Mood-Stabilizing Drugs in Depression

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Mood-stabilizing drugs including lithium, anticonvulsants, and antipsychotics have established effects in the management of bipolar disorder, especially in mania. However, these drugs also have been shown to be effective in depressed patients. For example, lithium is well established as an effective augmenting strategy with tricyclic antidepressants in refractory depression. This article will review a variety of effects of mood-stabilizing drugs in bipolar and unipolar depressed patients, which will include acute treatment, prevention of relapse and recurrence, and the management of refractory patients. The effects of antipsychotics (especially atypicals) and new research directions also will be reviewed.
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The effectiveness of mood-stabilizing drugs in the acute and maintenance treatment of bipolar disorder, especially mania, is well established.[1] However, what is less well validated is the efficacy of mood-stabilizing drugs for the management of major depression (either unipolar or bipolar). In this regard, there is scant but significant literature on the effectiveness of mood-stabilizing drugs in the treatment of patients with depression (Table 1). This article will review the existing literature on the effects of mood stabilizers in depression and the potential for new agents in the management of depressive disorders.

PREVENTION OF RELAPSE AND RECURRENCE

Mood-stabilizing drugs are used commonly for the prevention of depressive relapse and recurrence in bipolar patients. However, literature exists on their effectiveness in unipolar disorder as well. For example, Peselow et al.[2] studied the prophylactic effect of lithium in unipolar, bipolar II, and cyclothymic patients. In this study, the investigators retrospectively evaluated the charts of patients with these diagnoses who were treated with lithium and determined the probability of their remaining well (i.e., free of significant depressive symptoms) for periods of up to 36 months after initiating lithium treatment. The use of other drug interventions was not controlled. Two analyses of relapse were performed: one in which dropouts were considered relapsers (yielding a higher relapse figure) and a second in which they were not. Over an average of 2 years, 42% to 55% of patients with bipolar II disorder, 31% to 42% of those with unipolar depression, and 26% to 36% of those with cyclothymia remained depression-free. This relatively weak effect of lithium in preventing depressive relapse was somewhat inconsistent with previous and subsequent controlled clinical trials.[3–5]

Kane and colleagues[5] performed a prospective placebo-controlled study of the efficacy of lithium in preventing depressive relapse in recurrent unipolar (N = 27) and bipolar II (N = 22) patients. Subjects were randomly assigned to 1 of 4 treatment groups: lithium plus imipramine, lithium plus placebo, placebo plus imipramine, and placebo plus placebo. In both the placebo plus placebo and the placebo plus imipramine groups, depressive relapse was high (50%–100%). In fact, the imipramine alone samples exhibited the highest rates of relapse overall (100% of unipolar and 67% of bipolar II). In contrast, both lithium conditions showed low relapse rates. Lithium alone had relapse rates of 29% for unipolar and 25% for bipolar II patients, while lithium plus imipramine had relapse in 13% of unipolar and 17% of bipolar II patients. These results suggest that lithium, either as monotherapy or in combination with imipramine, substantially reduced relapse in both groups. However, the very small sample sizes within treatment conditions precluded any definite conclusions regarding efficacy.

How does lithium really compare with antidepressants in the prevention of depressive relapse? Janicak et al.[6] reviewed the controlled clinical trials of lithium and antidepressants in relapse prevention. In 8 studies of 287 patients summarized by these authors, lithium was effective in preventing relapse in 59% of subjects against 25% of placebo patients, a difference of 34%. By comparison, in 18 studies of 2225 subjects, antidepressants were effective in preventing relapse in 77% of depressives against 50% of placebo patients, a difference of 27%. Although antidepressants

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Table 1. The Potential Uses of Mood Stabilizers in Depressed Patients

Prevention of relapse/recurrence
Acute treatment
Refractory depression
Monotherapy
Augmentation

were effective in a larger proportion of depressed patients than lithium (77% vs. 59%), the drug-placebo differences were approximately the same. These summarized results support an effect of lithium in the prevention of relapse.

However, probably the most revealing study of lithium prophylaxis of depression is an earlier report by Prien and colleagues[7] from the National Institute of Mental Health collaborative study data. In this study, 117 bipolar patients and 150 unipolar patients were assigned to treatment with lithium alone, imipramine alone, or a combination of the 2. A subset of the unipolar patients were randomized to placebo treatment. For the bipolar patients, lithium and a combination of lithium and imipramine were equally effective in the prevention of manic episodes and were superior to both imipramine and placebo. Lithium, lithium plus imipramine, and imipramine alone were equally effective and superior to placebo in the prevention of depression. For unipolar depressives, however, imipramine and the lithium plus imipramine combination were effective and superior to lithium alone, which was not significantly different from placebo. The data then were analyzed by dividing the unipolar depressives into moderately and severely depressed subgroups. In the moderately depressed sample, lithium (64% successful maintenance) was more effective than the lithium plus imipramine (56%) and imipramine alone (57%) treatments. All groups were more successful than placebo (35%). However, in the more severely depressed subjects, imipramine (48%) and the imipramine plus lithium combination (42%) were more successful than lithium alone (12%) or placebo (6%) in preventing relapse. These data indicate that lithium is an effective maintenance treatment in the prevention of depressive relapse in bipolar patients and in moderately but not severely depressed unipolar patients.

In comparison with the relatively larger body of literature on the effectiveness of lithium in preventing depressive relapse, other mood-stabilizing drugs have been less studied. In an open prospective report of carbamazepine prophylaxis in depression, 15 depressed patients were treated for an average of 49.5 months.[8] The authors reported that 11 (73%) experienced substantial benefit. However, a careful literature review did not yield any other prospective assessment of the effects of anticonvulsants or other mood stabilizers in depression. Clearly, the prevention of depressive relapse in both bipolar and unipolar depressive groups is an area that is ripe for clinical investigation with anticonvulsant mood-stabilizing agents.

ACUTE TREATMENT

Lithium

There are 8 adequate studies of lithium in the acute treatment of bipolar depression, all using a prospective placebo-controlled crossover design.[9–16] All of these studies found lithium superior to placebo in acute treatment, yielding an average response rate of 79%.[17] However, when compared with antidepressant treatment, lithium has fared less well. For example, Fieve and colleagues[9] randomly assigned 29 bipolar I patients to lithium, imipramine, or placebo. Although lithium was superior to placebo treatment, it was less effective than imipramine, resulting in an average decrease in depression ratings of 32% against 58% for the imipramine group.[9] This single study indicates that lithium may not be an appropriate acute monotherapy treatment for bipolar depression and is consistent with the common clinical practice of combining antidepressants with mood stabilizers. Remarkably, after over 30 years of controlled clinical investigations, this important question has not been adequately addressed in a large-scale, placebo-controlled clinical trial.

Carbamazepine

There have been a number of acute trials of carbamazepine in depression.[18] Most have been uncontrolled open trials of small numbers of subjects. Post et al.[19] did conduct a prospective study of the blind introduction of carbamazepine after a lengthy ineffective placebo lead-in in bipolar and unipolar depressives. Ten (42%) of 24 bipolars and only 2 (18%) of 11 unipolars demonstrated marked response. These results suggest an overall relatively weak response rate to carbamazepine in contrast with antidepressants and also that bipolar depressives may be more responsive than unipolars to carbamazepine. However, this sample was described as relatively resistant to prior treatment. Therefore, the results cannot be generalized to a nonrefractory sample.

Valproate

Like carbamazepine, there has been very little study of valproate in the acute treatment of depression, in contrast with the excellent literature on its effectiveness in mania.[20] Early open studies have suggested some benefit in acute management of bipolar depressives.[21] However, in a review of the effectiveness of valproate in bipolar and schizoaffective patients, McElroy and Keck suggest a relatively weak antidepressant effect.[22]

There is a single prospective open trial of valproate monotherapy in 33 patients with unipolar major depression.[23] By week 4 of treatment, 15 (54%) of 28 completers exhibited significant improvement (defined as a 50% reduction in Hamilton Rating Scale for Depression scores or a total score of ≤ 9), and at week 8, 19 (86%) of 22 completers were improved. In the intent-to-treat analysis,

66% were defined as responders, a rate that could be equivalent to other antidepressant drugs. However, a controlled investigation has not been published.

REFRACTORY DEPRESSION

There is extensive literature on lithium augmentation of tricyclic antidepressants (TCAs) in refractory depression that has been reviewed extensively elsewhere.[24–27] Suffice it to say that lithium augmentation of TCAs is the best validated treatment for refractory depressed patients.[26] The evidence for the effectiveness of lithium augmentation of other antidepressants, including selective serotonin reuptake inhibitors (SSRIs), is more limited.[27] Delgado et al.[28] treated a mixed group of 18 patients with depression (16 unipolars, 2 bipolars) who had failed an initial trial of open-label fluvoxamine treatment. Fifty percent of subjects who had failed to respond to fluvoxamine responded to a combination of fluvoxamine plus lithium treatment. Neither bipolar patient responded, indicating that 9 (56%) of 16 patients with unipolar major depression responded to the combination. Dinan[29] conducted an open trial of augmentation of sertraline with lithium. Seven (63%) of 11 refractory depressed patients showed a positive early effect.

However, the largest trial of lithium augmentation of an SSRI is the study of Baumann et al.[30] Twenty-four nonresponders were identified after a prospective trial of citalopram. Citalopram was then combined in a randomized blinded fashion with lithium or placebo for only 1 week. Subsequently, all subjects were treated with the combined treatment regimen. During the initial double-blind week, the citalopram plus lithium combination resulted in a positive response in 6 (60%) of 10 subjects, while the placebo group resulted in a positive response in 2 (14%) of 14. These preliminary reports suggest that lithium augmentation may be effective with SSRIs, but further study is needed.

The acute trial of carbamazepine by Post et al.,[19] discussed earlier, was conducted in a sample of depressives considered to be relatively resistant to standard pharmacotherapies. In this study, 42% of refractory bipolar depressives, but only 18% of unipolars, were considered to be marked responders. These data suggest but do not confirm a beneficial effect of carbamazepine in refractory bipolar patients. Small case series, but no controlled clinical trials, also indicate a possible benefit from carbamazepine augmentation of antidepressants, particularly TCAs.[31,32]

ANTIPSYCHOTICS

Typical antipsychotics have an established benefit in major depression with psychotic features and tend to speed response to treatment when used in combination with antidepressants as compared with antidepressant therapy alone. However, there is older literature on the effectiveness of these drugs as single-therapy agents in depression.

Table 2. Research Directions of Mood Stabilizers in Major Depression[a]

Lithium: augmentation of SSRIs
Anticonvulsants and atypical antipsychotics (unipolar and bipolar)
Acute antidepressant effects
Augmentation of antidepressants in refractory depression
Prevention of depressive relapse
Mood stabilizers: effects on highly recurrent unipolar depression

[a]Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

Robertson and Trimble[33] reviewed 34 double-blind trials of antipsychotics as antidepressants. These studies support a modest benefit in depressed patients, especially in symptoms of psychosis and anxiety. However, the use of typical antipsychotics as maintenance treatment of patients with mood disorders is largely precluded because of the risk of tardive dyskinesia.

A promising avenue for the treatment of depression may be the atypical antipsychotics. Several lines of evidence suggest a potential for value of these drugs in depressed patients. A series of reports have indicated benefit from clozapine or risperidone in mixed bipolar, schizoaffective manic or depressed, or psychotically depressed patients,[34–39] although a recent review[40] suggested that the effects of clozapine may be greater in mania than depression. In contrast to this conclusion, Keck et al.[39] evaluated response in a mixed group of 144 state mental hospital patients treated with risperidone. Factors associated with a moderate-to-marked response to risperidone included a diagnosis of bipolar disorder or schizoaffective disorder, depressive subtype. However, an alternative indication that atypicals may be beneficial in depression is the fact that risperidone in moderate-to-high doses has been reported in a series of cases to induce mania.[41–44] With the recognition that atypical antipsychotics appear to induce tardive dyskinesia at rates that are far lower than typical antipsychotics, atypicals may emerge as viable alternatives in the treatment of patients with depressive disorders.

RESEARCH DIRECTIONS

As alluded to earlier in this article, there are a variety of research areas that deserve attention (Table 2). For example, although the effectiveness of lithium augmentation of TCAs in refractory depression is well established, TCAs no longer represent the mainstay of antidepressant drug therapy. Lithium augmentation of SSRIs has some support, as reviewed earlier. However, a large-scale placebo-controlled trial of lithium augmentation of an SSRI is sorely needed.

In addition, anticonvulsant agents like carbamazepine or valproate have gained widespread use in the management of bipolar disorder. However, the existing clinical trials have focused primarily on the acute and prophylactic management of mania. Studies of the use of these anticonvulsants for acute depression monotherapy, for augmentation of an-

tidepressants in refractory depression, and for the prevention of depressive relapse in both unipolar and bipolar populations is needed. In particular, the study of the effectiveness of anticonvulsant mood-stabilizing agents in highly recurrent unipolar major depression could produce a major advance.

Similar studies on the potency of atypical antipsychotics in the acute and prophylactic management of depression are needed. As noted earlier, the existing data are suggestive of a potential for benefit of these drugs, especially for bipolar patients and possibly for refractory unipolar major depressive patients. These agents represent a promising new avenue in the treatment of depression.

Drug names: carbamazepine (Tegretol and others), citalopram (Celexa), clozapine (Clozaril), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), risperidone (Risperdal), sertraline (Zoloft).

REFERENCES

1. Post RM, Ketter TA, Pazzaglia PJ, et al. Rational polypharmacy in the bipolar affective disorders. Epilepsy Res Suppl 1996;11:153–180
2. Peselow ED, Dunner DL, Fieve RR, et al. Lithium prophylaxis of depression in unipolar, bipolar II, and cyclothymic patients. Am J Psychiatry 1982;139:747–752
3. Davis JM. Overview, maintenance therapy in psychiatry, II: affective disorders. Am J Psychiatry 1976;133:1–13
4. Schou M. Lithium as a prophylactic agent in unipolar illness. Arch Gen Psychiatry 1979;36:847–849
5. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness. Arch Gen Psychiatry 1982;39:1065–1069
6. Janicak PG, Davis JM, Preskorn SH, et al. Principles and Practice of Psychopharmacotherapy. Baltimore, Md: Williams & Wilkins; 1993
7. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH collaborative study group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984; 41:1096–1104
8. Stuppaeck CH, Barnas C, Schwitzer J, et al. Carbamazepine in the prophylaxis of major depression: a 5-year follow-up. J Clin Psychiatry 1994; 55:146–150
9. Fieve RR, Platman SR, Plutchik RR. The use of lithium in affective disorders, I: acute endogenous depression. Am J Psychiatry 1968;125:79–83
10. Goodwin FK, Murphy DL, Bunney WE. Lithium carbonate treatment in depression and mania. Arch Gen Psychiatry 1969;21:486–496
11. Greenspan K, Schildkraut JJ, Gordon EK, et al. Catecholamine metabolism in affective disorders, III. J Psychiatr Res 1970;7:171–182
12. Goodwin FK, Murphy DL, Dunner DL, et al. Lithium response in unipolar versus bipolar depression. Am J Psychiatry 1972;129:76–79
13. Noyes R, Dempsey GM, Blum A, et al. Lithium treatment of depression. Compr Psychiatry 1974;15:187–193
14. Baron M, Gershon ES, Rudy V, et al. Lithium carbonate response in depression. Arch Gen Psychiatry 1975;32:1107–1111
15. Mendels J. Lithium in the treatment of depression. Am J Psychiatry 1976; 133:373–378
16. Donnelly EF, Goodwin FK, Waldman IN, et al. Prediction of antidepressant responses to lithium. Am J Psychiatry 1978;135:552–556
17. Zornberg GL, Pope HG. Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397–408
18. Kahn D. Carbamazepine and other antiepileptic drugs in refractory depression. In: Roose SP, Glassman AH, eds. Treatment Strategies for Refractory Depression. Washington, DC: American Psychiatric Press; 1990:77–107
19. Post RM, Uhde TW, Roy-Byrne PP, et al. Antidepressant effects of carbamazepine. Am J Psychiatry 1986;143:29–34
20. Bowden CL, Brugger AM, Swan AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918–924
21. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in 55 patients with rapid-cycling bipolar disorder. Am J Psychiatry 1990;147: 431–434
22. McElroy SL, Keck PE. Treatment guidelines for valproate in bipolar and schizoaffective disorders. Can J Psychiatry 1993;38(suppl 3):S6–S66
23. Davis LL, Kabel D, Patel D, et al. Valproate as an antidepressant in major depressive disorder. Psychopharmacol Bull 1996;32:647–652
24. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081–1097
25. Phillips KA, Nierenberg AA. The assessment and treatment of refractory depression. J Clin Psychiatry 1994;55(2, suppl):20–26
26. Austin MP, Souza FG, Goodwin GM. Lithium augmentation in antidepressant-resistant patients: a quantitative analysis. Br J Psychiatry 1991;159:510–514
27. Shelton RC. Treatment options for refractory depression. J Clin Psychiatry 1999;60(suppl 4):57–61
28. Delgado PL, Price LH, Charney DS, et al. Efficacy of fluvoxamine in treatment-refractory depression. J Affect Disord 1988;15:55–60
29. Dinan TG. Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. Acta Psychiatr Scand 1993;88:300–301
30. Baumann P, Nil R, Souche A, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307–314
31. Cullen M, Mitchell P, Brodaty H, et al. Carbamazepine for treatment-resistant melancholia. J Clin Psychiatry 1991;52:472–476
32. Post RM, Uhde TW. Carbamazepine as a treatment of refractory depressive illness and rapidly cycling manic-depressive illness. In: Zohar J, Belmaker RH, eds. Treating Resistant Depression. New York, NY: PMA Publishing; 1987:l75–235
33. Robertson MM, Trimble MR. Major tranquillizers used as antidepressants: a review. J Affect Disord 1982;4:173–193
34. McElroy SL, Dessain EC, Pope HG Jr, et al. Clozapine in the treatment of psychotic mood disorders, schizoaffective disorder, and schizophrenia. J Clin Psychiatry 1991;52:411–414
35. Suppes T, McElroy SL, Gilbert J, et al. Clozapine in the treatment of dysphoric mania. Biol Psychiatry 1992;32:270–280
36. Dassa D, Kaladjian A, Azorin JM, et al. Clozapine in the treatment of psychotic refractory depression. Br J Psychiatry 1993;163:822–824
37. Kimmel SE, Calabrese IR, Woyshville MJ, et al. Clozapine in treatment-refractory mood disorders. J Clin Psychiatry 1994;55(9, suppl B):91–93
38. Jacobsen FM. Risperidone in the treatment of affective illness and obsessive-compulsive disorder. J Clin Psychiatry 1995;56:423–429
39. Keck PE, Wilson DR, Strakowski SM, et al. Clinical predictors of acute risperidone response in schizophrenia, schizoaffective disorder, and psychotic mood disorders. J Clin Psychiatry 1995;56:466–470
40. Zarate CA Jr, Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. J Clin Psychiatry 1995;56:411–417
41. Sajatovic M, Di Giovanni SK, Bastani B, et al. Risperidone therapy in treatment refractory acute bipolar and schizoaffective mania. Psychopharmacol Bull 1996;32(1):55–61
42. Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder [letter]. Lancet 1994;344:554–555
43. Schaffer CB, Schaffer LC. The use of risperidone in the treatment of bipolar disorder [letter]. J Clin Psychiatry 1996;57:136
44. Koek RJ, Kessler CC. Probable induction of mania by risperidone [letter]. J Clin Psychiatry 1996;57:174

DISCLOSURE OF OFF-LABEL USAGE

The following off-label uses for drugs were described in this article: lithium prophylaxis and treatment of unipolar depression, lithium augmentation of antidepressants, carbamazepine as a mood stabilizer, carbamazepine prophylaxis and treatment of depression, carbamazepine augmentation of antidepressants, lithium for the acute treatment of depression, valproate for the acute treatment of depression, and antipsychotics for depression.