Tolerability Profiles of Atypical Antipsychotics in the Treatment of Bipolar Disorder

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Atypical antipsychotics have unequivocally advanced the pharmacotherapy of bipolar disorder. These broad-spectrum medications offer efficacy against core symptoms of mania, and evidence supports the use of several agents as treatment options in depressed and maintenance phases of the disorder. Atypical antipsychotics also have a reduced propensity for provoking acute or tardive neurologic adverse events compared with their therapeutic predecessors, the conventional antipsychotics. These agents are not, however, a panacea and are associated with several problematic tolerability and safety concerns. Although classified together, atypical antipsychotics are heterogeneous in their tolerability and safety profiles, an issue that is relevant to individualizing treatment selection. This article reviews relevant adverse events attributable to the use of atypical antipsychotic agents, with particular consideration of the bipolar disorder population. *(J Clin Psychiatry 2005;66[suppl 3]:28–36)*

Atypical antipsychotics are frequently prescribed for acute and preventative management of bipolar disorder, offering efficacy against the spectrum of bipolar symptomatology.[1–3] Individualizing the selection of atypical antipsychotics for bipolar disorder patients necessitates familiarity with their efficacy, tolerability, and safety profiles. The therapeutic evidence base for the efficacy, tolerability, and safety of these agents in various phases of bipolar disorder varies.

This article evaluates the impact on patients of the relevant adverse events (AEs) attributable to the use of atypical antipsychotics (Table 1), with particular consideration for the bipolar disorder population. The organization for this review categorizes relevant atypical antipsychotic–associated AEs into 6 areas: (1) metabolic: weight gain, dyslipidemia, and glucose disturbances; (2) neurologic: sedation/somnolence, extrapyramidal symptoms, seizures, and neuroleptic malignant syndrome; (3) cardiovascular: myocarditis/cardiomyopathy and corrected QT (QTc) prolongation; (4) hyperprolactinemia; (5) reproductive health and safety: pregnancy and lactation; and (6) affective symptom induction: precipitation or exacerbation of switches in mood states. Specific tactics and strategies for systematic screening, surveillance, and management of atypical antipsychotic–associated AEs will be provided.

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ATYPICAL ANTIPSYCHOTICS: AN OVERVIEW OF ADVERSE EVENTS

Metabolic

Weight gain. Over the past 2 decades an epidemic increase has occurred in the prevalence of obesity (body mass index [BMI] ≥ 30 kg/m^2), which currently exceeds 20% of the general population.[4] Obesity and overweight are associated with an increased prevalence of, in order of total direct treatment cost, diabetes mellitus, coronary artery disease, osteoarthritis, hypertension, gallbladder disease, and some forms of cancer. Obesity also has been related to dyslipidemia, sleep apnea, and increased all-cause mortality.[5] Patients with mood and psychotic disorders have a cluster of overweight risk factors (e.g., sedentary lifestyle, pharmacology-associated weight gain, comorbid binge-eating disorder) that predispose them to a relatively higher vulnerability to obesity.[6,7]

Obesity has been found to be present in up to 35% of patients with bipolar disorder.[8] Four studies have compared differences in weight and BMI (and associated risk factors) between persons with bipolar disorder and the general population (Table 2).[9–13] These studies indicate that persons with bipolar disorder are more likely to be obese than the general population and that their obesity is associated with a greater degree of depression and a higher risk for relapse.

A further concern is that the fat-patterning in bipolar disorder populations may be disproportionately centrally distributed (i.e., measured by the waist-hip ratio).[13] Central

Table 1. Adverse Events Associated With Atypical Antipsychotics[a]

Event	Clozapine	Olanzapine	Risperidone	Quetiapine	Ziprasidone	Aripiprazole
Metabolic						
Weight gain	++++	+++	++	++	+/0	+/0
Dyslipidemia	++	+++	+	+	0	0
Glucose dysregulation	++	++	+	+	0	0
Neurologic						
Somnolence/sedation	++++	+++	++	+++	+	+
Extrapyramidal symptoms	0	+	++	0	+	+
Cardiovascular						
Myocarditis/cardiomyopathy	+/0	0	0	0	0	0
QTc prolongation	+/0	+/0	+/0	+	+	0
Hormonal						
Prolactin	0	+/0	++	0	0	0

[a]Number of plus symbols signifies extent of adverse event.

Table 2. Obesity/Overweight Status in Studies of Patients With Bipolar Disorders

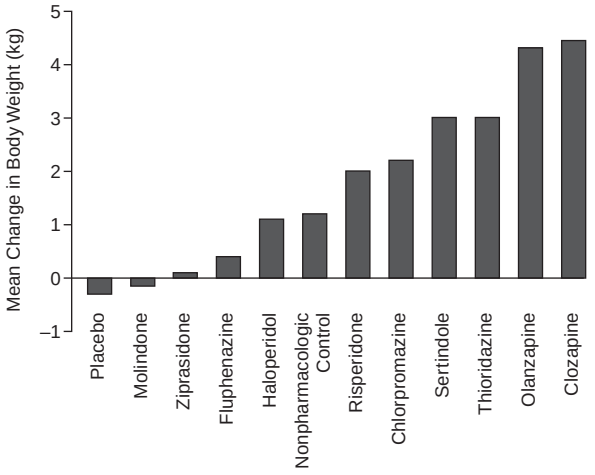
Author and Year	Study Design	Patients	Comments
Fagiolini et al[9] 2002	Retrospective chart review	N = 50 bipolar disorder (DSM-IV)	34/50 (68%) were obese/overweight 16/50 (32%) were obese Weight status associated with number of previous depressive episodes Most weight gain occurred during acute treatment Increase in BMI positively related to HAM-D Increase in BMI negatively related to baseline BMI
McElroy et al[10] 2002	Open-label, prospective	N = 644 outpatients bipolar disorder I/II (DSM-IV)	57% overweight/obese 21% overweight 5% extremely obese (BMI ≥ 40) American patients have higher mean BMI, obesity, extreme obesity than Europeans American women bipolar disorder patients have higher rates of obesity and extreme obesity than reference American men bipolar disorder patients have higher rates of overweight and obesity than reference Associations between excess BMI and age, annual income, comorbid binge-eating disorder, arthritis, diabetes mellitus, hypertension, consumption, weight gain–inducing psychotropic agents
Fagiolini et al[11] 2003	Post hoc analysis of randomized controlled trial	N = 175 bipolar disorder I (DSM-IV) Enrolled: 1991–2000	62 (35%) obese Overweight not reported Obese patients had fewer years of education More depressive than manic episodes Higher baseline HAM-D scores and required more time to achieve remission During maintenance, significantly higher rate of recurrence in obese (54%) vs nonobese (35%) Time to recurrence significantly shorter for obese patients Risk of relapse into depression greater than mania in obese patients
Elmslie et al[12,13] 2000, 2001	Open-label, observation cross-sectional	N = 89 euthymic bipolar disorder I (DSM-IV) N = 445 age-, sex-matched controls in New Zealand	Female patients significantly higher percentage overweight 44% vs 24% Obesity 20% vs 13% Abdominal obesity (waist-hip ratio > 0.8) 59% vs 17% Male patients higher rate of obesity 19% vs 10% Male abdominal obesity (waist-hip ratio > 0.9) 58% vs 35% Female patients receiving antipsychotics, alone or in combination, have a higher overall sugar intake

Abbreviations: BMI = body mass index, HAM-D = Hamilton Rating Scale for Depression.

adiposity (a proxy of visceral adipose tissue) exhibits relatively higher metabolic activity than peripheral adipose tissue and is a major risk factor for coronary artery disease.[14]

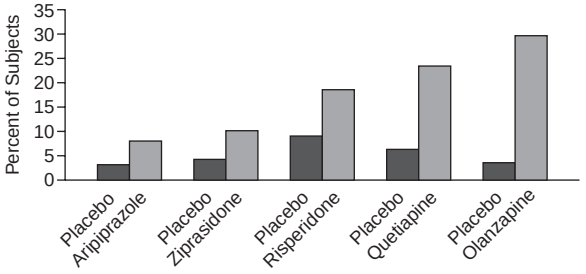
Antipsychotic-associated weight gain is a disturbing AE for patients. Although difficult to quantify, iatrogenic weight gain probably diminishes self-esteem and contributes to noncompliance with treatment regimens,[15,16] which increases the risk for affective relapse.[16,17] Weiden and colleagues[18] scrutinized heterogeneous variables associated with compliance in schizophrenia. Body mass index and subjective ratings of distress from weight gain were powerful predictors of noncompliance, with obese individuals more than twice as likely as persons with a normal BMI to

Figure 1. Estimated Mean Weight Gain at 10 Weeks on Standard Doses of Conventional and Atypical Antipsychotics[a]



[a]Reprinted with permission from McIntyre.[27]

Figure 2. Incidence of Weight Gain Reported in U.S. Package Inserts for Short-Term Studies[a]



[a]Reprinted with permission from Casey et al.[20] Clinically significant weight gain defined by the U.S. Food and Drug Administration as ≥ 7% of baseline weight.

report insufficient adherence to therapy. These results are probably applicable to bipolar disorder, given that in several studies weight gain has led to the discontinuation of lithium treatment in bipolar disorder patients.[18]

The differential liability of atypical antipsychotics for weight gain ranges from significant to minimal. Clozapine and olanzapine are associated with significant increases in weight, while ziprasidone and aripiprazole are associated with minimal weight change.[19,20] For example, after 10 weeks of treatment, clozapine, olanzapine, risperidone, and ziprasidone were associated with weight gains of 4.45 kg, 4.15 kg, 2.10 kg, and 0.04 kg, respectively (Figure 1).[19] Most available data describing atypical antipsychotic–associated weight gain were obtained from short-term studies in schizophrenia, with a relative dearth of long-term comparative data. Weight-gain data from studies conducted in bipolar disorder populations indicate a similar propensity for atypical antipsychotic–associated weight increase.[8]

Weight gain has been a correlate of both monotherapy and polypharmacotherapy with some atypical antipsychotics. For example, an analysis of pooled results from monotherapy trials with olanzapine at 15 mg/day indicated a mean weight increase of 11.8 kg after 1 year of treatment.[8] A review of data from short-term clinical trials with the atypical antipsychotics risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole showed that a higher percentage of patients who received olanzapine experienced weight gain than patients who received any of the other atypical antipsychotics (Figure 2).[20] Polypharmacotherapy, a frequent and increasing practice pattern in bipolar disorder, is associated with significantly greater weight gain from the short- and long-term use of medication. Thus, Tohen et al.[21] noted a weight increase of 2 kg over an 18-month relapse prevention phase with combination olanzapine and divalproex/lithium, compared with a loss of 1.8 kg in the monotherapy divalproex/lithium group. Clinically relevant increases in weight (≥ 7% change from baseline) were greater for patients who received combination therapy (27%) versus monotherapy (6%).[21]

Switching studies have demonstrated that atypical antipsychotic–associated weight gain may be reversible with some agents. For example, ambulatory patients insufficiently responsive to or poorly tolerant of a conventional antipsychotic, olanzapine, or risperidone were switched to open-label, flexible-dose ziprasidone.[22] Patients who successfully completed 6 weeks of ziprasidone monotherapy were eligible for entry into open-label extension studies in which ziprasidone was provided in flexible dosages of 40 to 160 mg/day for 52 weeks.[23] Improvements were noted in both psychopathologic and weight parameters. At study endpoint (week 58), patients switched from olanzapine to ziprasidone had a significant reduction (21.6 lb using a mixed-model analysis, $p < .0001$) in mean body weight, and those switched from risperidone to ziprasidone had a significant weight loss of 15.2 lb ($p < .005$). Patients switched from a conventional antipsychotic, usually haloperidol, which causes a relatively small amount of weight gain, did not have a significant change in mean weight.[23]

The mechanisms of atypical antipsychotic–associated weight gain are comprehensively reviewed elsewhere.[24] Most existing data describing mechanisms of antipsychotic-induced weight gain have emphasized changes in monoamine and histaminergic signaling.[7] Kroeze et al.[25] screened 17 conventional and atypical antipsychotic drugs for binding to 12 neurotransmitter receptors. Affinity for the histamine (H_1) receptor had the highest correlation with weight gain (Spearman $\rho = –0.72$; $p < .01$), followed by affinities for the α_{1A} adrenergic (Spearman $\rho = –0.54$; $p < .05$), 5-HT_{2C} (Spearman $\rho = –0.49$; $p < .05$), and 5-HT_6 (Spearman $\rho = –0.52$; $p < .005$) receptors. Ziprasidone and

Table 3. Atypical Antipsychotics and Metabolic Abnormalities[a]

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Ziprasidone	+/–	–	–
Aripiprazole	+/–	–	–

[a]Reprinted with permission from the American Diabetes Association.[1]
Abbreviation: D = discrepant results. Symbols: + = increased effect, – = no effect.

aripiprazole, which are associated with little weight gain, have minimal in vitro affinity for H_1 receptors.[25]

Dyslipidemia. There is growing concern about changes in the lipid profile associated with atypical antipsychotic use. The increased weight, especially abdominal weight, induced by some atypical antipsychotics is associated with elevated levels of triglycerides and small, dense, low-density lipoprotein particles as well as reduced levels of high-density lipoprotein. An elevated level of triglycerides is a risk factor for cardiovascular disease and insulin resistance, independent of weight gain. An adverse lipid profile increases the risk of atherosclerosis and cardiovascular diseases independent of factors such as diabetes mellitus and hypertension. The combination of diabetes mellitus and a lipid disorder synergistically elevates the risk of cardiovascular disease.[8]

Studies scrutinizing the effects of atypical antipsychotics on lipid parameters have predominantly included persons with schizophrenia, with relatively few studies in bipolar disorder populations. These studies indicate that clozapine, olanzapine, and quetiapine are associated with adverse lipid profiles. A 52-week, open-label, placebo-controlled study of inpatients with bipolar disorder (N = 210) found that treatment with ziprasidone was related to a decrease in triglyceride levels.[26] An adverse lipid profile should be corrected with a therapeutic goal of normalizing lipid levels and subsequently reducing susceptibility to other medical morbidities (e.g., diabetes mellitus).[8]

Glucose disturbances. Disturbances in glucose metabolism such as hyperglycemia, de novo type 2 diabetes mellitus, exacerbation of preexisting diabetes mellitus, and metabolic decompensation (i.e., diabetic ketoacidosis and hyperosmolar nonketotic coma) are heterogeneous in pathophysiology and etiology. Excess weight is a risk factor for type 2 diabetes mellitus in the general population. Weight gain increases insulin resistance, particularly when excess weight is in the abdominal compartment.[27]

The evidence base for the effects of atypical antipsychotics on glucose metabolism consists largely of case reports, chart reviews, pharmacovigilance databases, and pharmacoepidemiologic studies. Fewer rigorous studies have carefully scrutinized glucose handling (e.g., frequently sampled intravenous glucose tolerance tests). The topic of atypical antipsychotics and glucose metabolism has been comprehensively reviewed in several recent reports.[1,28]

Several conclusions can be drawn from the literature cited throughout this section on metabolic adverse events. The use of some atypical antipsychotics further increases a patient's risk of metabolic disturbances, including glucose metabolism and dyslipidemia. Metabolic disruption—as evidenced by weight gain, type 2 diabetes mellitus, and a worsening lipid profile—has been reported more often with clozapine and olanzapine than with other agents. Clinical studies with risperidone and quetiapine have had inconsistent results, with some studies showing an increased risk and others showing a minimal risk. Ziprasidone and aripiprazole have been associated with the lowest risk for weight gain, no increased risk for diabetes mellitus, and no worsening of the serum lipid profile. A recent statement from a consensus panel of members of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity[1] concluded that the available agents have a differential risk for metabolic disturbances (Table 3). The consortium position statement also provides recommendations for systematic screening, surveillance, and management of glucose metabolic and lipid disturbances in persons receiving atypical antipsychotics.[1]

Given that several atypical antipsychotics have been associated with the development of hyperglycemia and diabetes mellitus, the U.S. Food and Drug Administration (FDA) recently requested that the prescribing information for all atypical antipsychotics contain a warning about the risk of hyperglycemia and diabetes mellitus. The warning advises that hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients who received atypical antipsychotics. However, there have been few reports of hyperglycemia or diabetes mellitus with ziprasidone and aripiprazole.[29–33]

Neurologic

Sedation/somnolence. Sedation/somnolence are among the most frequently reported AEs associated with atypical antipsychotic usage. Sedation generally refers to diminished cognitive responsivity, while somnolence is often operationalized as subjective sleepiness. The co-occurrence of these phenomena is common, particularly in persons receiving polypharmacotherapy regimens.[34] The incidence and severity of sedation/somnolence are dissimilar among atypical antipsychotics. The differential affinity of atypical antipsychotics for H_1 receptors is probably the pharmacologic property most responsible for their dissimilarity in provoking sedation/somnolence.[27]

While sedation/somnolence may be helpful in the acute treatment of hospitalized patients with severe mania, it is a problematic side effect in the later stages of hospitalization and in the treatment of outpatients. Subjectively reported sedation/somnolence may impair the ability of ambulatory patients to function, reduce overall satisfaction with treatment, contribute to medication-discontinuation behavior, and subsequently increase risk of affective relapse. The severity of sedation/somnolence noted with acute therapy appears to diminish with some atypical antipsychotics during maintenance therapy.

The management of problematic sedation/somnolence begins by excluding other phenotypically similar syndromes (e.g., depression, dysphoria, hypothyroidism) and other iatrogenic causes (e.g., lithium-induced hypothyroidism).[27] Reducing an atypical antipsychotic's dose, if possible, and/or switching to another atypical antipsychotic with a lower propensity for sedation/somnolence would be the next therapeutic approach. The therapeutic usefulness of wake-promoting agents (e.g., modafinil, psychostimulants) has not been systematically studied in bipolar disorder populations.[35,36] Case reports of 3 patients (2 with schizophrenia and 1 with schizophrenia and mood disorder not otherwise specified) who were receiving modafinil for antipsychotic-induced sedation showed that modafinil reduced the amount of time patients slept without exacerbating psychotic symptoms.[36]

Extrapyramidal symptoms. Antipsychotic-induced movement disorders or extrapyramidal symptoms (EPS) are traditionally classified into acute syndromes, which include akathisia, dystonia, and parkinsonism, and tardive syndromes such as dyskinesia.[8,37] In studies that limited enrollment to persons with bipolar disorder, atypical antipsychotics provoked fewer EPS and posed a lower long-term risk of tardive dyskinesia than conventional antipsychotics.[38–42] Evidence suggests that persons with mood disorders may be at higher risk for tardive dyskinesia and other types of EPS than persons with schizophrenia, underscoring the relevance of improved neurologic safety of atypical antipsychotics in this patient population.[43,44] Some atypical antipsychotics, for example, risperidone and olanzapine, have a tendency to induce EPS at higher doses.[29,30,45]

Given the higher risk of EPS, the management of EPS in bipolar disorder includes increased monitoring and intermittent structured screening (i.e., Abnormal Involuntary Movement Scale), as well as patient education and counseling. Switching to and/or initiating an atypical antipsychotic with a reduced propensity for EPS is an alternative therapeutic avenue, while the use of adjuvant antiparkinsonian agents is reserved for occasional occurrences of EPS.

Seizures. A dose-dependent seizure risk has been established for clozapine.[46] Although clozapine has not been extensively studied in bipolar disorder, some evidence and clinical opinion support the use of this agent in treatment-refractory bipolar disorder populations.[47,48] The risk for seizure activity with atypical antipsychotics other than olanzapine, which also has a dose-dependent risk of seizure, does not appear to be higher than with placebo.[49] Factors associated with seizure activity include the use of concomitant agents that lower the seizure threshold, rapid dose titrations, slow drug metabolism, and drug-drug interactions.[50]

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS) has been reported less frequently with atypical than with conventional antipsychotics.[8,51] The classic symptoms of NMS are hyperthermia, muscle rigidity, changes in mental status, and autonomic dysfunction. The concomitant use of mood stabilizers (e.g., lithium) and other psychotropic agents in bipolar disorder patients may increase their susceptibility to this serious and potentially lethal event. As with most psychotropic agents, patients should be advised of the need for adequate hydration and avoidance of overheating while receiving atypical antipsychotic therapy.[52]

Cardiovascular

Myocarditis/cardiomyopathy. Symptomatic myocarditis usually occurs when a viral infection leads to lymphocytic infiltration. Myocarditis is not normally fatal: in 1990, the incidence of fatal myocarditis was calculated as 4 per million.[53,54] The risk of myocarditis in the first month of clozapine therapy has been estimated to be 10- to 20-fold greater than in the general population.[53] An association between clozapine and cardiomyopathy has also been described.[55] Case reports describing the risk of cardiomyopathy exist for some other atypical antipsychotics, some conventional antipsychotics, and some mood stabilizers (e.g., lithium).[55] The hazard rate for these other agents, however, has not been determined as the number of reports is relatively few.

It is recommended that practitioners promptly discontinue the use of clozapine upon suspicion of myocarditis.[46]

QTc prolongation. Modest prolongation of the QTc interval has been reported with some atypical antipsychotics, although the clinical significance of this effect is unknown. A randomized study[56] comparing thioridazine, haloperidol, risperidone, olanzapine, quetiapine, and ziprasidone found that 4 of the 6 drugs studied had a mean change in QTc interval from baseline of ≥ 10 ms, with thioridazine having the greatest mean change (30.1 ms) and olanzapine the least (1.7 ms). The mean increase in baseline-corrected QTc interval was observed at forecast C_{max} for all of the drugs. The coadministration of metabolic inhibitors with each of the agents did not augment QTc prolongation. None of the atypical antipsychotics prolonged the QTc interval by more than 16 ms. The use of atypical antipsychotics does not appear to be associated with an increased risk of cardiac events.[56]

Hyperprolactinemia

Prolactin has 2 main roles in the reproductive system. First, it stimulates the production of milk after the breast has been primed by estrogen. Second, it acts on the gonadotropin-releasing hormone pulse center in the hypothalamus to prevent the pituitary from releasing gonadotropins, an action that suppresses ovarian or testicular function. Although hyperprolactinemia is usually asymptomatic, it can produce symptoms in both women and men. Symptoms in women include menstrual irregularities, infertility, breast tenderness or engorgement, galactorrhea, migraine or tension headache syndrome, and estrogen-deficiency symptoms such as hot flashes. In men, hyperprolactinemia has been associated with reduced libido, erectile dysfunction, fatigue, and, occasionally, gynecomastia or galactorrhea.[8,57,58]

Hyperprolactinemia-associated amenorrhea may lead to health consequences, such as osteoporosis, which are related to estrogen deficiency. However, laboratory evidence of hyperprolactinemia in women with regular menses has not been reliably associated with an increase in developing metabolic bone disease.[8] Concerns have been expressed about hyperprolactinemia and the development of breast cancer. However, no conclusive evidence has been found that sustained hyperprolactinemia, in the absence of oral contraceptive usage, is associated with breast cancer.[59]

Risperidone has been associated with sustained hyperprolactinemia. In a review of controlled studies with risperidone administered at doses of as much as 6 mg/day, Cavallaro et al.[60] found sexual and endocrinologic side effects in 8% to 9% of women, erectile and ejaculatory dysfunction in 8% to 15% of men, and decreased libido variously reported at 2% to 12% for both sexes. An analysis of data from randomized, double-blind studies of risperidone in patients with chronic schizophrenia by Kleinberg et al.[61] estimated decreased libido at 1% in women and 10% in men. A recent comprehensive analysis failed to find any relation between risperidone-associated prolactin elevation and disturbances in growth and sexual maturation in children and adolescents with subaverage IQs.[62] Prolactin elevation with risperidone may be dose-dependent, although some persons exhibit prolactin elevation at lower doses. It is a testable hypothesis that higher prolactin responsivity may be related to dopamine-2 receptor gene polymorphisms.[63]

The differential diagnosis of hyperprolactinemia involves excluding pituitary microadenoma and the concomitant use of medications associated with prolactin increase (e.g., oral contraceptives, reserpine, haloperidol, and cimetidine). The management of hyperprolactinemia entails antipsychotic dose reduction, the concomitant use of a dopamine agonist (e.g., bromocriptine, cabergoline), or the use of an atypical antipsychotic not associated with sustained hyperprolactinemia.[8,58–60]

Reproductive Health and Safety

Pregnancy. Pregnancy is a period of heightened vulnerability for affective symptomatology and relapse in women with bipolar disorder. The selection of a psychotropic medication in pregnancy requires balancing the expected benefits against possible, often unknown, risks. Lithium and the anticonvulsant drugs (e.g., divalproex, carbamazepine) are associated with significant reproductive toxicity (i.e., structural malformations, growth retardation, perinatal toxicity, and adverse neurobehavioral sequelae).[64] Both classes of agents have been identified by the American Academy of Pediatrics (AAP) and FDA as category D (positive risk of human fetal teratogenicity has been demonstrated).[65,66]

The atypical antipsychotics have insufficient case registry data to inform definitive conclusions about their reproductive toxicity. They are largely classified by the AAP/FDA as class C (human fetal teratogenicity cannot be ruled out), with clozapine classified as B (no evidence of risk in humans).[66]

Clozapine, commercially available in Switzerland since 1961, does not raise prolactin levels, theoretically increasing the possibility of conception during clozapine therapy compared with conventional antipsychotics or risperidone.[67] Gestational diabetes mellitus, excessive weight gain, shoulder dystocia, floppy infant syndrome, hypotonia, and neonatal seizures have been described with clozapine.[68]

The case registry dataset for olanzapine is larger than that of other atypical antipsychotics. This dataset provides reassuring, albeit incomplete, data that the agent is not associated with any reproductive toxicity above the base rate of major congenital abnormalities (2% to 4%).[69,70] Currently, the human toxicity data are insufficient to suspect or not suspect risperidone, quetiapine, ziprasidone, and aripiprazole of fetal toxicity.[66]

Lactation. The postpartum period is a relatively high-risk period for an affective episode, especially for women with preexisting psychiatric disorders. An estimated 40% to 70% of women with bipolar disorder undergo postpartum mania or depression that is modifiable with mood-stabilizing therapies.[71–73] The AAP cautions against the use of lithium while breast-feeding, while valproate and carbamazepine are compatible with breast-feeding.[74]

No evidence has been found in clinical trials associating the atypical antipsychotics with fetal toxicity, but no evidence has been found demonstrating that this class of antipsychotics is not associated with fetal toxicity.[75] The AAP has designated clozapine as a drug "which may be of concern" during lactation.[74] Clozapine, some conventional antipsychotics, antianxiety agents, and antidepressants have long half-lives, which creates a risk that measurable amounts of the drug may accumulate in the plasma and tissue, including the brain, of nursing infants. For a comprehensive review of the risk of using atypical antipsychotics during reproductive years, with recommenda-

tions for monitoring and treatment during lactation, see Gentile[75] and the AAP Committee on Drugs.[74]

Polycystic ovarian syndrome. One other condition affecting reproductive-age women is polycystic ovarian syndrome (PCOS), an intrinsic pathologic process involving hyperandrogenism and ovulatory dysfunction occurring in 2% to 7% of women in their reproductive years. No data associate any of the available atypical antipsychotics with PCOS, although there have been reports of links between some atypical antipsychotics (i.e., clozapine and olanzapine) and metabolic syndrome, which may be a risk factor for the subsequent development of PCOS.[76] Valproate is the one medication for bipolar disorder that has been associated with PCOS.[73,77–81]

Affective Symptom Induction

Bipolar disorder is a multidimensional illness that requires effective treatments that target symptoms and avoid iatrogenic worsening of other dimensions of the illness. Concerns have been raised about affective symptom induction with a variety of psychotropic agents. Moreover, equivocal evidence suggests that genetic associations between some polymorphisms may be involved in medication-associated switches in bipolar disorder.[82,83] Interpreting switch data requires familiarity with naturalistic switch rates in bipolar disorder, which have been described since the prepharmacologic era.[84]

Although most practitioners are familiar with the possibility of antidepressant-destabilization of bipolar disorder,[85] there is growing concern that conventional antipsychotics may adversely affect symptoms in bipolar populations. Earlier studies evaluating the effectiveness of depot antipsychotic agents during the maintenance phase of bipolar disorder indicated that these agents may exacerbate and induce depressive symptoms in bipolar disorder patients.[86,87] Zarate and Tohen[88] explored the effectiveness of adjunctive continuation of the conventional antipsychotic perphenazine and a mood stabilizer in stabilized bipolar disorder patients (N = 37) in a randomized, placebo-controlled, 6-month study. Compared with patients who discontinued the combination therapy, patients who received perphenazine/mood stabilizer therapy were more likely to have less time to depressive relapse, discontinue the trial, and have elevated rates of dysphoria, depressive symptoms, and EPS.[88]

Data for the atypical antipsychotics in acute mania do not reveal any risk of postmania depression above the placebo rate (approximately 0%–10%). Randomized double-blind, placebo-controlled trials with olanzapine and quetiapine in bipolar depression also did not reveal evidence of manic switching. Moreover, maintenance studies of various designs with risperidone, olanzapine, ziprasidone, and aripiprazole have not found evidence of affective symptom aggravation into mania or depression and/or cycle acceleration.[21,28,89,90]

Taken together, data are reassuring, albeit incomplete, and indicate that atypical antipsychotics are not consistently associated with affective symptom induction or cycle acceleration in bipolar disorder. In contrast, conventional antipsychotics are associated with dysphoria, depressive symptom exacerbation, and affective relapse in short- and long-term studies in bipolar disorder. The apparent absence of a switch to another affective state with atypical antipsychotics is a distinct advantage compared with their therapeutic predecessors, the conventional antipsychotics, in the treatment of bipolar disorder. Similarly, antidepressants—including both the more recently developed selective serotonin reuptake inhibitors and the older tricyclic antidepressants—are associated with switches to manic states and cycle acceleration.[85] The potential advantage of atypical antipsychotics compared with conventional antipsychotics and antidepressants in the treatment of bipolar depression needs to be investigated further in controlled clinical studies.

CONCLUSION

The atypical antipsychotics are a class of agents that are heterogeneous in pharmacology, efficacy, tolerability, and safety. Their therapeutic index is an unequivocal advance compared with conventional antipsychotics in bipolar disorder. But atypical antipsychotics are not a panacea and are associated with several problematic tolerability and safety concerns. Improving the overall utility of these agents in bipolar disorder requires that practitioners be familiar with the major categories of AEs and how atypical antipsychotics differ in their propensity for inducing AEs.

Available atypical antipsychotics and novel atypical antipsychotics currently under investigation are being evaluated for various dimensions of bipolar disorder. As these treatments evolve and become cornerstone therapies in the management of bipolar disorder, there will be a further need to carefully characterize their effectiveness and overall safety in polypharmacotherapeutic regimens—a research vista for the future.

Drug names: aripiprazole (Abilify), bromocriptine (Parlodel and others), cabergoline (Dostinex), carbamazepine (Carbatrol, Tegretol, and others), chlorpromazine (Sonazine, Thorazine, and others), cimetidine (Tagamet and others), clozapine (Clozaril, Fazaclo, and others), divalproex (Depakote), fluphenazine (Prolixin and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), modafinil (Provigil), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), reserpine (Serpalan and others), risperidone (Risperdal), thioridazine (Intensol and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, bromocriptine and cabergoline are not approved by the U.S. Food and Drug Administration for the treatment of prolactin elevation; and carbamazepine, clozapine, fluphenazine, and perphenazine are not approved for the treatment of bipolar disorder.

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