Factors Influencing Acute Weight Change in Patients With Schizophrenia Treated With Olanzapine, Haloperidol, or Risperidone

Bruce R. Basson, M.S.; Bruce J. Kinon, M.D.; Cindy C. Taylor, Ph.D.; Keith A. Szymanski, Pharm.D.; Julie A. Gilmore, Ph.D.; and Gary D. Tollefson, M.D., Ph.D.

Objective: Clinical factors predicting weight change in patients with schizophrenia and related disorders during acute treatment with the antipsychotic drugs olanzapine, risperidone, and haloperidol were sought through retrospective analyses.

Method: Six-week body-weight data from 2 trials, study 1 comparing olanzapine and haloperidol (N = 1369) and study 2 olanzapine and risperidone (N = 268), were analyzed. Effects of 8 clinically relevant covariates—therapy, clinical outcome (Brief Psychiatric Rating Scale), baseline body mass index (BBMI), increased appetite, age, gender, race, and dose—on weight were compared.

Results: In study 1, olanzapine (vs. haloperidol) therapy, better clinical outcome, lower BBMI, and nonwhite race significantly affected weight gain. Effects of increased appetite and male gender on weight gain were significant for olanzapine but not for haloperidol. In study 2, better clinical outcome, lower BBMI, and younger age significantly affected weight gain. Increased appetite was more frequent during olanzapine treatment than during haloperidol, but not significantly different from risperidone. Significant differences in effect on weight change were found between olanzapine and haloperidol but not between olanzapine and risperidone. No evidence was found that lower antipsychotic drug doses were associated with lower weight gain.

Conclusion: This report identifies predictive factors of acute weight change in patients with schizophrenia. Similar factors across antipsychotic drugs in predicting greater weight gain included better clinical outcome, low BBMI, and nonwhite race. Factors differing between conventional (haloperidol) and atypical (olanzapine) agents included increased appetite and gender. Choice of atypical antipsychotic drug (olanzapine vs. risperidone) was of minor importance with regard to influence on acute weight gain.

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Reprint requests to: Bruce J. Kinon, M.D., Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 4133, Indianapolis, IN 46285.

There is compelling evidence that patients with schizophrenia often gain weight during pharmacologic intervention. Weight gain has been reported during treatment with many of the conventional agents, in particular the phenothiazines[1] and thioxanthenes,[2] as well as with most of the novel atypical agents including clozapine,[3–6] risperidone,[7,8] olanzapine,[9–11] sertindole,[12] and quetiapine.[13,14] Hypothetical mechanisms of action of these agents, such as serotonin 5-HT_{2C}[15,16] or histamine H_1[17] receptor antagonism, have been implicated.

Historically, investigators have observed that a decrease in body weight, perhaps secondary to decreased appetite or increased motor activity or agitation, often precedes overt signs of psychosis in patients with schizophrenia.[18,19] Early reports speculate that weight increase may result from an improved mental state in which patients feel and eat better.[20] The fact that weight loss has been shown to reverse itself with improvement in psychosis in some patients[18] suggests that weight gain in patients undergoing effective treatment may represent, in part, recovery from a disease-associated weight loss. However, in some patients, weight gain may be viewed as an undesirable effect and may have a potentially negative impact on the patient's overall health and treatment compliance.

The variability in patient experience with weight gain during antipsychotic drug treatment argues that this phenomenon is multifactorial, and so far the factors governing this relationship have not been clearly defined. Weight gain during antipsychotic drug treatment has been shown to correlate with excessive appetite[21–23] and has a tendency to plateau over time.[2,5,6,18,24] The effects of clinical outcome, baseline body mass index (BBMI), demographics, and dosing on weight change, though, have been less consistently demonstrated. Furthermore, whether or not these

potential influences differ between the conventional and the atypical antipsychotic drugs is unknown.

The purpose of these analyses was to determine if observed acute weight changes during treatment with olanzapine, haloperidol, and risperidone are predicted by relevant factors,[25] including clinical outcome, BBMI, increased appetite, age, gender, race, and dose. The degree to which these factors interact with therapy in the prediction of treatment-emergent weight gain could potentially aid clinicians in their management of patients with schizophrenia or related disorders who are undergoing initiation of an acute course of pharmacotherapy.

METHOD

Study Group

Patients were selected from 2 large, controlled, double-blind studies: a 6-week acute trial of olanzapine versus haloperidol (study 1)[10] and a 28-week trial of olanzapine versus risperidone (study 2).[26] Patients were diagnosed with DSM-III-R[27] (study 1) or DSM-IV[28] (study 2) schizophrenia, schizoaffective disorder, or schizophreniform disorder. Patients were at least 18 years of age and provided a written informed consent document after the details of the study had been fully explained.

In order to maintain consistency and also to allow qualitative comparisons between studies, data were truncated at 6 weeks, which not only represents the duration of most acute clinical trials but is also a relevant time frame used in clinical practice to determine treatment outcome and decide on treatment continuation. Since weight change is of primary interest in patients who continue into longer term therapy, only patients completing a full 6 weeks of observation were included in this retrospective analysis.

STUDY DESIGN

Study 1. Patients (N = 1996) were randomly assigned 2:1 to olanzapine (N = 1336) or haloperidol (N = 660). Since this was a flexible-dose study, 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). Patients began 6 weeks of double-blind therapy with a minimum Brief Psychiatric Rating Scale ($BPRS_{(0–6)}$) total score of 18 (mean = 33) and/or intolerance to current antipsychotic drug therapy (excluding haloperidol). Baseline and a 6-week postbaseline weight measurement were available for 1369 patients in study 1.

Study 2. Patients (N = 339) were randomly assigned 1:1 to either 15 mg/day of olanzapine (range, 10–20 mg/day; N = 172) or risperidone (initially 1.0 mg twice daily then titrated to a dose of 4–12 mg/day; N = 167). Patients had a minimum $BPRS_{(0–6)}$ total score of 24 (mean = 36) and were followed for up to 28 weeks. Baseline and a 6-week postbaseline weight measurement were available for 268 patients in study 2.

Assessments

Body mass index (weight [kg] divided by height [m^2])[29] was determined at baseline prior to study drug initiation. Outcome on the $BPRS_{(0–6)}$ extracted from the Positive and Negative Syndrome Scale (PANSS),[30] dose, and weight (kg) were recorded weekly. Appetite disturbance was collected on the Association for Methodology and Documentation in Psychiatry (AMDP-5)[43] adverse event scale, which recorded the severity rating for episodes of both excessive and decreased appetites. The difference in severity ratings of these 2 events was used to dichotomize patients as to whether or not increased appetite was reported. Where both excessive and decreased appetites were reported, the event occurring closest to the end of therapy was used. Patients reporting neither increased nor decreased appetite were classified as not increased.

Statistical Method

Statistical Analysis Software (SAS, version 6.09[31]) was used for all analyses. Histograms of change from baseline weight after 6 weeks were constructed, and the data were then modeled using analysis of variance (ANOVA), including 8 main effects and 7 therapy-by-factor interactions. Observed case weight-change data for 6-week completers were analyzed using repeated-measures ANOVA with time included as a class variable. In order to make comparisons of the relative importance of predictive factors, continuous predictors were reduced to 2-level class variables by using the median value for the study population to separate patients into 2 approximately equal-sized groups. Figures display differences in means adjusted for other factors in the model.

Data from the 2 studies were not combined. All tests were 2-sided and, unless otherwise noted, conducted at the .05 level of significance.

RESULTS

Patient Characteristics

Baseline patient characteristics for the populations examined are presented in Table 1. The only significant difference at baseline between therapy groups occurred in study 1 with patients on haloperidol therapy having a greater BBMI when compared with patients on olanzapine therapy (p = .002). Mean daily dose during the acute phase for these patient subgroups was olanzapine 11.2 ± 3.4 mg/day, haloperidol 10.8 ± 3.4 mg/day for study 1; and olanzapine 16.7 ± 2.4 mg/day, risperidone 6.8 ± 1.5 mg/day for study 2. There were no discontinuations due to weight gain as an adverse event for any drug in either study during the 6-week acute phase. Addition-

Table 1. Baseline Characteristics in Study 1 (Olanzapine vs. Haloperidol) and Study 2 (Olanzapine vs. Risperidone)[a]

	Study 1			Study 2		
Characteristic	Olanzapine (N = 1059)	Haloperidol (N = 310)	p Value	Olanzapine (N = 133)	Risperidone (N = 135)	p Value
Gender, N (%)						
Male	683 (64)	203 (65)	.787	89 (67)	81 (60)	.256
Female	376 (36)	107 (35)		44 (33)	54 (40)	
Race						
Nonwhite	197 (19)[b]	64 (21)[c]	.412	31 (23)[d]	33 (24)[e]	.886
White	862 (81)	246 (79)		102 (77)	102 (76)	
BBMI, mean ± SD	25.9 ± 4.9	27.0 ± 6.2	.002	26.7 ± 5.9	25.8 ± 5.8	.221
Age, mean ± SD, y	38.9 ± 11.6	38.0 ± 11.2	.218	36.0 ± 10.8	35.6 ± 10.3	.723
BPRS, mean ± SD	32.9 ± 10.6	33.5 ± 10.5	.387	37.0 ± 9.1	35.9 ± 9.0	.361

[a]Abbreviations: BBMI = baseline body mass index, BPRS = Brief Psychiatric Rating Scale.
[b]African American, 10%; Hispanic, 4%; other, 5%.
[c]African American, 12%; Hispanic, 5%; other, 4%.
[d]African American, 21%; Hispanic, 1%; other, 2% (percentages do not add to 23% due to rounding).
[e]African American, 20%; Hispanic, 1%; other, 4% (percentages do not add to 24% due to rounding).

Figure 1. Histogram of Weight Changes Among Study 1 Patients Completing 6 Weeks of Acute Therapy With Olanzapine or Haloperidol

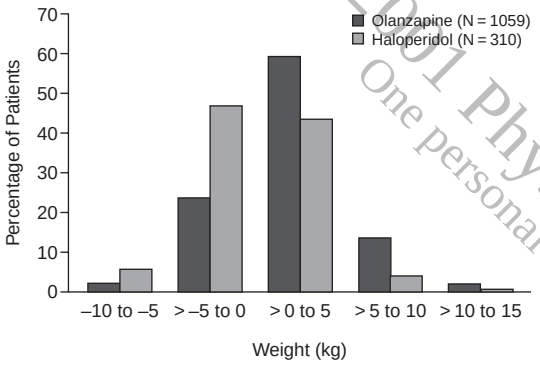
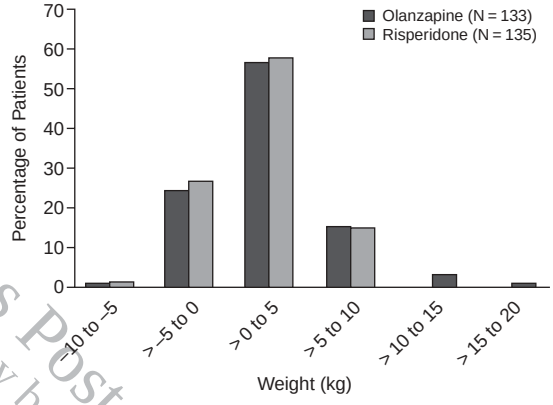


Figure 2. Histogram of Weight Changes Among Study 2 Patients Completing 6 Weeks of Acute Therapy With Olanzapine or Risperdal



ally, noncompleting patients did not have significantly higher weight gain at comparable timepoints than completing patients.

Overall Weight Change

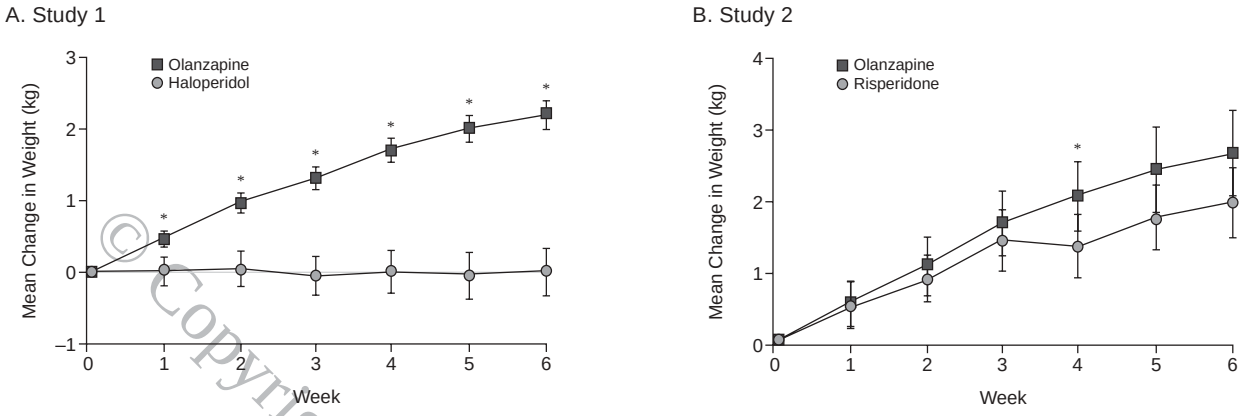
Histograms of the weight changes observed after 6 weeks in studies 1 and 2 are presented in Figures 1 and 2, respectively. In study 1, weight gain was significantly greater with olanzapine (2.24 ± 3.31 kg) compared with haloperidol (0.01 ± 2.97 kg; $p < .001$). In study 2, weight gain differences were not significant, averaging 2.66 ± 3.42 kg with olanzapine compared with 1.99 ± 2.77 kg with risperidone ($p = .081$). Figure 3 illustrates the mean weight change and the rate of weight change of patients completing the 6-week period for study 1 (panel A) and for study 2 (panel B). In study 1, olanzapine-treated patients experienced significantly more weight than haloperidol-treated patients at each week out to 6 weeks ($p < .05$). In study 2, olanzapine-treated patients experienced significantly more weight than risperidone-treated patients at week 4 only ($p < .05$).

Predictive Factors: Study 1 (Olanzapine vs. Haloperidol)

Figure 4 displays the mean difference in weight change between the 2 levels of each of the predictive factors examined in the study comparing olanzapine and haloperidol. The predictive factor with the greatest effect on weight change was found to be initial randomization to atypical versus conventional therapy, with olanzapine-treated patients gaining significantly greater weight than patients receiving haloperidol ($p < .001$). Clinical outcome and BBMI also had significant effects on weight change, such that patients completing the study with better clinical outcome (endpoint BPRS score ≤ 18) gained significantly more weight than patients with poorer clinical outcome (endpoint BPRS score > 18) ($p = .003$), and patients with low BBMI (≤ 25) gained more weight than patients with high BBMI (> 25; $p = .001$). The effects of clinical outcome and the effects of BBMI on weight change were consistent across olanzapine and haloperidol.

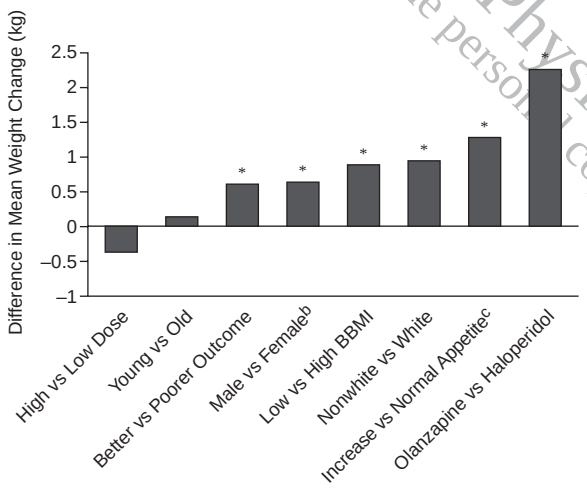
Increased appetite as compared to normal/decreased appetite also had a significant effect on weight change

Figure 3. Mean Change in Body Weight (kg) of Completing Patients Treated With Olanzapine or Haloperidol (panel A) and Olanzapine or Risperidone (panel B) From Baseline Out to 6 Weeks (observed cases)[a]



[a]Mean ± 2 SEM displayed.
*p < .05.

Figure 4. Effect of Factors Influencing Acute Antipsychotic Drug Weight Gain in Study 1, Olanzapine vs. Haloperidol[a]



[a]Displayed as differences in least-squares mean (set of parameters used in the model to minimize the distance between observed values and predicted values) weight change between groups.
[b]Significant gender-by-therapy interaction (p = .050).
[c]Significant appetite-by-therapy interaction (p = .005).
*p < .05.

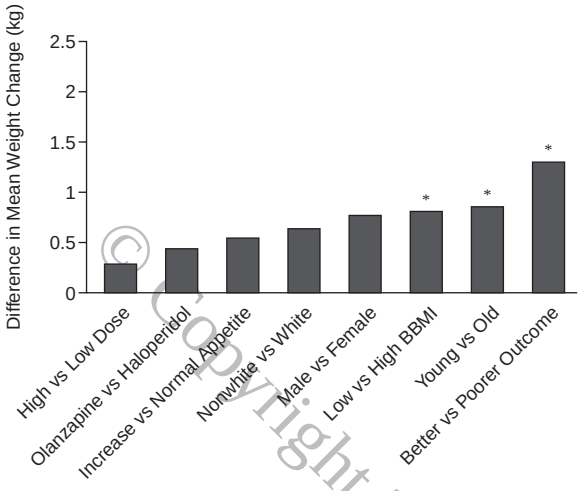
(p < .001), but this effect was not consistent for both therapy groups (interaction p = .005). Among patients taking olanzapine, those with increased appetites had greater weight gain than patients without (p < .001), while the effect of increased appetite on weight change was not significant among subjects receiving haloperidol (p = .259). Furthermore, the difference in the proportion of patients reporting increased appetite was significantly greater among olanzapine-treated patients (28.8%) compared with those treated with haloperidol (16.5%) (p < .001). Age was not a significant predictor of weight change in this study (p = .573). Younger patients (≤ 37.3 years) on olanzapine treatment had numerically greater weight gain than older patients (> 37.3 years), while the opposite was true for haloperidol-treated patients. Gender had a significant effect on weight change but only among patients taking olanzapine (overall p = .003; interaction p = .050). Males on olanzapine treatment gained significantly more weight than females on olanzapine treatment (p < .001), but the effect was not significant for haloperidol (p = .583). Nonwhite patients gained significantly more weight than white patients (p < .001), and this effect was consistent across both treatments. Differences between patients on below-median versus above-median dose of therapy were not significant (p = .059).

Predictive Factors: Study 2 (Olanzapine vs. Risperidone)

Figure 5 displays the mean difference in weight change between the 2 levels of each of the predictive factors examined. In contrast to study 1, differences in weight change between olanzapine and risperidone treatment groups were not significant (p = .387). Similar to study 1, though, clinical outcome was a significant predictor of weight change, whereby patients with better clinical outcome (endpoint BPRS scores ≤ 17) gained significantly more weight than those with poorer clinical outcome (endpoint BPRS scores > 17) (p = .001). Patients with lower BBMI (≤ 25) also gained significantly more weight than patients with higher BBMI (> 25) (p = .036). The effects of both clinical outcome and BBMI on weight change did not differ between olanzapine and risperidone treatment.

The effect of increased appetite on weight change was not significant in study 2 (p = .230), although patients with increased appetites gained numerically more weight than those with normal or decreased appetites. The fre-

Figure 5. Effect of Factors Influencing Acute Antipsychotic Drug Weight Gain in Study 2, Olanzapine vs. Risperidone[a]



[a]Displayed as differences in least-squares mean (set of parameters used in the model to minimize the distance between observed values and predicted values) weight change between groups.
*p < .05.

quency of increased appetite seen with olanzapine (25.6% of patients) was not significantly different from that seen with risperidone (23.0% of patients). The effect of age on weight gain was significant (p = .029), with patients < 34.7 years gaining significantly more weight than patients > 34.7 years, and this effect was not significantly different for the 2 treatments. The effect of gender on weight change was not significant (p = .057), although males had numerically greater weight gain than females for both compounds. The effect of race was also not significant (p = .154), although nonwhites gained numerically more weight than whites. Differences between patients taking high mean daily doses (above median) versus low doses (below median) were not significant. No significant effect-by-therapy interactions were seen, indicating that the effects on weight change of the covariates examined did not depend significantly on choice of therapy (olanzapine vs. risperidone).

DISCUSSION

Acute weight gain is a common occurrence for patients treated with antipsychotic drugs and must be considered by clinicians from the point of view of both patient compliance and the patient's general health status when initiating antipsychotic drug therapy. Weight gain is often viewed as a clinically significant untoward effect, and clinicians must balance striking improvements in clinical symptomatology against concerns over potential or actual changes in body mass. For many clinicians, the initial 6 weeks of antipsychotic drug therapy is a minimum time period in which to critically evaluate how patients are responding to a new course of therapy. Changes in efficacy, extrapyramidal symptoms, patient compliance, and vital sign and laboratory measurements such as weight and serum prolactin levels would all be assessed during this time frame. Data from the present studies address these issues by determining weight changes during both conventional and atypical antipsychotic drug treatment and by considering how clinical outcome, BBMI, appetite, demographic factors, and dose may affect these changes.

Weight Change Overall

Results from these analyses indicate that the overall magnitude and rate of weight change experienced after olanzapine treatment was significantly greater than that experienced after haloperidol treatment (2.24 kg during olanzapine treatment compared with 0.01 kg during haloperidol treatment). Additionally, the majority of olanzapine-treated patients experienced acute weight gain, while fewer haloperidol-treated patients appeared to gain weight during the first 6 weeks of treatment. The overall acute weight gain experienced during olanzapine treatment was numerically but not significantly greater than that experienced after risperidone treatment. Additionally, between olanzapine and risperidone, there was a similar distribution of patients gaining weight across treatments, and the rate of weight gain was not significantly different after 6 weeks.

Data from these 2 present studies are similar to others reported in the literature. Beasley et al.[9] observed a mean weight increase of 3.5 ± 3.9 kg following 6 weeks of treatment with 12.5 to 17.5 mg/day of olanzapine, while haloperidol was not seen to significantly alter weight. Other studies have reported a weight gain of 2 kg over 8 weeks with risperidone treatment.[7,8]

Weight and Clinical Outcome

For all 3 drugs examined, better clinical outcome was significantly associated with larger weight gain compared with poorer clinical outcome. In the study of 2 atypical agents, clinical outcome was more important when predicting weight changes that occurred during pharmacotherapy than choice of antipsychotic drug treatment (that is, olanzapine vs. risperidone). Clinicians must therefore balance the potentially better outcome seen with atypical agents against the chance that better responding patients may risk increased body mass. Furthermore, part of the weight gain seen with olanzapine-treated patients compared with haloperidol-treated patients may be tied to the greater clinical improvement seen in olanzapine-treated patients.[10] Further analysis of the relationship between clinical outcome and weight gain with respect to specific clinical symptoms would help to address this issue. While some early studies suggest an association between weight gain with conventional antipsychotic drugs and decreased psychosis,[1,20,32–34] others have failed to demonstrate such a relationship. It is somewhat intuitive that patients who are

less symptomatic may be more likely to engage in normal patterns of eating. Weight loss is also known to precede onset of psychopathology, and so the extent to which weight restoration may be a desirable outcome should be considered.

Weight and Baseline Body Mass Index

A relationship between lower BBMI and greater weight gain was indicated across haloperidol, olanzapine, and risperidone. Note that, in study 1, haloperidol patients had a significantly greater BBMI than did olanzapine patients, which would tend to lower weight gain estimates seen with haloperidol relative to olanzapine. In both studies, underweight patients who might have benefited from weight restoration were at higher risk for weight gain, while overweight patients tended to gain less weight. It is also consistent with the findings of Hummer et al.,[3] who demonstrated that patients with lower initial body weight (4% mean deviation from normal body weight) were at significantly higher risk for weight gain. Similarly, Umbricht et al.[4] reported that patients who were underweight prior to treatment gained significantly more weight with clozapine treatment than patients at normal or higher weights. It should be noted, however, that symptomatic improvement with antipsychotic drugs may also be associated with significant weight gain in patients who are normal weight or overweight at baseline.

Weight and Appetite

A significantly greater percentage of patients taking olanzapine reported increased appetite compared with those taking haloperidol, and those patients went on to register significantly greater weight changes than patients whose appetites were not increased. In study 2, patients treated with olanzapine and risperidone displayed similar frequencies of increased appetite, of similar order to that seen with olanzapine in study 1 and greater than that seen with haloperidol in study 1. This finding is suggestive that greater weight increases on olanzapine or risperidone relative to haloperidol might result in part from increased appetite. While the effect of increased appetite did not reach statistical significance in study 2, a variety of factors may account for this, including the smaller size of study 2 versus study 1.

Weight and Demographics

Data from these studies indicate that while males may gain significantly more weight than females under atypical antipsychotic treatment, gender did not affect weight change for the conventional antipsychotic drug. Although a previous report suggests gender is not significantly associated with weight gain,[3] other studies[35] have reported that gender may influence the degree of weight change. In contrast to the present study, Frankenburg et al.[35] reported that women gained more weight than men with clozapine treatment, but this may be partly explained by the fact that in that study women had a lower BBMI than men. Nonwhite patients had greater weight increase in both of the present studies when compared with white patients. The nonwhite group in our report was primarily African American and Hispanic, racial groups that may be more prone to weight gain during treatment with antipsychotic drugs[36] and to obesity in general. The present data also suggest that age may influence weight change, but primarily for the atypical antipsychotic drugs. Younger patients gained more weight on average than older patients when taking either olanzapine or risperidone, but not when taking haloperidol. This finding suggests that when initiating atypical antipsychotic drug treatment, weight gain may be less likely to occur in the older patient.

Weight and Dose

Previous reports suggest that a dose-response curve is absent with weight gain experienced after antipsychotic drug treatment.[3] In this report, which included 2 studies of variable-dose design, patients receiving high doses did not gain significantly greater amounts of weight than patients receiving low doses. While not a definitive finding, as patients were not randomized to low versus high dose and it is unknown whether weight change influenced dosing decisions, no evidence is provided that adjusting dosage in order to curb weight gain would be an effective strategy.

Mechanisms of Weight Gain

The mechanism of action of weight gain during treatment with antipsychotic drugs is poorly understood. Unlike haloperidol, both olanzapine and risperidone demonstrate relatively high affinity for serotonin 5-HT_{2C} and histamine H_1 receptors,[37] and it has been demonstrated that 5-HT_2 receptor deficient mice become overweight as a result of abnormal control of feeding behavior. Blockade of central H_1 receptors also increases food intake in rats fed a low protein diet.[17] The finding in our study that olanzapine produces greater levels of increased appetite than haloperidol suggests a possible receptor antagonist mechanism. Weight gain during treatment with atypical antipsychotic drugs could also be affected by preferential metabolism of carbohydrate over fat, resulting in increased fat storage.[38] Serum leptin levels, thought to signal the size of the adipose depot to brain and peripheral tissue, are increased following treatment with clozapine or olanzapine but are not increased with haloperidol.[39,40]

Interventions

Just as in the general population, management of weight can be challenging for patients with schizophrenia. However, these analyses suggest a number of possible courses of action open to clinicians wishing to prescribe atypical antipsychotic drugs but concerned over possible weight gain. First, patient reports of increased appetite

may be an early signal indicating a need for dietary intervention. One early study showed that reduced caloric intake in an inpatient setting promoted weight loss,[41] while a later study found that among olanzapine-treated patients, weight gain may be partially reversible with dietary and behavioral maneuvers.[36] Second, these analyses indicate that obese patients should not necessarily be denied newer atypical antipsychotic drug treatment because heavier patients are actually less vulnerable to further weight gain. Third, the profile of patients most at risk for weight gain during atypical antipsychotic drug treatment seems to be underweight, nonwhite males who are responding excellently to treatment, and so it is important for physicians to be sensitized to the potential for greater weight gain in patients with one or more of these characteristics and for whom an interruption of treatment would be countertherapeutic. Fourth, this study provides no evidence that lower antipsychotic drug doses produce any significant effect on weight change. Finally, it should be noted that switching among atypical antipsychotic drugs has not always been completely successful in resolving weight gain issues.[42] Further study of patients who do not gain weight during antipsychotic drug treatment may help to elucidate more promising interventions for treatment-emergent weight gain.

Limitations

The present analyses, and previous work in the field, have certain limitations. These findings represent retrospective rather than prospective investigations, and these trials did not utilize measures such as controlled diets, food preference, metabolic monitoring, or meal logs, which would better characterize important factors in weight change such as appetite and caloric intake. Although dose did not appear to affect weight change, further studies of fixed-dose design would be needed to confirm this finding. Additionally, this report is limited to the effects of acute treatment on weight change and may not apply to long-term therapy. Recent analyses, though, for predicting weight change during long-term therapy do suggest that the effects of BBMI and dose on longer term (out to 3 years) weight changes among olanzapine- and haloperidol-treated patients are similar to those described in the present report.[24] Last, these analyses are limited to factors predictive of acute weight gain and may not be extrapolated to predictors of long-term weight gain. Other analyses are ongoing to determine the potential health consequences of weight gain during antipsychotic treatment.

CONCLUSION

This report successfully identified predictive factors for weight change experienced after acute antipsychotic drug treatment in patients with schizophrenia or related disorders. Factors that were similar across the 3 antipsychotic drugs in predicting greater weight gain included better clinical outcome, low BBMI, and nonwhite race. Factors that appeared to differ between conventional (haloperidol) and atypical (olanzapine and risperidone) agents included increased appetite and gender. Choice of atypical antipsychotic drug (olanzapine vs. risperidone) was of minor importance compared with other predictive factors with regard to significant influence on weight gain. No evidence was found that lower doses of antipsychotic drugs were associated with lower weight gain. Appropriate intervention, such as advice on healthy living habits, diet, and moderate exercise or, in some circumstances, treatment discontinuation, should be considered if weight gain undermines clinical benefits or has adverse effects on the patient's health. Further exploration of a common underlying pharmacologic locus, especially among the novel agents, is encouraged.

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

REFERENCES

1. Klett CJ, Caffey EMJ. Weight changes during treatment with phenothiazine derivatives. J Neuropsychiatry 1960;2:102–108
2. Amdisen A. Drug-produced obesity: experiences with chlorpromazine, perphenazine and clopenthixol. Dan Med Bull 1964;11:182–189
3. Hummer M, Kemmler G, Kurz M, et al. Weight gain induced by clozapine. Eur Neuropsychopharmacol 1995;5:437–440
4. Umbricht DSG, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry 1994;55(9, suppl B):157–160
5. Lamberti JS, Bellnier T, Schwarzkopf SB. Weight gain among schizophrenic patients treated with clozapine. Am J Psychiatry 1992;149: 689–690
6. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72
7. Claus A, Bollen J, De Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand 1992;85:295–305
8. Owens DGC. Extrapyramidal side effects and tolerability of risperidone: a review. J Clin Psychiatry 1994;55(5, suppl):29–35
9. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacol 1996;14:111–123
10. 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
11. Beasley CM, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute-phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
12. Tamminga CA, Mack RJ, Granneman GR, et al. Sertindole in the treatment of psychosis in schizophrenia: efficacy and safety. Int Clin Psychopharmacol 1997;12(suppl 1):S29–S35
13. Small JG, Hirsch SR, Arvanitis LA, et al. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549–557
14. Borison RL, Arvanitis LA, Miller BG, et al. ICI204, 636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16:158–169
15. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2C serotonin receptors. Nature 1995;374:542–546
16. Simansky KJ. Serotonergic control of the organization of feeding and satiety. Behav Brain Res 1996;73:37–42
17. Mercer LP, Kelley DS, Humphries LL, et al. Manipulation of central ner-

vous system histamine or histaminergic receptors (H1) affects food intake in rats. J Nutr 1994;124:1029–1036
18. Krypsin-Exner W. Beitrage zum verlauf des korpergewichtes bei psychosen. Wiener Klin Wschr 1947;59:531–534
19. Rowntree DW, Kay WW. Clinical biochemical and physiological studies in cases of recurrent schizophrenia. J Ment Sci 1952;98:100
20. Planansky K. Changes in weight in patients receiving a "tranquilizing" drug. Psychiatr Q 1958;32:289–303
21. Mefferd RB, Labrosse EH, Gawienowski AM, et al. Influence of chlorpromazine on certain biochemical variables of chronic male schizophrenics. J Nerv Ment Dis 1958;127:167–179
22. Bernstein JG. Induction of obesity by psychotropic drugs. Ann N Y Acad Sci 1987;499:203–215
23. Brady KT. Weight gain associated with psychotropic drugs. South Med J 1989;85:611–617
24. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry 2001;62:92–100
25. Kinon BJ, Basson B, Szymanski K, et al. Factors associated with weight gain during olanzapine treatment. Presented at the 11th annual congress of the European College of Neuropsychopharmacology (ECNP); Oct 31–Nov 4, 1998; Paris, France
26. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
27. American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders, Third Edition. Washington, DC: American Psychiatric Association; 1987
28. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
29. Kuczmarski RJ, Flegal KM, Campbell SM, et al. Increasing prevalence of overweight among US adults. JAMA 1994;272:205–211
30. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
31. SAS Institute Inc. SAS/STAT User's Guide. 4th ed. Cary, NC: SAS Institute Inc; 1990
32. Holden JMC, Holden UP. Weight changes with schizophrenic psychosis and psychotropic drug therapy. Psychosomatics 1970;11:551–561
33. Singh MM, DeDios LV, Kline NS. Weight as a correlate of clinical response to psychotropic drugs. Psychosomatics 1970;11:562–570
34. Klett CJ, Caffey EM. Weight changes during treatment with phenothiazine derivatives. J Neuropsychiatry 1960;2:102–108
35. Frankenburg FM, Zanarini MC, Kando J, et al. Clozapine and body mass change. Biol Psychiatry 1998;43:520–524
36. Wirshing DA, Wirshing WC, Kysar L, et al. Novel antipsychotics: comparison of weight gain liabilities. J Clin Psychiatry 1999;60:358–363
37. Bymaster F, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996;14:87–96
38. Flatt JP. Steroids and obesity in rats. Int J Obes 1989;15:552b
39. Bromel T, Blum WF, Ziegler A, et al. Serum leptin levels increase rapidly after initiation of clozapine therapy. Mol Psychiatry 1998;3:76–80
40. Kraus T, Haack M, Schuld A, et al. Body weight and leptin plasma levels during treatment with antipsychotic drugs. Am J Psychiatry 1999;156:312–314
41. Gopalaswamy AK, Morgan R. Too many chronic mentally disabled patients are too fat. Acta Psychiatr Scand 1981;72:254–258
42. Bryden KE, Kopola LC. Body mass index increase of 58% associated with olanzapine [letter]. Am J Psychiatry 1999;156:1835–1836
43. AMDP. Arbeitsgemeinschaft für Methodik und Diagnostik in der Psychiatrie (Association for Methodology and Documentation in Psychiatry [AMDP]). Das AMDP-System. Manual zur Dokumentation psychiatrischer Befunde. 4th Aflage. Berlin, Heidelberg, New York; 1981