Novel Antipsychotics: Comparison of Weight Gain Liabilities

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Background: We performed a retrospective analysis of 122 clinical records of 92 male patients with DSM-III-R schizophrenia to examine the relative weight gain liabilities of clozapine, risperidone, olanzapine, and sertindole compared with haloperidol. We hypothesized that the unique pharmacodynamic profiles of these agents would contribute to different amounts and patterns of weight gain.

Method: Data were analyzed to determine differences in weight gain during treatment among patients receiving 5 different drug treatments (clozapine [N = 20], olanzapine [N = 13], risperidone [N = 38], haloperidol [N = 43], and sertindole [N = 8]). Measures of maximal weight gain, final weight, and duration to maximal weight gain were calculated.

Results: Repeated measures analyses of variance controlling for age, treatment duration, and initial weight revealed statistically significant differences between groups on all 3 measures. Clozapine and olanzapine had the greatest maximal weight gain liability ($F = 4.13$, $df = 4,23$; $p = .01$). Weight gain with clozapine, but not olanzapine or risperidone, appears to persist (as reflected by final weight) despite behavioral interventions (e.g., nutritional consultation, suggested exercise regimen; $F = 5.69$, $df = 4,23$; $p = .003$). Clozapine- and olanzapine-treated subjects appeared to gain weight over a prolonged period of time, whereas risperidone- and sertindole-treated subjects had a more limited period of weight gain ($F = 2.95$, $df = 4,25$; $p = .04$).

Conclusion: Clozapine and olanzapine caused the most weight gain, risperidone was intermediate, and sertindole had less associated weight gain than haloperidol. The relative receptor affinities of the novel antipsychotics for histamine H_1 appear to be the most robust correlate of these clinical findings.

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Many antipsychotic drugs have been associated with substantial weight gain and drug-induced obesity.[1–3] Studies indicate that antipsychotic drug–induced weight gain is a common cause of noncompliance and discontinuance of treatment, resulting in the return of psychotic symptoms.[1,2,4,5] Furthermore, excessive weight gain and obesity are associated with increased morbidity from coronary heart disease, diabetes, hypertension, gallbladder disease, and some forms of cancer.[6] Monitoring and combating antipsychotic drug–induced weight gain may therefore play a part in promoting treatment compliance and general health among psychotic patients.

Psychotropic drugs that influence serotonin (5-HT) neurotransmission have been reported to affect food intake and cause fluctuations in weight. Drugs that facilitate serotonin transmission have been found to reduce food consumption and cause weight loss.[7–9] In contrast, drugs that block serotonin transmission have been found to increase food intake and cause weight gain.[2,10–12]

It remains speculative which serotonin receptor type is responsible for stimulating food intake and weight gain. Aulakh et al.[13] suggested that both 5-HT_{1C} and 5-HT_2 receptors play an important role in the stimulation of food intake; these receptors are now referred to as 5-HT_{2C} and 5-HT_{2A}, respectively.[14] Tecott and colleagues[15] developed a strain of mice whose gene for the 5-HT_{2C} receptor was removed. These mice became obese and had a propensity for seizures.

In addition to animal models for the role of 5-HT_{2C} in eating behavior, the medication fenfluramine is thought to

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Table 1. Binding Affinity In Vitro of Antipsychotics for Neurotransmitter Receptor Subtypes[a]

Drug	5-HT_{2A}	5-HT_{2C}	D_{2L}	D_{2S}	α_1	H_1
Clozapine	9.6	13	192	147	23	0.23
Olanzapine	2.5	7.1	31	21	60	0.65
Risperidone	0.52	48	5.9	6.2	2.3	20
Haloperidol	196	> 10,000	2.2	1.8	19	790
Sertindole	0.39	1.9	7.0	5.8	1.8	130

[a]Reprinted with permission from reference 14. Binding affinity (K_i) values are shown in nmol/L.

exert its chemical activity as a 5-HT_{2C} (formerly 5-HT_{1C}) agonist, thus suppressing appetite.[16] Additionally, *m*-chlorophenylpiperazine (*m*-CPP), a serotonin agonist, decreases food intake when given to humans.[17] This adds further evidence that the serotonin blockade of novel antipsychotics may do the opposite, i.e., increase food intake.

Also, some of these novel agents, particularly clozapine, have strong affinity for histamine H_1 receptor sites.[18,19] Links between weight gain, use of antihistamines, and older conventional antipsychotic agents such as thioridazine and chlorpromazine have been demonstrated in humans.[2,3,20–22]

Clozapine, risperidone, sertindole, and olanzapine are novel antipsychotics that have been developed in an effort to increase antipsychotic efficacy with fewer side effects, particularly extrapyramidal side effects, than conventional antipsychotics. In comparison with conventional antipsychotics, these novel antipsychotics are pharmacologically characterized as potent serotonin receptor antagonists with a lower affinity for dopamine D_2 receptor sites.[23–26] Specifically, clozapine, risperidone, sertindole, and olanzapine have high binding affinities for 5-HT_{2C} and 5-HT_{2A}.[14,27,28] Clozapine also has a large amount of activity at cholinergic and histaminergic receptor sites.[18,19] Previous studies have indicated that clozapine, risperidone, and olanzapine are responsible for drug-induced weight gain in psychotic patients.[29–33] Table 1 shows the medications' binding affinities for neurotransmitter receptor subtypes.

In contrast, haloperidol is a conventional antipsychotic with a low affinity for serotonin receptor binding sites.[34] Studies indicate that haloperidol's serotonergic properties are significantly weaker than those exhibited by clozapine, risperidone, sertindole, and olanzapine.[25,27,35–37] It has been hypothesized that haloperidol's limited serotonergic properties are responsible for the drug's lower potential to induce weight gain[2] and that the different serotonergic affinities exhibited by the novel antipsychotics and haloperidol might explain the variation in the amount of weight gained by patients receiving these drugs.[38]

This study is a retrospective analysis of the relative weight gain liabilities of clozapine, risperidone, olanzapine, and sertindole compared with that of haloperidol. We hypothesized that the unique pharmacodynamic profiles of these agents will contribute to different amounts and different patterns of weight gain.

METHOD

Subjects and Procedures

The subjects were 92 male patients with schizophrenia (DSM-III-R criteria) who were participants in 8 different clinical drug trials conducted over 6 years in our research clinic: a study comparing clozapine with haloperidol, 2 different studies comparing risperidone with haloperidol, a study comparing sertindole with placebo, a study comparing olanzapine with placebo, a study comparing 4 dose levels of haloperidol decanoate, a study comparing clozapine with risperidone, and a study comparing olanzapine with risperidone. Thirty subjects participated in more than 1 study over the 6-year period. Thus, 122 clinical records were included in the analyses.

As noted above, some of these clinical trials included placebo controls during the initial double-blind phase. Placebo-control subjects were not entered into these analyses of weight gain because none of them were maintained on treatment with placebo longer than 6 weeks (see Table 2 for average duration of treatment). All studies were double-blind comparisons that were followed by open-label extension phases, with the exception of the haloperidol decanoate study (it had no open-label extension). The patients in the 2 clozapine-treatment studies and 1 of the risperidone versus haloperidol studies were classified as treatment resistant; the patients in 1 of the risperidone studies, the sertindole study, and both olanzapine studies were classified as treatment responsive; and the patients in the haloperidol decanoate study had a history of psychotic decompensation with a need to be maintained on treatment with antipsychotics. The drug studies were all conducted at the V.A. Greater Los Angeles Healthcare System. All the patients provided informed consent after receiving a full explanation of their respective study procedures.

At the time these data were collected, our clinic was running approximately 10 studies. The 8 studies chosen were selected because they had the greatest number of patients enrolled for the longest period of time. These studies have been conducted over a 6-year period.

Medical charts were reviewed to obtain the following information: age, ethnicity, diagnosis, weight changes, duration of treatment, and inpatient status. Demographic variables are summarized in Table 2. Patients were weighed as part of routine procedures using the same clinic scale.

All patients were subject to the following clinical management of weight control during the 6-year period: First, patients were instructed to weigh themselves and report their weight to our research clinical nurse specialist at each visit (every 1 to 4 weeks). If this simple feedback behavioral paradigm failed to maintain their weight (a gain of 10 lb [4.5 kg] in our subjects is generally considered sufficient to warrant further intervention), they were instructed

Table 2. Demographic Variables

Variable	Drug: Clozapine (N = 20)	Olanzapine (N = 13)	Risperidone (N = 38)	Haloperidol (N = 43)	Sertindole (N = 8)	Pairwise Comparisons
Age, y, mean ± SEM**	43.1 ± 1.0	44.5 ± 1.2	43.9 ± 1.0	41.1 ± 1.0	42.4 ± 1.4	Clozapine > haloperidol,** risperidone > haloperidol,** olanzapine > haloperidol**
Ethnicity, N (%)						
White	11 (55)	5 (38)	25 (66)	16 (37)	5 (62)	
African American	5 (25)	5 (38)	9 (24)	10 (23)	2 (25)	
Hispanic	4 (20)	1 (8)	1 (3)	11 (26)	0 (0)	
Other	0 (0)	2 (15)	3 (8)	6 (14)	1 (12)	
Treatment duration, wk, mean ± SEM**	27.2 ± 8.0	73.1 ± 9.9	25.8 ± 5.8	24.7 ± 5.4	42.5 ± 12.6	Olanzapine > clozapine,** olanzapine > risperidone,** olanzapine > haloperidol**

**p ≤ .01.

to keep a detailed diary of all food intake over a several week period. If this failed to maintain or decrease weight, they were then referred to our clinical nutritionist. Subsequent to this, they were referred to the "Wellness Clinic" at our medical center, which involves a more rigorous evaluation of both dietary and exercise habits and adds education, exercise classes, and group support. While it is true that not all subjects availed themselves of these services, there is no reason to think that any one drug group would have more or fewer "uncooperative" patients.

Statistical Methods

Maximal weight gain was defined as the maximum weight a subject obtained at any point in the study minus his initial weight. Percentage weight gain was defined as maximum weight minus initial weight, divided by initial weight. Of note, 12 patients lost weight during the study. Thus, the maximum weight change for these patients was negative. Final weight change was defined as the final weight observed minus the initial weight. Both maximal weight change and final weight change were studied to see if interventions resulted in a change between maximal and final weights. Repeated-measures analyses of variance (ANOVAs) were performed using the SAS statistical package.[39]

RESULTS

Subjects

There were statistically significant differences between the drug treatment groups on the demographic variables of age ($F = 4.96$, $df = 4,26$; $p = .004$) and duration of treatment ($F = 5.27$, $df = 4,26$; $p = .003$; see Table 2). There were no other statistically significant differences between groups on demographic variables.

Maximal Weight

Controlling for age, treatment duration, and initial weight, we determined average adjusted maximal weights for each group (Table 3). Clozapine- and olanzapine-treated patients had the highest maximal weight gains compared with other groups ($F = 4.26$, $df = 4,23$; $p = .01$). Figure 1 represents the percentage of subjects on each drug treatment who gained 10% or more of their baseline weight, less than 10%, and had no weight change. Patients taking olanzapine or clozapine gained weight over greater periods of time compared with risperidone- and sertindole-treated subjects ($F = 2.95$, $df = 4,25$; $p = .04$; see Table 3).

Final Weight

Controlling for age, treatment duration, and initial weight, we found that final weight change was different among groups ($F = 5.69$, $df = 4,23$; $p = .003$; Table 4). At the time of final weight measurement, clozapine-associated weight gain remained statistically significantly higher than that for all other medications. No other pairwise differences were seen.

Relationship Between Initial Weight and Weight Gain

Overall, there was no relationship between body weight status at baseline and either the maximum weight gained or the weight at endpoint. Of the 92 subjects, however, 2 who were thin at baseline were clearly outliers. These 2 patients gained 45 lb and 55 lb (20 kg and 25 kg), respectively, during treatment (with baseline weights of 128 lb and 151 lb [58 kg and 68 kg]). Including these outliers in a Pearson product moment correlation calculation gave only a meager suggestion of an inverse correlation between body weight index at baseline and weight gained ($r = –0.14$, $p = .19$). Excluding these outliers, however, caused even this suggestion to disappear completely.

Relationship Between Maximal Weight and Final Weight

The correlation between maximal and final weights was high for all drugs (overall: $r = 0.88$, $p = .0001$; clozapine: $r = 0.98$, $p = .0001$; haloperidol: $r = 0.90$, $p = .0001$; sertindole: $r = 0.94$, $p = .0004$) except olanzapine ($r = 0.83$, $p = .0001$) and risperidone ($r = 0.83$, $p = .0001$).

Table 3. Maximum Actual and Adjusted Weight Gain

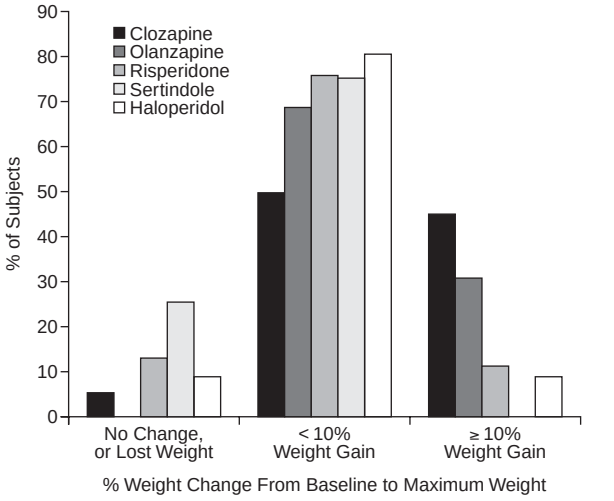
Variable	Drug					Pairwise Comparisons
	Clozapine	Olanzapine	Risperidone	Haloperidol	Sertindole	
Beginning weight, mean ± SD						n/a
lb	184.4 ± 33.5	190.0 ± 43.6	185.6 ± 38.0	186.0 ± 36.2	188.8 ± 30.1	
kg	83.0 ± 15.1	85.5 ± 19.6	83.5 ± 17.1	83.7 ± 16.3	84.9 ± 13.5	
Adjusted time to maximum weight gain, mean ± SEM, wk**	24.9 ± 3.1	21.2 ± 4.1	15.0 ± 2.3	18.5 ± 2.1	8.3 ± 4.9	Clozapine > risperidone,** clozapine > sertindole,** olanzapine > sertindole*
Maximum weight gain, mean ± SD						n/a
lb	16.8 ± 13.3	17.8 ± 13.3	9.1 ± 7.6	7.7 ± 9.0	5.6 ± 7.3	
kg	7.5 ± 6.0	8.0 ± 6.0	4.1 ± 3.4	3.5 ± 4.1	2.5 ± 3.3	
Maximum adjusted weight gain, mean ± SEM**						Clozapine > sertindole,* clozapine > haloperidol,** olanzapine > sertindole,* olanzapine > haloperidol**
lb	15.2 ± 1.8	15.0 ± 2.2	11.1 ± 1.4	8.2 ± 1.3	6.8 ± 2.8	
kg	6.9 ± 0.8	6.8 ± 1.0	5.0 ± 0.6	3.7 ± 0.6	3.1 ± 1.2	
Maximum % weight gain, mean ± SD	9.5 ± 8.1	10.5 ± 10.3	5.2 ± 4.4	4.1 ± 4.7	3.2 ± 4.5	n/a
Maximum adjusted % weight gain, mean ± SEM**	8.8 ± 1.1	8.8 ± 1.3	6.4 ± 0.8	4.4 ± 0.8	4.1 ± 1.7	Clozapine > sertindole,* clozapine > haloperidol,** olanzapine > sertindole,* olanzapine > haloperidol**

*p ≤ .05. **p ≤ .01.

Relationship Between 5-HT$_{2C}$ Receptor Affinity, H$_1$ Receptor Affinity, and Weight Gain

No relationship could be established between the relative 5-HT$_{2C}$ receptor affinities and weight gain. However, an exponential relationship was seen between the medications' H$_1$ receptor affinities and maximum weight gain (Figure 2).

Figure 1. Weight Gain as a Function of Drug



DISCUSSION

Novel antipsychotics vary in their weight gain liabilities. Clozapine and olanzapine appear to cause the most weight gain, risperidone is intermediate, and sertindole actually has less associated weight gain than haloperidol. Clozapine's effect on weight gain was sustained and unresponsive to interventions, whereas olanzapine's weight gain effect was somewhat reversible with dietary and other behavioral maneuvers. However, the possibility that this phenomenon may simply be an artifact of the much longer treatment duration of the olanzapine patients (73.14 weeks) compared with that of the clozapine patients (27.17 weeks) cannot be ruled out.

For those patients who did gain weight, the time course was distinct among treatment groups. Risperidone- and sertindole-treated subjects reached a weight plateau after a comparatively short initial time period (circa 10 weeks), whereas olanzapine- and clozapine-treated patients continued to gain weight over a more lengthy period (circa 20 weeks.)

The weight gain liabilities of these drugs appeared to be correlated with their relative affinities for the histamine H$_1$ receptor. Despite our speculation that weight gain from these new agents would be linked to serotonin receptor activity, no relationship could be established between clinical weight gain and 5-HT$_{2C}$ receptor affinity.

The literature is variable in terms of establishing a link between weight gain and dose of conventional antipsychotic medications.[40–43] Our sample size is too small to adequately address the issue of dosage. In future studies, we will attempt to have a larger sample to examine dosage issues.

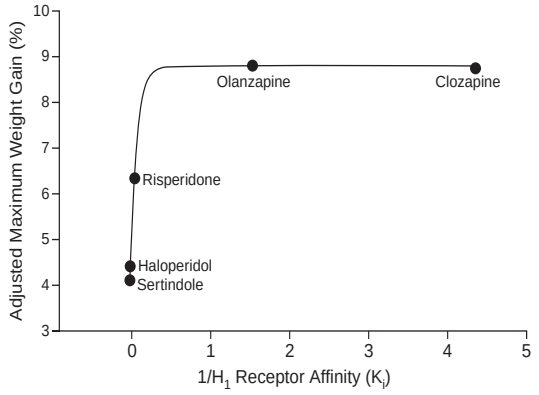
Other possible explanations for increased weight gain seen in the clozapine-treated patients compared with the haloperidol-treated patients may be that, clinically, the clozapine-treated patients were ill longer and were thus more sedentary. However, over half of the haloperidol-treated subjects in this retrospective study were matched for severity of illness with the clozapine-treated patients.

Table 4. Final Weight Gain

Variable	Drug					Pairwise Comparisons
	Clozapine	Olanzapine	Risperidone	Haloperidol	Sertindole	
Final weight gain, mean ± SD						n/a
lb	14.1 ± 13.5	6.2 ± 14.1	4.2 ± 9.2	3.0 ± 10.9	0.5 ± 8.6	
kg	6.3 ± 6.1	2.8 ± 6.4	1.9 ± 4.2	1.4 ± 4.9	0.2 ± 3.9	
Final adjusted weight gain, mean ± SEM**						Clozapine > risperidone,** clozapine > sertindole,**
lb	15.0 ± 2.3	5.3 ± 2.9	5.0 ± 1.8	3.4 ± 1.7	1.4 ± 3.7	clozapine > haloperidol,**
kg	6.8 ± 1.0	2.4 ± 1.3	2.3 ± 0.8	1.5 ± 0.8	0.6 ± 1.7	clozapine > olanzapine*
Final % weight gain, mean ± SD	8.0 ± 8.2	4.2 ± 9.8	2.5 ± 5.3	1.6 ± 5.7	0.6 ± 5.2	n/a
Final adjusted % weight gain, mean ± SEM**	8.7 ± 1.3	3.3 ± 1.6	3.1 ± 1.0	1.9 ± 1.0	1.2 ± 2.0	Clozapine > risperidone,** clozapine > sertindole,** clozapine > haloperidol,** clozapine > olanzapine**

*p ≤ .05. **p ≤ .01.

Figure 2. Weight Gain as a Function of H_1 Affinity[a]



[a]$y = 4.7[1 - e^{-12.5x}] + 4.1$ where y = adjusted maximum weight gain (%) and x = $1/H_1$ receptor affinity (K_i).

Additionally, the clozapine-treated patients had a better clinical response than the haloperidol-treated subjects.[38] Some researchers have postulated that an increase in weight during clozapine treatment is linked with good clinical response.[44] Although we have clinical response data for all these patient groups, different rating instruments were used to measure response in each study. Each subset of patients was selected for these studies for their different historical patterns of response; thus, comparisons across these studies would be unfair.

As adults age, weight can naturally increase.[45] We believe the weight gain seen in our patients treated with the new agents exceeds what would be expected as a normal aspect of aging. Indeed, some patients in each group gained over 30 lb (14 kg).

The fact that only men were included in this study is a limitation, as women may have different weight gain patterns. Another potential difficulty in interpreting our results is that 30 patients were involved in more than 1 study. Sequential participation may artificially minimize the actual weight gain a patient may have experienced with the second medication he was exposed to in the second trial.

A suggestion coming from pharmaceutical companies is that weight gain may be most significant in patients who were initially underweight. However, we examined this in our data set, and we saw no correlation between body weight index at baseline and weight gain.

Future prospective studies could be designed to actually measure caloric intake and assess the types of foods that patients eat, e.g., are they preferentially increasing carbohydrate intake or fat intake?

Although novel antipsychotic drugs have superiority over haloperidol both in increased effectiveness and in reduced side effects,[46,47] they carry the liability of potential weight gain. Of note, conventional antipsychotic medications were also notorious for this effect, particularly lower-potency agents.[1,2] Histamine receptor blockade was speculated to play a role in this in the past.[48] Antihistamines are well known to cause weight gain,[2,3,20–22] so antihistamine properties of clozapine and olanzapine may, in part, account for the increase in weight caused by these medications.[30] Indeed, we saw the strongest correlation between weight gain and relative histamine H_1 receptor affinities of the novel agents.

Clinicians should be aware of this potential liability of the new agents. Patients should have nutritional counseling and referral to exercise programs while taking these medications. Weight should be monitored carefully over the course of treatment. Primary care practitioners, family members, and other caregivers should be alerted to this risk, as the potential complications of weight gain in patients with schizophrenia can be serious. Of note, several of our patients who have had enormous weight gain on treatment with novel antipsychotic medications have developed diabetes.[49] Greater risk for heart disease may also result in patients who develop significant weight gain. It is essential that we educate our patients to minimize the risks of this important side effect.

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

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