

# Long-Term Changes in Weight and Plasma Lipids during Maintenance Treatment with Ziprasidone

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To measure the long-term changes in weight and plasma lipids after switching antipsychotic treatment to ziprasidone, three 52-week, open-label extension studies of ziprasidone in outpatients ( $N=185$ ) with schizophrenia or schizoaffective disorder successfully completing one of three, 6-week switch studies were carried out. Pre-switch treatment consisted of risperidone ( $n=43$ ), olanzapine ( $n=71$ ), or conventional antipsychotic agents ( $n=71$ ). The maximum length of exposure to ziprasidone was 58 weeks. Nonfasting total cholesterol and triglyceride levels were obtained at baseline and at weeks 6, 19, 32, 45, and 58. Weight was measured at baseline and during each follow-up visit; height was recorded at baseline for the purpose of body mass index (BMI) calculation. Efficacy measures included the Positive and Negative Syndrome Scale and Clinical Global Impression—Severity scale which were obtained at baseline and major follow-up points. Clinically significant sustained improvements in weight, BMI, total cholesterol, and triglyceride levels were observed among patients switched to ziprasidone from risperidone or olanzapine. Switching from conventional antipsychotics was not associated with significant changes in weight and lipid parameters. Mean reductions in weight from baseline to study endpoint were 9.8 kg ( $p<0.001$ ) and 6.9 kg ( $p<0.005$ ) for patients previously treated with olanzapine and risperidone, respectively. These findings demonstrate that switching from risperidone or olanzapine to ziprasidone is associated with sustained, clinically significant improvements in weight and plasma lipids.

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## INTRODUCTION

Among individuals with schizophrenia, there is an increased prevalence of obesity (American Diabetes Association, 2004; Fontaine *et al*, 2001), dyslipidemia (Koro *et al*, 2002a), diabetes mellitus (Koro *et al*, 2002b), and related conditions such as cardiovascular disease (Brown *et al*, 2000; Casey *et al*, 2004). Contributing factors may include lower socioeconomic class (Baxter, 1996), lack of exercise, poor diet, and smoking (Brown *et al*, 1999). In addition, some of the medications used for the management of schizophrenia are associated with clinically significant increases in weight (Allison *et al*, 1999; Casey and Zorn, 2001; Lieberman *et al*, 2005; Newcomer, 2005) and adverse alterations in serum lipid levels (Casey and Zorn, 2001; Eyre *et al*, 2004; Meyer and Koro, 2004). The relative contribution of nonpharmacologic factors and the specific con-

tribution of antipsychotic medications to weight gain and dyslipidemia observed in patients with schizophrenia have both been the subject of considerable scrutiny, with an emerging consensus about the importance of risk-reduction strategies (American Diabetes Association, 2004; Meyer and Koro, 2004; Jin *et al*, 2004; Ryan *et al*, 2003; Wirshing *et al*, 1999).

Modest improvements in weight and adiposity (NHLBI, 1998) and plasma lipids (NCEP, 2001, 2002; Hennekens, 1998) can significantly lower the risk for cardiovascular disease. This has led to heightened public health interest in behavioral and pharmacologic strategies to lower body weight and harmful lipid fractions (NHLBI, 1998; NCEP, 2001). Behavioral approaches such as changing diet and increasing activity levels are usually associated with modest reductions in body weight of 3–5% over 1 year in general medical populations (Norris *et al*, 2004; Sheppard *et al*, 1991). In psychiatric populations, behavioral approaches may require more intensive and costly efforts to achieve even this level of weight reduction; however, few studies have addressed these issues (Brar *et al*, 2005; Menza *et al*, 2004). Weight reduction achieved with currently approved antiobesity drugs is similarly modest over the long term (approximately 5% of initial body weight (McMahon *et al*,

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2000)), and these drugs may be associated with adverse effects that can limit their use in psychiatric patients (eg anxiety, insomnia, or anal leakage (Casey *et al*, 2003)).

An alternative approach to the management of weight and dyslipidemia in patients requiring ongoing antipsychotic medication is the use of antipsychotic drugs less associated with such adverse effects. While this may be a straightforward prevention strategy, it has not yet been established that switching from a higher- to a lower-risk antipsychotic medication can favorably affect long-term weight and lipid profiles. Previous studies, including the initial, 6-week, ziprasidone-switch studies, that suggest the short-term utility of this approach indicated statistically significant reductions in body weight and body mass index (BMI) over 6-weeks after a switch from risperidone or olanzapine to ziprasidone (Weiden *et al*, 2003a) or 8-weeks for aripiprazole (Casey *et al*, 2003). The ziprasidone-switch studies also detected significant reductions in nonfasting total plasma cholesterol and triglycerides in patients switched from both olanzapine and risperidone but not conventional antipsychotic drugs (Weiden *et al*, 2003a). These short-term results, however, left open questions about the long-term course, sustainability, and effect size of any treatment-related changes in weight or lipids.

To address these questions, we report here changes in body weight, BMI, and nonfasting lipids during 52 weeks of ziprasidone monotherapy, following a previously reported 6-week switch to ziprasidone from prior maintenance treatment ( $\geq 3$  months) with risperidone, olanzapine, or a conventional antipsychotic drug (Weiden *et al*, 2003a).

## METHODS

### Design

All patients included in this analysis participated in a 1-year extension of one of three identically designed 6-week medication-switch studies. These studies were conducted simultaneously between 1997 and 1999, before ziprasidone's commercial availability. The design of these studies has been described elsewhere (Weiden *et al*, 2003b) and is therefore summarized briefly below.

Participants were outpatients with schizophrenia or schizoaffective disorder based on psychiatrist diagnostic evaluation using DSM-IV criteria. The patients were clinically stable but experiencing symptoms or adverse events sufficient to warrant a change in antipsychotic therapy. The pre-switch treatment groups were risperidone ( $n = 43$ ), olanzapine ( $n = 71$ ), and conventional antipsychotic drugs ( $n = 71$ ). Participants were randomized to one of three different cross-titration methods, with each method resulting in complete discontinuation of the pre-switch antipsychotic medication within 1 week of starting ziprasidone. Benzodiazepine use was restricted to lorazepam for anxiety; use of zolpidem tartrate for insomnia was discouraged but not prohibited. No adjunctive behavioral or pharmacologic interventions for weight reduction were provided during the study.

All patients in this report had successfully completed one of three short-term switch trials and agreed to participate in a 52-week, open-label extension study of maintenance

ziprasidone, such that the maximum length of ziprasidone exposure was 58 weeks.

### Assessments

Nonfasting plasma total cholesterol and triglyceride levels were obtained at baseline (just before switching to ziprasidone) and at 6, 19, 32, 45, and 58 weeks. Specific HDL-C and LDL-C values were not collected. Samples were analyzed at a central laboratory. Weight was measured at baseline and at each follow-up visit. Height was recorded at baseline to enable the calculation of BMI. Efficacy measures were obtained at baseline and major follow-up points using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression—Severity (CGI-S) scale. Extrapyramidal symptoms were assessed with the Simpson–Angus Rating Scale (SARS), Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movements Scale (AIMS). Adverse events were recorded at each visit; an electrocardiogram was recorded at baseline and endpoint. The corrected QT interval was measured manually and calculated according to Bazett's formula:  $QT_c = QT/(RR)^{1/2}$  (Bazett, 1920).

### Statistical Analyses

All patients who entered the extension studies were included in the analyses. Pooled data were used to summarize demographic characteristics, treatment duration, and daily ziprasidone dose.

Careful consideration was given to the method used for data analysis, especially in light of the discontinuation rates observed in longitudinal trials of patients with schizophrenia. Because we hypothesized that weight change could be dependent on the length of time elapsed since last exposure to a weight-gain-promoting medication, we selected the mixed-model repeated measures (MMRM) analysis *a priori* as the most appropriate method for evaluating the primary outcomes. MMRM was used to estimate changes in weight, BMI, and plasma lipid levels (total cholesterol and triglycerides) from baseline to the time of each follow-up visit. The resultant slopes provided an estimate of change, not an observed mean, at each visit.

Mixed-model repeated measures models used for these analyses always included fixed effects from protocol (ie pre-switch antipsychotic drug), baseline BMI, the number of days of maintenance therapy with ziprasidone, and the interaction between the pre-switch medication and the number of days of maintenance therapy. Individual intercept and slope for each subject were used as random effects in the model, with an unrestricted covariance matrix structure. On the basis of the pattern of weight and plasma lipid changes seen in the short-term ziprasidone switch studies, we hypothesized that differences in weight and plasma lipid outcomes would be related to prior antipsychotic status. As the group treated with conventional antipsychotic drugs had shown minimal changes in weight and plasma lipids, the group whose prior treatment was a conventional was assigned to be the reference value in the regression models.

A step-wise procedure selected significant fixed effects from possible influential baseline characteristics that were hypothesized in *post hoc* model constructions. These

baseline characteristics included age, race, sex, weight, height, total plasma cholesterol and triglyceride levels, PANSS total score, PANSS positive and negative symptom subscale scores, SARS score for parkinsonism, and CGI-S scores. All statistical tests of significance were two-tailed, with the significance level set at 0.05. The analysis and results presented are based on a 58-week (6 plus 52 weeks) MMRM analysis. Sensitivity MMRM analyses were also performed using 32 weeks, rather than 58 weeks, as the final data point in a *post hoc* test of the influence of a shorter maintenance treatment period. The 32-week results were very similar to the 58-week endpoint results and are not reported here. Effect size (Cohen's *d* (the mean change in the variable of interest over the pooled standard deviation)) was calculated for each variable. The term baseline is used to refer to the core study baseline.

Last observation carried forward (LOCF) and observed case (OC) analyses were performed as secondary analyses, and are presented here for comparison purposes. Analysis of covariance was performed separately using the LOCF endpoint and observed value at each visit. The analysis of covariance model included the treatment effect and baseline as covariates. All calculations were performed with SAS (SAS version 8.2; Cary, NC, USA).

## RESULTS

### Subjects

Demographics and baseline characteristics for the 185 patients included in the analyses are shown in Table 1. The treatment groups comprised patients switched from risperidone (*n* = 43), olanzapine (*n* = 71), or conventional

antipsychotic drugs (*n* = 71). Baseline nonfasting plasma triglyceride and glucose levels were higher, and age younger, in the patients switched from olanzapine; these were the only differences between the treatment groups in relevant variables at baseline.

The mean baseline BMI for each group, while high (range 30.29–32.01), is similar to other samples of patients with schizophrenia and schizoaffective disorder studied over the past 5–10 years (Coodin, 2001; McEvoy *et al*, 2005). A total of four patients from the olanzapine, one from the risperidone, and one from the conventional antipsychotic group were using a statin at baseline. No patient in any group used any anorectic medication before, or subsequent to, ziprasidone switch.

Of the 185 patients who entered the extension studies, 100 (54%) remained in the study at week 32 and 72 (39%) remained at week 58. Discontinuation rates in the pre-switch conventional antipsychotic, olanzapine, and risperidone groups were 58, 64, and 58%, respectively. The median duration of ziprasidone treatment was 40.6 weeks. Of the 113 patients (61%) who discontinued therapy before the 58-week endpoint, 34 (30%) discontinued for treatment-related reasons (adverse events, *n* = 16; efficacy-related, *n* = 18). Of the 77 patients who discontinued for reasons not related to the study drug, 25 did so due to adverse events, 34 defaulted, and another 18 discontinued for other unknown reasons. There was no assessment of sedation other than that reported as a spontaneous adverse event. The pattern of discontinuation after switching to ziprasidone was similar in each study and was consistent with overall discontinuation rates. The pooled median daily dose of ziprasidone at study endpoint was 120 mg.

**Table 1** Baseline Demographics and Illness Characteristics

Variable	Conventional antipsychotic drugs ( <i>n</i> = 71)	Risperidone ( <i>n</i> = 43)	Olanzapine ( <i>n</i> = 71)	Overall ( <i>n</i> = 185)	<i>p</i> -value for difference between groups
Weight, kg (SD)	89.93 (18.48)	88.40 (19.32)	95.41 (20.95)	91.68 (19.62)	0.118 <sup>a</sup>
BMI (SD)	30.41 (6.57)	30.29 (6.24)	32.01 (6.67)	31.00 (6.60)	0.251
Total cholesterol, mg/dl (SD) <sup>b</sup>	195.40 (40.09)	213.77 (44.21)	203.34 (53.58)	202.80 (46.9)	0.127
Triglycerides, mg/dl (SD) <sup>c</sup>	186.39 (136.82)	236.07 (136.66)	262.44 (201.62)	227.30 (167.40)	0.023
Glucose, mg/dl (SD) <sup>d</sup>	100.4 (27.7)	103.9 (29.0)	116.8 (49.6)	107.55 (38.4)	0.030
Men, <i>n</i> (%)	47 (66.2)	27 (62.8)	49 (69.0)	123 (66.5)	0.791 <sup>e</sup>
Mean age, years (range)	40.0 (18–61)	39.2 (18–61)	36.0 (19–57)	38.3 (18–61)	0.049
Schizophrenia (%)	73	86	71	75	0.156 <sup>e</sup>
Schizoaffective disorder (%)	27	14	29	25	0.156 <sup>e</sup>
PANSS					
Total score, mean ± SD	59.5 ± 15.3	59.4 ± 16.5	56.4 ± 15.4	58.3 ± 15.6	0.433
Positive score, mean ± SD	13.4 ± 4.6	13.4 ± 5.3	12.5 ± 4.7	13.0 ± 4.8	0.466
Negative score, mean ± SD	17.1 ± 5.9	16.2 ± 6.0	16.0 ± 5.8	16.4 ± 5.9	0.509

<sup>a</sup>F-test (all comparisons except those noted by 'e').

<sup>b</sup>Recommended level <200 mg/dl.

<sup>c</sup>Recommended level <150 mg/dl.

<sup>d</sup>Recommended level <126 mg/dl (nonfasting).

<sup>e</sup>χ<sup>2</sup> test.

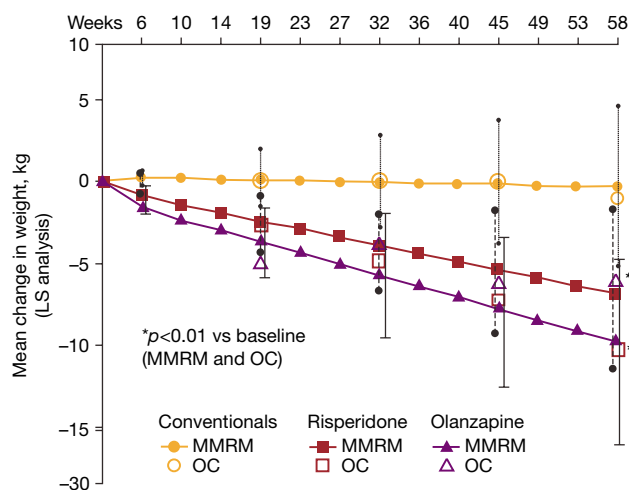
## Efficacy and Safety

In the pooled intent-to-treat (ITT) population ( $n=185$ ), statistically significant improvement from pre-switch baseline to endpoint (LOCF) was observed in mean scores for CGI-S ( $-0.3$ ,  $t=-3.5$ ,  $df=177$ ,  $p<0.001$ ), PANSS total ( $-4.3$ ,  $t=-2.6$ ,  $df=121$ ,  $p<0.01$ ), and PANSS negative symptom subscale ( $-2.4$ ,  $t=-4.9$ ,  $df=121$ ,  $p<0.0001$ ) but not the PANSS positive subscale ( $-0.7$ ,  $t=-1.5$ ,  $df=121$ ,  $p=NS$ ). Statistically significant mean improvement in PANSS negative symptom score (ITT, LOCF) was also observed for each of the three groups:  $-2.2$  (0.8),  $t=-2.9$ ,  $df=44$ ,  $p<0.01$  for those switched from conventional antipsychotic drugs;  $-3.5$  (1.0),  $t=-3.6$ ,  $df=30$ ,  $p<0.01$  for those switched from risperidone; and  $-1.7$  (0.8),  $t=-2.1$ ,  $df=45$ ,  $p<0.05$  for those switched from olanzapine. Mean improvement in PANSS total score was significant for the group previously treated with conventional antipsychotic drugs ( $-6.3$  [2.3],  $t=-2.7$ ,  $df=44$ ,  $p<0.01$ ) but not for the groups previously treated with olanzapine ( $-3.5$  [2.7],  $t=-1.3$ ,  $df=45$ ,  $p=0.20$ ) or risperidone ( $-2.6$  [3.9],  $t=-0.7$ ,  $df=30$ ,  $p=0.51$ ). The reduction in PANSS positive scores was less than 1.5 points and not significant for any of the three groups.

In the safety population ( $n=185$ ), scores improved significantly on all movement disorder measures (SARS:  $-2.1$ ,  $t=-6.6$ ,  $df=65$ ,  $p<0.0001$ ; BAS:  $-1.1$ ,  $t=-6.5$ ,  $df=40$ ,  $p<0.0001$ ; and AIMS:  $-1.1$ ,  $t=-2.4$ ,  $df=43$ ,  $p<0.05$ ). One patient had a QTc interval  $\geq 450$  ms at baseline, six had a QTc interval  $\geq 450$  ms at some point during the study, and three had a QTc interval  $\geq 450$  ms at study endpoint. No patient had a QTc interval  $\geq 500$  ms at any time during the study.

## Effect on Body Weight

MMRM analysis indicated a gradual, continuous reduction in weight, beginning in the first 6 weeks and continuing over the ensuing 52 weeks of ziprasidone maintenance among patients switched from risperidone or olanzapine



**Figure 1** Time course of weight change over 58 weeks after switch to ziprasidone. LS, least-squares analysis; MMRM, mixed-model repeated measures analysis; OC, observed cases analysis.

but not from conventional antipsychotic drugs (Figure 1). Mean estimated weight loss at 58 weeks for patients switched from olanzapine was 10.3% of the mean initial pre-switch body weight (baseline, 95.4 kg; total weight loss, 9.8 kg; Cohen's  $d$ , 1.00); mean estimated monthly weight loss was 0.69 kg per month. For patients switched from risperidone, the corresponding reduction in weight was 7.8% (baseline, 88.4 kg; total weight loss, 6.9 kg; Cohen's  $d$ , 0.70); mean estimated monthly weight loss was 0.5 kg per month. LOCF analyses also showed substantial, statistically significant reductions in weight at 58 weeks that were, as expected, not as large as those seen in the MMRM analyses due to the time dependence of observed changes (eg LOCF mean weight loss  $\pm$  SE: olanzapine pretreatment,  $4.5 \pm 6.1$  kg,  $t=-6.3$ ,  $df=70$ ,  $p<0.01$ ; risperidone pretreatment,  $5.1 \pm 10.1$  kg,  $t=-3.3$ ,  $df=42$ ,  $p<0.01$ ), supporting *a priori* concerns that LOCF analyses may systematically underestimate change in effects that are time dependent.

Using the group treated with conventional antipsychotic drugs as the point of reference, the pre-switch medication was a significant predictor of weight loss for patients switched from olanzapine ( $p<0.01$ ) but not from risperidone ( $p=0.17$ ) (Table 2). The duration of ziprasidone treatment was a significant predictor of weight loss for patients previously treated with either olanzapine ( $p<0.01$ ) or risperidone ( $p<0.01$ ) but not for those previously treated with conventional antipsychotic drugs ( $p=0.67$ ) (Table 2). Sex, age, and baseline BMI, PANSS, CGI, or adverse event ratings did not significantly predict changes in weight.

## Effect on BMI

The mean baseline BMIs of all three groups (range 30.41–32.01 kg/m<sup>2</sup>) indicated a patient sample that was already obese (BMI  $> 30$  kg/m<sup>2</sup>). The pattern of reduction in BMI was by definition proportional to that for weight loss, with large decreases at 58 weeks observed in patients switched

**Table 2** Regression Analysis of Predictors of Change in Weight during Maintenance Ziprasidone Therapy

Variable	$\beta$	SE	df	t	p
Pre-switch BMI <sup>a</sup>	-0.00024	0.02361	1980	-0.01	0.99
Pre-switch antipsychotic drug					
Conventional	0	—	—	—	—
Risperidone	-0.5476	0.4020	1980	-1.36	0.17
Olanzapine	-0.8951	0.3536	1980	-2.53	0.01
Duration of ziprasidone treatment					
From conventional	-0.00168	0.003969	1980	-0.42	0.67
From risperidone	-0.01626	0.004950	1980	-3.29	<0.01
From olanzapine	-0.02258	0.003953	1980	-5.71	<0.01
Intercept	0.3014	0.7606	181	0.40	0.69

Abbreviations: BMI, body mass index; df, degrees of freedom.

<sup>a</sup>Because baseline BMI did not differ significantly between groups, the BMI variable was collapsed and entered as one baseline variable.

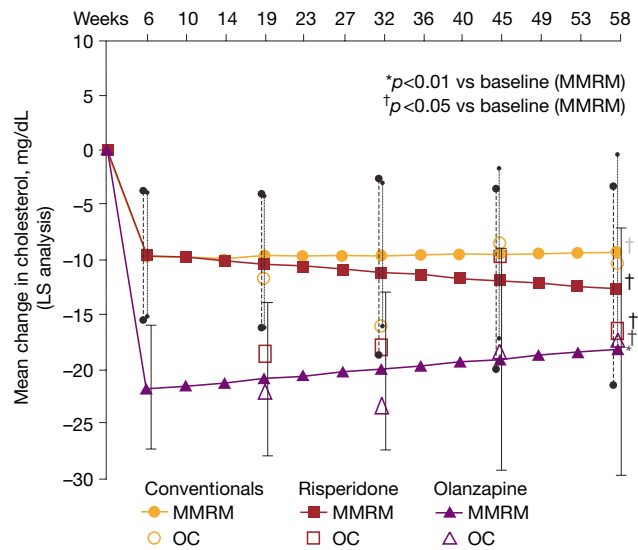
from either olanzapine (baseline, 32.0; reduction,  $-3.2$ ;  $t = -6.0$ ,  $df = 1980$ ,  $p < 0.01$ ; Cohen's  $d$ , 0.97) or risperidone (baseline, 30.3; reduction,  $-2.5$ ;  $t = -3.7$ ,  $df = 1980$ ,  $p < 0.01$ ; Cohen's  $d$ , 0.74) (Figure 2). LOCF analysis again underestimated long-term change but the decreases at 58 weeks were still clinically and statistically significant (LOCF mean BMI change  $\pm$  SE: olanzapine pretreatment,  $-1.5 \pm 2.0$ ,  $t = -6.1$ ,  $df = 69$ ,  $p < 0.01$ ; risperidone pretreatment,  $1.8 \pm 3.5$ ,  $t = -3.4$ ,  $df = 42$ ,  $p < 0.01$ ). Results of the regression analysis using the fixed-effects model were comparable with that for weight reduction.

### Effect on Total Plasma Cholesterol Levels

In contrast to the more gradual course of change in weight and BMI, the improvement in cholesterol levels occurred rapidly upon switching to ziprasidone. At 6 weeks, mean total cholesterol had declined significantly in all three patient groups, including the group that switched from conventional antipsychotic drugs. These reductions were then sustained with no further decrease over the entire 52-week extension period (Figure 3). The median change for total cholesterol at the LOCF endpoint ( $n = 185$ ) was  $-17.00$ ,  $-13.00$ , and  $-11.00$  for olanzapine, risperidone, and conventional antipsychotics, respectively. The median change for total cholesterol at the end of the 52-week extension (completer analysis,  $n = 72$ ) was  $-17.50$ ,  $-12.00$ , and  $-11.00$  for olanzapine, risperidone, and conventional antipsychotics, respectively. As a proportion of baseline levels, LOCF endpoint decreases at 58 weeks were 9.2% for the olanzapine (baseline, 203.3; endpoint, 184.6 mg/dl;  $t = -4.5$ ,  $df = 70$ ,  $p < 0.0001$ ; Cohen's  $d = 0.59$ ), 7.6% for the risperidone (baseline, 213.8; endpoint 197.5 mg/dl;  $t = -4.0$ ,  $df = 42$ ,  $p = 0.0002$ ; Cohen's  $d$ , 0.51), and 5.1% (baseline, 195.4; endpoint, 185.5 mg/dl;  $t = -2.7$ ,  $df = 69$ ,  $p = 0.01$ ; Cohen's  $d$ , 0.31) for the conventional antipsychotic drugs pre-switch groups.

Pre-switch antipsychotic medication was a significant predictor of reduction in total plasma cholesterol levels in the olanzapine group (Table 3). Baseline total cholesterol

level was significantly associated with the change in total cholesterol level for all three pre-switch groups. The PANSS depression subscale score at baseline also predicted reduction in total cholesterol level for all three groups. Sex, age and baseline BMI, CGI, and PANSS (except for



**Figure 3** Time course of change in total plasma cholesterol level from baseline to 58 weeks after switch to ziprasidone. LS, least-squares analysis; MMRM, mixed-model repeated measures analysis; OC, observed cases analysis.

**Table 3** Regression Analysis of Predictors of Change in Total Plasma Cholesterol Levels during Maintenance Ziprasidone Therapy

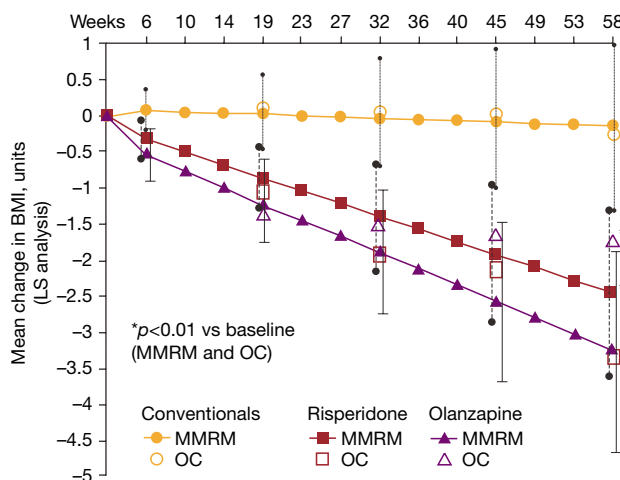
Baseline variable	$\beta$	SE	df	t	p
Pre-switch BMI <sup>a</sup>	-0.0825	0.2406	1017	-0.34	0.73
Baseline cholesterol <sup>b</sup>	-0.2692	0.0335	1017	-8.04	<0.01
PANSS depression <sup>c</sup>	-1.3015	0.4704	1017	-2.77	<0.01
<i>Pre-switch antipsychotic</i>					
Conventional	0	—	—	—	—
Risperidone	0.8174	4.2377	1017	0.19	0.85
Olanzapine	-12.2324	3.7121	1017	-3.30	<0.01
<i>Duration of ziprasidone treatment</i>					
From conventional	0.0016	0.0098	1017	0.17	0.87
From risperidone	-0.0087	0.0128	1017	-0.68	0.50
From olanzapine	0.0100	0.0104	1017	0.96	0.34
Intercept	58.3598	10.3283	177	5.65	<0.01

Abbreviations: BMI, body mass index; df, degrees of freedom.

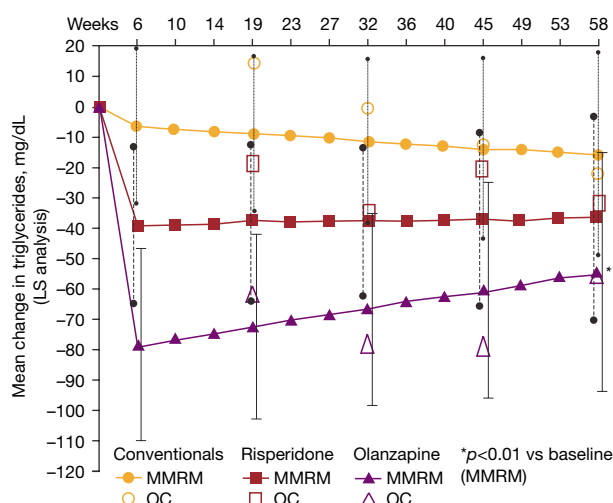
<sup>a</sup>Because baseline BMI did not differ significantly between groups, the BMI variable was collapsed and entered as one baseline variable.

<sup>b</sup>Nonfasting.

<sup>c</sup>Includes G1, G2, G3, and G6 on PANSS.



**Figure 2** Time course of BMI change over 58 weeks after switch to ziprasidone. LS, least-squares analysis; BMI, body mass index; MMRM, mixed-model repeated measures analysis; OC, observed cases analysis.



**Figure 4** Estimated change in plasma triglyceride level after switch to ziprasidone. LS, least-squares analysis; MMRM, mixed-model repeated measures analysis; OC, observed cases analysis.

depression subscale), duration of ziprasidone treatment or adverse event ratings did not significantly predict change in total cholesterol levels.

### Effect on Plasma Triglyceride Levels

Similar to the time course of cholesterol change, rapid improvements in triglyceride levels occurred within 6 weeks of the switch to ziprasidone. Plasma triglycerides decreased (MMRM) significantly in the groups previously treated with olanzapine (decrease of 78.0 mg/dl from a baseline of 262.4 mg/dl;  $t = -6.7$ ,  $df$  1017,  $p < 0.0001$ ; Cohen's  $d$ , 0.59) and risperidone (decrease of 39.2 mg/dl from a baseline of 236.1 mg/dl;  $t = -2.7$ ,  $df$  1017,  $p < 0.01$ ; Cohen's  $d$ , 0.30) groups. Repeated assessments over the next 52 weeks showed sustained triglyceride improvements (Figure 4). In the group previously treated with conventional antipsychotic drugs, triglyceride levels were not statistically different to baseline at 6 and 58 weeks. Triglyceride reductions at 58 weeks, as a proportion of baseline levels, were 20.8% (54.5 mg/dl) and 15.8% (36.7 mg/dl) for the pre-switch olanzapine and risperidone groups, respectively. The median change in triglycerides at the LOCF endpoint ( $n = 185$ ) was  $-41.00$ ,  $-28.00$ , and  $-2.5$  for olanzapine, risperidone, and conventional antipsychotics, respectively. The median change in triglycerides at the end of the 52-week extension (completer analysis,  $n = 72$ ) was  $-14.50$ ,  $-11.00$ , and  $-10.00$  for olanzapine, risperidone, and conventional antipsychotics, respectively.

In the LOCF analyses, a significant reduction in triglyceride levels at 58 weeks was also shown for the group previously treated with olanzapine ( $-76.5 \pm 176.6$  mg/dl;  $t = -3.7$ ,  $df$  70,  $p < 0.01$ ) and a trend was shown for the group previously treated with risperidone ( $-35.1 \pm 115.2$  mg/dl;  $t = -2.0$ ,  $df$  69,  $p = 0.052$ ). The mean decrease in triglyceride levels at 58 weeks for the pre-switch risperidone group was similar across all analyses (estimated changes were  $-35.1$ ,  $-36.66$  and  $-31.12$  from LOCF, MMRM, and OC analyses, respectively).

**Table 4** Regression Analysis of Predictors of Change in Plasma Triglycerides during Maintenance Ziprasidone Therapy

Baseline variable	$\beta$	SE	df	t	p
Pre-switch BMI <sup>a</sup>	0.7373	1.0450	1017	0.71	0.48
Baseline cholesterol <sup>b</sup>	0.3985	0.1505	1017	2.65	<0.01
Baseline triglycerides <sup>b</sup>	-0.4672	0.0046	1017	-0.47	<0.01
CGI-S	18.7789	8.8701	1017	2.12	0.03
Sex (female)	-33.6730	14.5249	1017	-2.32	0.02
<i>Pre-switch antipsychotic</i>					
Conventional	0	—	—	—	—
Risperidone	-33.8526	19.2282	1017	-1.76	0.08
Olanzapine	-75.1119	16.9374	1017	-4.43	<0.01
<i>Days on maintenance ziprasidone</i>					
From conventional	-0.0249	0.0356	1017	-0.70	0.48
From risperidone	0.0068	0.0467	1017	0.15	0.88
From olanzapine	0.0643	0.0379	1017	1.70	0.09
Intercept	-54.4191	53.8501	175	-1.01	0.31

Abbreviations: BMI, body mass index; CGI-S, Clinical Global Impressions—Severity;  $df$ , degrees of freedom.

<sup>a</sup>Because baseline BMI did not differ significantly between groups, the BMI variable was collapsed and entered as one baseline variable.

<sup>b</sup>Nonfasting.

Of all potentially explanatory variables entered into the fixed-effects model, baseline triglyceride and cholesterol levels were the best predictors of subsequent reduction in triglyceride levels, with higher baseline values associated with greater reductions. Prior treatment with olanzapine was also associated with reduction in plasma triglyceride lowering (Table 4). In addition, female sex and greater baseline CGI-S scores significantly predicted decreases in triglyceride levels for all three pre-switch groups. There was no significant effect of baseline BMI, PANSS, duration of ziprasidone treatment, adverse event ratings, or age on triglyceride levels.

### DISCUSSION

This is the first long-term study of weight and lipid changes associated with a therapeutic substitution of antipsychotic medications. The three 6-week, medication-switch studies reported improvements in weight, BMI, and lipid profiles after therapeutic substitution of ziprasidone for olanzapine or risperidone (Weiden *et al*, 2003a). Short-term studies involving substitution of aripiprazole for olanzapine or risperidone also reported improvements in weight and BMI (Casey *et al*, 2003). However, these data did not establish whether these initial improvements could be sustained during long-term antipsychotic treatment.

The present study demonstrated that weight loss continued throughout an additional 1 year of maintenance ziprasidone treatment. Furthermore, estimated weight loss was both statistically significant and clinically relevant, with



large effect size estimates (Cohen's *d*) for decreases in body weight and BMI for patients switched from olanzapine (1.00 and 0.97, respectively) and risperidone (0.70 and 0.74, respectively).

Patients who switched from conventional antipsychotic drugs as a group did not experience weight loss. This group serves as an important point of comparison with patients switched from risperidone and olanzapine. This contrast, together with the results of the regression analysis showing that the weight loss in the groups previously treated with olanzapine or risperidone was most strongly associated with the time elapsed since last exposure to these medications, suggests that the observed improvements in weight and BMI were primarily related to removal of the prior antipsychotic drug. Supporting this inference, the 58-week estimate of weight loss for patients switched to olanzapine in this study (−9.8 kg) was similar to published estimates of the amount of weight gained over 1 year in patients initiating therapy with olanzapine (Nemeroff, 1997). Furthermore, the mean baseline weight and BMI of those switched from conventional antipsychotic drugs was similar to those who switched from atypical antipsychotic drugs, strongly suggesting patient weight loss was not simply a result of regression to the mean.

Data were not available to determine whether patients switching from conventional antipsychotics agents had been previously exposed to atypical agents. It is therefore difficult to identify the underlying causes of the elevated BMI status of the group treated with conventional antipsychotics before the switch. However, patients with schizophrenia tend to weigh more and have higher BMIs than matched controls in the general population (Coodin, 2001). Although the reasons for this are not well understood, it is likely due to a combination of factors including the underlying illness, lifestyle, diet, lack of exercise, and antipsychotic medication effects (Henderson *et al*, 2006; Brown *et al*, 1999; Daumit *et al*, 2005; Newcomer and Haupt, 2006; Goldman, 1999; Wirshing, 2004; Farwell *et al*, 2004). It is possible that ziprasidone may tend to reverse weight gain associated with atypical antipsychotic treatment but has a more limited effect on weight gain associated with other lifestyle-related factors.

Another important observation was that the significant reductions in lipid levels observed 6 weeks after starting ziprasidone were sustained over the ensuing year of maintenance treatment. The largest decrease observed was the mean (MMRM) reduction in triglycerides in the pre-switch olanzapine group (30% at 6 weeks; 21% at 58 weeks). This finding is similar to the improvement that can be expected among patients treated with statins (Hebert *et al*, 1997). Decreases in triglycerides in the pre-switch risperidone group (17% at 6 weeks; 16% at 58 weeks) were also clinically relevant. The reduction in total cholesterol in all three groups was not as large (4–11% at 6 weeks, 5–9% at 58 weeks) but was nonetheless statistically significant and sustained. Consistent with the current results are data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. In CATIE phase 1, ziprasidone was the only study medication associated with improvements in all weight and metabolic variables (Lieberman *et al*, 2005, p 1215). In CATIE phase 2, patients who discontinued their phase 1 study medication experienced a decrease in total

cholesterol and triglyceride levels when switched to either ziprasidone or risperidone compared when switching to either olanzapine or quetiapine (Stroup *et al*, 2005).

The relatively rapid, marked decreases in plasma lipid levels followed by sustained effects in all three groups were notably different from the gradual but continuous reduction in weight and BMI observed in the pre-switch olanzapine and risperidone groups. This finding is consistent with previous studies that have demonstrated that antipsychotic medication-related increases in lipid levels (Newcomer, 2005; Meyer and Koro, 2004; Newcomer *et al*, 2002) and insulin resistance (Casey *et al*, 2004; Meyer and Koro, 2004; Newcomer *et al*, 2002) can occur independently of changes in weight or adiposity.

Reductions in weight, BMI, and lipid levels of the magnitude seen in this study are associated with significant reductions in cardiovascular events and mortality (NHLBI, 1998; NCEP, 2001). These results have important implications for patients with schizophrenia, among whom cardiovascular disease accounts for almost one quarter of excess mortality (Brown *et al*, 2000).

The weight loss associated with 58 weeks of ziprasidone treatment in patients previously treated with olanzapine (10.3% of initial body weight, MMRM) or risperidone (7.8% of initial body weight, MMRM) is greater than that reported in other long-term studies of pharmacologic approaches to weight reduction. Placebo-controlled studies which assessed the efficacy of metformin (Baptista *et al*, 2006) over 14 weeks or sibutramine (Henderson *et al*, 2005, 2007) over 12 weeks in reducing weight gain associated with several atypical antipsychotics found no clinically or statistically significant weight loss in the treatment groups *vs* placebo. In the metformin trial, a worsening of the lipid profile was noted in the placebo group but improvements were not noted in the active comparator group; markers of insulin resistance improved in both treatment and placebo groups (Baptista *et al*, 2006; Faulkner *et al*, 2007). Additionally, weight loss of only about 5% of initial body weight was observed after 1 year in nonpsychiatric populations using agents such as orlistat or sibutramine (Padwal *et al*, 2004). The weight loss noted above in this study was also greater than that reported in studies of diet and exercise programs of equal duration among nonpsychiatric populations specifically seeking weight loss. In those studies, mean weight loss was typically around 5% of initial body weight (Norris *et al*, 2004; Sheppard *et al*, 1991). Moreover, a recent Cochrane review reported very small effect sizes for patients treated with metformin, sibutramine, and psychosocial interventions (Faulkner *et al*, 2007).

The addition of psychosocial interventions to reduce weight among patients treated with atypical antipsychotics has also been evaluated. In a 6-month controlled study by Littrell *et al*, patients (*N* = 70) were randomized to receive weekly education classes or standard care. At study endpoint, the mean change in weight of the intervention group was −0.06 lb, while the mean change in weight of the standard care group was 9.57 lb (Littrell *et al*, 2003). Brar *et al* (2005) found a significant reduction (*p* < 0.05) in weight among patients receiving behavioral treatment (−4.4 lb) *vs* standard care (−2.42 lb) over a 14-week period. Despite the improvements in subject weight observed during these trials, it still remains unclear whether such

gains would be maintained over longer periods of time. Furthermore, the role of dietary and lifestyle changes and the effect, if any, on the lipid profile were not examined.

A 52-week trial examined the effect of a multimodal weight control program in a small population ( $n=31$ ) of subjects with schizophrenia (Menza *et al*, 2004). This trial evaluated weight and BMI as primary efficacy variables as well as change in hemoglobin A<sub>1C</sub>, blood pressure, and lipids. The findings from the intervention group were compared to the charts of patients ( $n=20$ ) at the same institutions for which height and weight data were available during the same time period in which the intervention study was carried out. A statistically significant mean weight loss of 6.6 lb was observed in the intervention group compared to a mean weight gain of 7.0 lb in the control group ( $p=0.01$ ). This correlates to a mean decrease in BMI of 1.7 vs an increase of 2.6 for the reference group ( $p=0.01$ ). No statistically significant changes in lipids were noted.

As yet, there are no published reports on the long-term ( $\geq 6$  months) use of pharmacotherapy for weight loss in patients taking atypical antipsychotic medications. Independent of any benefits that might be observed, it remains unclear whether anorectic agents would need to be given continuously in order for the weight loss to be sustained, or whether adverse effects and drug interactions would complicate the use in this population. The robust effect of certain therapeutic substitutions on body weight should provide an important point of comparison with respect to efficacy, risks, and cost when considering any alternative approach to weight reduction in the schizophrenia patient population.

The patients switched to ziprasidone from predominantly high-potency conventional antipsychotic drugs served as an important comparison with the patients switched from second-generation agents. The lack of significant change in weight, BMI, and triglyceride levels in the patients switched from high-potency conventional agents is consistent with prior research demonstrating limited effects of these agents on weight and lipids (Allison *et al*, 1999) and argues against a nonspecific effect of study participation on the changes observed after the switch to ziprasidone from olanzapine or risperidone.

The patients studied were drawn from a variety of outpatient clinical settings. Other than the change in antipsychotic medication, there were no other psychosocial or pharmacologic interventions that were part of the protocol, suggesting that changes in weight, BMI, and lipid levels are likely to be related to the change in antipsychotic medication. The change in weight and lipid levels associated with the three pre-switch medication regimens studied are consistent with the published literature on the rank order of relative risks these agents pose for weight gain and adverse effects on metabolic variables (Newcomer, 2005; Arato *et al*, 2002; Bobes *et al*, 2003; McIntyre *et al*, 2003).

Limitations of this study include the lack of a control group or groups that did not change medication. In addition, the baseline sample may overrepresent patients who experienced weight gain while on their prior medications. However, even if such a selection bias did occur, the findings remain relevant to the management of patients who experience weight gain during a course of treatment with second-generation antipsychotic drugs. Alternatively, because inclusion in the study was not limited to patients who had experienced weight gain or hyperlipidemia in their

prior course of treatment, the current results may provide a conservative estimate of changes in body weight or lipids that could occur in patients undergoing a similar medication switch specifically for these reasons.

The fact that only patients who had successfully completed a short-term switch study were eligible for the extension studies may have skewed the composition of the extension-period population toward patients who had already lost weight while taking ziprasidone. This is unlikely, however, as patients switched from conventional antipsychotic drugs were equally likely to continue with ziprasidone despite the absence of any overall effect on body weight.

Other limitations include a lack of control for patient lifestyle factors such as diet and exercise regimens, lack of laboratory data to evaluate glucose homeostasis and insulin resistance, a nonrandom effect of nonfasting blood work (ie time to last meal and size of last meal) in relationship to pre-switch antipsychotic, and a lack of data regarding reason for the switch (ie weight gain, dyslipidemia, or unrelated to these primary outcome variables).

Finally, we assessed nonfasting, rather than fasting, lipid levels. While fasting triglyceride levels are preferred as an indication of insulin resistance, nonfasting triglyceride levels have shown utility as predictors of cardiovascular disease and are at least as useful as fasting levels for this purpose (Eberly *et al*, 2003). Similarly, several recent studies have demonstrated that differences between fasting and nonfasting measurements of serum cholesterol fractions are not substantial, and have concluded that nonfasting levels are adequate for most clinical purposes (Weiss *et al*, 2003; Desmeules *et al*, 2005; Craig *et al*, 2000).

In this study, the mean daily ziprasidone dose was 120 mg. This dose is similar to the mean modal dose in phase 1 of the CATIE trial (Lieberman *et al*, 2005). The optimal ziprasidone dose for patients with schizophrenia is thought to be in the range of 120–160 mg/day (Nemeroff *et al*, 2005; Joyce *et al*, 2006; Mamo *et al*, 2004). Further studies are needed to determine whether doses of ziprasidone  $>120$  mg/day can provide additional efficacy in patients with schizophrenic illness.

The results from this study suggest that therapeutic replacement of an antipsychotic drug more associated with a risk for weight gain and dyslipidemia with one less associated with these adverse events may favorably affect weight, BMI, and lipid fractions associated with adverse health outcomes. The magnitude of beneficial effects on weight is comparable with those observed with existing diet and exercise regimens, with or without adjunctive pharmacotherapy to promote weight loss. Similarly, the magnitude of beneficial effects on lipid levels associated with such therapeutic substitutions is similar to benefits obtained with existing lipid-lowering treatments. Future research, particularly involving risk-benefit and cost analyses, should directly compare therapeutic substitution of antipsychotic medications with alternative behavioral and pharmacologic approaches to weight loss and lowering of lipid levels in this patient population.

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## DISCLOSURES

Dr Lebovitz is a consultant to Amylin Pharmaceuticals Inc.; a member of the Speaker Bureau for Amylin Pharmaceuticals Inc., GlaxoSmithKline, Sanofi Aventis Pharmaceuticals Inc., Bayer Corporation; stock or investment holder: Amylin Pharmaceuticals Inc., GlaxoSmithKline, Bayer Corporation, and Bristol-Myers Squibb Company.

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Dr Yang is an employee of Pfizer Inc.

## REFERENCES

- Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC *et al* (1999). Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* **156**: 1686–1696.
- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity (2004). Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* **27**: 596–601.
- Arato M, O'Connor R, Meltzer HY (2002). A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol* **17**: 207–215.
- Baptista T, Martinez J, Lacruz A, Rangel N, Beaulieu S, Serrano A *et al* (2006). Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. *Can J Psychiatry* **51**: 192–196.
- Baxter DN (1996). The mortality experience of individuals on the Salford psychiatric case register. I. All-cause mortality. *Br J Psychiatry* **168**: 772–779.
- Bazett HC (1920). An analysis of the time-relations of electrocardiograms. *Heart* **7**: 353–370.
- Bobes J, Rejas J, Garcia-Garcia M, Rico-Villademoros F, Garcia-Portilla MP, Fernandez I *et al* (2003). Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. *Schizophr Res* **62**: 77–88.
- Brar JS, Ganguli R, Pandina G, Turkoz I, Berry S, Mahmoud R (2005). Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* **66**: 205–212.
- Brown S, Birtwistle J, Roe L, Thompson C (1999). The unhealthy lifestyle of people with schizophrenia. *Psychol Med* **29**: 697–701.
- Brown S, Inskip H, Barraclough B (2000). Causes of the excess mortality of schizophrenia. *Br J Psychiatry* **177**: 212–217.
- Casey DE, Carson WH, Saha AR, Liebeskind A, Ali MW, Jody D *et al* (2003). Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. *Psychopharmacology (Berl)* **166**: 391–399.
- Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M *et al* (2004). Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* **65**(Suppl 7): 4–18.
- Casey DE, Zorn SH (2001). The pharmacology of weight gain with antipsychotics. *J Clin Psychiatry* **62**(Suppl 7): 4–10.
- Coodin S (2001). Body mass index in persons with schizophrenia. *Can J Psychiatry* **46**: 549–555.
- Craig SR, Amin RV, Russell DW, Paradise NF (2000). Blood cholesterol screening influence of fasting state on cholesterol results and management decisions. *J Gen Intern Med* **15**: 395–399.
- Daumit GL, Goldberg RW, Anthony C, Dickerson F, Brown CH, Kreyenbuhl J *et al* (2005). Physical activity patterns in adults with severe mental illness. *J Nerv Ment Dis* **193**: 641–646.
- Desmeules S, Arcand-Bosse JF, Bergeron J, Douville P, Agharazi M (2005). Nonfasting non-high-density lipoprotein cholesterol is adequate for lipid management in hemodialysis patients. *Am J Kidney Dis* **45**: 1067–1072.
- Eberly LE, Stamler J, Neaton JD (2003). Mortality after 16 years for participants randomized to the Multiple Risk Factor Intervention Trial. *Arch Intern Med* **163**: 1077–1083.
- Eyre H, Kahn R, Robertson RM (2004). Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Diabetes Care* **27**: 1812–1824.
- Farwell WR, Stump TE, Wang J, Tafesse E, L'Italien G, Tierney WM (2004). Weight gain and new onset diabetes associated with olanzapine and risperidone. *J Gen Intern Med* **19**: 1200–1205.
- Faulkner G, Cohn T, Remington G (2007). Interventions to reduce weight gain in schizophrenia. *Cochrane Database Syst Rev* **1**: CD005148.
- Fontaine KR, Heo M, Harrigan EP, Shear CL, Lakshminarayanan M, Casey DE *et al* (2001). Estimating the consequences of antipsychotic induced weight gain on health and mortality rate. *Psychiatry Res* **101**: 277–288.
- Goldman LS (1999). Medical illness in patients with schizophrenia. *J Clin Psychiatry* **60**(Suppl 21): 10–15.
- Hebert PR, Gaziano JM, Chan KS, Hennekens CH (1997). Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* **278**: 313–321.
- Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D *et al* (2006). Dietary intake profile of patients with schizophrenia. *Ann Clin Psychiatry* **18**: 99–105.
- Henderson DC, Copeland PM, Daley TB, Borba CP, Cather C, Nguyen DD *et al* (2005). A double-blind, placebo-controlled trial of sibutramine for olanzapine-associated weight gain. *Am J Psychiatry* **162**: 954–962.
- Henderson DC, Fan X, Copeland PM, Borba CP, Daley TB, Nguyen DD *et al* (2007). A double-blind, placebo-controlled trial of sibutramine for clozapine-associated weight gain. *Acta Psychiatr Scand* **115**: 101–105.
- Hennekens CH (1998). Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. *Circulation* **97**: 1095–1102.
- Jin H, Meyer JM, Jeste DV (2004). Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* **71**: 195–212.
- Joyce AT, Harrison DJ, Loebel AD, Carter CT, Ollendorf DA (2006). Effect of initial ziprasidone dose on length of therapy in schizophrenia. *Schizophr Res* **83**: 285–292.
- Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J *et al* (2002a). An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. *Arch Gen Psychiatry* **59**: 1021–1026.
- Koro CE, Fedder DO, L'Italien GJ, Weiss SS, Magder LS, Kreyenbuhl J *et al* (2002b). Assessment of independent effect

- of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 325: 243.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO *et al* (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353: 1209–1223.
- Littrell KH, Hilligoss NM, Kirshner CD, Petty RG, Johnson CG (2003). The effects of an educational intervention on antipsychotic-induced weight gain. *J Nurs Scholarsh* 35: 237–241.
- Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F *et al* (2004). A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. *Am J Psychiatry* 161: 818–825.
- McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L *et al* (2005). 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* 80: 19–32.
- McIntyre RS, Trakas K, Lin D, Balshaw R, Hwang P, Robinson K *et al* (2003). Risk of weight gain associated with antipsychotic treatment: results from the Canadian National Outcomes Measurement Study in schizophrenia. *Can J Psychiatry* 48: 689–694.
- McMahon FG, Fujioka K, Singh BN, Mendel CM, Rowe E, Rolston K *et al* (2000). Efficacy and safety of sibutramine in obese white and African American patients with hypertension: a 1-year, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med* 160: 2185–2191.
- Menza M, Vreeland B, Minsky S, Gara M, Radler DR, Sakowitz M (2004). Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. *J Clin Psychiatry* 65: 471–477.
- Meyer JM, Koro CE (2004). The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 70: 1–17.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2001). Executive summary of the third report of the National Cholesterol Education Program (NCEP). *JAMA* 285: 2486–2497.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002). Third report of the National Cholesterol Education Program (NCEP)—final report. *Circulation* 106: 3143–3421.
- National Heart, Lung and Blood Institute (1998). *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—the Evidence Report*. National Institutes of Health: Bethesda, MD.
- Nemeroff CB (1997). Dosing the antipsychotic medication olanzapine. *J Clin Psychiatry* 58(Suppl 10): 45–49.
- Nemeroff CB, Lieberman JA, Weiden PJ, Harvey PD, Newcomer JW, Schatzberg AF *et al* (2005). From clinical research to clinical practice: a 4-year review of ziprasidone. *CNS Spectr* 10: S1–S20.
- Newcomer JW (2005). Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 19(Suppl 1): 1–93.
- Newcomer JW, Haupt DW (2006). The metabolic effects of antipsychotic medications. *Can J Psychiatry* 51: 480–491.
- Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP *et al* (2002). Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* 59: 337–345.
- Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, Serdula M *et al* (2004). Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. *Am J Med* 117: 762–774.
- Padwal R, Li SK, Lau DC (2004). Long-term pharmacotherapy for obesity and overweight. *Cochrane Database Syst Rev* 3: CD004094.
- Ryan MC, Collins P, Thakore JH (2003). Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psychiatry* 160: 284–289.
- Sheppard L, Kristal AR, Kushi LH (1991). Weight loss in women participating in a randomized trial of low-fat diets. *Am J Clin Nutr* 54: 821–828.
- Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA *et al* (2005). Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 163: 611–622.
- Weiden PJ, Daniel DG, Simpson G, Romano SJ (2003a). Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. *J Clin Psychopharmacol* 23: 595–600.
- Weiden P, Simpson G, Potkin S, O'Sullivan RL (2003b). Switching to ziprasidone from conventional antipsychotics, olanzapine, or risperidone in stable outpatients with schizophrenia. *J Clin Psychiatry* 64: 580–588.
- Weiss R, Harder M, Rowe J (2003). The relationship between nonfasting and fasting lipid measurements in patients with or without type 2 diabetes mellitus receiving treatment with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Ther* 25: 1490–1497.
- Wirshing DA (2004). Schizophrenia and obesity: impact of antipsychotic medications. *J Clin Psychiatry* 65(Suppl 18): 13–26.
- Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J *et al* (1999). Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry* 60: 358–363.