# Changes in Weight, Plasma Lipids, and Glucose in Adults Treated With Ziprasidone: A Comprehensive Analysis of Pfizer-Initiated Clinical Trials

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**ABSTRACT**

***Background:*** Elevated cardiometabolic morbidity and mortality in patients with schizophrenia and bipolar disorder have been attributed to multiple sources, including antipsychotic treatment, which may adversely affect cardiometabolic risk factors. We therefore present here a comprehensive set of analyses of changes in metabolic parameters from ziprasidone clinical trials.

***Method:*** The comprehensive set of analyses of metabolic changes conducted here was considered post hoc and exploratory. Changes in weight, fasting lipids, and fasting glucose from baseline to study end (last observation carried forward [LOCF]) for adult subjects in Pfizer-sponsored oral monotherapy randomized placebo-controlled ziprasidone clinical trials were analyzed by using an analysis of covariance model. In addition, available weight, fasting lipids, and fasting glucose data from all ziprasidone-treated subjects from all controlled and uncontrolled oral monotherapy studies of ziprasidone (102 studies; N = 12,599) conducted from 1992 to 2009 were analyzed similarly.

***Results:*** In short-term randomized controlled trials (RCTs) (duration ≤ 12 weeks), least squares mean ± SD change from baseline to end of study (LOCF) in weight was 0.64 ± 0.12 kg in ziprasidone-treated subjects (n = 1,386) versus −0.02 ± 0.14 kg in placebo-treated subjects (n = 747) ($P < .0001$); in long-term RCTs (duration > 12 weeks), the corresponding values were −0.96 ± 0.68 kg for ziprasidone (n = 363) and −1.68 ± 0.80 kg for placebo (n = 142) ($P = .24$). Mean ± SD weight change in ziprasidone-treated subjects from all controlled and uncontrolled studies ranged from 0.2 ± 5.6 kg at 6 weeks (n = 3,156) to 1.7 ± 10.1 kg at 36 months (n = 178). There were no significant differences between the ziprasidone and placebo groups in fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or glucose in the controlled studies, and there were minimal changes in ziprasidone-treated subjects in all controlled and uncontrolled studies.

***Conclusions:*** This comprehensive analysis of data from the ziprasidone clinical trial database demonstrates limited evidence of any clinically significant adverse effects of ziprasidone on weight and consistent evidence of a neutral effect on fasting plasma lipids and glucose.

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Evidence indicates that average life expectancy for individuals with major mental illness is up to 30 years less than that of the general population.[1–4] A recent study involving data from the public health systems of several US states examined life expectancy for people with a major mental illness, including affective disorders, such as major depression and bipolar disorder, attention-deficit/hyperactivity disorders, schizophrenia, and schizoaffective disorders. The results indicated that mean age at death was 25 to 30 years lower than that observed in the general population over the same years in the same states.[2] Significantly, the leading cause of death in the mentally ill in this study was coronary heart disease. Overall, cardiovascular disease (encompassing coronary heart disease, cerebrovascular disease, and peripheral vascular disease) was associated with more than 35% of deaths in this population (suicide was associated with fewer than 5%). In a separate study, Saha and colleagues[5] examined the distribution of relative risk for mortality, measured as all-cause standardized mortality ratios, in 37 trials involving schizophrenia patients. Median all-cause standardized mortality ratio was 2.58, compared with the general population. Increased standardized mortality ratios were detected for most causes of death, with overall standardized mortality ratios noted to be increasing over the past 3 decades, suggesting an increasing gap between mortality rates in schizophrenia versus those in the general population.[5]

Studies like these have focused attention on the high prevalence and risk of cardiovascular disease among those with major mental illness. Although mortality attributable to cardiovascular disease in the general population has markedly declined in recent decades (from more than 50% to approximately 36% of underlying cause of deaths in the United States, for example), similar improvements have not extended to individuals with major mental illness. In patients with schizophrenia, for example, cardiovascular disease is the leading cause of mortality, with schizophrenia patients more likely to experience premature cardiovascular disease mortality than individuals in the general population.[6] Increased rates of cardiovascular disease risk among those with major mental illnesses like schizophrenia are influenced by a number of factors, including the increased prevalence of established modifiable cardiovascular disease risk factors, such as elevated blood pressure, dyslipidemia, overweight and obesity, hyperglycemia and diabetes, and smoking.[7–12] For example, obesity is approximately twice as prevalent in people with severe mental illnesses such as schizophrenia in comparison to the general population.[8] Similarly, a number of studies of individuals with bipolar disorder have reported

increased rates of obesity, smoking, diabetes, hypertension, dyslipidemia, and metabolic syndrome, with standardized mortality ratios ranging from 1.5 to 3 relative to the general population.[13–17]

While increases in cardiometabolic morbidity and mortality in this population can be attributed to multiple sources,[18] the effect of antipsychotic treatment on key risk factors like weight and adiposity has been recognized as a key contributor to risk.[19] This background, along with pharmacoepidemiological studies suggesting increased risk of diabetes mellitus in association with some second-generation antipsychotics, led to initial US Food and Drug Administration (FDA) review of available clinical trials and adverse event reports for hyperglycemia and diabetes with these medications and, in 2003 and 2004, an FDA requirement for the addition of a class warning to the product labeling concerning risk for hyperglycemia, diabetes, and related metabolic disturbances for all second-generation antipsychotic drugs. At that time, Pfizer undertook a number of analyses to determine the extent to which ziprasidone, a second-generation antipsychotic agent used in the management of schizophrenia and acute bipolar mania, may pose such risks. Comprehensive analyses of existing clinical trial data were performed and presented at the American Psychiatric Association (APA) annual meetings in 2007[20] and 2008,[21] several switch studies were conducted and published,[22,23] and data were presented and analyzed at the American Diabetes Association/APA consensus development conference in 2004.[24] In October 2007, the FDA prescribing information for olanzapine was further altered to incorporate warnings about increased risk of weight gain, hyperglycemia, and hyperlipidemia associated with olanzapine use compared with other agents in its class. In 2008, the FDA requested that all manufacturers of second-generation antipsychotics provide specific analyses to the FDA for the purpose of evaluating the extent to which each of these agents may contribute to these metabolic adverse events.

We present here a summary of the results of the most current set of comprehensive analyses of metabolic data from all Pfizer-sponsored monotherapy clinical trials of oral ziprasidone in adults with bipolar disorder or schizophrenia. Because the results of placebo-controlled, double-blind studies constitute class I evidence and are the only data that can be interpreted precisely in terms of drug-attributable effect, this report focuses on these data. However, given the importance of long-term outcomes, results of uncontrolled studies are also presented. Taken together, these data—accumulated over the course of a clinical trial program extending over 18 years—provide a transparent and comprehensive assessment of the effects of ziprasidone on weight and metabolic parameters.

## METHOD

Overall, analyses of metabolic data were performed on pooled data drawn from a database comprising all Pfizer-sponsored clinical studies of oral ziprasidone monotherapy for the treatment of schizophrenia and schizoaffective disorder or bipolar disorder in adults (102 studies; N = 12,599). These studies include 8 phase 1 and 94 phase 2, 3, and 4 studies, ranging from 1 to 156 weeks in duration, with database locks before June 2009. Patients in these studies were treated with doses of ziprasidone ranging from 10 to 200 mg daily. The first subject, first visit for the earliest trial occurred on August 6, 1990, and the first subject, first visit for the earliest phase 3 trial was on June 5, 1992. Results of many of these studies have been published previously.[20,25–28]

Studies were excluded from the analyses if they lacked a ziprasidone monotherapy arm, lasted < 7 days, had a relapse-prevention study design in which subjects had ziprasidone exposure prior to randomization, or were designed to evaluate ziprasidone using non-oral routes of drug delivery (eg, intramuscular, intravenous). Also excluded were trials recruiting only patients aged over 65 years, where underlying weight loss in the subject population may lead to underestimates of drug effects on weight gain and other metabolic parameters in the general adult population.

For the purpose of these analyses, studies were grouped as follows: (1) placebo-controlled short-term studies (≤ 12 weeks); (2) placebo-controlled long-term studies (≥ 52 weeks); and (3) all controlled and uncontrolled studies. As these analyses were considered post hoc and exploratory, no adjustments were made to CI or *P* values to adjust for multiple statistical comparisons.

For short-term randomized controlled trials (RCTs), least squares mean change from baseline to study end in weight; fasting triglycerides; fasting total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; and fasting glucose was determined for ziprasidone-treated and placebo-treated patients by using an analysis of covariance model, with treatment and protocol as independent variables (last-observation-carried-forward [LOCF] method was used to handle missing data).

A categorical summary of change from baseline to any postbaseline measurement (baseline, n; any postbaseline measurement, n [%]), in which some of the key categories

**Clinical Points**

- This work is the first to report the metabolic effects of a second-generation antipsychotic that incorporates data from an entire clinical trial program.
- These analyses provide compelling evidence that ziprasidone is a low-risk agent in terms of liability for weight gain when used in the treatment of adults with schizophrenia or bipolar disorder and that it has a neutral effect on fasting plasma lipids and glucose.
- Given the importance of cardiometabolic risk factors in contributing to major morbidity and mortality in patients with major mental illness, therapeutic options with the lowest likelihood of contributing to risk are clinically desirable.


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specified by the FDA were used, is presented for fasting lipids and fasting glucose in short-term RCTs. This summary includes changes in plasma concentration greater than a threshold amount, shift from borderline to high plasma concentration values, and shift from normal to high values. Categories of interest for triglycerides were an increase ≥ 50 mg/dL; shift from borderline to high, defined as an increase from ≥ 150 mg/dL and < 200 mg/dL to ≥ 200 mg/dL; and shift from normal to high, defined as an increase from < 150 mg/dL to ≥ 200 mg/dL. Corresponding categories were defined for change in fasting total, LDL, and HDL cholesterol. For fasting plasma glucose, categories of interest were defined as a shift from borderline to high (≥ 100 and < 126 mg/dL to ≥ 126 mg/dL) and a shift from normal to high (< 100 mg/dL to ≥ 126 mg/dL); a threshold value was not applied.

For long-term RCTs, there were no available data for fasting lipids or glucose; only weight data were analyzed for this group of studies.

For all controlled and uncontrolled studies, mean change from baseline to last measurement for weight; fasting triglycerides; fasting total, LDL, and HDL cholesterol; and fasting glucose levels were estimated for all subjects receiving ziprasidone. Although all studies had weight data, the majority of studies did not have fasting glucose or fasting lipid data; only those studies that collected such data were included in the corresponding analyses. For each analysis, descriptive statistics (n, mean ± SD change from baseline to last measurement, median duration of treatment exposure, and mean ± SD modal dose) were obtained. For the analyses of fasting lipids and fasting glucose, studies were divided into those lasting up to 12 weeks and those lasting at least 48 weeks. Summary statistics for weight change are presented for periods of ziprasidone exposure of 6 weeks, 6 months, 12 months, 24 months, and 36 months.

A categorical summary of change in fasting lipids and fasting glucose is presented for subjects receiving ziprasidone from all controlled and uncontrolled studies using the same cut-offs as were used in the analyses of data from the short-term RCTs. Weight change was summarized by using some of the key categories specified by the FDA: no change in weight, weight gain between 0 and 30 kg (in increments of 5 kg, reflecting World Health Organization categories for weight change), and weight gain > 30 kg. Additionally, the incidence of weight gain ≥ 7% from baseline was estimated.

## RESULTS

Demographic characteristics of the subjects included in these analyses are shown in Table 1.

**Table 1. Demographic Characteristics of All Subjects in the Controlled and Uncontrolled Adult Oral Monotherapy Ziprasidone Clinical Trials**

| Variable | Ziprasidone (n = 11,558) | Placebo (n = 1,041) |
|---|---|---|
| Age, y | | |
| Mean ± SD | 38.0 ± 11.5 | 40.2 ± 12.5 |
| Range | 18.0–98.0 | 18.0–92.0 |
| Gender, n (%) | | |
| Male | 7,309 (63.2) | 622 (59.8) |
| Female | 4,249 (36.8) | 419 (41.2) |
| Race, n (%) | | |
| White | 7,497 (64.9) | 734 (70.5) |
| Black | 1,402 (12.1) | 196 (18.8) |
| Asian | 1,041 (9.0) | 51 (4.9) |
| Hispanic | 314 (2.7) | 8 (0.8) |
| Other | 512 (4.4) | 52 (5.0) |
| Missing | 792 (6.9) | 0 (0.0) |
| Weight, kg | | |
| Arithmetic mean ± SD | 77.5 ± 19.2 | 80.2 ± 20.1 |
| Range | 33.0–216.7 | 39.3–188.2 |
| Median time of exposure to treatment, d | | |
| Median | 54 | 62 |
| Quartile 1 | 28 | 24 |
| Quartile 3 | 127 | 64 |
| Range | 1–2,406 | 5–69 |

### Short-Term RCTs

***Weight (14 studies).*** The estimated difference in least squares mean weight change from baseline to end of study (LOCF) between subjects treated with ziprasidone (n = 1,386) and those treated with placebo (n = 747) was 0.66 kg (95% CI, 0.36–0.95; $P < .0001$) (Table 2). Mean ± SD modal dose of ziprasidone was 102 ± 53 mg/d, and median duration of study drug exposure was 28 days.

***Lipids (4 studies).*** For all lipid parameters, the difference between treatment groups was not statistically significant (Table 2). Median duration of study drug exposure was 42 days, and mean modal ziprasidone dose ranged from 95 mg/d to 99 mg/d.

A summary of the categorical change in fasting lipids by treatment is displayed in Table 3. In both groups, the most commonly occurring categorical shift was from borderline to high fasting triglycerides (ziprasidone, 31.9%; placebo, 28.8%), and the least frequent shift was from normal to high fasting LDL cholesterol (ziprasidone, 0.0%; placebo, 1.1%).

***Glucose (4 studies).*** The estimated mean change in fasting glucose was similar (and not significantly different) for ziprasidone and placebo groups (least squares mean ± SE: 2.60 ± 1.85 mg/dL and 2.19 ± 2.11 mg/dL in the ziprasidone and placebo groups, respectively) (Table 2).

A shift from normal to high fasting glucose concentration occurred in 2.0% of subjects in the ziprasidone group and 0.9% in the placebo group) (Table 3).

### Long-Term RCTs

***Weight (4 studies).*** Least squares mean change in weight from baseline to end of study (LOCF) was –0.96 ± 0.68 kg in the ziprasidone group (n = 363) and –1.68 ± 0.80 kg in the placebo group (n = 142); the estimated difference between treatment groups was 0.72 (95% CI, –0.48 to 1.92; $P = .24$) (Table 2). The mean ± SD modal dose of ziprasidone was 82 ± 44 mg/d; the median duration of exposure to ziprasidone was 272 days, compared with 103 days for placebo.

There were no data for fasting lipids or fasting glucose in the long-term RCTs.

**Table 2. Summary of Change in Metabolic Parameters in Adults From Placebo-Controlled Oral Ziprasidone Monotherapy Trials**

| Outcome Variable | Study Duration, wk | Change From Baseline to End of Study, LOCF, LS Mean ± SE (n) | | Treatment Difference, LS Mean (95% CI), kg | *P* Value |
|---|---|---|---|---|---|
| | | Ziprasidone | Placebo | | |
| Weight, kg | ≤ 12 | 0.64 ± 0.12 (1,386) | −0.02 ± 0.14 (747) | 0.66 (0.36 to 0.95) | < .0001 |
| | ≥ 52 | −0.96 ± 0.68 (363) | −1.68 ± 0.80 (142) | 0.72 (−0.48 to 1.92) | .24 |
| Glucose, mg/dL | ≤ 12 | 2.60 ± 1.85 (406) | 2.19 ± 2.11 (297) | 0.40 (−3.04 to 3.85) | .82 |
| Fasting triglycerides, mg/dL | ≤ 12 | 0.27 ± 5.85 (429) | 10.90 ± 6.46 (331) | −10.63 (−23.10 to 1.84) | .09 |
| Fasting total cholesterol, mg/dL | ≤ 12 | 3.35 ± 2.09 (429) | 4.10 ± 2.30 (331) | −0.75 (−5.20 to 3.69) | .74 |
| Fasting LDL cholesterol, mg/dL | ≤ 12 | −3.14 ± 1.47 (359) | −1.93 ± 1.67 (270) | −1.20 (−5.59 to 3.18) | .59 |
| Fasting HDL cholesterol, mg/dL | ≤ 12 | −0.05 ± 0.44 (371) | −0.87 ± 0.49 (286) | 0.83 (−0.47 to 2.12) | .21 |

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, LOCF = last observation carried forward, LS = least squares, SE = standard error.

**Table 3. Categorical Change From Baseline in Fasting Lipids and Glucose in Short-Term Randomized Controlled Trials**

| Laboratory Analyte (fasting) | Category Change From Baseline (at least once), mg/dL | Ziprasidone | | Placebo | |
|---|---|---|---|---|---|
| | | Baseline, n | Any Postbaseline Measurement, n (%) | Baseline, n | Any Postbaseline Measurement, n (%) |
| Triglycerides | Increase by ≥ 50 | 429 | 82 (19.1) | 331 | 77 (23.3) |
| | Normal to high (< 150 to ≥ 200) | 258 | 20 (7.8) | 212 | 18 (8.5) |
| | Borderline to high (≥ 150 and < 200 to ≥ 200) | 69 | 22 (31.9) | 52 | 15 (28.8) |
| Total cholesterol | Increase by ≥ 40 | 429 | 43 (10.0) | 331 | 18 (5.4) |
| | Normal to high (< 200 to ≥ 240) | 244 | 6 (2.5) | 181 | 3 (1.7) |
| | Borderline to high (≥ 200 and < 240 to ≥ 240) | 119 | 14 (11.8) | 99 | 15 (15.2) |
| LDL cholesterol | Increase by ≥ 30 | 359 | 39 (10.9) | 270 | 17 (6.3) |
| | Normal to high (< 100 to ≥ 160) | 115 | 0 (0.0) | 89 | 1 (1.1) |
| | Borderline to high (≥ 100 and < 160 to ≥ 160) | 193 | 18 (9.3) | 141 | 14 (9.9) |
| HDL cholesterol | Normal to low (≥ 40 to < 40) | 283 | 22 (7.8) | 220 | 24 (10.9) |
| Glucose | Normal to high (< 100 to ≥ 126) | 305 | 6 (2.0) | 219 | 2 (0.9) |
| | Borderline to high (≥ 100 and < 126 to ≥ 126) | 80 | 12 (15.0) | 72 | 7 (9.7) |

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

### All Controlled and Uncontrolled Studies

***Weight (102 studies).*** Mean ± SD changes from baseline to specified time point (observed cases) for ziprasidone-treated subjects were 0.2 ± 5.6 kg at 6 weeks (n = 3,156); −0.9 ± 9.4 kg at 6 months (n = 1,171); −0.8 ± 10.0 kg at 12 months (n = 1,301); 1.1 ± 9.2 kg at 24 months (n = 338); and 1.7 ± 10.1 kg at 36 months (n = 178).

Categorical changes in weight are shown in Supplementary eFigure 1 (available at Psychiatrist.com). Subjects who lost weight or stayed the same weight comprised the largest category at each time point (range, 56.9% at 12 months to 46.1% at 36 months). The incidence of ≥ 7% weight gain from baseline was 5.4% at 6 weeks, 10.8% at 6 months, 16.7% at 12 months, 26.6% at 24 months, and 29.2% at 36 months.

***Lipids (18 studies).*** In subjects treated with ziprasidone for up to 12 weeks, fasting lipid values declined, except for HDL cholesterol, for which higher values are better (Table 4). Subjects receiving ziprasidone for at least 48 weeks demonstrated slightly more beneficial changes in all lipid parameters than those receiving ziprasidone for up to 12 weeks (Table 4). Categorical shift in fasting lipids is shown in Table 5.

***Glucose (24 studies).*** Mean ± SD change in fasting glucose was 1.3 ± 19.6 mg/dL in subjects receiving ziprasidone for at least 48 weeks (median duration of exposure of 438 days), compared with 0.7 ± 26.8 mg/dL in those who received medication for up to 12 weeks (median duration of exposure of 42 days) (Table 4).

Although the number of subjects receiving ziprasidone for at least 48 weeks was small, the proportion shifting from normal to high was greater than that seen in those receiving ziprasidone for up to 12 weeks (4.5% vs 3.2%), whereas the percentage shifting from borderline to high was smaller (8.8% vs 12.2%) (Table 5).

## DISCUSSION

This summary of key analyses of the metabolic effects of ziprasidone, based on the complete clinical trial database spanning studies from 1992 to 2009, provides compelling evidence that ziprasidone is a low-risk agent in terms of liability for weight gain, hyperlipidemia, or hyperglycemia. Pooled data from short-term placebo-controlled double-blind trials in adults demonstrated minimal differences between ziprasidone-treated and placebo-treated patients for all measured variables in all analyses. Analyses of the integrated data set comprising all controlled and uncontrolled studies revealed small mean changes in ziprasidone-treated subjects in all measured variables at all time points.

**Table 4. Summary of Change in Metabolic Parameters in All Adult Patients Receiving Oral Ziprasidone Monotherapy: Controlled and Uncontrolled Trials**

| Outcome Variable | Study Duration, wk | n | Change From Baseline to Specified Exposure Duration, Observed Cases,[a] Mean ± SD | Duration of Treatment Exposure, Median, d | Modal Dose, Mean ± SD, mg/d |
|---|---|---|---|---|---|
| Fasting glucose, mg/dL | ≤ 12 | 1,854 | 0.7 ± 26.8 | 42 | 111 ± 45 |
| | ≥ 48 | 149 | 1.3 ± 19.6 | 438 | 104 ± 45 |
| Fasting triglycerides, mg/dL | ≤ 12 | 1,475 | −10.6 ± 102.0 | 43 | 112 ± 42 |
| | ≥ 48 | 136 | −12.0 ± 99.0 | 440 | 105 ± 46 |
| Fasting total cholesterol, mg/dL | ≤ 12 | 1,494 | −6.1 ± 32.9 | 43 | 112 ± 42 |
| | ≥ 48 | 138 | −9.3 ± 38.3 | 445 | 104 ± 45 |
| Fasting LDL cholesterol, mg/dL | ≤ 12 | 1,324 | −4.6 ± 28.6 | 43 | 113 ± 42 |
| | ≥ 48 | 117 | −9.6 ± 36.8 | 421 | 102 ± 47 |
| Fasting HDL cholesterol, mg/dL | ≤ 12 | 1,434 | 0.4 ± 9.7 | 43 | 113 ± 42 |
| | ≥ 48 | 127 | 0.8 ± 11.1 | 428 | 102 ± 46 |

[a]For lipids and glucose, last available measurement.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

**Table 5. Categorical Change From Baseline in Fasting Lipids and Glucose in Adults Receiving Ziprasidone in All Monotherapy Controlled and Uncontrolled Studies**

| | | ≤ 12 Weeks' Exposure | | ≥ 48 Weeks' Exposure | |
|---|---|---|---|---|---|
| Laboratory Analyte (fasting) | Category Change From Baseline (at least once), mg/dL | Baseline, n | Any Postbaseline Measurement, n (%) | Baseline, n | Any Postbaseline Measurement, n (%) |
| Triglycerides | Increase by ≥ 50 | 1,475 | 256 (17.4) | 136 | 22 (16.2) |
| | Normal to high (< 150 to ≥ 200) | 882 | 60 (6.8) | 85 | 6 (7.1) |
| | Borderline to high (≥ 150 and < 200 to ≥ 200) | 250 | 60 (24.0) | 21 | 4 (19.0) |
| Total cholesterol | Increase by ≥ 40 | 1,494 | 124 (8.3) | 138 | 15 (10.9) |
| | Normal to high (< 200 to ≥ 240) | 845 | 24 (2.8) | 82 | 3 (3.7) |
| | Borderline to high (≥ 200 and < 240 to ≥ 240) | 430 | 45 (10.5) | 34 | 5 (14.7) |
| LDL cholesterol | Increase by ≥ 30 | 1,324 | 140 (10.6) | 117 | 16 (13.7) |
| | Normal to high (< 100 to ≥ 160) | 416 | 3 (0.7) | 32 | 1 (3.1) |
| | Borderline to high (≥ 100 and < 160 to ≥ 160) | 734 | 59 (8.0) | 62 | 2 (3.2) |
| HDL cholesterol | Normal to low (≥ 40 to < 40) | 1,044 | 130 (12.5) | 85 | 18 (21.2) |
| Glucose | Normal to high (< 100 to ≥ 126) | 1,422 | 46 (3.2) | 112 | 5 (4.5) |
| | Borderline to high (≥ 100 and < 126 to ≥ 126) | 343 | 42 (12.2) | 34 | 3 (8.8) |

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

To our knowledge, this is the first report of the metabolic effects of any second-generation antipsychotic that incorporates data from the entire clinical trial program. All Pfizer-sponsored trials, and all subjects from these trials who met the criteria for each analysis, were included. Wherever possible, placebo-controlled data were used to evaluate possible drug-attributable effects, and uncontrolled data were reported to provide additional empirical evidence, suggesting the presence or absence of metabolic effects, particularly during long-term treatment. The total exposed population data set had much larger numbers of subjects at 6 and 12 months and sufficient numbers at 24 and 36 months to allow for assessment of longer-term metabolic effects. The categorical and descriptive analyses of these data demonstrated outcomes that were similar to the analyses of the placebo-controlled studies. Because these data were mostly uncontrolled, any observed changes cannot be solely attributed to drug effect. However, the minimal changes in laboratory values and weight over periods of up to 1 year or more are strongly suggestive of an absence of clinically significant adverse drug effects.

The only difference between placebo and ziprasidone groups in the short-term RCTs that was statistically significant was change in weight from baseline to end of study. However, least squares mean ± SE change in weight was minimal for both placebo-treated and ziprasidone-treated subjects: 0.64 ± 0.12 kg for ziprasidone versus –0.02 ± 0.14 kg for placebo. The magnitude of the absolute weight gain and weight gain relative to placebo is very small and unlikely to be of clinical significance. More importantly, data from the long-term RCTs showed that ziprasidone-treated subjects lost 0.96 kg (least squares mean change from baseline to end of study), which was not significantly different compared with placebo. Further, among ziprasidone-treated patients receiving medication for at least 12 months, the mean ± SD weight change remained negative (–0.8 ± 10.0 kg). Taken together, these data constitute strong evidence that ziprasidone has minimal adverse effects on weight over a duration of exposure up to 1 year. Our results are consistent with what has been reported to date in large clinical trials not sponsored by Pfizer, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).[29] For example, in that

well known trial of second-generation antipsychotics in the treatment of schizophrenia, ziprasidone treatment was associated with a mean weight loss of –1.6 kg.

With respect to fasting values for serum glucose, triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol, there were no differences between ziprasidone and placebo groups in the least squares mean change from baseline to end of study in the short-term RCTs. In all cases, the change from baseline to end of study was minimal. These results, especially given that the laboratory values are fasting and the number of subjects is relatively large, provide strong evidence that ziprasidone has a neutral effect on blood glucose and lipids. The uncontrolled long-term data are supportive of this interpretation, as the mean change from baseline for a median duration of exposure of more than 400 days was in a favorable direction for all lipid parameters and was greater than that seen at a median duration of exposure of approximately 40 days. The mean change in glucose was just 1.3 mg/dL for a median exposure period of 428 days. Again, results of CATIE are similar in both magnitude and direction to the changes in lipids and glucose reported here.[29]

There did appear to be a time-dependent effect on change in weight in the uncontrolled data, with those remaining on medication for 24 or 36 months having a greater likelihood of gaining weight. This could be due in part to a drug effect, but, in the absence of a control group, this cannot be separated from nonpharmacologic effects. For example, there has been a secular trend toward weight gain in adults in the United States for the period during which these trials were conducted.[30] One can also infer that patients remaining on study drug long-term tended to be doing relatively well clinically and may have therefore been more likely to be eating more regularly, though not necessarily more healthily. The initial observation of increased rates of overweight and obesity in the schizophrenia population, reviewed in the introduction, predates the introduction of second-generation antipsychotics.[6] These nondrug effects may also have contributed to the small percentage of subjects who had a categorical change in glucose values in the all-studies group.

Several limitations of this study warrant mentioning. First, there were a relatively small number of subjects with long-term exposure to ziprasidone in the controlled analyses. This was primarily due to the fact that the majority of RCTs of ziprasidone in patients with schizophrenia, schizoaffective disorder, and bipolar disorder were short-term, usually between 3 and 8 weeks in duration, as has been the case for all second-generation antipsychotics. More problematically, there were no data for fasting glucose and lipid analyses from the placebo-controlled, double-blind, long-term studies. The main reason for this shortcoming is that most of these trials were conducted in the 1990s and early 2000s, prior to the time when focus was placed on weight and metabolic complications with second-generation antipsychotics. At that time, measuring serum lipids and glucose, fasting or not, beyond baseline screening, was not a routine component of clinical trials in schizophrenia or bipolar disorder.

## CONCLUSIONS

The need for better understanding of causes and contributors to medical morbidity and mortality in patients with major mental illness has become increasingly clear in recent years. Of particular interest is the relationship between antipsychotic therapy, increased cardiovascular risk, and poor outcomes in individuals with bipolar disorder and schizophrenia, which is recognized as complex and, at least in part, potentially treatment related. The life-long nature of treatment necessitates careful appraisal of the risks versus benefits of therapy and appropriate tailoring of treatment to avoid causing or exacerbating medical comorbidities. Avoidance of, and reduction in, risk of cardiovascular disease is a particularly important clinical consideration in the management of major mental disorders, in order to achieve improvements in cardiovascular outcomes equivalent to those observed in recent decades in the general population.

The results of all of the analyses presented here add to the body of evidence supporting the minimal risk profile of ziprasidone at all dosages when used in adults with bipolar disorder or schizophrenia. These analyses confirm previous findings that treatment with ziprasidone in adults with these disorders does not produce clinically relevant negative effects on mean changes for a range of metabolic parameters, including weight, total and fractionated cholesterol, triglycerides, and glucose. This information describing the metabolic profile of ziprasidone should be valuable to physicians and other health care professionals in making appropriate risk-benefit evaluations when considering atypical antipsychotic therapy for their patients. Given the importance of cardiometabolic risk factors in contributing to major morbidity and mortality among sufferers of major mental illness, therapeutic options with the lowest likelihood of contributing to risk in this area are clinically desirable.

***Drug names:*** olanzapine (Zyprexa and others), ziprasidone (Geodon and others).
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***Potential conflicts of interest:*** **Dr Pappadopulos** is an employee of Pfizer and had received grant support from the National Institute of Mental Health (NIMH). **Dr Newcomer** has received research grant support from the NIMH, National Alliance for Research on Schizophrenia and Depression, Bristol-Myers Squibb, and Pfizer; has served as a consultant to Boehringer-Ingelheim, AstraZeneca, Bristol-Myers Squibb, Lundbeck, Obecure, Otsuka, Pfizer, Sepracor/Sunovion, and Teva; has served on data safety monitoring committees of Dainippon Sumitomo Pharma America, Organon/Schering-Plough/Merck, Bristol-Myers Squibb, and Vivus; has been a consultant to litigation; and has received royalties/other income from Compact Clinicals/Jones and Bartlett Publishing. **Dr Kolluri** is an employee of Pfizer.
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***Additional information:*** The Pfizer database is not publicly accessible. Readers may request access to the data by contacting Dr Pappadopulos.
***Supplementary material:*** See accompanying pages.



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## REFERENCES


1. Casey DE, Haupt DW, Newcomer JW, et al. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry*. 2004;65(suppl 7):4–18, quiz 19–20.
2. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.
3. Jeste DV, Gladsjo JA, Lindamer LA, et al. Medical comorbidity in schizophrenia. *Schizophr Bull*. 1996;22(3):413–430.
4. Miller BJ, Paschall CB 3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv*. 2006;57(10):1482–1487.
5. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123–1131.
6. Curkendall SM, Mo J, Glasser DB, et al. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *J Clin Psychiatry*. 2004; 65(5):715–720.
7. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19(suppl 1): 1–93.
8. 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(4):215–220.
9. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*. 2005;80(1):45–53.
10. McCreadie RG; Scottish Schizophrenia Lifestyle Group. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183(6):534–539.
11. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32.
12. Subramaniam M, Chong SA, Pek E. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. *Can J Psychiatry*. 2003;48(5):345–347.
13. Birkenaes AB, Opjordsmoen S, Brunborg C, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. *J Clin Psychiatry*. 2007;68(6):917–923.
14. Correll CU, Frederickson AM, Kane JM, et al. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. *Bipolar Disord*. 2008; 10(7):788–797.
15. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. *Bipolar Disord*. 2004;6(5):368–373.
16. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry*. 2002; 63(3):207–213.
17. Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*. 2006;63(7):824–830.
18. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA*. 2007;298(15):1794–1796.
19. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11): 1686–1696.
20. Folks DG, Lombardo I, Loebel AD, et al. Effect of ziprasidone on weight and metabolic parameters at various fixed doses in patients with schizophrenia or schizoaffective disorder. Presented at: American Psychiatric Association Annual Meeting; May 19–24, 2007; San Diego, CA. Poster NR512.
21. Newcomer JN, Mandel FS, Lombardo I. Ziprasidone treatment effects on weight and lipids in patients with metabolic risk. Presented at: American Psychiatric Association Annual Meeting; May 3–8, 2008; Washington, DC. Poster NRA 052.
22. Weiden PJ, Simpson GM, Potkin SG, et al. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. *J Clin Psychiatry*. 2003;64(5):580–588.
23. Weiden PJ, Newcomer JW, Loebel AD, et al. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. *Neuropsychopharmacology*. 2008;33(5):985–994.
24. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.
25. Daniel DG, Zimbroff DL, Potkin SG, et al; Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20(5):491–505.
26. Keck PJ Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/ day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. *Psychopharmacology (Berl)*. 1998;140(2):173–184.
27. Keck PEJ Jr, Versiani M, Potkin S, et al. Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003;160(4):741–748.
28. Potkin SG, Keck PE Jr, Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005;25(4):301–310.
29. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
30. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295(13): 1549–1555.


Supplementary material follows this article.

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# Supplementary Material

**Article Title:** Changes in Weight, Plasma Lipids, and Glucose in Adults Treated With Ziprasidone: A Comprehensive Analysis of Pfizer-Initiated Clinical Trials

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## List of Supplementary Material for the article

1. eFigure 1 Categorical Change From Baseline in Weight in Adults Receiving Ziprasidone in All Monotherapy Controlled and Uncontrolled Studies

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Supplementary eFigure 1: Categorical Change From Baseline in Weight in Adults Receiving Ziprasidone in All Monotherapy Controlled and Uncontrolled Studies