Weight Gain and Antipsychotic Medication: Differences Between Antipsychotic-Free and Treatment Periods

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Background: We performed a retrospective analysis of data involving 121 inpatients to examine the rate of weight gain during antipsychotic-free periods and during treatment with various antipsychotic drugs.

Method: Data were analyzed to determine differences in weekly weight change during antipsychotic-free (N = 65), typical antipsychotic (N = 51), or atypical antipsychotic (N = 130) treatment periods. Atypical antipsychotic treatment periods were further subdivided into olanzapine (N = 45), clozapine (N = 47), or risperidone (N = 36) treatment periods. A paired comparison was conducted on 65 patients who had an antipsychotic-free treatment period preceding or following a neuroleptic drug treatment period. In addition, patients were classified as either non-obese (with a body mass index [BMI] ≤ 29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2) to test whether the rate of weight gain during treatment periods was related to initial BMI.

Results: Across all treatment periods, weekly weight gain was as follows: 0.89 lb/wk (0.40 kg/wk) on atypical antipsychotic medication, 0.61 lb/wk (0.27 kg/wk) on typical antipsychotic medication, and 0.21 lb/wk (0.09 kg/wk) on no antipsychotic medications. The atypical antipsychotic versus antipsychotic-free comparison was significant (F = 3.51; df = 2,231; p = .031), while the typical antipsychotic versus antipsychotic-free comparison was not. Among the individual atypical antipsychotic medications, significantly more weight gain occurred during olanzapine treatment (1.70 lb/wk) (0.76 kg/wk) than with either clozapine (0.50 lb/wk) (0.22 kg/wk) or risperidone (0.34 lb/wk) (0.15 kg/wk) treatments (F = 7.77; df = 2,117; p = .001). In the paired analysis with patients serving as their own controls, the difference between weekly weight gain during atypical antipsychotic treatment and antipsychotic-free treatment was significant (t = –3.91; df = 44; p = .001), while the difference between weight gain during typical antipsychotic treatment and antipsychotic-free treatment was not significant. With the individual drugs, treatment with both olanzapine and clozapine caused significantly higher weekly weight gain than antipsychotic-free treatment (p = .001 and p = .036, respectively), while treatment with risperidone did not. Non-obese patients (BMI < 29.9 kg/m^2) and obese patients (BMI > 30.0 kg/m^2) did not differ significantly in their weight gain during typical or atypical antipsychotic treatment.

Conclusion: Treatment with atypical antipsychotics was associated with more weight gain than treatment with typical antipsychotics. Among the atypical drugs, olanzapine was associated with more weight gain than either clozapine or risperidone. The patient's admission BMI was not associated with the amount of weight gained during subsequent antipsychotic treatment.

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One of the great advances in psychopharmacology of the past decade has been the advent of the atypical antipsychotic medications that display both increased antipsychotic efficacy and fewer adverse side effects, particularly extrapyramidal, than typical antipsychotics.[1–4] Olanzapine, clozapine, risperidone, and other atypical antipsychotic medications are an integral part of the therapeutic program for many individuals with schizophrenia and other psychotic disorders. However, although these drugs have some significant advantages over the typical antipsychotic medications in terms of their therapeutic effects and side effect profiles, a significant disadvantage that has emerged is their potential, as a class, to produce weight gain.[5–11] Among the atypical antipsychotics, the extent of weight gain varies and has been

hypothesized to be due to differing degrees of drug action on the serotonergic,[12–16] dopaminergic,[16–19] cholinergic,[20,21] histaminergic,[20,21] and other neurotransmitter systems.

Drug-induced obesity is a significant problem in the schizophrenic population for 2 main reasons, health risk and treatment adherence. Treatment with atypical antipsychotics has been shown to be associated with elevated triglyceride levels,[22–25] increased insulin levels,[22,26] and new-onset diabetes.[22,27–30] Furthermore, excessive weight gain and obesity are associated with increased morbidity from coronary heart disease, hypertension, gallbladder disease, sleep apnea, osteoarthritis, and some forms of cancer.[31]

Second, not only is weight gain undesirable as a health hazard, but such a noticeable and culturally unacceptable side effect may cause patients to discontinue their medications, increasing their risk for relapse.[32–37] While there are many reasons that patients taking neuroleptics decide to discontinue them, significant weight gain, particularly in the long term, contributes to patients' decisions to discontinue their medications.[32,38] Monitoring and preventing antipsychotic-induced weight gain may, therefore, play a role in promoting treatment compliance and general health among psychotic patients.

This study is a retrospective analysis of the potential of treatment with typical or atypical antipsychotics to be associated with weight gain. By comparing each patient's weight change while taking medication to his/her weight change during an antipsychotic-free period, this study controls for the effects of treatment setting, thus overcoming a major limitation of previous studies.

METHOD

Subjects and Procedure

A review of the charts of all patients admitted to the Schizophrenia Research Unit of the New York Psychiatric Institute, New York, N.Y., during the years 1994 to 1999 was conducted. All weight data used in the study were obtained from patients participating in Institutional Review Board–approved studies that included an antipsychotic-free period. The New York Psychiatric Institute requires all patients provide written consent prior to participation in any studies with an antipsychotic-free period. Typically, the patients in our study were admitted to the unit, stabilized, attempted an antipsychotic-free period of 2 to 4 weeks, and then received 1 or more courses of treatment with an antipsychotic medication. The data were excluded from the following treatment periods: treatment periods of less than 2 weeks, treatment periods in which the patient was simultaneously treated with more than 1 antipsychotic medication, and treatment periods with insufficient documentation of weight. During antipsychotic-free periods, patients received no antipsychotic medications but could receive anxiolytic, antidepressant, and/or mood stabilization medications as needed, most commonly lorazepam, benztropine, or lithium salts. Anxiolytic, antidepressant, and mood stabilization medications were constant throughout the hospital course, and for within-subject comparison we eliminated cases in which these medications were started or stopped during or between treatment episodes of interest.

Table 1. Demographic Variables of Study Subjects

Characteristic	Subjects (N = 121)
Age (y), mean ± SD	33.2 ± 11.1
Gender, N	
Male	69
Female	52
Ethnicity, N	
White	68
Hispanic	30
Black	17
Other	6
DSM-IV diagnosis, N	
Schizophrenia	70
Schizoaffective disorder	31
Other[a]	20
Admission values, mean ± SD	
Weight (lb)	169 ± 38
Height (in)	66.6 ± 4.0
Body mass index (kg/m^2)	26.8 ± 6.1
Duration of illness (y)	11.2 ± 9.3

[a]Diagnoses within "other" category include schizophreniform personality disorder, bipolar I disorder, schizoid personality disorder, and schizophrenia residual and psychotic disorder (not otherwise specified).

The following information was obtained from the medical charts: age, gender, ethnicity, DSM-IV diagnosis, duration of treatment and dosage, height, and weight. Demographic variables are summarized in Table 1. Body weight was measured on admission, at discharge, and weekly during the patient's stay by the nursing staff. Patient weights were taken at 7:00 a.m. prior to breakfast using a balance-beam scale. The body mass index (BMI) was computed as body weight (in kilograms)/square of height (meters). For classifications, BMIs less than or equal to 29.9 kg/m^2 were considered non-obese and BMIs greater than or equal to 30.0 kg/m^2, clinically obese. In all, 121 patients were included in this study, and data from 246 treatment episodes were analyzed.

Statistical Methods

The 121 patients contributed 65 antipsychotic-free periods, 51 typical antipsychotic medication treatment periods, and 130 atypical antipsychotic medication treatment periods. Each antipsychotic-free and antipsychotic medication treatment period was characterized by the amount of weight change per week (expressed as lb/wk), as well as the initial and final BMI and the length of treatment period. In some cases, patients completed as many as 4 separate treatments that were included in our analysis. Because this was a retrospective analysis of naturalistic

inpatient treatment, treatment periods were not designed to occur in a specific order.

The variables of interest were as follows: weight change per week, number of weeks of treatment, initial BMI, final BMI, starting weight, and final weight. These variables were analyzed using a 3 (treatments = antipsychotic-free, typical antipsychotic, and atypical antipsychotic) × 2 (BMI groups = non-obese and obese) univariate analysis of variance (SPSS Version 10.0.5). When the analysis revealed significant between-group effects, additional post hoc univariate analyses of variance (ANOVAs) were performed to identify specifically which groups accounted for the differences. In addition, an analysis of covariance (ANCOVA) similar to the ANOVA described above was performed using raw BMI data as the covariate rather than categorized BMI data.

Led by the results of the first ANOVA, 2 additional grouping factors were created: the first to specifically look at the 3 atypical treatments separately (olanzapine, clozapine, and risperidone), and the second a reanalysis using 4 treatment groups (antipsychotic-free, typical antipsychotics, atypical antipsychotics [not including olanzapine], and olanzapine). In cases where the Ns were reasonable to assess for weight-change-per-week differences within the same subjects across treatment periods, paired 2-tailed *t* tests were performed with alpha set at .05. Such data existed for the following comparisons: antipsychotic-free treatment versus typical antipsychotic treatment, antipsychotic-free treatment versus atypical antipsychotic treatment, antipsychotic-free treatment versus individual atypical antipsychotic treatment (olanzapine, clozapine, and risperidone), and typical antipsychotic treatment versus atypical antipsychotic treatment. For the paired analysis of antipsychotic-free versus neuroleptic treatment periods within individual patients, the antipsychotic-free period immediately preceded or followed the comparison neuroleptic treatment period. Overall, 61 of the 65 antipsychotic-free periods occurred immediately before or after an antipsychotic treatment period.

Secondary analyses were also conducted to account for the possibility that weight change might be dependent on the length of the treatment interval. ANOVAs were performed for each of the treatment groupings by the number of weeks of treatment. The treatment interval categories were as follows: 1 = 2 weeks; 2 = 3–4 weeks; 3 = 5, 6, and 7 weeks; and 4 = 8 or more weeks of treatment. This categorizing scheme yielded approximately 25% of the cases into each category.

Finally, a regression analysis was performed using weight change per week as the dependent variable with the following independent variables: the 4 treatment grouping variable (antipsychotic-free, typical antipsychotics, atypical antipsychotics [not including olanzapine], and olanzapine), initial BMI, diagnostic group (schizophrenia, schizoaffective disorder, or other), gender, age, number of weeks of treatment interval, and treatment order/number. The probability to enter and to be removed from the equation was set at p = .10 and p = .15, respectively.

RESULTS

Subjects

Table 1 presents the demographic data of the 121 patients taking part in the study. There were no statistical differences between the antipsychotic-free (N = 65), typical antipsychotic medication (N = 51), and atypical antipsychotic medication (N = 130) treatments for patient age, gender, admission weight, height, duration of treatment, ethnic background, or DSM-IV diagnosis. The distribution of gender across the 3 treatment periods did differ; the male-to-female ratio of patients treated with typical antipsychotic medication was much higher than with atypical antipsychotic medication or antipsychotic-free periods ($\chi^2 = 5.90$, df = 2, p = .052). Treatment order/number across the individual atypical antipsychotic treatments also differed significantly. Within the atypical grouping, clozapine treatment as opposed to olanzapine, risperidone, or typical antipsychotic treatment was more likely to occur as the third or greater (later) treatment period during a patient's overall stay ($\chi^2 = 31.15$, df = 4, p < .0001).

Relationship Between Weight Change and Treatment Type

We began by determining the mean weight change per week (lb/wk) for each subject during each treatment period (Table 2). During treatments with atypical antipsychotics (olanzapine, clozapine, risperidone, or quetiapine) patients gained significantly more weight per week than during antipsychotic-free treatments (F = 3.51; df = 2,231; p = .031; see Table 2). There was no significant difference between the rate of weight gain between the antipsychotic-free and typical antipsychotic treatment periods, or between typical and atypical antipsychotic treatment periods. Among the 3 atypical antipsychotic treatments, olanzapine treatment resulted in a significantly higher rate of weight gain than either clozapine or risperidone treatment (F = 7.77; df = 2,117; p = .001; Table 3). There was no significant difference between the rates of weight gain in patients while taking clozapine versus risperidone. When analyzed separately, olanzapine treatment was also associated with a significantly higher rate of weight gain compared with antipsychotic-free treatment, typical antipsychotic treatment, and treatment with other atypical antipsychotic medications (F = 7.17; df = 3,228; p = .001; see Tables 2 and 3).

Relationship Between Weight Change and Body Mass Index

In addition to studying the effect of different treatment types on weekly weight gain, we also determined if a

Table 2. Body Mass Index (BMI) and Weight Change During Antipsychotic-Free Treatment or During Treatment With Typical or Atypical Antipsychotic[a]

	Type of Treatment												Treatment Phase			
	Antipsychotic-Free (N = 65)				Typical Antipsychotic[b] (N = 51)				Atypical Antipsychotic[c] (N = 130)							Treatment
Value	Mean	SD	95% CI	%	Mean	SD	95% CI	%	Mean	SD	95% CI	%	F	df	p	Post Hoc
Initial weight (lb)	169	34	160 to 177		167	41	156 to 179		169	36	163 to 176		0.34	2,231	.71	
Final weight (lb)	169	33	161 to 178		171	39	160 to 182		175	37	169 to 182		0.15	2,231	.857	
Percent change in weight				0				2.4				3.5				
Weight change (lb/wk)	0.21	2.56	–0.42 to 0.84		0.61	1.46	0.20 to 1.02		0.89	1.75	0.58 to 1.20		3.51	2,231	.031	Antipsychotic-free < atypical antipsychotic
Initial BMI (kg/m^2)	26.0	5.0	24.7 to 27.2		26.5	6.6	24.6 to 28.3		27.0	5.2	26.0 to 27.9		0.66	2,231	.516	
Final BMI (kg/m^2)	26.1	4.9	24.9 to 27.3		27.1	6.4	25.2 to 28.9		27.9	5.3	27.0 to 28.8		1.89	2,231	.153	
Duration of treatment period (wk)	3.3	2.0	2.8 to 3.8		6.4	4.2	5.2 to 7.6		6.8	4.5	6.0 to 7.5		12.4	2,231	.001	Antipsychotic-free < typical antipsychotic and atypical antipsychotic

[a]BMI code was included in the analysis of variance but showed no significant differences across BMI code nor interaction with treatment number, so data were not included in table.
[b]Typical antipsychotics (N, mean dosage ± SD) are as follows: haloperidol (30, 9.0 ± 6.5 mg/d), fluphenazine (17, 34.2 ± 10.3 mg/d), perphenazine (9, 23.8 ± 17.7 mg/d), trifluoperazine (3, 23.3 ± 2.9 mg/d), thiothixene (3, 27.7 ± 28.2 mg/d), pimozide (2, 2.5 ± 0.7 mg/d), molindone (1, 50 mg/d), thioridazine (1, 200 mg/d), and chlorpromazine (1, 100 mg/d).
[c]Atypical antipsychotics (N, mean ± SD dosage) are as follows: olanzapine (45, 15.8 ± 7.6 mg/d), clozapine (47, 323 ± 194 mg/d), risperidone (36, 5.78 ± 3.41 mg/d), and quetiapine (2, 384.4 ± 283.4 mg/d).

Table 3. Body Mass Index (BMI) and Weight Change During Treatment With Different Atypical Antipsychotics[a]

	Olanzapine (N = 45)				Clozapine (N = 47)				Risperidone (N = 36)				Treatment Phase			Treatment
Value	Mean	SD	95% CI	%	Mean	SD	95% CI	%	Mean	SD	95% CI	%	F	df	p	Post Hoc
Initial weight (lb)	174	40	162 to 186		170	31	161 to 179		165	39	151 to 178		0.31	2,117	.733	
Final weight (lb)	184	38	172 to 196		173	32	163 to 182		168	39	155 to 182		1.15	2,117	.319	
Percent change in weight				5.7				1.8				1.8				
Weight change (lb/wk)	1.70	2.00	1.10 to 2.30		0.50	1.39	0.09 to 0.91		0.34	1.70	–0.24 to 0.91		7.77	2,117	.001	Olanzapine > clozapine and risperidone
Initial BMI (kg/m^2)	27.3	5.5	25.6 to 28.9		26.3	4.3	25.0 to 27.6		27.2	6.3	25.0 to 29.3		0.60	2,117	.552	
Final BMI (kg/m^2)	28.8	5.0	27.3 to 30.3		26.7	4.5	25.4 to 28.1		27.7	6.4	25.5 to 30.0		0.43	2,117	.649	
Duration of treatment period (wk)	6.5	4.2	5.2 to 7.8		6.7	4.3	5.4 to 8.0		6.5	4.9	4.9 to 8.2		0.22	2,122	.806	

[a]Dosages (mean ± SD) are as follows: olanzapine (15.8 ± 7.6 mg/d), clozapine (323 ± 194 mg/d), and risperidone (5.8 ± 3.5 mg/d). BMI code was included in the analysis of variance but showed no significant differences across BMI code nor interaction with treatment number, so data were not included in table.

patient's initial weight influenced the amount of weight gained during treatment. We found no significant difference in weight gain between non-obese and obese patients during antipsychotic-free, typical antipsychotic, or atypical antipsychotic treatment periods. In addition, raw BMI data (used as a covariate) exhibited no significant association with treatment groupings or weekly weight change.

Within-Subject Comparisons

To substantiate the initial findings described above, we further restricted our analysis to patients who completed an antipsychotic-free period of at least 2 weeks and used these patients as their own control to compare weight change per week on antipsychotic medication to weight change per week during an adjacent antipsychotic-free phase (Table 4). Within this subgroup, 20 patients had

Table 4. Paired Analysis of Weight Change During Antipsychotic-Free and Drug Treatment Periods in Subjects Receiving Both Types of Treatments

Type of Treatment	N	Antipsychotic-Free (lb/wk) Mean	SD	Drug (lb/wk) Mean	SD	t	df	p
Typical antipsychotic	20	–0.07	2.75	0.69	1.73	–0.95	19	.353
Atypical antipsychotic	45	–0.05	2.07	1.39	2.04	–3.91	44	.001
Olanzapine	26	–0.47	2.13	2.10	2.21	–5.53	25	.001
Clozapine	9	–0.53	1.21	0.67	0.71	–2.51	8	.036
Risperidone	13	0.64	2.34	0.81	1.93	–0.22	12	.833

a treatment with a typical antipsychotic medication adjacent to an antipsychotic-free period, and 45 patients had a treatment with an atypical antipsychotic medication adjacent to an antipsychotic-free period. We found a significant difference between a patient's weekly weight gain while taking an atypical antipsychotic as compared with the antipsychotic-free period ($p = .001$), while there was no significant difference between a patient's weekly weight gain on a typical antipsychotic versus the antipsychotic-free period (see Table 4). An identical paired analysis with the individual atypical antipsychotics showed that olanzapine and clozapine were both associated with significantly higher weekly weight gains compared with the antipsychotic-free period ($p = .001$ and .036 respectively; see Table 4). Weekly weight gain on risperidone treatment did not differ significantly from the antipsychotic-free period.

Predictors of Weight Gain

Regression analysis determined that gender, age, patient's starting BMI, number of weeks of treatment interval, and treatment order/number between the antipsychotic-free, atypical antipsychotic, and typical antipsychotic treatments did not predict weekly weight gain. We did find that treatment type, i.e., antipsychotic-free, typical, atypical, or olanzapine (F to change = 11.71, df = 1,235; $p = .001$), duration of illness ($F = 6.93$, df = 1,234; $p = .009$), and diagnosis ($F = 4.18$, df = 1,233; $p = .042$) were all associated with weight change. Longer duration of illness was associated with decreased weight gain during treatment, and the schizoaffective group exhibited less weight gain compared with the schizophrenia and "other" groups (mean weight change: schizoaffective disorder = 0.17 ± 1.6 lb [0.08 ± 0.72 kg], schizophrenia = 0.78 ± 2.0 lb [0.35 ± 0.90 kg], "other" = 1.07 ± 2.3 lb [0.48 ± 1.04 kg]). Further multivariate analysis indicated that diagnosis predicted weight gain at only a trend level ($p = .097$).

Secondary Analyses

Secondary analyses addressing the length of the treatment intervals also revealed no significant association between length of treatment and weight gain. We did find a significant correlation between duration of illness (years) and admission BMI ($r = 0.275$, df = 119, $p < .01$). To further explore this relationship, we performed a partial correlation on duration of illness and admission BMI controlling for age. When controlling for age, the partial correlation coefficient indicated a trend relationship between duration of illness and admission BMI ($r = 0.153$, df = 118, $p = .096$).

DISCUSSION

The present study confirms that atypical antipsychotics are associated with greater weight gain in patients than typical antipsychotics.[10,11] Our analysis also indicated that gender, age, initial BMI, and the order that patients receive different treatment types did not predict weekly weight gain, emphasizing that the type of drug itself seems the strongest indicator of potential weight gain. Consistent with previous reports,[39,40] we found that among the atypical antipsychotics, olanzapine and clozapine were associated with greater weight gain than risperidone, although only the olanzapine treatment reached statistical significance when compared with typical antipsychotic treatment. In fact, weight gain may be the most common adverse effect of olanzapine. Beasley et al.[41] reported that 40% of patients taking olanzapine gained 7% or more of their body weight compared with 12.4% of those taking haloperidol and 3.1% taking placebo.

A unique strength of this study is that in addition to comparing the weight gain associated with atypical and typical antipsychotics, we were able to control for any weight change that occurred during an antipsychotic-free phase within the identical inpatient environment. In fact, as expected, the mean weight gain for patients during the antipsychotic-free period was significantly lower than the mean weight gain during atypical antipsychotic treatment. In an analysis of just those patients who completed an antipsychotic-free period of at least 2 weeks adjacent to an antipsychotic treatment period, we observed the same trends in weight gain: atypical antipsychotic treatment was associated with significantly more weight gain per week than antipsychotic-free treatment, and both olanzapine and clozapine treatments individually were associated with significantly more weight gain than antipsychotic-free treatment. Thus, we are confident that in the patients we studied, the weight gain associated with the atypical antipsychotic treatment was a mechanism of the drugs themselves rather than a nonspecific effect of the inpatient environment.

Even though the inclusion of an antipsychotic-free period was a significant methodological improvement in this study compared with similar other studies, there were still obvious limitations. Because this was a naturalistic, retrospective chart review, the patients were not randomly

assigned to drug, which limited the numbers of patients in some of the individual antipsychotic medication categories and does not address whether there were differences in the inpatient environment over certain time periods. The period of observation for all treatment groups was relatively short considering that the weight gain associated with many of the antipsychotic medications may not be linear, in which case a window of several weeks could exaggerate or minimize the long-term effect on a patient's weight. Moreover, most patients were also taking anxiolytics, antidepressants, and/or mood stabilizers simultaneous to receiving antipsychotic medications. Certain drugs in each of these families have been shown to cause weight gain independently,[42] and thus may be responsible for some of the weight gain attributed to the antipsychotics, although use of these medications was normally consistent throughout the entire patient stay. The above limitations in study design potentially minimize the ability to detect significant differences in inducing weight gain in patients between antipsychotic medication categories and antipsychotic and antipsychotic-free treatment periods.

Weight gain associated with the use of antipsychotics is not only a clinical concern for the patient but a broader public health issue as well. Future studies are needed to adequately address the time course, variability, reversibility, and predictive factors of weight gain associated with antipsychotic medications. Additional study is also required to assess weight gain induced by concomitant administration of multiple antipsychotic drugs, since in practice up to one fourth of all patients on antipsychotics are taking more than one simultaneously.[43] Careful studies are also needed to measure energy intake and expenditure in patients taking various antipsychotics in order to determine the exact mechanism of these drugs for inducing weight gain. Similarly, some studies have suggested that weight gain correlates with treatment response.[8] Further studies are required to confirm this association, to better understand its mechanism, and to explore whether preventing weight gain interferes in any way with drug efficacy. Finally, future studies are needed that assess the role of weight management for minimizing the health risks associated with obesity and maximizing compliance and continuation of treatment in patients benefiting from antipsychotic treatment.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane), trifluoperazine (Stelazine and others).

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