GUIDELINE WATCH: PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH BIPOLAR DISORDER, 2ND EDITION

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APA's *Practice Guideline for the Treatment of Patients With Bipolar Disorder,* 2nd Edition, was published in April 2002 (1). Since that time, a number of controlled treatment studies on aspects of bipolar disorder have been completed and published or are in press, including studies of second-generation (atypical) antipsychotics as monotherapy and as adjunctive treatment (with more traditional mood stabilizers) for the acute treatment of mania, studies of antiepileptic agents for the acute treatment of mania, trials for three medications for the acute treatment of bipolar depression, four monotherapy and one combination therapy relapse prevention studies, and studies of psychosocial interventions for maintenance. The evidence from these studies supports a substantially expanded set of options for clinicians who treat patients with bipolar disorder. This guideline watch briefly reviews the most important of the studies. The majority of the studies were industry supported.

PSYCHIATRIC MANAGEMENT

Recently completed epidemiological studies have estimated the lifetime prevalence of bipolar I and II disorders in the general population to be 3.7%–3.9% (2, 3). The prevalence in samples of patients presenting with depression is much higher, ranging from 21% (4) to 26% (5) in primary care settings and from 28% (6) to 49% (7) in psychiatric clinics. Use of a screening instrument, such as the Mood Disorder Questionnaire, can substantially improve recognition of patients with bipolar disorder, particularly among depressed patients (8).

The American Psychiatric Association (APA) practice guidelines are developed by expert work groups using an explicit methodology that includes rigorous review of available evidence, broad peer review of iterative drafts, and formal approval by the APA Assembly and Board of Trustees. APA practice guidelines are intended to assist psychiatrists in clinical decision making. They are not intended to be a standard of care. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available. Guideline watches summarize significant developments in practice since publication of an APA practice guideline. Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent opinion of the authors and approval of the Executive Committee but not policy of the APA. Suggested citation: Hirschfeld RMA: *Guideline Watch: Practice Guideline for the Treatment of Patients With Bipolar Disorder.* Arlington, VA: American Psychiatric Association. Available online at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

Acute treatment

Manic or mixed episodes

Two randomized, double-blind, controlled studies have shown olanzapine monotherapy to be significantly better than placebo for the acute treatment of patients with mania or mixed episodes, with initial dosing of either 10 mg/day or 15 mg/day (9, 10). Somnolence, dry mouth, dizziness, and weight gain occurred significantly more frequently in the olanzapine group than in the placebo group. In another randomized, double-blind study, olanzapine was equivalent to haloperidol for patients with acute mania and was superior to haloperidol for patients whose index episode did not include psychotic features (11). Olanzapine monotherapy has also been compared with divalproex monotherapy in two randomized, double-blind, controlled studies. In one there was equivalent efficacy (12), and in the other olanzapine had superior efficacy (13). However, the side-effect profile for divalproex was more benign.

Olanzapine has also been studied as an adjunctive agent to traditional mood stabilizers. In a double-blind, randomized, controlled trial, olanzapine added to divalproex or lithium was superior to divalproex or lithium alone in patients who had had an inadequate response to at least 2 weeks of lithium or valproate monotherapy (14). Side effects included somnolence, hyperkinesia, and nausea.

The efficacy of risperidone monotherapy for the acute treatment of mania has been demonstrated in three randomized, double-blind, placebo-controlled trials. Risperidone monotherapy was superior to placebo in all three studies. In the three studies patients were started on 3 mg/day of risperidone, with titration to a maximum of 6 mg/day. Onset of action in one study was seen at day 3 (15), and in another at 1 week (16). In the third study, risperidone was equivalent to haloperidol and superior to placebo (17). Side effects included somnolence, hyperkinesia, and nausea.

Two randomized, double-blind, placebo-controlled studies examined the adjunctive use of risperidone with traditional mood stabilizers (i.e., lithium or divalproex) (18, 19). In both studies the combination of risperidone with mood stabilizer outperformed mood stabilizer alone. The addition of risperidone substantially increased the prevalence of extrapyramidal symptoms.

The efficacy of ziprasidone as monotherapy in the acute treatment of patients with manic or mixed episodes was tested in two randomized, double-blind, placebo-controlled studies, with initial dosing of 40 mg twice a day (20, 21). Ziprasidone had an onset of action at day 2 in both trials and was superior to placebo at endpoint. The mean dosage in the two studies was 130 mg/day and 112 mg/day, respectively. Side effects included somnolence, dizziness, extrapyramidal syndrome, nausea, akathisia, and tremor.

Two studies of aripiprazole monotherapy in the acute treatment of mania have been published (22, 23). In a randomized, double-blind, controlled study, aripiprazole at a starting dosage of 30 mg/day was compared with placebo in patients with manic or mixed episodes (22). Aripiprazole was superior to placebo in efficacy, beginning at day 4. Side effects included nausea, dyspepsia, somnolence, vomiting, insomnia, and akathisia. A second study compared aripiprazole and haloperidol over 12 weeks (23). The drugs performed similarly regarding improvement in manic symptoms, but substantially more aripiprazole patients completed the study. Extrapyramidal symptoms were much higher for haloperidol.

The efficacy of quetiapine in patients with manic episodes has been studied in two different 12-week randomized, double-blind, placebo-controlled trials—one against lithium and the other against haloperidol (24, 25). Quetiapine was initiated at 100 mg on day 1, with an upward titration to 800 mg/day or higher. Quetiapine was equivalent in efficacy to the two active comparators, and both were superior to placebo at day 21. Side effects included dry mouth, somnolence, weight gain, and dizziness.

In another study, adjunctive quetiapine or placebo was given to acutely manic patients who were still manic after at least 7 days of treatment with lithium or divalproex. Quetiapine was initiated at 100 mg and titrated to 400 mg/day by day 4, with a target dose of 200–800 mg/day (26).

The quetiapine treatment group had a significantly higher response rate and reduction in manic symptoms. The mean last-week dosage in all patients receiving quetiapine was 504 mg/day.

There have been two recently published randomized, double-blind, placebo-controlled studies of the extended-release formulation of the anticonvulsant carbamazepine for the acute treatment of manic or mixed episodes (27, 28). In both studies, carbamazepine extended-release was initiated at 400 mg in divided doses on day 1 and increased as tolerated up to 1,600 mg/day. The mean final dosages were 756 mg/day (27) and 643 mg/day (28), respectively. An onset of action was seen at day 14 in the first trial and at day 7 in the second trial, and both trials found carbamazepine extended-release to be superior to placebo at endpoint. Side effects included dizziness, somnolence, nausea, vomiting, ataxia, blurred vision, dyspepsia, dry mouth, pruritus, and speech disorder.

The many monotherapy and adjunctive therapy studies of mania since 2002 provide a number of new options for clinicians in the acute treatment of patients with mania.

A significant clinical concern is metabolic effects associated with second-generation antipsychotics (29). Clozapine and olanzapine are associated with increased risks of developing diabetes mellitus and dyslipidemia. A recent comparative antipsychotic trial in schizophrenia suggested significantly greater weight gain for olanzapine than for the other antipsychotics studied (i.e., perphenazine, quetiapine, risperidone, and ziprasidone) (30). Clozapine and olanzapine are associated with the most weight gain, risperidone and quetiapine with moderate weight gain, and ziprasidone and aripiprazole with minimal weight change. Because of these risks, clinicians have been advised to monitor weight, waist circumference, blood pressure, glucose, and lipids at baseline and at monthly intervals in patients on these medications (31).

Depressive episodes

The impact (in terms of duration of episodes and quality of life) of depressive episodes in bipolar patients is substantially worse than the impact of manic episodes (32, 33). Unfortunately, far less research attention has been paid to the treatment of bipolar depression (34, 35). This section reviews three studies published since the 2002 publication of the second edition practice guideline.

In an 8-week placebo-controlled, double-blind study, olanzapine monotherapy and the combination of olanzapine and fluoxetine were examined in the acute treatment of bipolar I depression (36). Although both olanzapine and the combination of olanzapine and fluoxetine were superior to placebo in efficacy, the response in the combination group was much greater, and only the combination of olanzapine and fluoxetine received an indication from the Food and Drug Administration for the acute treatment of bipolar depression. The first separation from placebo occurred at week 1 and continued throughout the trial. The mean dosage in the combination group was 7.4 mg/day of olanzapine and 39.3 mg/day of fluoxetine. By the end of the study, 8 of 10 core symptoms of depression had improved relative to placebo. Side effects included somnolence, weight gain, increased appetite, dry mouth, asthenia, and diarrhea. Neither olanzapine monotherapy nor the combination of olanzapine and fluoxetine caused switching into mania or hypomania.

A large randomized, double-blind, placebo-controlled trial supported the efficacy of quetiapine monotherapy for the treatment of bipolar I or II depression (37). Quetiapine initiated at 50 mg/day and titrated to either 300 mg/day or 600 mg/day within 1 week was found to be effective compared with placebo at both doses, with no significant difference in efficacy between the two dosage groups. Onset of action occurred by 1 week and continued throughout the trial. Statistical significance was achieved at endpoint in 9 of 10 core features of depression. Side effects included dry mouth, sedation, somnolence, dizziness, and constipation and were substantially greater in the 600 mg/day group compared with the 300 mg/day group. Incidence of treatment-emergent mania did not differ from that of placebo.

A single-blind, randomized, nonplacebo-controlled comparison of venlafaxine and paroxetine was conducted with patients with bipolar disorder who were currently presenting with a major depressive episode and who were currently taking a mood stabilizer (38). Both medications yielded significant improvements in depressive symptomatology with no significant differences in safety measures. Among the patients treated with paroxetine, 3% switched to hypomania or mania, compared with 13% in the venlafaxine group.

Two small, controlled studies of the adjunctive use of the dopamine agonist pramipexole in the treatment of bipolar depression suggest efficacy (39, 40). Both studies were 6-week placebo-controlled studies of pramipexole (mean peak dosage = 1.7 mg/day) added to the therapeutic levels of traditional mood stabilizers. Results were strongly positive in both studies, with few adverse events.

In conclusion, medications having the strongest evidence for efficacy for acute treatment of depression in patients with bipolar I disorder are the olanzapine-fluoxetine combination, quetiapine, and lamotrigine. There is suggestive evidence that the adjunctive use of pramipexole may be helpful. Evidence for the efficacy of an antidepressant with adjunctive mood stabilizer is modest. Prescription of antidepressants in the absence of a mood stabilizer is not recommended for bipolar I patients.

Maintenance treatment

Since publication of the second edition practice guideline, new studies have been published on the long-term treatment of patients with bipolar disorder.

Pharmacological interventions

Two large randomized, double-blind studies examined the utility of lamotrigine in the maintenance treatment of patients with bipolar I disorder (41, 42). Both studies were placebo controlled and included lithium monotherapy as an active comparator. In one study, patients had most recently suffered a depressive episode (41) and, in the other, a manic or hypomanic episode (42). Both studies involved an open-label stabilization period of 8–16 weeks followed by an 18-month trial of lamotrigine monotherapy, lithium monotherapy, or placebo in patients who had recovered and were stable.

In the study of recently depressed patients (41), both lamotrigine (200 mg/day or 400 mg/day) and lithium (0.8–1.1 meq/liter) were superior to placebo in preventing any mood episode. Lamotrigine, but not lithium, was superior to placebo in preventing a depressive episode. Lithium, but not lamotrigine, was superior to placebo in preventing a manic, hypomanic, or mixed episode. With the exception of rash, there were no side effects of lamotrigine that exceeded placebo. There were no serious rashes. For the lithium group, the incidence of somnolence and tremor exceeded that of placebo.

In the study of recently manic or hypomanic patients (42), both lamotrigine (target dosage of 200 mg/day) and lithium (0.8–1.1 meq/liter) were superior to placebo in delaying onset of any mood episode. Lithium, but not lamotrigine, was superior to placebo in prevention of a manic episode, but neither agent was superior to placebo in preventing depressive episodes. There were no adverse events for which lamotrigine statistically exceeded placebo. Lithium exceeded placebo for diarrhea only.

When the data from both studies were pooled, lamotrigine was superior to placebo in time to intervention for any mood episode, as well as for prevention of depressive episodes and manic, hypomanic, or mixed episodes (43). Similarly, lithium was superior to placebo in time to intervention for a mood episode and for prevention of a manic, hypomanic, or mixed episode. Lithium was not superior to placebo in prevention of a depressed episode.

Given the results from these studies, both lamotrigine and lithium appear to have substantial utility in the maintenance treatment of patients with bipolar disorder. The utility of lamotrigine was somewhat greater for the prevention of depressive compared with manic episodes, and the opposite is true for lithium.

A 47-week, randomized, double-blind study of olanzapine versus divalproex for manic or mixed episodes was completed (44). The median time to remission was shorter for olanzapine than for divalproex, although the remission rates at the end of the study did not differ between agents. Adverse events for olanzapine included somnolence, dry mouth, increased appetite, weight gain, akathisia, and high alanine aminotransferase levels, while adverse events for divalproex were nausea and nervousness.

A randomized, double-blind, controlled trial compared the efficacy of olanzapine and lithium for the prevention of relapse or recurrence of a manic or mixed episode (45). In this study patients currently experiencing a manic or mixed episode were treated acutely with olanzapine and lithium for 6–12 weeks. Patients who achieved remission were randomly assigned to 52 weeks of olanzapine or lithium monotherapy. A relapse into mania or depression occurred in 30% of the olanzapine-treated patients and in 39% of the lithium-treated patients—an insignificant difference. Olanzapine was superior to lithium in rates of symptomatic recurrence of mania or mixed episodes (14% vs. 28%), but rates of depression recurrence did not differ. Treatment-emergent insomnia was higher in the lithium group than in the olanzapine group. Among the lithium group, 26% discontinued treatment because of side effects, compared with 19% of the olanzapine group.

A randomized, double-blind, controlled study examined the utility of continued combination treatment with a mood stabilizer (lithium, carbamazepine, or valproate) and a first-generation (typical) antipsychotic (perphenazine) (46). Immediately following remission from a manic episode, patients were randomly assigned to remain on the combination therapy or to receive the mood stabilizer plus placebo. Among those on continued combination therapy, there was shorter time to depressive relapse, a higher rate of discontinuation, and higher rates of dysphoria, depressive symptoms, and extrapyramidal symptoms. The study concluded that there were no short-term benefits with the continuation of the first-generation antipsychotic with a mood stabilizer; in fact, its continued use was associated with the aforementioned detrimental effects.

However, a similar study of the second-generation antipsychotic olanzapine plus mood stabilizer versus mood stabilizer plus placebo had somewhat different results (47). In this randomized, double-blind, controlled study, patients who achieved remission after 6 weeks of treatment with olanzapine plus either lithium or valproate received continued lithium or valproate plus olanzapine or plus placebo for 18 months. There were no differences in time to relapse into mania or depression between the monotherapy and combination therapy groups, but combination therapy was significantly better for prevention of symptomatic relapse. Combination therapy was associated with increased somnolence, weight gain, and tremor.

Psychosocial interventions

Knowledge of the utility of psychosocial interventions has expanded recently. Family-focused therapy is a manualized psychosocial program involving all available family members in which weekly psychoeducation, communication enhancement training, and problem-solving skills training occur adjunctively with pharmacotherapy. A 2-year randomized, controlled study of family-focused therapy plus pharmacotherapy versus a crisis management intervention and pharmacotherapy (supported by grants from the National Institute of Mental Health, the National Alliance for Research on Schizophrenia, and the MacArthur Foundation) found that postepisode symptomatic adjustment and drug adherence were enhanced with the family-focused therapy and pharmacotherapy combination compared with the other (48). Patients in the group receiving family-focused therapy had fewer relapses and longer survival intervals.

Another randomized, controlled study examined the utility of cognitive therapy in conjunction with pharmacotherapy over a 12-month period (49). Those treated with cognitive therapy and pharmacotherapy had significantly fewer bipolar episodes, days in an episode, and number of admissions.

Two controlled studies (supported by grants from the Stanley Medical Research Institute, the Instituto de Salud Carlos III, the Fundació Marató de TV3, and the Fundació María Francisca Roviralta) of a longitudinal (21-session) psychoeducational program were conducted in Spain (50, 51). In both studies psychoeducation reduced recurrences over 2 years. Psychoeducation enhanced lifestyle regularity and early syndrome detection.

A recent study (supported by grants from the National Institute of Mental Health) found that a psychosocial intervention focused on addressing interpersonal problems and regulating social rhythms during acute treatment in bipolar I patients extended the time to new episode and reduced the likelihood of recurrence (52).

CONCLUSION

Since the publication in 2002 of the *Practice Guideline for the Treatment of Patients With Bipolar Disorder,* 2nd Edition, new options for the acute treatment of manic, mixed, or depressive episodes have emerged. Knowledge of pharmacological and psychosocial interventions for maintenance has also increased.

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