Treatment of Bipolar Disorder: The Evolving Role of Atypical Antipsychotics

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Abstract

Management of bipolar disorder (BPD) may require multiple medications, including lithium, anticonvulsants, and antipsychotics (both conventional and atypical). Updated treatment guidelines reflect an expanded role for atypical antipsychotics (AAPs) in BPD treatment. Five AAPs—olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole—are approved by the US Food and Drug Administration (FDA) as monotherapy for first-line treatment of acute manic and (except for quetiapine) mixed episodes. Two AAPs—olanzapine (in fixed-dose combination with fluoxetine) and quetiapine—are also FDA approved for bipolar depression. For long-term maintenance therapy, one option is to continue effective, well-tolerated acute phase treatment; however, only olanzapine and aripiprazole are FDA approved for maintenance, based on evidence from randomized, placebo-controlled clinical trials.

Although head-to-head comparisons are scarce, meta-analysis data suggest that olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole have similar antimanic efficacy; therefore, AAP selection for this indication should be guided by other considerations such as safety, tolerability, and cost. Safety and tolerability issues to consider when selecting an AAP include metabolic dysfunction (weight gain, type 2 diabetes, and dyslipidemia); hyperprolactinemia; extrapyramidal symptoms; QTc prolongation; and pharmacokinetic drug interactions.

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Treatment of bipolar disorder (BPD) is challenging in part because of the diversity of presenting symptoms. These may include full *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) episodes of mania, depression, and mixed states (in which patients meet criteria for both mania and depression simultaneously); any of these may be accompanied by psychotic symptoms. Patients may also present with milder periods of hypomania or subthreshold depression, or with symptoms of comorbidities such as anxiety disorders, substance abuse disorders, attention-deficit/hyperactivity disorder,[1] eating disorders,[2] and impulse control disorders,[3] all of which are quite common among bipolar individuals.

To manage these manifestations, an array of medications from multiple classes is available. Currently, 11 drugs are approved by the US Food and Drug Administration (FDA) for use in some aspect of BPD (**Table**),[4-16] while others are widely used off-label based on varying degrees of evidence. Furthermore, agents approved for one phase of BPD are used off-label in other phases (eg, a drug approved for acute mania may be continued as maintenance therapy).

Commonly prescribed treatments in BPD include lithium; anticonvulsants such as divalproex, carbamazepine, or lamotrigine; and antipsychotics, both conventional and atypical. Adjunctive agents include benzodiazepines (in acute mania) and antidepressants (in depressive episodes).

Nonpharmacologic approaches also have a role in BPD treatment. Psychosocial interventions that address illness management (eg, treatment adherence, lifestyle change, early recognition of prodromal symptoms) and interpersonal difficulties are an important adjunct to pharmacotherapy.[17] These interventions may include psychoeducation; cognitive behavioral or other psychotherapy; group therapy; family therapy; and support groups.[17,18] Electroconvulsive therapy is an option in life-threatening manic, mixed, or depressive episodes; for treatment-resistant illness; or as an alternative to medication (eg, during pregnancy).[17]

Because of the protean nature of BPD and the many treatment options, clinical decision-making can be complex. To assist the clinician,

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Table. Drugs Approved by the FDA for Treatment of Bipolar Disorder

Drug Class	Drug	FDA-approved Indications	References
—	Lithium carbonate (Eskalith; Lithobid)	Treatment of acute manic episodes of manic-depressive illnesses	4, 5
		Maintenance therapy in manic-depressive patients with a history of manias	4, 5
Anticonvulsants	Divalproex sodium (Depakote)*	Treatment (up to 3 weeks) of acute manic episodes associated with bipolar disorder	6
	Divalproex sodium extended release (Depakote ER)*	Treatment (up to 3 weeks) of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features	7
	Lamotrigine (Lamictal)	Maintenance treatment (up to 18 months) of bipolar I disorder in patients treated for acute episodes with standard therapy	8
	Carbamazepine extended release (Equetro)	Treatment (up to 3 weeks) of acute manic and mixed episodes associated with bipolar I disorder	9
Antipsychotics, conventional (first generation)†	Chlorpromazine (Thorazine)	To control the manifestations of the manic type of manic-depressive illness	10
Antipsychotics, atypical (second generation)‡	Olanzapine (Zyprexa)	Acute monotherapy: short-term (3-4 weeks) treatment of acute mixed or manic episodes associated with bipolar I disorder	11
		Maintenance monotherapy after achieving responder status	11
		Acute combination therapy with lithium or valproate: short-term (up to 6 weeks) treatment of acute mixed or manic episodes associated with bipolar I disorder	11
	Olanzapine for injection (Zyprexa IntraMuscular)	Treatment of agitation associated with bipolar I mania	11
	Risperidone (Risperdal)	Short-term (up to 3 weeks) treatment of acute manic or mixed episodes associated with bipolar I disorder, as monotherapy (in adults and in children and adolescents ages 10-17 years) or in combination with lithium or valproate (in adults)	12
	Quetiapine (Seroquel)	Treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy (up to 12 weeks) or in combination with lithium or divalproex (up to 3 weeks)	13
		Treatment (up to 8 weeks) of depressive episodes associated with bipolar I or II disorder	13
	Ziprasidone (Geodon)	Treatment (up to 3 weeks) of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features	14
	Aripiprazole (Abilify)	Treatment of acute manic and mixed episodes associated with bipolar disorder	15
		Maintenance therapy in patients with bipolar I disorder who have been stabilized and maintained for at least 6 weeks after a recent manic or mixed episode	15
Atypical anti-psychotic + SSRI antidepressant	Olanzapine and fluoxetine (Symbyax)	Treatment (up to 8 weeks) of depressive episodes associated with bipolar disorder	16

*Although divalproex is not FDA approved for long-term maintenance therapy in bipolar disorder, it is widely used off-label for this indication.
†Chlorpromazine is the only first-generation antipsychotic that is FDA approved for bipolar disorder. However, other conventional antipsychotics such as haloperidol (Haldol) are widely used off-label.
‡Clozapine (Clozaril) is not FDA approved for bipolar disorder, but is used off-label in treatment-resistant bipolar disorder.
FDA indicates US Food and Drug Administration; SSRI, selective serotonin reuptake inhibitor.

various groups have developed guidelines. In the United States, these include:

- the 2002 American Psychiatric Association (APA) practice guideline,[17] which is to be updated in the coming year
- the 2004 update of the Expert Consensus Guideline Series[19]
- the Texas Medication Algorithm Project (TMAP), last updated in 2005[20]

Because nearly all the research addresses bipolar I disorder (BPD I), evidence-based recommendations for bipolar II disorder (BPD II) are not available.[20] However, the Expert Consensus Guideline Series includes some consensus-based recommendations for BPD II.[19]

General Approaches to Treatment

All of the published guidelines note that effective decision-making requires accurate monitoring of the patient's symptoms and clinical state. Rather than relying on memory and general impressions, systematic measurement provides greater precision in monitoring treatment response, helps avoid errors of omission, and facilitates informed patient participation.[1]

TMAP is an example of a measurement-based care model. The TMAP algorithms were developed as part of a comprehensive program that includes systematic assessment of symptoms and drug adverse effects (AEs) at each clinic visit to guide treatment adjustments.[21] The clinician-administered Brief Bipolar Disorder Symptom Scale (BDSS) was developed for clinical use and evaluated as part of the TMAP program.[22,23]

Another measurement-based model is the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).[1] Measurement tools provided by this program—including a clinician-administered Clinical Monitoring Form, a Clinical Self Report Form that patients can fill out in the waiting room at each visit, and a Mood Chart for tracking data between visits—are available online at **www.manicdepressive.org.**

One major shift in treatment in the past several years has been the increasing application of atypical antipsychotics (AAPs). The remainder of this article focuses on the roles of 5 AAPs—olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole—in the treatment of bipolar mania, bipolar depression, and mixed states. Although clozapine has been used to treat refractory BPD, it is not FDA approved for this purpose and a discussion of its use in BPD is beyond the scope of this article.

AAP Efficacy in Bipolar Disorder

Acute manic and mixed episodes. *Monotherapy.* Randomized, double-blind, placebo-controlled (RDBPC) trials have demonstrated efficacy of 5 AAPs as monotherapy for acute mania, with or without psychosis: olanzapine,[11,24,25] risperidone,[12,26,27] quetiapine,[13,28-30] ziprasidone,[14,31,32] and aripiprazole.[15,33,34] All 5 agents are approved by the FDA for mania, and all but quetiapine are approved for mixed episodes (the quetiapine trials did not include patients with current mixed episodes).[11-15]

Results of several randomized, double-blind (RDB), active-comparator trials suggest that AAP monotherapy is as effective as monotherapy with other antimanic agents, including lithium,[28,35,36] divalproex,[36,37] and haloperidol.[29,36,38,39] Two RDB studies (olanzapine vs divalproex[40] and aripiprazole vs haloperidol[41]) suggest superiority of AAPs.

Combination therapy. RDBPC trials have demonstrated efficacy in combination with either lithium or valproate (divalproex) for olanzapine,[42] risperidone,[43] and quetiapine.[44-46] These 3 AAPs have been approved by the FDA for use with lithium or valproate/divalproex.[11-13]

In contrast, in one RDBPC trial of risperidone combined with either lithium, valproate, or carbamazepine, mania symptom scores were significantly improved with risperidone compared with placebo at week 1, but not at endpoint. Post-hoc analysis suggested that the subset of patients taking carbamazepine was responsible for the lack of difference at endpoint; this subgroup also had reduced risperidone blood levels, suggesting that lack of efficacy was due to carbamazepine induction of risperidone metabolism.[12,47] (See also ***Pharmacokinetic drug interactions*** under **AAP Safety and Tolerability Issues** below.)

Ziprasidone and aripiprazole are not currently FDA approved for combination therapy.

Relative efficacy of AAPs in acute mania. There is one published head-to-head trial comparing differ-

ent AAPs in BPD. In a 3-week RBD comparison of risperidone versus olanzapine for manic or mixed episodes without psychotic features, both drugs produced similar improvement in mania scores.[48]

Because head-to-head trials are scarce, the best available comparative information comes from a meta-analysis of RDBPC studies of AAPs for acute mania. Data from 12 monotherapy and 6 combination therapy trials, involving a total of 4304 patients, were analyzed. Olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole all demonstrated efficacy compared with placebo. Pairwise comparisons failed to identify any significant efficacy differences among the 5 AAPs.[49]

The investigators concluded that the 5 AAPs have similar efficacy for bipolar mania. Thus, AAP selection may best be guided by other factors such as safety and tolerability, evidence of maintenance efficacy, and cost.[49] (See **AAP Safety and Tolerability Issues** below.)

Acute depressive episodes. AAP efficacy in bipolar depression has been demonstrated for olanzapine and quetiapine. Olanzapine (in fixed-dose combination with fluoxetine) was the first AAP to be approved by the FDA for bipolar depression. Recently, quetiapine was also approved for this indication.

Olanzapine. Efficacy of olanzapine/fluoxetine combination (OFC) for bipolar depression was established in 2 identically designed 8-week RDBPC trials, comparing OFC versus olanzapine alone versus placebo. In both studies, the OFC group fared significantly better than those assigned to either monotherapy or placebo.[16] A pooled analysis of the 2 studies showed that, while olanzapine monotherapy is better than placebo, OFC is superior to both olanzapine monotherapy and placebo. The risk of treatment-emergent mania did not differ among the groups.[50]

A secondary analysis of these trials showed significantly greater improvement in health-related quality of life (HRQOL) with OFC versus olanzapine alone, and with either active treatment versus placebo.[51]

OFC has also been compared with lamotrigine in a 7-week RDB trial involving 410 patients with bipolar I depression. The OFC group had modestly but significantly greater improvement in depressive symptoms. Although the percentage of responders was similar in both groups, time to response was significantly shorter with OFC.[52]

Quetiapine. Efficacy of quetiapine for bipolar depression was established in 2 identically designed 8-week RDBPC trials (BOLDER I and II) that included patients with either bipolar I or II disorder. In both trials, quetiapine was superior to placebo from the end of the first week onward.[53,54] In BOLDER I, there was no significant between-group difference in the incidence of treatment-emergent mania[53]; in BOLDER II, the incidence of treatment-emergent mania/hypomania was lower in the quetiapine group (statistically significant by post-hoc analysis).[54]

Long-term maintenance. Olanzapine and aripiprazole have demonstrated long-term maintenance efficacy in RDBPC trials, and currently are the only AAPs approved by the FDA for that indication. However, open-label evidence suggests that quetiapine and ziprasidone may also be effective for maintenance.

Olanzapine. Efficacy of olanzapine maintenance monotherapy was demonstrated in 361 patients with manic or mixed episodes who had responded to open-label olanzapine and were then randomized to double-blind olanzapine or placebo for an additional 48 weeks. Times to relapse into manic, mixed, and depressive episodes were all significantly longer in the olanzapine group.[11,55]

RDB comparisons with other active agents suggest that olanzapine is at least as effective as lithium[56] or divalproex[57] for long-term maintenance.

Long-term olanzapine efficacy is also supported by a 49-week open-label extension[58] of one of the pivotal mania trials.[24] One hundred thirteen patients entered the extension phase. Olanzapine was associated with significant additional improvement in mania score, as well as HRQOL improvements in several dimensions. Furthermore, compared with the previous 12 months, olanzapine maintenance saved nearly $900 per month per patient, primarily due to reduced hospitalization costs.[58]

Olanzapine has also been studied in long-term combination therapy with lithium or valproate. In

a continuation[59] of the pivotal combination therapy trials in acute mania,[42] 99 patients who had achieved syndromic remission (ie, by *DSM-IV* criteria) with olanzapine plus either lithium or valproate were randomized to double-blind olanzapine versus placebo for 18 months while continuing to receive open-label lithium or valproate. Time to syndromic relapse into either mania or depression was not significantly different between the groups; however, olanzapine was superior to placebo in preventing symptomatic relapse (ie, by mania and depression scale scores).[59]

Quetiapine. There have been no published double-blind trials of quetiapine for maintenance. However, in an open-label study, 28 patients were randomized to either quetiapine or other mood stabilizers (primarily valproate or lithium) for 12 months. Both groups had similar outcomes, with significant improvement compared with baseline.[60]

Ziprasidone. There have been no double-blind maintenance trials with ziprasidone. However, in a 52-week open-label extension of an acute mania trial, ziprasidone monotherapy was associated with significant and sustained global symptom improvement compared with baseline.[61]

Aripiprazole. Efficacy of aripiprazole monotherapy for long-term maintenance was established in a 26-week RDBPC trial in 161 patients with a recent manic or mixed episode, who had been stabilized on open-label aripiprazole for ≥6 weeks. Aripiprazole was superior to placebo in delaying time to manic relapse, but there was no significant between-group difference in time to depressive relapse.[15,62]

AAP Safety and Tolerability Issues

This section briefly summarizes selected AAP safety and tolerability issues.

Weight gain, hyperglycemia, dyslipidemia. Some AAPs have been linked to weight gain, type 2 diabetes, and dyslipidemia.[63-65] This AAP-associated metabolic disturbance may exceed that observed with lithium, anticonvulsants, or conventional antipsychotics. In double-blind comparisons, olanzapine has been associated with significantly more short-term weight gain than divalproex[37,40,57] or haloperidol,[38] and with significantly more long-term weight gain than lithium.[56] In a cross-sectional study of 125 bipolar patients, those taking AAPs (olanzapine, quetiapine, or risperidone) had higher rates of metabolic syndrome (defined as 3 or more of: abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein [HDL] cholesterol) than those taking conventional mood stabilizers.[66]

There have been many reports of new-onset or worsening diabetes in patients taking AAPs. This may, at least in part, result from weight gain and/or changes in body fat distribution.[67] However, in some individuals glucose intolerance appears to be independent of adiposity, suggesting a direct effect on insulin secretion and/or sensitivity.[67,68] In particular, case reports of rapid-onset, and often rapidly reversible, severe hyperglycemia or diabetic ketoacidosis (DKA) suggest a possible direct effect on beta-cell function.[68]

In general, AAP-associated dyslipidemia—including elevated triglycerides, elevated low-density lipoprotein (LDL) and total cholesterol, and reduced HDL cholesterol—appears to be consistent with weight gain.[67]

AAPs differ in their propensity to cause metabolic dysfunction. Based on available evidence, olanzapine appears to have the greatest metabolic effects, ziprasidone and aripiprazole the least, with quetiapine and risperidone intermediate.[67,68]

The majority of published studies—including case reports, retrospective chart reviews, large database analyses, and randomized controlled trials—provide consistent evidence that olanzapine increases the risk of substantial weight gain, insulin resistance, diabetes, and dyslipidemia (especially elevated triglycerides).[68] Of the 5 AAPs, olanzapine has been associated with the most weight gain and has most often been involved in case reports of diabetes and DKA.[63-65]

Quetiapine and risperidone have been associated with moderate weight gain (quetiapine somewhat more than risperidone) during short- and long-term treatment, but have not consistently been associated with diabetes or dyslipidemia.[68]

Ziprasidone and aripiprazole appear to have minimal effects on weight and adiposity, and there is

little or no evidence that they increase the risk of glucose intolerance, diabetes, or dyslipidemia.[68] However, long-term experience with these 2 newest AAPs is limited.

While the product labels of all 5 AAPs carry a warning about hyperglycemia and diabetes,[11-15] reports of DKA and hyperosmolar coma are mentioned only with olanzapine, risperidone, and quetiapine.[11-13]

An accompanying article in this issue, "Metabolic Syndrome and Mental Illness," by John W. Newcomer, MD, reviews metabolic syndrome in psychiatric disorders, including recommendations for monitoring patients on antipsychotic therapy.

Hyperprolactinemia. Hyperprolactinemia occurs frequently with conventional antipsychotics, and also has been observed with AAPs. Prolactin elevation may be asymptomatic, or may result in symptoms including gynecomastia (in men); menstrual abnormalities, infertility, acne, and hirsutism (in women); galactorrhea and sexual dysfunction (in both sexes). Some of these symptoms (eg, galactorrhea) result from direct effects of prolactin on target tissues. Others (eg, amenorrhea) result from disruption of the hypothalamic-pituitary-gonadal axis, leading to reduction of estrogen levels in women and of testosterone levels in men. Thus, osteoporosis is a potential long-term complication. Animal and epidemiological data suggest that hyperprolactinemia may also increase breast cancer risk.[69]

Except for risperidone, AAPs are less likely than conventional antipsychotics to increase prolactin levels.[65,69,70] Risperidone causes marked, sustained elevation of prolactin levels in a substantial percentage of patients.[69] In at least one double-blind trial, prolactin levels were higher with risperidone than with haloperidol (statistical significance not stated).[39] In contrast, olanzapine-induced prolactin increase is milder than that of haloperidol, and does not persist with chronic dosing.[71] Ziprasidone has been observed to cause slight, transient prolactin elevations that return to baseline within the dosing interval.[72,73] In clinical trials, quetiapine[28,29,46,74] and aripiprazole[33,34,62,75] have not been associated with increased mean prolactin levels compared with placebo.

Extrapyramidal symptoms (EPS). EPS are categorized as either acute (including dystonia, parkinsonism, and akathisia) or tardive (onset ≥3 months after initiation of therapy, including tardive dyskinesia and tardive dystonia).[76] These movement disorders can cause discomfort, disfiguration, and functional impairment, and are thought to be an important cause of treatment refusal and nonadherence.[76] BPD patients may be at higher risk for EPS than those with schizophrenia.[64,65]

EPS are frequent with conventional antipsychotics; although they also occur with AAPs, the risk with AAPs appears to be substantially lower at recommended doses.[65,76] For example, in RDB trials in BPD patients, haloperidol was associated with more EPS than olanzapine,[38] risperidone,[43] quetiapine,[29] and aripiprazole.[41] Although long-term prospective data are limited, tardive as well as acute EPS risk appears to be relatively low with AAPs.[65,76] Improvements of both acute and tardive EPS have been observed after switching from a conventional antipsychotic to an AAP.[76]

The comparative potential of different AAPs to cause EPS is not reliably known. Current evidence suggests that risperidone may carry the greatest risk, especially at doses >4-6 mg/d.[76]

QTc prolongation. Prolongation of the electrocardiographic QTc interval is associated with an increased risk of torsades de pointes (TdP), a life-threatening ventricular arrhythmia. QTc prolongation has been reported to occur with AAPs; in an open-label, randomized evaluation that included 4 AAPs, the order of mean QTc prolongation was: ziprasidone > quetiapine > risperidone > olanzapine.[77] The ziprasidone product label carries a warning that ziprasidone should be avoided in the presence of other factors that prolong QTc or otherwise increase TdP risk.[14] Although ziprasidone is the only AAP that carries such a warning, similar considerations may apply to the other AAPs.[78] It should be noted that the risk of AAP-associated TdP, if any, appears to be very low.[78] No cases of TdP or sudden death were reported in clinical trials of ziprasidone monotherapy, nor in a review of 50 cases of ziprasidone overdose.[79] Rare cases of TdP have been reported in patients taking AAPs, including ziprasidone[80] and quetiapine,[81] but causation is difficult to determine because these cases involved multiple confounding and contributing factors.

Pharmacokinetic drug interactions. Olanzapine, risperidone, quetiapine, and aripiprazole are metabolized primarily via cytochrome P450 (CYP) pathways and, therefore, may interact with drugs that inhibit or induce CYP enzymes. For example, coadministration with carbamazepine, a CYP inducer, may increase clearance of these AAPs by ≥50%,[11-13,15] significantly reducing their blood levels. In contrast, less than one third of ziprasidone metabolism is mediated by CYP enzymes.[14] While clinically significant interactions between ziprasidone and CYP inhibitors are considered unlikely, carbamazepine has been shown to reduce ziprasidone exposure by approximately 35%.[14]

The Evolving Role of AAPs in Bipolar Disorder

Acute manic or mixed episodes. The 2002 APA guidelines recommend either lithium, divalproex, or an antipsychotic (eg, olanzapine) as first-line therapy. In less severe cases, they may be applied as monotherapy, while in more severe cases, lithium or divalproex may be combined with an antipsychotic.[17]

Since the APA guidelines were published, 4 additional AAPs (risperidone, quetiapine, ziprasidone, and aripiprazole) have been approved by the FDA for acute mania or mixed episodes. These expanded options are reflected in the 2005 updated TMAP algorithm. Based on efficacy evidence, the algorithm recommends first-line monotherapy with either lithium, divalproex, or any of the 5 AAPs for euphoric or irritable mania/hypomania; and with any of the above except lithium or quetiapine for dysphoric mania or mixed states.[20] TMAP specifies that olanzapine is considered an alternate choice of AAP because currently available evidence suggests it may have greater potential for causing metabolic disturbances.[20] Carbamazepine is also considered an alternate choice because of its AE profile.[20]

If there is no response to the initial agent, a different first-line agent should be tried. While this has not been studied in depth, TMAP specifies that lack of response to one AAP does not preclude response to a different AAP.[20]

If monotherapy results in a partial response, a combination of 2 first-line agents (but not 2 AAPs) is recommended. Aripiprazole is excluded at this stage because there have been no published positive combination trials, and carbamazepine is excluded because it can induce the metabolism of other antimanic agents.[20]

If combination therapy does not result in remission, the third step is combination therapy with expanded options, including aripiprazole. Conventional antipsychotics are also an option at this stage, although AAPs are preferred because they are less likely to cause EPS.[20]

Step 4 options include either adding clozapine or using a 3-drug combination (lithium, an anticonvulsant, and an AAP).[20]

Acute depressive episodes. The 2002 APA guidelines recommend either lithium or lamotrigine as first-line therapy[17]; at that time, there was no established role for AAPs in bipolar depression. OFC was not approved by the FDA for bipolar depression until 2003, and quetiapine not until 2006.

The 2005 TMAP algorithm recommends lamotrigine—either as monotherapy or added to existing antimanic therapy—as first-line treatment; AAPs are not recommended initially.[20] However, an accompanying commentary suggests that olanzapine could be a first-line alternative, based on strength of evidence; and that lithium could also be considered, based on weight of evidence as well as data suggesting an antisuicide benefit.[82]

In the TMAP algorithm, use of an AAP—either OFC or quetiapine—is recommended as a second-line option. If this does not produce the desired response, the third step is combination therapy with 2 of the following: lithium, lamotrigine, quetiapine, OFC. Steps 4 and 5 involve expanded options for mood stabilizer and antidepressant combinations.[20]

Long-term maintenance. The 2002 APA guidelines noted that the maintenance options most supported by evidence were lithium or valproate, with lamotrigine or carbamazepine as possible alternatives. It was recommended that any conventional antipsychotics used during acute episodes should be tapered and discontinued if possible, due to the risk of tardive dyskinesia. AAPs could be considered as an alternative, but at that time there was no definitive evidence of AAP maintenance efficacy comparable to that of lithium or valproate.[17]

Since then, 2 AAPs (olanzapine and aripiprazole) have gained FDA approval for maintenance. Expanded options are reflected in the 2005 TMAP

algorithm. The algorithm notes that one option is to remain on effective, well-tolerated acute-phase treatment. Otherwise, maintenance options differ depending on whether the most recent episode was manic or depressed.[20]

If the most recent episode was manic, mixed, or hypomanic, TMAP considers olanzapine a first-line alternative to lithium or valproate, with aripiprazole as a second-line option.[20] (The FDA approval of aripiprazole for maintenance occurred after the TMAP algorithm was updated.) For illness resistant to those agents, level 3 options are carbamazepine or clozapine. Quetiapine, risperidone, or ziprasidone are recommended at level 4, based on limited data; and at level 5, conventional antipsychotics may be considered.[20]

For maintenance when the most recent episode was depressed, the evidence is less clear. TMAP recommends lamotrigine, with or without an antimanic agent, as first-line therapy; lithium as second line. At level 3, a combination of a previously effective antimanic and antidepressant (eg, OFC) is recommended. Level 4 options include any of the AAPs, including clozapine; and at level 5, conventional antipsychotics may be considered.[20]

Summary

Management of BPD may require multiple medications including lithium, anticonvulsants, and antipsychotics, as well as adjunctive agents. Updated treatment guidelines reflect an expanded role for AAPs in the treatment of BPD.

Based on data from RDBPC trials, 5 AAPs—olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole—are approved by the FDA as monotherapy for first-line treatment of bipolar mania. All except quetiapine are also approved for mixed episodes. The antimanic efficacy of these AAPs is similar to that of other widely used agents such as lithium, divalproex, and haloperidol. Olanzapine, risperidone, and quetiapine have also demonstrated efficacy as add-on therapy with lithium or divalproex.

Of the AAPs, only olanzapine (in fixed-dose combination with fluoxetine) and quetiapine are approved by the FDA for bipolar depression.

Olanzapine and aripiprazole have demonstrated long-term maintenance efficacy in RDBPC trials, and both are FDA approved for that indication. However, open-label evidence suggests that quetiapine and ziprasidone also have maintenance efficacy.

Clozapine is the only AAP not FDA approved for BPD. It is used off-label in treatment-resistant BPD.

Although head-to-head comparisons are scarce, meta-analysis data suggest that olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole have similar efficacy for acute mania. Therefore, AAP selection for this indication should be guided by other considerations such as AE profiles and cost.

Safety and tolerability issues with AAPs (excluding clozapine) include:

- **Weight gain, type 2 diabetes, and dyslipidemia.** Available evidence suggests that the risk may be highest with olanzapine and lowest with ziprasidone and aripiprazole; however, experience with the latter 2 is limited.
- **Hyperprolactinemia.** Risperidone can cause marked, sustained hyperprolactinemia, greater than that seen with haloperidol. Prolactin increases with the other AAPs are relatively mild and transient.
- **EPS.** AAPs cause fewer acute EPS than conventional antipsychotics; the risk of tardive EPS with AAPs awaits clarification with long-term data.
- **QTc prolongation.** Ziprasidone prolongs the QTc interval more than other AAPs, and is the only AAP whose product label carries a warning about QTc prolongation. However, TdP has rarely been reported in patients taking ziprasidone or other AAPs, and only in the presence of other predisposing factors.
- **Pharmacokinetic drug interactions.** Ziprasidone is less likely than other AAPs to have clinically important interactions with CYP inhibitors or inducers.

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