

# Psychotropic Drugs and Adverse Events in the Treatment of Bipolar Disorders Revisited

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Psychopharmacology research aims to expand the therapeutic ratio between efficacy, on the one hand, and adverse events and safety, on the other. The novel antipsychotics are now the antipsychotics of choice in the treatment of bipolar disorders. They have the advantages of potential antidepressant properties and low risks of extrapyramidal side effects and, especially, of tardive dyskinesia. However, novel antipsychotics may also have varying propensities to cause side effects, such as somnolence, hyperprolactinemia, weight gain (sometimes significant), and possibly diabetes mellitus. The increasing use of these novel agents requires careful assessment and monitoring of emergent side effects and diligent consideration of associated medical complications. Two new anticonvulsants, lamotrigine and topiramate, have recently shown promise in the treatment of bipolar disorders. Most of their adverse effects can be avoided by slow titration toward the recommended doses. In contrast to carbamazepine and valproic acid, topiramate may be associated with weight loss.

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The fundamental goal of psychopharmacology research is to expand the therapeutic ratio between efficacy, on one hand, and adverse events and safety, on the other. New medications, such as novel antipsychotics and anticonvulsants, are showing a great deal of promise in the treatment of bipolar disorders, but these agents are not without side effects. Moreover, since combination therapy is the rule rather than the exception in the treatment of bipolar disorders, the risk and frequency of side effects are potentially multiplied for these patients. This

article will review the adverse-event profiles of the novel antipsychotics and anticonvulsants that are being used in treating patients with bipolar disorders.

## NOVEL ANTIPSYCHOTIC AGENTS

Novel antipsychotics are now the antipsychotics of choice for patients with bipolar affective disorders, having displaced the conventional antipsychotic agents.<sup>1</sup> Controlled data using risperidone, olanzapine, and ziprasidone all suggest that the incidence of extrapyramidal side effects (EPS) associated with these drugs is similar to placebo EPS rates. Although the novel antipsychotics are not devoid of EPS risk, the phenomenon appears to be dose related and manageable.<sup>2,3</sup> For example, doses of risperidone below 4 mg daily have the usual “atypical” receptor affinity profile, in which EPS risk is relatively minimal.<sup>4</sup> U.S. and international multicenter placebo-controlled trials comparing risperidone with haloperidol and placebo (in addition to a mood stabilizer) have shown rates of EPS with risperidone to be comparable to placebo (Figure 1).<sup>5,6</sup> In a Spanish trial investigating the safety and efficacy of risperidone in patients diagnosed with bipolar disorders (N = 527), the incidence of various extrapyramidal symptoms was seen to decline steadily over time (Figure 2).<sup>7</sup> Similarly, an analysis of data from 3 actively controlled, blinded studies found a very low risk of long-term treatment-emergent dyskinetic events associated with olanzapine (1%) compared with haloperidol (4.5%).<sup>8</sup>

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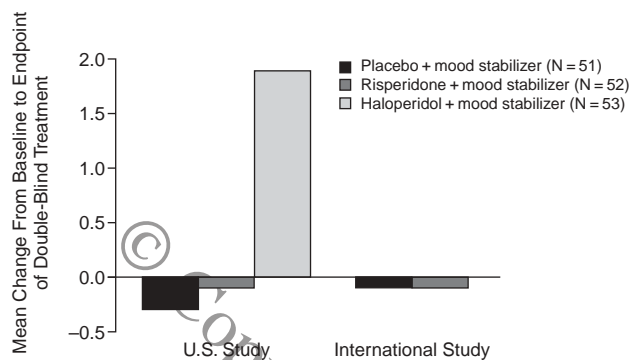
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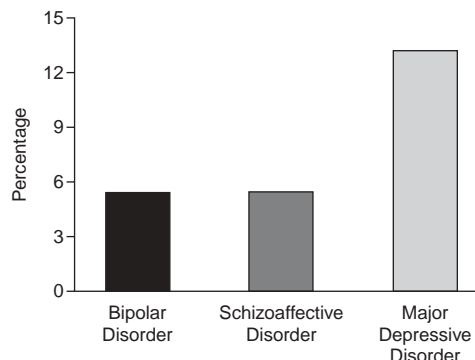
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**Figure 1. U.S. and International Risperidone Studies: Extrapyramidal Symptoms Rating Scale (ESRS) Score<sup>a</sup>**



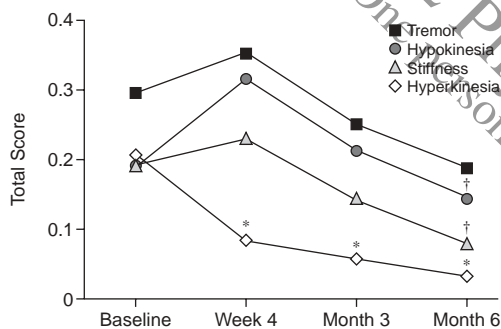
<sup>a</sup>Data from Sachs<sup>5</sup> and Yatham.<sup>6</sup>

**Figure 3. Patients With Tardive Dyskinesia Risk Receiving Conventional Antipsychotics in Mood Disorders<sup>a</sup>**



<sup>a</sup>Adapted with permission from Kane.<sup>10</sup>

**Figure 2. Risperidone in 527 Patients With Bipolar Disorder: Extrapyramidal Symptoms (EPS) Over 6 Months<sup>a</sup>**



<sup>a</sup>Data from Vieta et al.<sup>7</sup>  
\*p < .001 vs. baseline.  
†p < .05 vs. baseline.

The rate of tardive dyskinesia in young patients with schizophrenia is about 5% annually for the first few years of treatment with a conventional antipsychotic.<sup>9</sup> The rate of tardive dyskinesia among some mood disorder populations receiving conventional antipsychotics may be considerably higher (Figure 3).<sup>10</sup> In contrast, the tardive dyskinesia rate associated with the novel antipsychotics seems to be at about the 1% annual rate of spontaneous tardive dyskinesia seen in the general psychiatric population.<sup>9,11-13</sup> Indeed, in small studies that have described the utility of risperidone and olanzapine in the setting of bipolar disorders, no tardive dyskinesia has been noted.

Some recent reviews have concluded that the potential for somnolence imparted by an antipsychotic medication is correlated with its affinity for histamine receptors.<sup>14</sup> Inducing somnolence may be a desirable short-term effect for acutely manic and highly irritable patients, but it is obviously problematic in the longer term, particularly for

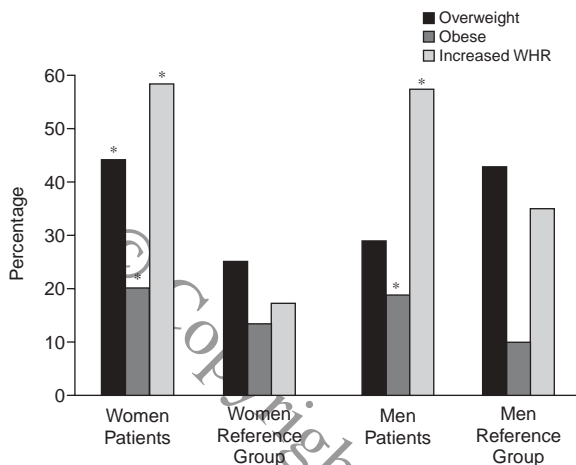
higher-functioning patients. In any case, the clinician should remove or reduce the amounts of concurrent central nervous system (CNS)-depressing agents and also rule out other causes of somnolence (for example, depression or lithium-induced hypothyroidism) before attributing the symptom solely to the antipsychotic medication.

The depressogenic potential of conventional antipsychotics has frequently been noted by clinicians. There are no data to prove that conventional antipsychotics cause depression directly—instead, they may unmask or induce a syndrome that is phenotypically similar (yet different) from depression. One plausible mechanism for the phenomenon is that conventional antipsychotics block endogenous dopaminergic reward systems in the brain. In contrast, novel antipsychotics are not depressogenic, and some novel antipsychotics, such as risperidone and olanzapine, may have antidepressant properties.

Scattered case reports in the literature claim that novel antipsychotics may induce mania.<sup>15-17</sup> However, the physician should interpret these findings with caution. For example, in one report of risperidone-induced mania,<sup>18</sup> the doses used were far higher than recommended, and mood stabilizers had recently been discontinued. There is no evidence from controlled trials involving novel antipsychotics that they induce mania.

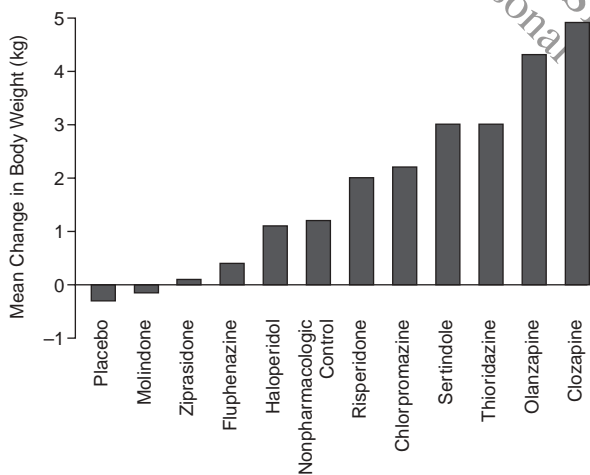
Like the conventional antipsychotics, risperidone<sup>19</sup> may produce hyperprolactinemia in a dose-dependent fashion. However, the serum level of prolactin correlates very poorly with clinical symptoms such as galactorrhea or menstrual or sexual dysfunction.<sup>20</sup> It is important to rule out secondary causes such as pituitary adenomas, but apart from this, asymptomatic hyperprolactinemia needs only to be monitored closely. For symptomatic patients, the options include decreasing the dose of the antipsychotic drug, adding a dopamine agonist, or, if necessary, switching medications.

Figure 4. Prevalence of Overweight and Obesity in Bipolar Patients<sup>a,b</sup>



<sup>a</sup>Data from Elmslie et al.<sup>22</sup> Abbreviation: WHR = waist:hip ratio.  
<sup>b</sup>N = 89 patients vs. 445 reference subjects.  
 \*p < .05.

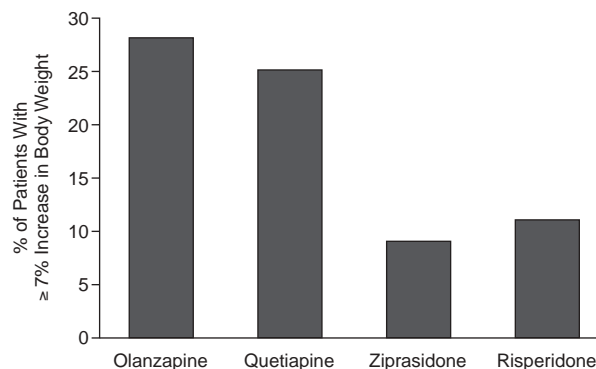
Figure 5. Estimated Mean Weight Gain at 10 Weeks<sup>a</sup>



<sup>a</sup>Adapted with permission from Allison et al.<sup>26</sup>

The past few decades have seen an unprecedented increase in the prevalence of overweight and obesity in the general North American population; currently, an estimated 50% of the Canadian and U.S. populations have body mass index (BMI) > 25 (normal BMI = 20 to 25). Although BMI is the most common measure of obesity, waist circumference is more closely correlated with central obesity, which is associated with increased health risks. Waist circumferences > 102 cm (40.2 in.) in men and > 88 cm (34.6 in.) in women are linked to cardiovascular morbidity.<sup>21</sup>

Figure 6. Controlled Trials of Antipsychotics: Weight Gain ≥ 7% From Baseline After 8 Weeks of Treatment<sup>a</sup>



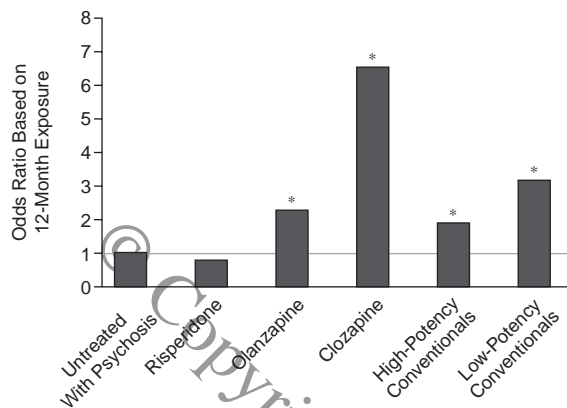
<sup>a</sup>Data from Conley and Mahmoud,<sup>27</sup> Garver,<sup>28</sup> and the FDA Psychopharmacological Drugs Advisory Committee.<sup>29</sup>

Among patients taking antipsychotic agents, a number of factors—including lack of previous exposure to antipsychotic medication—are risk factors for weight gain, but interestingly, dosage is not a reliable predictor. A recent study of 89 ambulatory bipolar patients<sup>22</sup> revealed higher BMIs and waist-to-hip ratios than the general population (Figure 4). The latter, a surrogate marker for abdominal adiposity, independently predicts coronary artery disease and diabetes mellitus. Moreover, data are accumulating that persons with chronic mental disorders are often overweight and obese.<sup>23</sup> Persons with persistent mental illness have high rates of adverse health behaviors (such as smoking and alcohol use) and often fail to receive adequate medical treatment.<sup>24,25</sup> This perilous combination of factors may be lethal.

That antipsychotic medications differ in their propensity to cause weight gain has been reported since the mid-1950s. Novel antipsychotics as a class are more likely to cause weight gain than conventional antipsychotics, and among the former, a meta-analysis suggests that clozapine and olanzapine are associated with the most weight gain, while risperidone and ziprasidone are associated with less (Figure 5).<sup>26</sup> Data from controlled studies<sup>27-29</sup> also indicate that olanzapine and quetiapine are associated with a higher proportion of patients gaining ≥ 7% of body weight during an 8-week treatment period than are ziprasidone or risperidone (Figure 6). The propensity for weight gain with some agents may be correlated with in vitro affinity for 5-HT<sub>2C</sub> and histamine H<sub>1</sub> receptors.<sup>30</sup> However, it should be kept in mind that weight gain is a “final common phenotype” that is probably the culmination of a complex series of events.

Weight gain is difficult to manage, and therefore, primary prevention should be the preferred strategy. Behavioral interventions can be a useful part of a primary or secondary prevention strategy. Almost no systematic

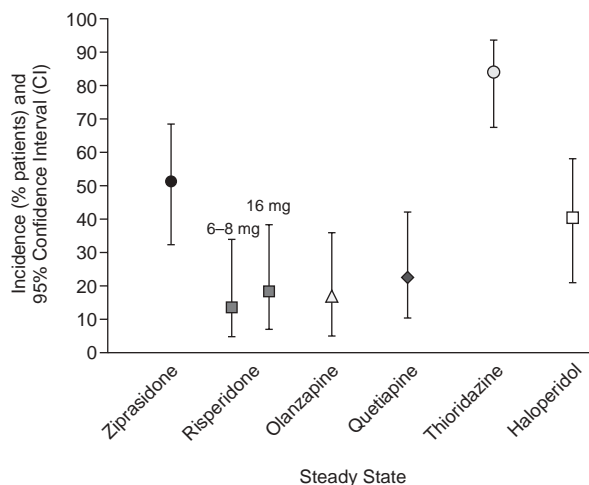
**Figure 7. Differential Effects of Antipsychotics on Type 2 Diabetes: Findings From a Large Health Plan Database<sup>a</sup>**



<sup>a</sup>Data from Mahmoud et al.<sup>35</sup> for 2.5 million lives analyzed; adjusted for age, prior medication exposure, 8-month preexisting type 2 diabetes.

\*Statistically significant compared with untreated psychotic patient group;  $p < .05$ .

**Figure 8. Incidence of QTc Increases  $\geq 30$  msec at Steady State; Study 054<sup>a</sup>**



<sup>a</sup>Adapted from the FDA Psychopharmacological Drugs Advisory Committee briefing document for Zeldox capsules.<sup>29</sup>

study of contemporary weight loss agents (i.e., orlistat, sibutramine) in individuals with mental disorders has been performed, although new reports are emerging that suggest the new anticonvulsant topiramate may cause weight loss.<sup>31</sup> Psychiatrists should ensure that their patients' weights, fasting blood glucose levels, and lipid profiles are monitored periodically.

Currently, the relationship between glucoregulatory abnormalities and novel antipsychotics is under active investigation. Most studies of apparent novel antipsychotic-induced diabetes mellitus are case reports involving clozapine<sup>32,33</sup> or olanzapine.<sup>34</sup> It appears that the relative risk of diabetes is elevated 2- to 4-fold in patients with schizophrenic or bipolar disorders. According to recent data from a large health plan database, which included more than 15,000 patients receiving treatment for psychosis,<sup>35</sup> there are substantial differences in the relative risk of diabetes among the available antipsychotic therapies. It was determined that patients receiving clozapine, conventional antipsychotics, or olanzapine had a 2-fold higher prevalence of type 2 diabetes (Figure 7) than the untreated patients. Although weight gain may be a risk factor for diabetes, other variables are also relevant. In 1 study of 82 patients with schizophrenia receiving clozapine, 38% developed diabetes after 60 months. Notably, the occurrence of diabetes was not related to weight gain.<sup>36</sup>

QT interval prolongation has received increased attention since the recent issuance of regulatory warnings about thioridazine. Study 054<sup>29</sup> (Figure 8) is a comparative study conducted by Pfizer, Inc., of the use of antipsychotic medications in 164 patients. Only thioridazine

was observed to cause QTc increases  $\geq 75$  msec (a significant increase), and only ziprasidone and thioridazine caused QTc increases  $\geq 60$  msec. Although all of the novel antipsychotics examined were associated with some prolongation of the QT interval, there were no statistical differences between them, and none of the prolongations (including those provoked by ziprasidone) were deemed to be pathologic. The QT interval is influenced by a great many variables, and there is a dearth of well-designed direct comparative studies that control for these.<sup>37</sup>

### ANTICONVULSANT AGENTS

The use of the anticonvulsants carbamazepine and valproic acid to treat bipolar disorder is now familiar to psychiatrists. The most commonly reported side effects of carbamazepine include CNS-related problems such as drowsiness, headache, dizziness, ataxia and diplopia, gastrointestinal upset, allergic skin reactions, leukopenia, and elevated liver enzymes, particularly  $\gamma$ -glutamyltransferase. Most of these adverse events are early and transient and can be managed by beginning treatment at low doses. However, the possibility of rare and serious blood dyscrasias and of hepatic failure requires careful ongoing monitoring. In long-term trials involving bipolar patients, the most frequent side effects of valproic acid have been somnolence, tremor, headache, weakness, and gastrointestinal upset. The most frequent adverse effects associated with discontinuation were nausea, tremor, somnolence, and alopecia.<sup>38</sup>

Two new anticonvulsants have recently shown promise in the treatment of bipolar disorder. The most common

side effects of lamotrigine are dizziness, tremor, somnolence, headache, nausea, and rash.<sup>39</sup> The rash varies in appearance and severity ranging from a measles-like condition to Stevens-Johnson syndrome and toxic epidermal necrolysis. However, the incidence of rash is lower in adults than in children, and it is now known that if the drug is started at the recommended low doses and titrated slowly, the incidence of serious rash is greatly reduced.<sup>40</sup> The most common adverse events reported with topiramate are paresthesias (as expected for a carbonic anhydrase inhibitor), dizziness, anxiety, and fatigue. Most of these side effects can be avoided by slow titration to the recommended doses. For acute treatment of mania, the suggested doses are 200 to 400 mg/day titrated over 4 to 10 days, while the typical maintenance or add-on doses are 50 to 400 mg/day with a titration of approximately 25 mg/wk. Interestingly, new reports are emerging that suggest that, in contrast to carbamazepine and valproic acid, topiramate may be associated with weight loss.<sup>31</sup>

## CONCLUSION

In conclusion, the new treatment options that are now routinely being used in bipolar disorders appear to impart a lower rate of serious adverse events than do the older antibipolar therapies. It would seem that at least some of the new agents offer the desired expanded therapeutic ratio between efficacy and safety.

*Drug names:* carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lamotrigine (Lamictal), molindone (Moban), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia), topiramate (Topamax), valproic acid (Depakene), ziprasidone (Geodon).

## REFERENCES

- Canadian Disease and Therapeutic Index (CDTI); Montreal, Canada: IMS Health; 2000
- Miller CH, Umbricht DSG, Lieberman JA, et al. The prevalence and severity of acute extrapyramidal side effects in patients treated with clozapine, risperidone or conventional antipsychotics. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 8, 1996; New York, NY. Abstract NR542:217-218
- Rosebush PI, Mazurek MF. Neurologic side effects in neuroleptic-naïve patients treated with haloperidol or risperidone. *Neurology* 1999;52:782-785
- Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT<sub>2</sub> and D<sub>2</sub> receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiatry* 1999;156:286-293
- Sachs GS. Safety and efficacy of risperidone versus placebo in combination with lithium or valproate in the treatment of the manic phase of bipolar disorder [poster]. Presented at the 22nd annual meeting of the Congress of the College of International Neuropsychopharmacology; July 9-13, 2000; Brussels, Belgium
- Yatham L. Safety and efficacy of risperidone as combination therapy for the manic phase of bipolar disorder: preliminary findings of a randomized, double-blind study (Ris-Int-46) [poster]. Presented at the 22nd annual meeting of the Congress of the College of International Neuropsychopharmacology; July 9-13, 2000; Brussels, Belgium
- Vieta E, Herraiz A, Fernández A, et al. Risperidone as add on therapy in bipolar disorder [poster]. Presented at the 38th annual meeting of the American College of Neuropsychopharmacology; Dec 12-16, 1999; Acapulco, Mexico
- Tollefson GD, Beasley CM Jr, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry* 1997;154:1248-1254
- Kane JM, Woerner MG, Pollack S, et al. Does clozapine cause tardive dyskinesia? *J Clin Psychiatry* 1993;54:327-330
- Kane JM. Tardive dyskinesia in affective disorders. *J Clin Psychiatry* 1999;60(suppl 5):43-47
- Lemmens P, Brecher M, Van Baelen B. Extrapyramidal symptoms in patients treated with risperidone [abstract]. Presented at the 35th annual meeting of the American College of Neuropsychopharmacology; Dec 9-13, 1996; San Juan, Puerto Rico
- Tollefson GD, Beasley CM, Tamura RN. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. *Am J Psychiatry* 1997;154:1248-1254
- Woerner MG, Kane JM, Lieberman JA, et al. The prevalence of tardive dyskinesia. *J Clin Psychopharmacol* 1991;11:34-42
- Zarate CA. Antipsychotic drug side effect issues in bipolar manic patients. *J Clin Psychiatry* 2000;61(suppl 8):52-63
- Koek RJ, Kessler CC. Probable induction of mania by risperidone. *J Clin Psychiatry* 1996;57:174-175
- Gelenberg AJ. Can risperidone trigger mania? *Biol Ther Psychiatry News* 1996;19:18-19
- Fitz-Gerald MJ, Pinkofsky HB, Brannon G, et al. Olanzapine-induced mania [letter]. *Am J Psychiatry* 1999;156:1114
- Dwight MM, Keck PE Jr, Stanton SP, et al. Antidepressant activity and mania associated with risperidone treatment of schizoaffective disorder. *Lancet* 1994;344:554-555
- Kleinberg DL, Davis JM, de Coster R, et al. Prolactin levels and adverse events in patients treated with risperidone. *J Clin Psychopharmacol* 1999;19:57-61
- Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. *J Clin Psychiatry* 1999;60(suppl 10):5-14
- Lean M, Anderson A. Clinical strategies for obesity management. *Diabet Med* 1988;5:515-518
- Elmslie JL, Silverstone JT, Mann JJ, et al. Prevalence of overweight and obesity in bipolar patients. *J Clin Psychiatry* 2000;61:179-184
- Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 1999;60:215-220
- Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. *J Nerv Ment Dis* 1999;187:496-502
- Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med* 1998;338:1516-1520
- Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686-1696
- Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2001;158:765-774
- Garver DL. Review of quetiapine side effects. *J Clin Psychiatry* 2000;61(suppl 8):31-35
- FDA Psychopharmacological Drugs Advisory Committee: briefing document for Zeldox (ziprasidone hydrochloride capsules). July 19, 2000, 1-173. Available at: <http://www.fda.gov/ohms/dockets/ac/00/backgrd/3619b1a.pdf>. Accessed Aug 9, 2000
- Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 1999;60:358-363
- McIntyre RS, Mancini D, McCann S, et al. Topiramate vs bupropion SR added to mood stabilizer therapy for the depressive phase of bipolar disorder: a single-blind study. Presented at the Hormone, Brain, and Neuro-psychopharmacology Congress; July 16-19, 2000; Rhodes, Greece
- Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. *Am J Psychiatry* 1994;151:1395
- Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. *Am J Psychiatry* 1994;151:1520-1521
- Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and

- diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* 1999;40:438–443
35. Mahmoud R, Gianfancesco F, Grogg A, et al. Differential effects of antipsychotics on type 2 diabetes: findings from a large health plan database [poster]. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
  36. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* 2000;157:975–981
  37. Welch R, Chue P. Antipsychotic agents and QT changes. *J Psychiatry Neurosci* 2000;25:154–160
  38. Canadian Pharmaceutical Association. *Compendium of Pharmaceuticals and Specialties* 2001. 36th ed. Ottawa, Ontario, Canada: Canadian Pharmaceutical Association; 2001
  39. Calabrese JR, Bowden CL, McElroy SL, et al. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. *Am J Psychiatry* 1999;156:1019–1023
  40. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. *Ann Pharmacother* 1999;33:1037–1042

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