occurs as frequently in bipolar I as in bipolar II patients, and about 15% of patients in a large research lithium clinic had the rapid-cycling form of bipolar disorder.[39]

Although rapid-cycling patients may be less responsive to lithium maintenance therapy than non-rapid-cycling patients, I prefer to begin with lithium maintenance treatment in the uncomplicated noncomorbid patient. Roughly 50% of rapid cyclers will respond to lithium maintenance alone. If there is no response to lithium maintenance therapy, I suggest the addition of an anticonvulsant mood stabilizer such as carbamazepine or valproic acid after approximately a 6-month trial of lithium alone. The anticonvulsant plus lithium therapy should proceed for another 6 months, and, if there is no response at that time, patients should be switched to an alternate anticonvulsant to be administered with lithium. I also try to avoid the use of antidepressant pharmacotherapy in rapid-cycling bipolar patients. The notion of antidepressants inducing mania, and mania perpetuating the cycle ("highs cause lows"), suggests that patients might show more improvement if antidepressants are avoided and only antimanic mood stabilizers are used.

In the past, my colleagues and I advocated the use of antipsychotic medications such as thioridazine for the treatment of rapid-cycling patients. However, some of these patients, so treated, developed tardive dyskinesia, and I no longer recommend the use of the older neuroleptics. The efficacy of newer neuroleptics in the treatment of rapid cycling is not well supported by research studies. However, clozapine has been reported to be of some use in intractable patients.[40] Other medical treatments, such as thyroid hormone and electroconvulsive therapy, may be of assistance in refractory patients.[41–44]

I also advise rapid-cycling patients to keep a daily mood calendar. If there is a regular and predictable switch time from depression to hypomania, then increasing the mood-stabilizing medication just prior to the switch may prevent the hypomanic episode from evolving and lead to

greater stabilization of illness. Additionally, I recommend that patients have a regular structure to their day, getting up at the same time, going to bed at the same time, and eating meals at the same time. This is an attempt to regularize biological rhythms, which have been hypothesized to underlie the rapid-cycling condition. Since antidepressant pharmacotherapy is not being applied, the use of psychotherapy to target the depression may be beneficial.

Lithium Maintenance in Cyclothymic Disorder and Ultra Rapid Cycling

Cyclothymic disorder is a long-term (greater than 2 years) mood disorder characterized by frequent and brief mood alternations. Most patients who have uncomplicated cyclothymic disorder respond well to lithium maintenance therapy.[45–47]

In my experience, patients who have a cyclothymic-like condition of relatively short duration should be investigated for the possibility of head trauma, neuroendocrine dysfunction, multiple sclerosis, and substance abuse, since they may have a secondary bipolar disorder. Secondary bipolar disorder can be viewed as bipolar mood swings that occur after head trauma, seizure disorder, substance abuse, and endocrine dysfunction, or with central nervous system tumors, infections, and multiple sclerosis.[48] Such patients often present with very brief (within a day or an hour) bipolar mood swings termed *ultra rapid cycling*. A thorough medical workup is indicated before treatment to determine the cause of the ultra rapid-cycling condition. It would appear that there has been a change in the presentation of mania throughout the years to include a greater percentage of patients who have mixed bipolar disorder or ultra rapid cycling as part of their clinical picture possibly as a consequence of substance abuse.[49–52] Such patients have been described as less responsive to lithium than the classic patient who was seen in lithium centers 20 to 30 years ago and it has been suggested that patients with histories of mixed bipolar disorder or ultra rapid cycling may be preferable candidates for mood stabilization with anticonvulsant mood stabilizers rather than with lithium carbonate.

Maintenance Response and Sequence of Episodes

Kukopulos and colleagues[53] separated bipolar patients by course of illness. Mania-depression-interval (MDI) patients had mania followed by depression followed by euthymia. Depression-mania-interval (DMI) patients had depression, then mania, then euthymia. A third group had a continuous circular (CC) course with euthymia. In assessing the response to lithium maintenance treatment, the MDI group had a significantly better outcome than the DMI group. Sixty-one percent of the MDI group, compared with only 33% of the DMI group, showed a beneficial outcome with lithium therapy. This finding has been replicated by several groups,[54–56] but was not found in the data analysis performed by my colleagues and me.[57] Goodwin and Jamison[16] note that prior tricyclic antidepressant treatment in the DMI group may have a negative impact on lithium outcome.

Lithium in Unipolar Depression

The use of lithium as maintenance therapy for unipolar recurrent depression is supported by research studies but remains controversial. Goodwin and Jamison[16] reviewed the available data that showed a 65% relapse rate with placebo and a 22% relapse rate with lithium in unipolar recurrent depression. A major criticism of the studies of lithium maintenance in unipolar recurrent depression relates to the relative short duration of these trials (about 1 year) and heterogeneity of the unipolar samples studied. Prien et al.[58] reported better maintenance effects for imipramine than lithium in their study. The finding may be related to their unipolar sample being more severely ill than the samples in other studies.[16]

The use of lithium as an augmenting agent in treatment-resistant unipolar depression has also been supported by research studies.[59,60] Responders to lithium augmentation may be more likely to have bipolar tendencies (positive family history of mania or cyclic histories) than nonresponders.

Use of Lithium in the Elderly

Use of lithium in the elderly should be approached cautiously since renal function is often compromised, and higher blood levels per unit dose are likely to occur in elderly versus younger patients. Therefore, elderly patients require a lower daily dose of lithium, and multiple daily dosing is preferred over single dosing. The dangers of lithium toxicity developing are higher in the elderly than in younger patients. In addition, the elderly are more likely to be taking other medications that may have interactions with lithium.

Family History and Lithium Response

Some studies support the notion that patients who have a negative family history of mania show a poorer response to lithium maintenance treatment than patients with a positive family history.[61–64] This notion has been perplexing, and not all data sets support this hypothesis. For example, rapid cyclers—patients who have notoriously poor lithium outcomes compared with other bipolar patients—show the same degree of mania in relatives as non-rapid-cycling patients.[38] Furthermore, a patient can become a nonresponder by having a breakthrough episode, which can occur at any time. Also, a patient's family history can become positive if a member of the family develops mania. These changes in status in regard to lithium response and family history would work toward negating the notion of correlating lithium response with family history.

DISCONTINUATION

Three aspects to lithium discontinuation are recurrence of illness, development of lithium discontinuation refractoriness, and increasing mortality. Several studies that demonstrated maintenance effects for lithium had a discontinuation design[5,6,9]; that is, the subjects who were stabilized on lithium treatment were randomly assigned on a double-blind basis to continue taking lithium or switch to placebo treatment. These and other studies indicate a relapse rate that is much higher during placebo treatment than during continuation of lithium.[65] Indeed, the study by Fleiss et al.[21] found that patients who discontinued lithium after stabilization had the same episode frequency as patients who had never taken lithium or patients who were initially treated with placebo rather than lithium. Similar results were noted by Schou.[66] Thus, lithium discontinuation results in a return to the patient's underlying episode frequency, whereas continuation of lithium treatment results in continued reduction in frequency and severity of bipolar disorder. Several studies also suggest that rapid discontinuation may result in an earlier relapse than tapering.[66–68]

The mortality of bipolar patients is higher than that of the general population, and the increase in mortality rates is largely accounted for by suicide.[69] Goodwin and Jamison[16] summarize several studies that reported suicide ranges from 4.7% to 50% of all deaths. Their calculations of the ratio of observed versus expected mortality in bipolar disorder was 2.28. Lithium treatment has been shown to decrease the mortality rate.[70–72] Thus, lithium discontinuation, which results in an increased episode frequency, is also likely to be associated with increased mortality.

The notion of lithium discontinuation refractoriness is supported by studies noting that patients who repetitively stopped lithium ultimately became less responsive to treatment.[73–76] However, not all studies agree.[77,78] An earlier study from my colleagues and me[57] suggested that patients who continued on lithium therapy showed greater benefit after initial relapse and that second episodes were delayed further. Thus, there are advantages to continuing lithium long term in patients and not in interrupting treatment. However, it should be pointed out that many patients who start lithium stop it on their own, often because they wish to take control of their own illness. Such patients often suffer a relapse and restart treatment with a resulting successful stabilization of mood. It is possible that patients described as having lithium discontinuation refractoriness have other factors associated with failure to show lithium response. These factors may include greater degrees of psychosis, secondary disorders, or the possibility of having bipolar disorder that may in itself be less lithium responsive than that seen in other patients. Further research in this area would seem to be warranted.

SUMMARY

The treatment of mood disorders with lithium carbonate has made a significant impact on the health of patients who have these disorders and on the nature of psychiatry itself. Further research into bipolar disorder has been somewhat complicated because of the beneficial effect of lithium that has resulted in patients who have uncomplicated disorders being treated in primary care settings. Thus, the lithium clinic of the 1970s and 1980s has largely disappeared from academic centers. Those bipolar patients still being treated at academic centers generally have complicated forms of bipolar disorder. The uncomplicated populations that one would like to access for modern studies of bipolar disorder are no longer available. In spite of this, lithium remains an important first-line therapy for modulation of mood in patients who have bipolar disorder and perhaps for other mood disorders as well.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), imipramine (Tofranil and others), lithium sustained-release (Lithobid, Eskalith CR), thioridazine (Mellaril and others), valproic acid (Depakene and others).

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