Lithium Combinations in Acute and Maintenance Treatment of Unipolar and Bipolar Depression

Jan A. Fawcett, M.D.

Bipolar illness and unipolar depression are both affective disorders associated with high lifetime morbidity and premature mortality due to suicide. Numerous double-blind, placebo-controlled trials have shown that lithium augmentation therapy is effective in treating acute episodes of bipolar depression, refractory major depression, and delusional depression as well as in reducing recurrences of these illnesses. Lithium is the only agent approved by the U.S. Food and Drug Administration for maintenance treatment of bipolar disorder. Further research is needed to specifically address whether the antidepressant effect of adding lithium is greater in bipolar disorder or in unipolar depressions. This article will summarize available evidence and clinical considerations regarding the use of lithium augmentation in acute and maintenance treatment of unipolar and bipolar depressions.

(J Clin Psychiatry 2003;64[suppl 5]:32–37)

Bipolar disorder and unipolar depression are recurrent illnesses that have devastating effects on patients' lives. Both disorders are associated with an increased mortality rate,[1] and the World Health Organization ranks unipolar major depression as fourth in importance in global disability and mortality—far exceeding the ranking of any other psychiatric illness.[2] The bipolar depressive phase of bipolar disorder, or the episode of major depression occurring in patients who meet the criteria for bipolar I or bipolar II, can be very disabling as well. Symptoms range from mild physical and mental slowing with little cognitive or perceptive distortion to extreme depressive symptoms, hallucinations, delusions, and clouding of consciousness.[3]

While patients and physicians should decide together whether long-term treatment for bipolar disorder is warranted, maintenance treatment should almost always be prescribed for patients who have had at least 2 mood episodes. The American Psychiatric Association[4] recently published its revised guidelines (Table 1) to aid physicians in determining which therapies are most effective for patients' long-term treatment. These guidelines recommend that continuation and maintenance treatment be considered for patients with bipolar II disorder and initiated after patients remit from a manic episode. Lithium and valproate are recommended with the highest level of clinical confidence, and the case for lithium is supported by substantial evidence from controlled studies.

Clinical studies and anecdotal evidence indicate that lithium can be efficacious when used alone or in combination with antidepressants in both reducing relapses of unipolar major depression[5] and in treating acute bipolar depressive episodes.[6] This article will review research regarding the efficacy of lithium augmentation therapy in the treatment of patients suffering from bipolar disorder (with an emphasis on depression) as well as recurrent and delusional major depression.

LITHIUM IN BIPOLAR DEPRESSION

Lithium is currently considered to be the most appropriate treatment for acute bipolar depression. According to the Expert Consensus Guidelines[7] for the treatment of bipolar disorder, which surveyed 61 experts and asked them to rate mood stabilizer regimens, lithium monotherapy was the only first-line recommendation for achieving antidepressant effects. In a review of available studies on the acute treatment of nonpsychotic bipolar depression, Zornberg and Pope[6] reported that in 8 of 9 controlled comparisons, which comprised a total of 145 patients, lithium was more effective than placebo. The response rate to lithium was approximately 79%, with a clearly pronounced response in 36% of the patients.

From the Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque.

This article is derived from the roundtable "Achieving Success in the Management of Bipolar Disorder: Is Lithium Sufficient?" which was held May 9–10, 2002, in Washington, D.C., and supported by an unrestricted educational grant from GlaxoSmithKline.

Corresponding author and reprints: Jan A. Fawcett, M.D., Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM 87131 (e-mail: jfawcett@salud.unm.edu).

Table 1. American Psychiatric Association Practice Guidelines for Maintenance Treatment for Bipolar Disorder[a]

Maintenance Treatment Guideline	Level of Clinical Confidence
When warranted	
After a manic episode	I
After a depressive episode	II
Medication monotherapy	
Lithium	I
Valproate	I
Lamotrigine	II[b]
Carbamazepine	II[b]
Olanzapine	II[b]
Medication augmentation	
Additional maintenance medication	II
Atypical antipsychotic	III
Antidepressant	III
Psychotherapy	II
Support group	I
Electroconvulsive therapy	II[c]

[a]Data from the American Psychiatric Association.[4]
[b]Use as monotherapy if this medication was effective for acute treatment of the last episode (I).
[c]Consider its use during maintenance treatment if it was effective for acute treatment of the last episode (II).
Symbols: I = substantial, II = moderate, III = varies with individual circumstances.

Table 2. Benefits of Lithium Maintenance Treatment in Patients With Bipolar Disorder by Decade[a]

		Percentage of Patients	
Decade	N	Improved ≥ 50%[b]	Episode-Free[c]
1970s	90	66.7	25.6
1980s	148	65.5	31.8
1990s	122	64.8	38.5
Total	360	65.6	32.5

[a]Reprinted with permission from Baldessarini and Tondo.[8]
[b]$r = -0.23$; $p = .23$.
[c]$r = 0.03$; $p = .86$.

Baldessarini and Tondo[8] conducted a 2-part study to determine whether lithium treatment continues to be as effective as it has been in former years. According to their research, no suggested mood-stabilizing treatment has as much evidence as does lithium that confirms its ability to reduce mortality risk in patients with bipolar illness or substantiates its long-term efficacy in treating both type I and type II bipolar disorders. In the first part of the study, they conducted a meta-analysis using 11 controlled and 13 open long-term lithium treatment trials for mixed major affective and bipolar disorders that demonstrated recurrence rates with and without lithium treatment. The long-term findings revealed no loss in the effectiveness of long-term lithium maintenance treatment; but in fact, in recent years there has been some decrease in recurrence rates of bipolar disorder (Table 2). The authors noted that lithium is unmatched in research support for long-term clinical effectiveness against morbidity and mortality associated with mania or depression in bipolar I and II disorders.

In the second part of their study, Baldessarini and Tondo[8] attempted to evaluate whether lithium was still an effective treatment modality against the morbidity and mortality that is associated with bipolar disorders. They analyzed the clinical effect of lithium on 360 patients with DSM-IV bipolar I (N = 220) and bipolar II (N = 140) disorders. All of the patients in the sample had begun lithium maintenance treatment (essentially as monotherapy) in the years following 1970 and had continued on the treatment for a minimum of 12 months. The authors found that lithium was as effective as it had been in studies prior to the 1970s for recurrence rates and patient improvement of 50% or more during maintenance therapy in a stable clinic setting. Baldessarini and Tondo concluded that long-term lithium treatment for bipolar disorder in compliant patients, though imperfect, remains effective.

LITHIUM AUGMENTATION IN REFRACTORY MAJOR DEPRESSION

Although antidepressant treatment is effective in many patients with major depression, up to one third of all patients with depression may not respond to an adequate trial of antidepressive treatment.[9] Currently, lithium may be the most effective adjunct in refractory depression with older antidepressants and for serotonin selective reuptake inhibitors (SSRIs). When administered concomitantly with antidepressants, lithium has proven to be effective in treating unipolar depression and preventing recurrent depression in both older and younger patients. Elderly patients, however, may need lower doses, because older patients have lower rates of renal clearance of lithium. It is believed that the combination of lithium and antidepressants is efficacious because lithium augments serotonin metabolism. Numerous placebo-controlled, double-blind trials have revealed that lithium is effective at reducing relapses in unipolar major depression when given as maintenance therapy, and it can help maintain remission achieved during electroconvulsive therapy (ECT).[5] Lithium and ECT are rarely administered together, however, due to the potential for harmful interaction.

Acute Treatment

A number of trials have established that lithium augmentation is more effective in managing refractory unipolar depression than acute antidepressant monotherapy. De Montigny et al.[10] presented one of the first reports on the addition of lithium to augment absent or partial response to tricyclic antidepressants (TCAs). In the first of 3 trials conducted by the researchers, the effect of lithium addition was studied in 34 TCA-resistant patients with unipolar depression. A psychiatric examination was conducted before TCA treatment was initiated and immediately before and 48 hours after lithium was added to all of the patients' drug regimens. Eight patients underwent a second phase in which the lithium was discontinued, another TCA drug was substituted for the first, and another

lithium trial was undertaken. Therefore, a total of 42 observations were made. Within 48 hours, in 30 of the 42 observations, the lithium brought about a greater than 50% improvement of the depression based on Hamilton Rating Scale for Depression (HAM-D) scores.

In the second of the 3 trials,[10] the effects of lithium addition were compared in 5 patients who failed to respond after 3 weeks of amitriptyline treatment and 5 patients who showed no improvement after receiving 3 weeks of placebo. Only 48 hours after beginning the lithium augmentation, all 5 patients receiving the amitriptyline showed a greater than 50% improvement, whereas only 1 patient in the placebo group showed a marked response. The third trial[10] studied the effect of lithium withdrawal in 9 TCA-resistant patients who had shown a noticeable improvement 48 hours after lithium augmentation. In this study, 5 of the patients relapsed 5 days after discontinuation. The researchers concluded that the antidepressant effect of lithium augmentation in TCA-resistant patients might be mediated by enhancing serotonin neurotransmission.

Heninger et al.[11] assessed whether lithium augmentation would potentiate a response in 15 treatment-refractory patients who had been receiving antidepressant treatment with desipramine, amitriptyline, or mianserin. In the placebo-controlled, double-blind study, 15 treatment-refractory patients who had received at least 21 days of antidepressant drug therapy continued to receive the same daily dose and were given either lithium (N = 8) or placebo (N = 7) augmentation. In comparison with placebo, lithium produced a small but significant ($p < .02$) improvement during the first 2 days of treatment. By days 7 through 12, lithium produced a significant ($p < .02$) and clinically meaningful improvement. On day 13 of the trial, the group receiving the placebo received lithium instead of placebo, and their rate of improvement matched that of the 8 patients who had received lithium initially. Heninger and colleagues concluded that lithium does augment the antidepressant effect when added to the long-term antidepressant treatment of nonresponding patients.

A study by Price et al.[12] reported trials of lithium augmentation with 84 treatment-refractory patients with major depression who were refractory to primary antidepressant treatment. Upon admission to the study, all psychotropic drugs were discontinued. Patients who had not recently received an adequate trial with an available antidepressant were given desipramine, nortriptyline, amitriptyline, or trazodone. Another group of patients who had not responded to prior adequate treatment was given adinazolam, bupropion, fluvoxamine, or mianserin. All of the patients were then treated with 2 to 3 weeks of placebo, followed by 4 to 6 weeks of active primary antidepressant alone. On determination of refractoriness in each patient, 900 mg/day of lithium was added to the ongoing antidepressant (it was subsequently increased up to 1500 mg/day to maintain serum levels of 0.5 to 1.3 mEq/L) and continued for at least 10 days. After 24 days, 26 patients (31%) had a marked response, 21 (25%) showed a partial response, 33 (39%) had no change, and 4 (5%) had an adverse response. In sum, 56% of patients had a significant positive response and 44% were nonresponders. Study results indicated that response to lithium augmentation may be variable, and a trial of at least 3 weeks is necessary to assess full benefit.

Recent studies have focused on augmenting SSRI treatment with lithium. In an attempt to establish whether lithium augmentation is more effective than SSRI monotherapy, Katona et al.[13] added either lithium or placebo on a double-blind basis to the drug regimen of 62 patients who had major depressive illness and had failed to respond to a controlled trial of lofepramine or fluoxetine. The trial lasted 6 weeks and response was defined as a HAM-D score of < 10. While rapid response was not consistently observed, response was seen in 15 (52%) of 29 patients taking lithium and only 8 (25%) of 32 patients taking the antidepressant alone ($p = .05$). The results appeared to confirm that lithium augmentation is a useful strategy in the treatment of resistant major depression; however, partial response was also frequently observed during continued SSRI treatment alone.

In a recent literature review, Zullino and Baumann[14] determined that for depressed patients not responding to SSRIs, lithium augmentation may be an effective and well-tolerated treatment for acute depression. They found an overall response rate of at least 50% following a 1- to 2-week, or sometimes 6-week, treatment period. However, they warned that the available studies varied in methodology, and thus, results are insufficient to confirm a rapid improvement after lithium introduction. They also added that special care should be taken when treating elderly patients due to a higher risk of adverse effects.

Bauer and Dopfmer[15] conducted a meta-analysis to investigate lithium augmentation of antidepressants that included only double-blind studies that had utilized acceptable diagnostic criteria for depression and response criteria. Out of 11 placebo-controlled, double-blind trials, 9 were included in the meta-analysis. Initially, the authors found that 3 aggregated studies comprising 110 patients with a minimum treatment duration of 2 weeks revealed a pooled odds ratio of 3.31 during lithium augmentation (of at least 800 mg/day) when compared with placebo. The absolute improvement in response rate was 27%. Inclusion of the 6 other studies (for a total of 234 patients) that met the same criteria but in which subjects were treated with lithium augmentation for less than 2 weeks or with a lower lithium dose resulted in even higher estimates.

Rouillon and Gorwood[16] reviewed 9 placebo-controlled studies, 22 case reports, 5 open comparisons, and 6 other studies (for a total of 969 patients) in which antidepressants were added to or co-administered with lithium to treat refractory depression. They combined all of these

studies and found that at doses of 600 to 900 mg/day, lithium augmentation was efficacious. They recommended starting with low doses (600 to 900 mg/day) and, if necessary, subsequently increasing the dose until the usual therapeutic range of blood level range (0.8 to 1.2 mEq/L) is reached. Because some patients require more time to respond, the authors suggested that lithium be prescribed for at least 3 to 6 weeks, and they concluded that all refractory depressed patients can potentially benefit from lithium augmentation.

Maintenance Treatment to Prevent Recurrence

There is a strong likelihood that an individual who has suffered one episode of depression will experience a second. According to most consensus statements,[17,18] during the episode of depression that has responded to treatment, patients may need to begin continuation treatment to prevent a relapse and should continue this treatment for at least 6 months after clinical recovery. This second phase of treatment is particularly necessary if patients have had 2 or 3 previous attacks because the chances of a further relapse are so great that long-term maintenance treatment is justified. Lithium can be used in continuation therapy after recovery from a depressive illness, functioning as a prophylactic agent in recurrent depressive illnesses.

Two studies provide some evidence that a beneficial effect of lithium augmentation in treating refractory depression not only occurs acutely but can be maintained—an important factor in any affective disorder that tends to be recurrent. In a follow-up study of patients with depression and documented refractoriness to antidepressants who had been successfully treated with lithium augmentation, Nierenberg et al.[19] followed 66 patients in a retrospective, naturalistic design for a mean ± SD 29.0 ± 15.3 months. Of the 66 patients, 19 (29%) had a poor outcome, defined as hospitalization, suicide attempt, death by suicide, or death as a complication of antidepressant treatment; 15 (23%) had a fair outcome, defined as the return of depressive symptoms that persisted for at least 2 weeks and met criteria for either minor depression or moderate depression; and 32 (48%) had a good outcome, defined as a course in which criteria for a poor or fair outcome were not met. An acute marked positive response to lithium appeared to predict a good subsequent treatment course, while acute partial responders and nonresponders were less likely to have a benign outcome despite subsequent treatment. The authors suggested that an acute marked response to lithium augmentation might be sustained regardless of the duration of time in which the lithium is taken, but they warned that this postulate should be regarded as speculative.

In an effort to determine the long-term outcome and optimal management of patients with treatment-refractory depression treated with lithium augmentation, Shergill et al.[20] conducted a 4- to 8-year naturalistic follow-up of patients treated with lithium augmentation in 2 controlled studies. The researchers were able to obtain outcome data on 53 of the 76 patients originally included in their study and reported a good outcome in 38 (72%) of the patients. A positive outcome appeared to be associated with a less endogenous nature of depression and an absence of prior hospitalizations. However, the authors noted that the incomplete follow-up of the total original sample and lack of objective medication and symptom data limited the conclusions for the intervening period.

The prophylactic efficacy of lithium compared with placebo was examined in a double-blind study[21] in 28 patients with unipolar recurrent depression who were followed up from 3 months to 4 years. The patients were diagnosed with unipolar recurrent depression by 2 diagnosticians, and each had a history of at least 2 depressive episodes during the previous 5 years as well as an absence of symptoms of hypomania lasting longer than 2 days. Blood drug levels in patients receiving lithium were measured periodically in order to achieve a lithium ion concentration between 0.7 and 1.2 mEq/L. Indexes of prophylactic efficacy revealed a statistically significant ($p < .05$) decrease in episode frequency and depth of depressive episodes as well as increased clinic attendance rates in the lithium group compared with the placebo group.

In a double-blind placebo-controlled study, Sackeim et al.[22] studied the use of antidepressants alone compared with antidepressants plus lithium augmentation to prevent recurrent depression in patients who had undergone ECT. Of 290 patients with major depression who completed an open ECT treatment phase, 159 met remitter criteria and 84 were eligible and willing to participate in the continuation study. Those 84 patients were then randomly assigned to receive 24 weeks of continuation treatment with placebo (N = 29), nortriptyline (N = 27), or nortriptyline plus lithium (N = 28). The outcome was measured by the rate of relapse of major depressive episodes among the 3 continuation groups. Within 6 months, 24 patients (84%) of the placebo group relapsed; 16 patients (60%) that were maintained on nortriptyline alone relapsed; and of those maintained on both nortriptyline and lithium, 11 patients (39%) relapsed. Relapse with nortriptyline and lithium occurred within 5 weeks of ECT termination in all but 1 case, while relapse occurred throughout treatment with placebo or nortriptyline alone. Medication-resistant, female patients and those who had more severe depressive symptoms following ECT treatment had more rapid relapse. This study involved a highly treatment-refractory sample of patients, yet lithium augmentation appeared to be effective in the majority. According to this study, lithium may be a viable treatment option for managing recurrent depression. Nierenberg et al.[23] recently reported that lithium augmentation of nortriptyline compared with placebo did not reveal a significant improvement in patients with depression resistant to multiple antidepressant medications. They

raised a question whether lithium is useful in patients refractory to multiple treatments.

LITHIUM IN DELUSIONAL DEPRESSION

Lithium has been shown to be effective in the management of treatment-refractory delusional depression, in some cases to the exclusion of ECT, which otherwise would have been the treatment of choice. Patients with delusional depression often refuse to acknowledge that they are ill and understandably may refuse to accept ECT. Since treatment with lithium is usually more acceptable—in these cases—lithium treatment may improve patient compliance.

To test the efficacy of lithium in treating delusional depression, Pai et al.[24] studied 5 patients who were suffering from delusional depression and were resistant to tricyclic antidepressant treatment. Of the 5 patients, 4 had previously suffered at least 1 depressive episode; of those 4 patients, 1 had recovered without treatment, and 3 had improved after ECT treatment. All 5 patients refused ECT for their current episode of depression. The patients were all treated with lithium, with blood levels maintained between 0.5 and 1.0 mmol/L. Two of the patients continued concomitant antidepressant treatment. All of the patients demonstrated a noticeable improvement after receiving the lithium treatment for 2 weeks, and in follow-up interviews throughout the next year, researchers determined that all 5 of the patients had been successfully treated with the lithium.

Another study[25] measured the response to lithium augmentation in 6 inpatients with psychotic depression who were refractory to a neuroleptic and tricyclic antidepressant combination treatment. While none of the 6 patients met DSM-III criteria for schizophrenia, they all had mood congruent psychotic features—5 were delusional and the sixth was paranoid and almost mute—and all had failed combined neuroleptic-tricyclic treatment. Following lithium augmentation of the antipsychotic-antidepressant combination, 3 of the 6 patients had a definite response, 2 of the patients manifested a gradual improvement over a 3-week period significant enough to enable discharge from the hospital, and 1 patient was unresponsive. Of the 3 definite responders, 1 improved dramatically within 48 hours, 1 improved within 7 days, and 1 within 2 weeks. While the authors determined that the success of lithium in this group of delusionally depressed patients is of particular importance due to the severity of the depressive illness, they also noted that further similar research should be placebo-controlled.

A group of 88 female patients with recurrent depression or repeated manic-depressive episodes were selected to participate in a study conducted by Baastrup and Schou[26] to determine the prophylactic action of lithium. All of the patients were observed for 6 months while lithium was administered for periods varying from 1 to 5 years. Calculations were made based on relapse frequency (average number of episode starts per year) and the psychosis rate (average number of months per year the patient spent in a psychotic state). The results were compared for periods with and without lithium treatment. The researchers determined that without lithium treatment, the manic-depressive patients spent an average of 13 weeks per year in a psychotic state, while with lithium treatment the average time spent in a psychotic state per year was less than 2 weeks. Concerning recurrent depression, the researchers determined that independent of the illness duration, lithium appeared to prevent relapses into depression in patients with recurrent depression as effectively as it prevented relapse of manic-depressive psychosis in patients with manic-depressive disorder.

CONCLUSION

It appears that lithium augmentation therapy and monotherapy is effective in treating acute episodes of bipolar depression, recurrent major depression, and delusional depression as well as in reducing recurrences of these illnesses. The sum of the previous studies indicates that the effect of lithium in depression is quite strong, and educators, psychiatrists, and physicians should inform colleagues, students, and patients that lithium does have antidepressant potential in the acute and continuation treatment phases of various depressive disorders.

Drug names: amitriptyline (Elavil), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Tegretol, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), mianserin (Tolvin and Bolvidon), nortriptyline (Aventyl and others), olanzapine (Zyprexa), trazodone (Desyrel).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, lithium and fluvoxamine are not approved by the U.S. Food and Drug Administration for the treatment of depression; carbamazepine and lamotrigine are not approved for the treatment of bipolar disorder; lithium is not approved for suicidality; and mianserin is not approved for use in the United States.

REFERENCES

1. Angst J, Baastrup P, Grof P, et al. The course of monopolar depression and bipolar psychoses. Psychiatr Neurol Neurochir 1973;76:489–500
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436–1442
3. Goodwin FK, Jamison KR. Manic-Depressive Illness. New York, NY: Oxford University Press; 1990
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002;159: 1–50
5. Coppen AC. Lithium in unipolar depression and the prevention of suicide. J Clin Psychiatry 2000;61(suppl 9):52–56
6. Zornberg GL, Pope HG. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408
7. Compton MT, Nemeroff CB. The treatment of bipolar depression. J Clin Psychiatry 2000;61(suppl 9):57–67
8. Baldessarini RJ, Tondo L. Does lithium treatment still work? evidence of stable responses over three decades. Arch Gen Psychiatry 2000;57:

187–190
9. Klein DF, Davis JM. Diagnosis and Drug Treatment of Psychiatric Disorder. Baltimore, Md: Williams and Wilkins; 1969
10. de Montigny C, Cournoyer G, Morissette R, et al. Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression: correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. Arch Gen Psychiatry 1983;40:1327–1334
11. Heninger GR, Charney DS, Sternberg DE. Lithium carbonate augmentation of antidepressant treatment: an effective prescription for treatment-refractory depression. Arch Gen Psychiatry 1983;40:1335–1342
12. Price H, Charney DS, Heninger G. Variability of response to lithium augmentation in refractory depression. Am J Psychiatry 1986;143:1387–1392
13. Katona CL, Abou-Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 1995; 166:80–86
14. Zullino D, Baumann P. Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. Pharmacopsychiatry 2001;34:119–127
15. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. J Clin Psychopharmacol 1999;19:427–434
16. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):40–41
17. Bohacek N, Bunney WE, Coppen A, et al. Pharmacotherapy of depressive disorders: a WHO consensus statement. J Affect Disord 1989;17:197–198
18. Montgomery SA, Racagni G, Coppen A, et al. Impact of neuropharmacology in the 1990s: strategies for the therapy of depressive illness. Task force of the Collegium Internationale Neuro-Psychopharmacologicum (CINP). Eur Neuropsychopharmacol 1993;3:153–156
19. Nierenberg AA, Price LH, Charney DS, et al. After lithium augmentation: a retrospective follow-up of patients with antidepressant-refractory depression. J Affect Disord 1990;18:167–175
20. Shergill SS, Robertson MM, Stein G. Outcome in refractory depression. J Affect Disord 1999;54:287–294
21. Fieve RR, Dunner DL, Kumbarachi T, et al. Lithium carbonate in affective disorders, 4: a double-blind study of prophylaxis in unipolar recurrent depression. Arch Gen Psychiatry 1975;32:1541–1544
22. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001;285:1299–1307
23. Nierenberg AA, Papakostas GI, Petersen T, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol 2003;23:92–95
24. Pai M, White AC, Deane AG. Lithium augmentation in the treatment of delusional depression. Br J Psychiatry 1986;148:736–738
25. Price LH, Conwell Y, Nelson JC. Lithium augmentation of combined neuroleptic-tricyclic treatment in delusional depression. Am J Psychiatry 1983;140:318–322
26. Baastrup PC, Schou M. Lithium as a prophylactic agent. Arch Gen Psychiatry 1967;16:162–172