Long-Term Olanzapine Treatment: Weight Change and Weight-Related Health Factors in Schizophrenia

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Background: Weight change and the weight-related health factors of nonfasting serum glucose, serum cholesterol, and diastolic blood pressure levels were analyzed in patients with DSM-III-R schizophrenia and related disorders who received treatment with olanzapine for up to 3 years, and comparisons were made to patients treated with haloperidol. Baseline body mass index (BBMI; kg/m^2) and dose (mg/day) were investigated as predictors of long-term weight change experienced during olanzapine treatment.

Method: This analysis retrospectively examined 573 patients receiving olanzapine and 103 patients receiving haloperidol for 39 weeks or more from a study of 1996 patients randomly assigned 2:1 to either olanzapine, 5 to 20 mg/day, or haloperidol, 5 to 20 mg/day. After 6 weeks of acute therapy, patients continued for 1 year or more with either double-blind or open-label olanzapine therapy or double-blind haloperidol therapy.

Results: Mean weight gain for olanzapine-treated patients observed for a median of 2.54 years trended toward a plateau after the first 39 weeks of treatment with a last-observation-carried-forward mean weight change of 6.26 kg (13.8 lb) and a median of 5.90 kg (13.0 lb). This was significantly higher than that for haloperidol-treated patients, whose mean weight gain was 0.69 kg (1.5 lb) after 1.15 years ($p < .001$). Patients with higher BBMI (> 27.6) gained significantly less weight during treatment with olanzapine than their lighter counterparts (BBMI < 27.6) ($p < .001$). The effect of olanzapine dose on weight was not significant ($p \geq .183$). Median serum glucose at endpoint was not significantly associated ($p = .096$) with weight change for olanzapine. Median serum cholesterol and diastolic blood pressure for olanzapine-treated patients at endpoint showed a relationship with weight change that was statistically ($p \leq .001$) but not clinically significant. The difference in incidence of elevated serum glucose, cholesterol, or diastolic blood pressure between olanzapine and haloperidol therapy groups was not different ($p > .05$).

Conclusion: Mean weight gain during olanzapine treatment trended toward a plateau after the initial 39 weeks of treatment with no further significant gain out to 3 years. Higher BBMI was predictive of a lower long-term weight gain, while dose was not a significant predictor of greater longer term weight change. The relationship between weight change and glucose was not statistically significant. The association between weight change and changes in cholesterol as well as changes in diastolic blood pressure was statistically significant but not considered clinically relevant based on the ranges observed.

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An improved treatment for schizophrenia has emerged with the development of novel atypical antipsychotic drugs. Unlike conventional antipsychotic drugs, novel agents have been shown to improve positive, negative, and mood symptoms of schizophrenia. Olanzapine is an atypical antipsychotic drug and has been demonstrated to safely and effectively decrease each of these dimensions of the overall psychopathology of schizophrenia,[1–3] and there are preliminary indications of efficacy in the cognitive symptoms of schizophrenia.[4] However, as with several of its conventional and atypical counterparts, weight change has occurred after olanzapine treatment in a proportion of patients undergoing pharmacotherapy.[5,6]

Weight change has been a reported side effect of antipsychotic drug use for over 30 years[7] and has been shown to occur during both conventional (for example, haloperidol and chlorpromazine) and novel (for example, risperidone, sertindole, quetiapine, and clozapine) antipsychotic drug treatment,[8] although in general the phenomenon is self-limiting in that it appears to plateau over time.[9,10] Recent reports suggest an association between antipsychotic drug treatment and diabetes mellitus[11,12] and cardiovascular disease.[13,14] It is, however, important to note that the base rate of such disorders in schizophrenia has been speculated to be higher than that seen in the general population.[15–17] In fact, a recently published study found that

the rates of diagnosed diabetes in schizophrenia exceeded the trend of the general population well before the widespread use of the new antipsychotic medications.[18] It therefore remains unclear whether any possible association between olanzapine and diabetes exceeds the expected incidence of diabetes in the general population. Moreover, previous reports have been confined to relatively short observation periods and relatively small sample sizes, and there is a paucity of published information on the long-term effects of novel antipsychotic drug treatment and weight change or weight-related health factors.

The objective of the present study was to investigate weight changes in patients with schizophrenia or related disorders who received treatment with olanzapine for up to 3 years, the most extensive observation period to date, and to determine whether 2 commonly implicated factors, baseline body mass index (BBMI) and dose, were significant predictors of long-term weight change. Contrasts with haloperidol were considered to provide meaningful comparisons between an atypical antipsychotic drug and a conventional antipsychotic drug, and these comparisons were made whenever possible depending on the availability of patients at relevant timepoints. An additional goal of this analysis was to determine whether there was an association between the amount of weight gained and patients' endpoint nonfasting serum glucose, serum cholesterol, and diastolic blood pressure levels. The use of endpoint analyses may provide a relevant outcome risk after chronic treatment over time. These analyses are limited to the more specific effects of olanzapine treatment and weight change and do not necessarily lend themselves to further inference of metabolic issues related to olanzapine treatment in general or to haloperidol treatment in general.

METHOD

Study Design and Patient Population

These analyses retrospectively examined a sample of patients from a study of 1996 patients diagnosed with DSM-III-R schizophrenia, schizoaffective, or schizophreniform disorders. Six hundred seventy-six patients (35%) of 1936 patients with evaluable weight-change data were included in this analysis; 573 received olanzapine and 103 patients received haloperidol. Patients were randomly assigned in a 2:1 ratio to either olanzapine, 5 to 20 mg/day, or haloperidol, 5 to 20 mg/day. Patients began 6 weeks of double-blind therapy with a minimum Brief Psychiatric Rating Scale (BPRS) total score of 36 (1 to 7 scale) and/or intolerance to current antipsychotic therapy (excluding haloperidol), after which patients who met predetermined response criteria (40% decrease from baseline in BPRS [0 to 6 scale] and at least 3 study weeks completed) were eligible to continue double-blind olanzapine or haloperidol treatment. Patients not meeting the response criteria were eligible to enter an open-label extension during which they received olanzapine only. Three years of study data were deemed an adequately long follow-up period with a sufficiently large number of olanzapine-treated patients (N = 147) observed at the 3-year timepoint to draw meaningful conclusions. Written informed consent was obtained from all participants, and institutional review board approval was given at each of the study sites.

Statistical Method

SAS version 6.09 (SAS Institute, Cary, N.C.) was used for all statistical analyses. Observed case weight-change data were analyzed using repeated measures analysis of variance (ANOVA) with time included as a class variable. Weight, glucose, cholesterol, and standing diastolic blood pressure data from weekly, monthly, or bimonthly timepoints were grouped into 3- to 6-month intervals (labeled as 13, 26, and 39 weeks and 1, 1.5, 2, 2.5, and 3 years) in order to facilitate model convergence. For each patient, the last recorded observation in each interval was used. To further characterize weight gain, the percentage of patients experiencing an increase of 7% or more of body weight was determined.

Body mass index (BMI; weight [kg]/height [m^2]) data were collected and categorized into thirds based on the distribution of values at baseline (BBMI) in this population: ≤ 23.6 (low), > 23.6 to 27.6 (medium), and > 27.6 (high). Mean daily dose was determined for each patient over the entire observation period and categorized according to the nearest 5 ± 2.5-mg increment (5, 10, 15, and > 15 mg/day). Both dose and BBMI factors were then evaluated as predictors of weight change.

Prevalence and incidence of laboratory and vital sign parameters above cutoff (≥ 160 mg/dL random nonfasting glucose,[19] ≥ 240 mg/dL random nonfasting blood cholesterol,[20] diastolic blood pressure ≥ 90 mm Hg[20]) and median values at baseline and endpoint for these parameters were calculated. The relationship between last-observation-carried-forward (LOCF) weight change and LOCF laboratory and vital sign values was determined using the Kruskal-Wallis test,[21] and the relationship between weight change and incidence of elevated laboratory/vital sign parameters was determined using the Cochran-Mantel-Haenszel test.[22] Fasting laboratory values were not measured in this study due in part to the difficulty of obtaining reliable samples in this clinical population and because it was not required in the objective of the original protocol.

RESULTS

Weight Change During Long-Term Treatment

Of 573 olanzapine-treated patients, 293 were observed for between 2.5 and 3 years, with 147 observed at the final 3-year timepoint. Of 103 haloperidol-treated patients, the maximum time observed was 100 weeks (1.9 years). Study group characteristics are presented in Table 1.

Table 1. Study Group Characteristics[a]

Characteristic	Haloperidol (N = 103)	Olanzapine (N = 573)
Length of treatment, median, wk	60	132
Age, mean ± SD, y	38.4 ± 11.7	39.4 ± 11.5
Gender		
Male, N (%)	64 (62%)	367 (64%)
Female, N (%)	39 (38%)	206 (36%)
Baseline BPRS score, mean ± SD	33.5 ± 11.6	32.2 ± 10.2
Baseline BMI, mean ± SD	26.9 ± 5.9	26.2 ± 5.0
Daily dose (mg/d), mean ± SD	12.7 ± 5.0	15.1 ± 4.7

[a]There were no statistically significant differences in patients' characteristics between olanzapine and haloperidol groups except for median length of treatment ($p < .001$). Abbreviations: BMI = body mass index, BPRS = Brief Psychiatric Rating Scale.

Figure 1. Mean Change in Body Weight (kg) of Patients Treated With Olanzapine (N = 573) or Haloperidol (N = 103) From Baseline Out to 3 Years (observed cases)

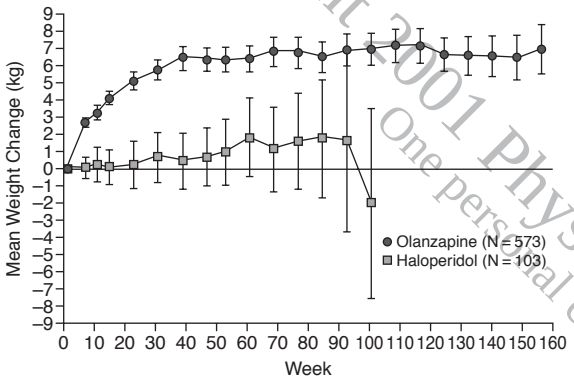


Figure 1 illustrates the mean weight change over the 3-year period. A plateau in the olanzapine weight-change data was defined to be that timepoint after which no further significant pairwise differences in weight-change data were seen. Accordingly, the within-group mean weight change for olanzapine-treated patients at 39 weeks was not significantly different from that seen at any of the subsequent timepoints ($p \geq .077$). Furthermore, there were no significant differences in mean weight change during olanzapine treatment seen between any of the timepoints between 1 and 3 years, inclusively ($p \geq .140$ for all comparisons). Weight change experienced during haloperidol treatment remained below that of olanzapine at all timepoints. Among 147 olanzapine-treated patients who completed the entire 3-year observation period, no significant differences between adjacent timepoints were seen after 39 weeks ($p \geq .186$ for all comparisons) (Figure 2), and a level of plateau was similar to that demonstrated in Figure 1.

Mean LOCF weight change for olanzapine-treated patients at endpoint after a median of 2.54 years of treatment was 6.26 kg (13.8 lb) with a median of 5.90 kg (13.0 lb).

Figure 2. Mean Change in Body Weight (kg) of Patients Treated With Olanzapine (N = 147) Who Completed the Entire 3-Year Observation Period (observed cases)

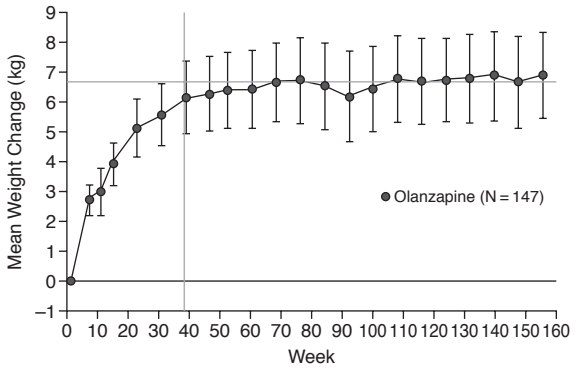
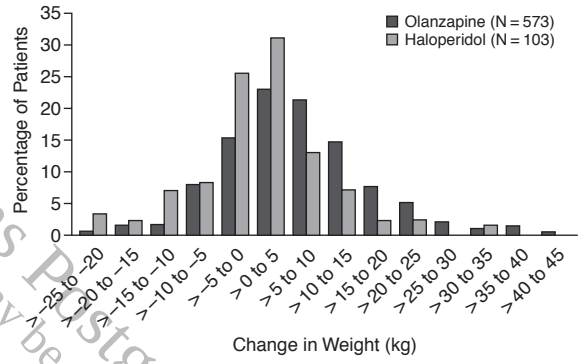


Figure 3. Mean Change in Body Weight (kg) of Olanzapine-Treated Patients (N = 573) and Haloperidol-Treated Patients (N = 103) at Endpoint[a]



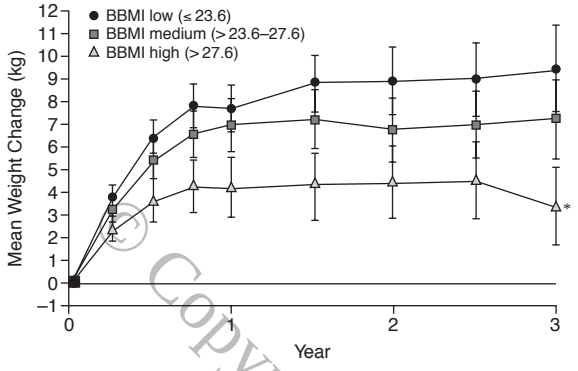
[a]Patients were observed for 39 weeks or more (last observation carried forward [LOCF]; median = 2.54 years).

This was significantly higher than that for haloperidol-treated patients, who gained a mean of 0.69 kg (1.5 lb) after a median of 1.15 years ($p < .001$). As shown in Figure 3, 26% of olanzapine-treated patients lost weight or gained no weight, 44% of patients gained > 0 to 10 kg, 22% gained > 10 to 20 kg, and 9% gained more than 20 kg. For haloperidol, 47% of patients lost weight or gained no weight, 44% gained > 0 to 10 kg, 9% gained >10 to 20 kg, and 3% gained more than 20 kg. Fifty-two percent of olanzapine-treated patients gained > 7% of their body weight, compared with 26% of haloperidol-treated patients.

Influence of BBMI and Dose on Weight Change With Olanzapine

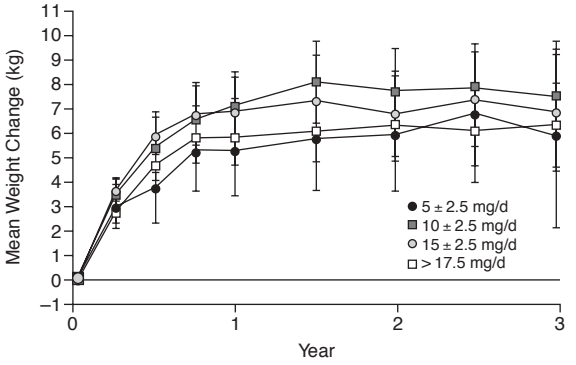
The effect of BBMI on weight change in olanzapine-treated patients was significant at all timepoints after 13 weeks ($p \leq .002$) (Figure 4). Patients with high BBMI values (> 27.6) had a mean weight change that was significantly less than that for patients with medium BBMI

Figure 4. Mean Change in Body Weight (kg) by Baseline Body Mass Index (BBMI) of Olanzapine-Treated Patients Observed for 39 Weeks or More[a]



[a]Patients were categorized by BBMI tertiles: low (≤ 23.6; N = 187), medium (> 23.6 to 27.6; N = 192), and high (> 27.6; N = 186) (observed cases).
*High BBMI group gained significantly less weight than low or medium groups ($p < .001$).

Figure 5. Mean Change in Body Weight (kg) by Mean Olanzapine Dose (mg/day) of Olanzapine-Treated Patients Observed 39 Weeks or More[a]



[a]5 ± 2.5 mg/day: N = 47; 10 ± 2.5 mg/day: N = 124; 15 ± 2.5 mg/day: N = 147; > 17.5 mg/day: N = 255 (observed cases). No significant differences between mean daily dose categories over the entire study period.

Table 2. Median Baseline/Endpoint Glucose, Cholesterol, and Diastolic Blood Pressure Levels for Corresponding Weight Changes for Olanzapine-Treated Patients Observed for 39 Weeks or More (LOCF)

	Glucose, mg/dL					Cholesterol, mg/dL					Diastolic Blood Pressure, mm Hg				
	Baseline			Endpoint		Baseline			Endpoint		Baseline			Endpoint	
Weight Change	N	Median	Interquartile Range	Median	Interquartile Range	N	Median	Interquartile Range	Median	Interquartile Range	N	Median	Interquartile Range	Median	Interquartile Range
Lost to 0	147	91.9	20.5	97.3	26.5	147	211.0	62.0	199.5	57.4	145	80.0	16.0	80.0	14.0
>0 to 10	252	93.0	20.8	98.5	25.9	252	199.3	61.3	203.4	58.3	249	80.0	16.0	80.0	18.0
>10 to 20	123	92.0	19.8	99.1	24.1	124	206.0	59.9	216.0	61.8	123	80.0	14.0	82.0	16.0
>20 to 30	38	89.5	19.8	104.7	27.3	38	193.5	45.5	226.3	57.1	38	80.0	20.0	85.5	13.0
>30 to 40	10	88.5	14.9	103.1	18.0	10	211.0	58.0	247.5	54.1	10	82.0	16.0	89.0	18.0
>40 to 50	1	86.5	0	100.9	0	1	269.9	0	288.9	0	1	70.0	0	80.0	0
Total	571	92.0	20.5	99.1	25.3	572	205.0	61.4	205.7	61.0	566	80.0	18.0	80.0	18.5

values (>23.6 to 27.6) or low BBMI values (≤ 23.6) ($p < .001$; both). Mean LOCF weight changes were 3.82 kg, 6.88 kg, and 8.07 kg for patients with high, medium, and low BBMI, respectively. Of patients with low BBMI, 85.0% had an endpoint BMI of either low or medium.

Dose was not a significant predictor of long-term changes in weight with olanzapine treatment. As shown in Figure 5, there were no significant differences in weight change between flexible mean daily dose categories up to 3 years ($p \geq .183$).

Because of the minimal weight gain experienced by a minority of haloperidol-treated patients, predictive analyses of BBMI and dose on weight gain were not reported for haloperidol.

Weight Change and Nonfasting Serum Glucose, Serum Cholesterol, and Diastolic Blood Pressure Levels

Median nonfasting serum glucose for olanzapine-treated patients (Table 2) at endpoint was significantly higher than for haloperidol-treated patients (Table 3) (99.1 mg/dL vs. 93.7 mg/dL, respectively; $p = .010$). Of 545 olanzapine-treated patients whose nonfasting glucose was < 160 mg/dL at baseline, 4.6% had a nonfasting glucose level ≥ 160 mg/dL at endpoint irrespective of loss or gain in weight. For haloperidol-treated patients, of 100 patients whose nonfasting glucose was < 160 mg/dL at baseline, 5.0% had a nonfasting glucose level ≥ 160 mg/dL at endpoint irrespective of loss or gain in weight. The difference in incidence of glucose levels ≥ 160 mg/dL at endpoint (in patients with glucose levels < 160 mg/dL at baseline) between the therapy groups was not significant ($p = .798$). Because of the minimal weight gain experienced by a minority of haloperidol-treated patients, analyses exploring the relationship between weight change and nonfasting glucose, cholesterol, and diastolic blood pressure were not statistically analyzed for the haloperidol treatment group but are shown descriptively in Table 3. No significant association was observed among olanzapine-treated patients between weight change and median nonfasting blood glucose at endpoint ($p = .096$). The association between weight change and the incidence of

Table 3. Median Baseline/Endpoint Glucose, Cholesterol, and Diastolic Blood Pressure Levels for Corresponding Weight Changes for Haloperidol-Treated Patients Observed for 39 Weeks or More (LOCF)

		Glucose, mg/dL		Cholesterol, mg/dL		Diastolic Blood Pressure, mm Hg	
Weight Change	N	Median Baseline	Median Endpoint	Median Baseline	Median Endpoint	Median Baseline	Median Endpoint
Lost to 0	46	93.7	94.2	210.9	214.6	80.0	80.0
>0 to 10	45	95.5	94.0	193.0	189.9	80.0	80.0
>10 to 20	9	91.0	91.0	176.7	180.6	80.0	82.0
>20 to 30	2	287.1	135.4	191.1	241.2	85.0	80.0
>30 to 40	1	94.0	91.0	155.0	211.0	74.0	80.0
>40 to 50	0	...	...	...	...	...	...
Total	103	94.0	93.7	197.6	189.9	80.0	80.0

nonfasting glucose ≥ 160 mg/dL at endpoint was also not significant (p = .091), nor was the incidence of glucose ≥ 160 mg/dL for patients gaining ≤ 10 kg (4.0%) significantly different from that for patients gaining > 10 kg (6.0%) (p = .299).

Median nonfasting serum cholesterol at endpoint was significantly higher for olanzapine-treated patients (Table 2) than for haloperidol-treated patients (Table 3) (205.7 mg/dL vs. 189.9 mg/dL, respectively; p = .002). Of 447 olanzapine-treated patients whose cholesterol was < 240 mg/dL at baseline, 15.7% had a cholesterol level ≥ 240 mg/dL at endpoint irrespective of loss or gain in weight. For haloperidol-treated patients, of 84 patients whose cholesterol was < 240 mg/dL at baseline, 8.3% had a cholesterol level ≥ 240 mg/dL at endpoint irrespective of loss or gain in weight. The difference in incidence of cholesterol levels ≥ 240 mg/dL at endpoint between the therapy groups was not significant (p = .091). There was a statistically significant association observed among olanzapine-treated patients between weight gain and median serum cholesterol at endpoint (p = .001). The incidence of cholesterol ≥ 240 mg/dL at endpoint was significantly more likely in the group gaining > 10 kg compared with those gaining ≤ 10 kg (24.3% vs. 11.6%; p < .001). In the respective groups with incident high cholesterol, for those gaining < 10 kg (N = 35), the median cholesterol at endpoint was 251.0 mg/dL (range, 240.1–399.0 mg/dL), while in the group gaining > 10 kg (N = 35), the median cholesterol at endpoint was 257.0 mg/dL (range, 241.0–297.8 mg/dL).

Median diastolic blood pressure at endpoint was not significantly different for olanzapine-treated patients (Table 2) compared with haloperidol-treated patients (Table 3) (80 mm Hg vs. 80 mm Hg, respectively; p = .994). Of 437 olanzapine-treated patients whose diastolic blood pressure was < 90 mm Hg at baseline, 20.4% had a diastolic blood pressure level ≥ 90 mm Hg at endpoint irrespective of loss or gain in weight. For haloperidol-treated patients, of 81 patients whose diastolic blood pressure was < 90 mm Hg at baseline, 18.5% had a diastolic blood pressure ≥ 90 mm Hg at endpoint irrespective of loss or gain in weight. The difference in incidence of diastolic blood pressure levels ≥ 90 mm Hg at endpoint between the therapy groups was not significant (p = .765). There was also a statistically significant association observed among olanzapine-treated patients between weight gain and endpoint diastolic blood pressure (p < .001). The incidence of diastolic blood pressure ≥ 90 mm Hg at endpoint was significantly more likely among patients gaining > 10 kg compared with patients gaining ≤ 10 kg (29.5% vs. 16.1%; p < .001). In the respective groups with incident high diastolic blood pressure, for those gaining ≤ 10 kg (N = 48), the median endpoint diastolic blood pressure was 92 mm Hg (range, 90–100 mm Hg), while in the group gaining > 10 kg (N = 41), the median endpoint diastolic blood pressure was also 92 mm Hg (range, 90–106 mm Hg).

DISCUSSION

The population of individuals with schizophrenia, in general, exhibits a higher prevalence of obesity than individuals without schizophrenia.[23] The prevalence of obesity (BMI ≥ 30) in the general population worldwide has been increasing significantly over the past 10 years and trends are generally similar for all age, gender, and race-ethnic groups.[24] The proportion of adults of both sexes defined as "overweight" has changed from 1 in 4 in the early 1970s to 1 in 3 in 1990 (25% to 33%),[25] and this has raised the subject of being overweight as a public health problem.

However, despite literature reports associating both conventional and novel antipsychotic drug use with weight change,[8] antipsychotic agents remain the cornerstone of therapy for individuals suffering from schizophrenia and related disorders. It also may be inferred that since weight loss can accompany acute psychotic decompensation,[26] restorative weight gain may accompany effective antipsychotic drug treatment. One possible mechanism for weight gain during antipsychotic treatment may be related to specific receptor antagonism. Drugs that block serotonergic transmission have been shown to increase food consumption and may cause weight gain.[27–30] While some clinical reports have shown no relationship between 5-HT_{2C} and weight change,[31] more recent preclinical data in 5-HT_{2C} receptor null mutant mice have suggested a role for 5-HT_{2C} receptors in the serotonergic regulation of body weight and food intake.[32]

More detailed between-drug comparisons of basic pharmacology, efficacy profile, and longer term compliance patterns will be necessary to better characterize the relative risk of weight gain. The present post hoc analyses were performed to investigate weight changes in patients with schizophrenia or related disorders who received treatment with olanzapine or haloperidol for up to 3 years,

and to determine whether BBMI and dose were significant predictors of long-term weight change. Further, these analyses were performed to determine whether there was an association between weight gain and endpoint nonfasting serum glucose, serum cholesterol, and diastolic blood pressure. Patients treated with haloperidol, a conventional antipsychotic drug reported to have minimal effect on weight change, were included in this study to determine whether weight gain experienced during olanzapine treatment affected these laboratory parameters differently from treatment with a conventional antipsychotic. These analyses offer clinicians the unique opportunity to investigate the effects of long-term antipsychotic drug treatment on a large cohort of patients with schizophrenia.

Weight Change During Long-Term Treatment

Olanzapine-treated patients gained significantly more weight than haloperidol-treated patients (6.26 kg after 2.54 years of olanzapine treatment vs. 0.69 kg after 1.15 years of haloperidol treatment). Fifty-two percent of olanzapine-treated patients gained >7% of their body weight, compared with 26% of haloperidol-treated patients. This differential emphasizes one of the challenges posed by utilization of one of the novel antipsychotic drugs as compared to the older conventional antipsychotic drugs.

There is a certain amount of confusion in the literature regarding the time course of weight gain during antipsychotic drug treatment. In general, the literature indicates that the majority of weight gain occurs during the first 3 months.[9,33] However, in one report[34] weight gain occurred most frequently after longer term exposure (> 18 months). In addition, plateauing of weight gain during antipsychotic drug treatment has been reported.[35] The present study indicates that mean weight gain during olanzapine treatment for this population trended toward a plateau after approximately 39 weeks of treatment and remained stable thereafter up to 3 years of observation. The rate of weight gain appeared most rapid during the first 12 weeks of olanzapine treatment. This relatively rapid onset of weight gain may suggest the importance of early intervention for weight gain mitigation. Methods of weight management should emphasize this early rapid weight gain and utilize psychoeducational strategies to control appetite, make healthy dietary choices, and encourage appropriate exercise regimens. The benefits of proactive interventions may result in weight stabilization at a lower plateau. The effectiveness of these interventions needs to be studied further. In addition, the potential for rapid and excessive weight gain suggests that clinicians should consider monitoring glucose and lipid levels and vital signs as clinically indicated.

Since this report focuses on the weight changes seen in a subgroup of olanzapine-treated patients, an important question is whether the choice of subgroup was appropriate and especially whether patients observed for shorter periods gained more weight before dropping out of the trial. A comparison of the olanzapine-treated patients treated > 39 weeks (N = 573) described in this report compared with the olanzapine-treated patients observed ≤ 39 weeks (N = 731; not shown) revealed that the mean weight gain for shorter term patients at comparable timepoints was significantly lower than that of longer term patients. This information helps to establish that patients were not discontinuing the study due to weight gain.

A second question is whether, among the patients selected for analysis, a dropout phenomenon contributed to the appearance of a weight gain plateau. However, since the subgroup of patients (N = 147) completing 3 years of observation show a similar plateauing of weight change to that seen in the full sample, the notion of dropouts as a reason for the plateau is discounted.

Together, these data suggest that after an acute period of relatively rapid weight gain, olanzapine-treated patients tend to be at progressively lower risk for further weight gain as they continue into maintenance pharmacotherapy at least up to 3 years.

A previous study of acute weight change during antipsychotic drug treatment suggests that one of the most robust predictors of weight gain is low BBMI.[36] This observation is supported by the present study in that lighter-set patients gained significantly more weight and plateaued with a higher increase than heavier-set patients. While part of this result may be due to a regression to the mean phenomenon (i.e., greater likelihood that patients with room for greater weight change will thus demonstrate the greatest weight change), this observation is still important since among some low BBMI patients, favorable antipsychotic drug–response may drive a process of weight restoration. However, the unique non-overlapping plateau curves associated with each BBMI category (see Figure 4) suggest that a regression to a single population mean is unlikely. Similarly, this phenomenon may be explained by low BBMI patients experiencing a greater weight shift even though their caloric intake increases to the same extent as the high BBMI patients; this interpretation would need further investigation to validate. Furthermore, the population already at risk of longer term cardiovascular health risks (higher BBMI) also appears to be the population that gains the least amount of weight.

Dose is a second factor of interest surrounding weight change. In this study, olanzapine maintenance dose was not found to be significantly predictive of changes in weight. This absence of a dose-response relationship is consistent with previous olanzapine reports[36] and, in general, with reports of other antipsychotic drugs.[33] This information is especially important in clinical practice in that it suggests the ineffectiveness of dosage reduction as a means of attenuating or reversing weight gain.

Weight Change and Nonfasting Serum Glucose, Serum Cholesterol, and Diastolic Blood Pressure Levels

Effect of weight change on serum glucose. For many years, case reports have associated conventional and, more recently, novel antipsychotic drugs with new onset or exacerbation of diabetes.[11,12,33,37,38] Clozapine has been among the most widely investigated of the class, although case reports also describe diabetes occurring in olanzapine-treated patients,[39] risperidone-treated patients,[40] and quetiapine-treated patients.[41] Although a review of these studies suggests that many of these patients entered therapy with existing risk factors for diabetes, the significance of these reports awaits further study.

In the present report, neither endpoint nonfasting serum glucose levels nor the incidence of nonfasting glucose ≥ 160 mg/dL at endpoint was significantly associated with weight change during olanzapine treatment. The incidence of nonfasting glucose levels above this cutoff (≥ 160 mg/dL) was 4.6% for olanzapine-treated patients after 2.54 years and 5.0% for haloperidol-treated patients after 1.15 years, irrespective of weight change. These data suggest that the incidence of endpoint hyperglycemia in a schizophrenic patient cohort is similar whether exposed to long-term treatment with an atypical antipsychotic drug or a conventional antipsychotic drug. Since this criterion is less strict than that required for a diagnosis of diabetes, that is, a random nonfasting blood glucose of ≥ 160 mg/dL confirmed with fasting plasma glucose levels ≥ 126 mg/dL on 2 subsequent days,[19] weight change as noted in this study does not seem to be associated with an abnormality of glycemic control.

Effect of weight change on serum cholesterol. Excess weight is one of the correlates of an elevated blood cholesterol.[25] In the present study, median endpoint values in serum cholesterol were comparable to those seen at baseline. However, there was a significant association between weight gain during olanzapine treatment and median serum cholesterol at endpoint, and additionally, median nonfasting serum cholesterol at endpoint was significantly higher for olanzapine-treated patients than for haloperidol-treated patients (205.7 mg/dL versus 189.9 mg/dL, respectively; $p = .002$). These data indicate that the proportion of patients experiencing greater weight gain were more at risk for elevated serum total cholesterol. Although most olanzapine-treated patients (97%) did not have elevations above 300 mg/dL, a minority did experience levels reaching 400 mg/dL. The association between weight gain and cholesterol on olanzapine therapy does not appear to be the predominant driver of increased cholesterol in treated schizophrenic patients, as the incidence of elevated cholesterol was not significantly different between olanzapine and haloperidol. In any event, increasing weight should alert the clinician to the possibility of rising cholesterol. Furthermore, the 8% to 16% incidence of elevated cholesterol irrespective of treatment suggests that schizophrenia may be associated with a substantial risk of hypercholesterolemia over time.

Effect of weight change on diastolic blood pressure. Hypertension has an estimated prevalence of 24% in the U.S. population, and it has been reported that increased levels of BMI may be associated with the increased cardiovascular risk factor of high blood pressure.[25] In this study, although median endpoint values in diastolic blood pressure were comparable to those seen at baseline, there was also a statistically significant association between weight gain and endpoint diastolic blood pressure. Additionally, the median diastolic blood pressure at endpoint was significantly higher for olanzapine-treated patients than for haloperidol-treated patients. Although the majority (97%) of olanzapine-treated patients' diastolic blood pressure did not go above 100 mm Hg, increasing weight with treatment would indicate the prudence of monitoring such patients for hypertension. In addition, the approximately 20% incidence of elevated diastolic blood pressure in this study population after long-term olanzapine or haloperidol treatment suggests a further health risk associated with schizophrenia in general.

Study limitations

This retrospective data analysis has several limitations. Results were obtained from a flexible-dose clinical trial as opposed to a usual clinical practice setting. As a result, concomitant medications, such as antidepressants and mood stabilizers that may possibly contribute to weight gain, were generally proscribed. Further, because dose was not fixed, the lack of a relationship between dosing and weight change during this clinical trial is not a definitive finding.

Also, only a routine laboratory panel including random glucose and cholesterol was performed in this study. Obtaining verifiable fasting glucose and cholesterol measurements in this patient population might be difficult due to dietary compliance issues, specifically with those patients who are outpatients. The scope of these analyses was limited to weight gain and its potential association with glucose, cholesterol, and diastolic blood pressure. It was not the intent of these analyses to explore the consequences of long-term olanzapine treatment in general on these metabolic factors. Future studies should implement more definitive laboratory assessments to better examine the relationship between weight and health-related factors.

Patients were followed with regular weight assessments, and this may have identified subjects with particular weight management problems that may have initiated a therapeutic dialogue around appetite, diet, and exercise. Such an intervention may have had a more significant impact on the responding patients who continued in the long-term extension clinical study, as contrasted with nonresponding patients who would have been excluded from

participating in this study but not necessarily from treatment in the community. It should be noted that the literature does contain reports of weight gain during antipsychotic drug treatment that may be managed by dietary control[7] and also cases in which weight gain appeared to be reversible.[42–44] Also important to note is the lack of equally distributed long-term data across treatment groups. Of olanzapine-treated patients, 293 were observed for between 2.5 and 3 years, with 147 observed at the final 3-year timepoint, compared with 103 haloperidol-treated patients for whom the maximum time observed was 100 weeks (1.9 years).

Although the size and scope of this investigation are the most comprehensive to date, it may be argued that a longer period of observation may be needed to make more definitive conclusions regarding weight change and weight-related health factors. Further prospective studies of long-term weight change during antipsychotic drug treatment and its clinical consequences are indicated. Such studies should utilize more detailed assessments of appetitive behaviors and more comprehensive assessments of individual disease-specific risk factors and of relevant laboratory parameters. Finally, the results presented relate to generalized findings from a controlled clinical trial; any individual experiencing excessive weight change should be medically evaluated for glucose, lipid, and vital sign changes as clinically indicated.

CONCLUSION

Olanzapine-treated patients gained significantly more weight than haloperidol-treated patients. Further characterization of weight gain during olanzapine treatment indicated that weight gain trended toward a plateau, patients with lower BBMI tended to gain more weight than those with higher BBMI, and dose was not a significant predictor of weight gain. The relationship between nonfasting serum glucose levels and weight gain was not significant; however, the association between weight increase and elevation in nonfasting serum cholesterol and diastolic blood pressure was statistically significant. The incidence of elevated serum glucose, cholesterol, or diastolic blood pressure levels was not statistically different from that seen with haloperidol therapy. These data indicate that the greater weight gain experienced during olanzapine treatment is not necessarily the predominant driver of laboratory changes seen in schizophrenic patients nor of the increased values of glucose, cholesterol, or diastolic blood pressure occurring over time regardless of atypical or conventional antipsychotic drug treatment. Further prospective studies of long-term weight change during antipsychotic drug treatment and its clinical consequences are indicated. The present study findings offer clinicians a global overview of the effects of long-term olanzapine treatment and weight change and may aid the development of weight interventions for patients. In view of the initial rapid increase in weight that can be experienced by olanzapine-treated patients, early interventions including therapeutic dialogue regarding weight management techniques and healthier lifestyle choices may be prudent.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Beasley CM Jr, Tollefson GD, Tran PV, et al. Efficacy of olanzapine: an overview of pivotal clinical trials. J Clin Psychiatry 1997;58(suppl 10): 7–12
2. Beasley CM Jr, Tollefson GD, Tran PV, et al. Safety of olanzapine. J Clin Psychiatry 1997;58(suppl 10):13–17
3. Tollefson GD, Beasley CM, Tran P, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
4. Purdon SE, Jones BDW, Stip E, et al. Neuropsychological change in early phase schizophrenia over twelve months of treatment with olanzapine, risperidone, or haloperidol. Arch Gen Psychiatry 2000;57:249–258
5. Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. Br J Psychiatry 1998;153:214–217
6. Rockwell WJK, Ellinwood EH Jr, Trader DW. Psychotropic drugs promoting weight gain: health risks and treatment implications. South Med J 1983;76:1407–1412
7. Stanton JM. Weight gain associated with neuroleptic medication: a review. Schizophr Bull 1995;21:463–472
8. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686–1696
9. Lamberti JS, Bellnier T, Schwarzkopf SB. Weight gain among schizophrenic patients treated with clozapine. Am J Psychiatry 1992;149: 689–690
10. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
11. Koval MS, Rames LJ, Christie S. Diabetic ketoacidosis associated with clozapine treatment. Am J Psychiatry 1994;151:1520–1521
12. Popli AP, Konicki PE, Jurjus GJ, et al. Clozapine and associated diabetes mellitus. J Clin Psychiatry 1997;58:108–111
13. Casey DE. The relationship of pharmacology to side effects. J Clin Psychiatry 1997;58(suppl 10):55–62
14. Burggraf GW. Are psychotropic drugs at therapeutic levels a concern for cardiologists? Can J Cardiol 1997;13:75–80
15. McKee HA, D'Arcy PF, Wilson PJK. Diabetes and schizophrenia: a preliminary study. J Clin Hosp Pharm 1986;11:297–299
16. Muckherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. Compr Psychiatry 1996;37:68–73
17. Keskiner A, Toumi AE, Bousquet T. Psychotropic drugs, diabetes and chronic mental patients. Psychosomatics 1973;16:176–181
18. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000;26:903–912
19. American Diabetes Association. Screening for type 2 diabetes. Diabetes Care 2000;23(1, suppl):S20–S23
20. Schwartz LM, Woloshin S. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988–1994. Eff Clin Pract 1999;2:76–85
21. Kruskal WH, Wallis WA. Use of ranks in one-criterion variance analysis. J Am Stat Assoc 1952;47:583–621
22. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–748
23. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
24. Flegal KM, Carroll MD, Kuczmarski RJ, et al. Overweight and obesity in the United States: prevalence and trends, 1990–1994. Int J Obes Relat Metab Disord 1998;22:39–47
25. Ernst ND, Obarzanek E, Clark MB, et al. Cardiovascular health risks related to overweight. J Am Diet Assoc 1997;97(7, suppl):S47–S51

26. Krypsin-Exner W. Beitrage zum verlauf des korpergewichtes bei psychosen. Wien Klin Wochenschr 1947;59:531–534
27. Goodall E, Oxtoby C, Richards R, et al. A clinical trial of the efficacy and acceptability of D-fenfluramine in the treatment of neuroleptic-induced obesity. Br J Psychiatry 1998;153:208–213
28. Silverstone T, Goodall E. Serotoninergic mechanisms in human feeding: pharmacologic evidence. Appetite 1986;7:85–97
29. Fletcher PJ. Increased food intake in satiated rats induced by the 5-HT antagonists methysergide, metergoline and ritanserin. Psychopharmacology (Berl) 1988;96:237–242
30. Bernstein JG. Psychotic drug induced weight gain: mechanism and management. Clin Neuropharmacol 1988;11:S194–S206
31. Rietschel M, Naber D, Fimmers R, et al. Efficacy and side-effects of clozapine not associated with variation in the 5-HT_{2C} receptor. Neuroreport 1997;8:1999–2003
32. Heisler LK, Chu HM, Tecott LH. Epilepsy and obesity in serotonin 5-HT_{2C} receptor mutant mice. Ann N Y Acad Sci 1998;861:74–78
33. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. Eur Neuropsychopharmacol 1995;5:437–440
34. Harris E, Eth S. Weight gain during neuroleptic treatment. Int J Nurs Stud 1981;18:171–175
35. Klett CJ, Caffey EMJ. Weight changes during treatment with phenothiazine derivatives. J Neuropsychiatry 1960;2:102–108
36. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing weight change in patients with schizophrenia treated with olanzapine versus haloperidol or risperidone [abstract]. Presented at the 51st Institute on Psychiatric Services; Oct 29, 1999; New Orleans, La
37. Kamran A, Doraiswamy PM, Jane JL, et al. Severe hyperglycemia associated with high doses of clozapine [letter]. Am J Psychiatry 1994;151:1395
38. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. J Clin Psychiatry 1983;44:347–348
39. Wirshing DA, Spellberg BJ, Erhart SM, et al. Novel antipsychotics and new onset diabetes. Biol Psychiatry 1998;44:778–783
40. Croarkin PE. Diabetic ketoacidosis associated with risperidone treatment? Psychosomatics 2000;41:369–370
41. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment [letter]. J Clin Psychiatry 1999; 60:556–557
42. Ayd FJ. Prolonged administration of chlorpromazine (Thorazine) hydrochloride. JAMA 1959;169:1296–1301
43. Gordon HL, Groth C. Weight change during and after hospital treatment. Arch Gen Psychiatry 1964;10:187–191
44. Amdisen A. Drug-produced obesity: experiences with chlorpromazine, perphenazine and clopenthixol. Dan Med Bull 1964;11:182–189