

Weight Gain Associated With Antipsychotic Drugs

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Weight gain has been reported with nearly every antipsychotic drug on the market (molindone is an exception). Weight gain occurs no matter what the patient's age, sex, or race and is seen with both oral and depot drug formulations. Numerous studies have found that patients gain weight when treated with a conventional antipsychotic, such as chlorpromazine, fluphenazine, and haloperidol. The newer, novel antipsychotics offer advantages over conventional antipsychotics, especially a relative lack of extrapyramidal symptoms, but some still have the disadvantage of causing weight gain. Clozapine and olanzapine in particular appear to cause substantial weight gain, much more so than do most conventional neuroleptics and novel agents such as risperidone. Given the risks to health and treatment compliance associated with weight gain and obesity, clinicians should monitor weight during the course of antipsychotic therapy and consider switching agents if excessive weight gain occurs.

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We have known for some time that treatment with antipsychotic drugs is associated with weight gain. A few years after the first neuroleptic medications were introduced, researchers were reporting clinically significant gains in weight among patients treated with these drugs.¹ Today, we have available several newer antipsychotic medications, which offer advantages over conventional neuroleptics in that they are less likely to cause extrapyramidal symptoms, tardive dyskinesia, and certain other adverse effects. Yet weight gain remains a problem with many of these newer agents.

Clinicians treating patients with schizophrenia and other psychotic disorders now have many psychotropic drugs from which to choose. Since the efficacy of each of these agents has been demonstrated (although individual patients may have varying responses to the same drug), drug selection becomes a matter of comparing adverse effect profiles. In this brief literature review, the goal is to examine weight gain reported with conventional neuroleptics and with newer antipsychotics and to determine which drugs might be the best choice for preventing or minimizing antipsychotic-associated weight gain.

CONVENTIONAL NEUROLEPTICS

One of the earliest studies to examine weight gain associated with antipsychotic drugs in a large number of patients was conducted by Klett and Caffey.¹ This study evaluated changes in weight in 396 men with chronic schizophrenia who were treated with chlorpromazine, promazine, phenobarbital, or placebo for 12 weeks, followed by a 12-week crossover between some patients in the antipsychotic and placebo groups. Although by week 6 slight differences in weight gain were apparent between the patients treated with the phenothiazines chlorpromazine and promazine and those receiving a control medication (phenobarbital or placebo), clear evidence of considerable weight gain in the phenothiazine groups compared with the control groups was seen at week 12. The patients who gained the most weight were those who were treated with a phenothiazine throughout the 24-week study period. Among patients whose medication was switched from a phenothiazine to phenobarbital or placebo for the last 12 weeks of the study, weight tended to return to pre-treatment levels.

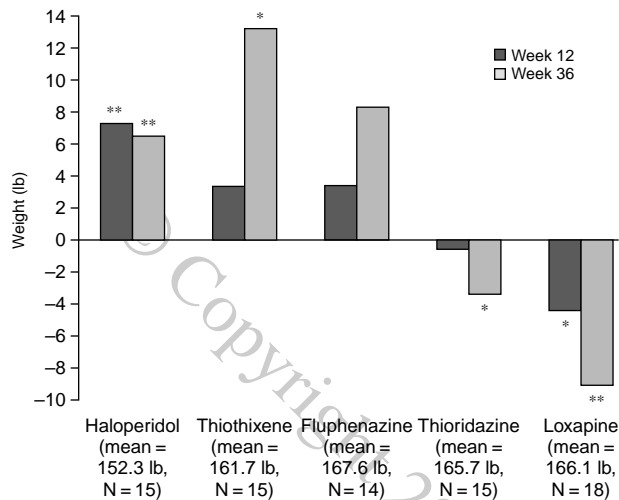
In a study conducted 10 years later, Holden and Holden² used a somewhat complicated study design to evaluate the effects of chlordiazepoxide, thioridazine, and a combination of these drugs on weight and clinical changes in 22 men with chronic schizophrenia. Each patient was randomly assigned to 1 of 3 medication sequences. The first group received in order placebo, chlordiazepoxide, placebo, chlordiazepoxide plus thioridazine, placebo, and thioridazine, each for a consecutive 8-week period. The other two groups received the same medications but in a different order. This study design allowed

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Figure 1. Baseline Weight and Change in Weight at 12 and 36 Weeks in Patients Treated With Selected Antipsychotic Agents^a



^aData from reference 4. All N = week 36.

* $p < .05$ vs. baseline. ** $p < .01$ vs. baseline.

investigators to evaluate changes in weight during 66 episodes of treatment with active drug and 66 episodes of treatment with placebo. During the periods when patients were treated with chlordiazepoxide, thioridazine, or both, weight gain averaged between 5 and 11 lb. There were no statistically significant differences in weight gain between chlordiazepoxide and thioridazine given alone. During the placebo periods, patients lost an average of 5 lb, with the greatest average weight loss (7.5 lb) occurring during the first placebo period.

Dufresne et al.³ conducted a 6-week study in which patients with schizophrenia were randomly assigned to receive haloperidol (N = 12), molindone (N = 10), or thioridazine (N = 13). At the end of the study period, patients receiving molindone lost a mean of 5 lb, those in the thioridazine group gained a mean of 6 lb, and those in the haloperidol group had no change in weight. Doss,⁴ however, reported significant weight loss in patients treated with thioridazine. In this retrospective chart review, the author reviewed data on body weight for 78 randomly selected patients with schizophrenia who had been treated with haloperidol, thiothixene, fluphenazine, thioridazine, or loxapine. Weights were recorded at baseline and after 12 and 36 weeks of treatment. As shown in Figure 1, patients treated with haloperidol, thiothixene, and fluphenazine all gained weight, while those receiving thioridazine and loxapine lost weight. Weight gain with haloperidol appeared to plateau by week 36, which was not the case for thiothixene and fluphenazine; patients taking these drugs continued to gain weight throughout the study period. Patients taking thioridazine had little change in weight at week 12 but lost a significant amount by week 36. Patients

treated with loxapine lost weight progressively over the 36-week treatment period.

Weight gain with conventional neuroleptics is just as likely with depot formulations as with oral tablets, as Johnson and Breen reported in 1979.⁵ In this prospective study of 132 outpatients with schizophrenia attending a depot clinic, 55% of patients treated with depot flupenthixol or fluphenazine gained a significant amount of weight, with 28% gaining more than 6.6 lb and 7% gaining more than 15.4 lb within 6 months. Expressed as a percentage of body weight, 11% of patients gained more than 10% of their initial body weight, 26% gained more than 5% of initial body weight, and 46% gained more than 2% of initial body weight. There was no significant difference in weight change between the flupenthixol and fluphenazine groups. There was a trend toward less weight gain with lower doses of each drug, but overall the correlation between weight and dose was not statistically significant.

My colleagues and I have also examined the relationship between weight and use of depot neuroleptics (M.B. Lake, M.D., R. Ganguli, M.D., unpublished data, 1996). The study included 125 patients with schizophrenia whose psychotic symptoms were being well controlled with depot injections of haloperidol or fluphenazine. Data on height, weight, and dose of medication were obtained as part of the patients' routine care, and body mass index (BMI) was calculated for each patient. Seventy-six of the 125 patients were asked to complete a questionnaire, which asked whether the patients believed they were overweight and to what they attributed their weight gain. We found that 42% of male patients and 49% of female patients were classified as obese (defined as a BMI > 28 kg/m² for men and > 27 kg/m² for women). Of the 76 patients surveyed, 54 (71%) believed they were overweight, with more women than men considering themselves overweight. Of those who thought of themselves as overweight, 34 (63%) attributed their obesity to the antipsychotic medication. There was no overall correlation between the weekly dose of medication and BMI or between duration of treatment and BMI, although we did note a trend toward an inverse correlation between dose of haloperidol and BMI (i.e., patients taking higher doses of haloperidol were less likely to have an unhealthy BMI). Thus, our recent findings support Johnson and Breen's⁵ earlier conclusion that, in general, weight change and dose of depot medication are not significantly related. As a result, administering lower doses of depot haloperidol, fluphenazine, or flupenthixol would not necessarily be an effective means of preventing or minimizing weight gain.

Early studies of conventional neuroleptics gave the impression that weight gain was tied to symptom improvement.⁶ Holden and Holden,² for example, noted that greater clinical improvement was significantly associated with greater weight gain ($p < .01$) and that greater clinical deterioration was associated with greater weight loss

($p < .01$). Leadbetter et al.⁷ reported that patients who gained the most weight while taking clozapine had the greatest improvements in scores on the positive and negative symptom subscales of the Brief Psychiatric Rating Scale (BPRS). Such findings have led many experts to believe that weight gain is necessary to achieve efficacy. Recent evidence, however, indicates that weight gain is not associated with clinical improvement in patients with schizophrenia.^{8,9}

NEWER ANTIPSYCHOTICS

Of all currently available antipsychotics, including the conventional neuroleptics, clozapine and olanzapine are associated with the greatest gains in weight. In a 1975 study,¹⁰ 9 of 13 adolescent patients with behavioral problems or acute schizophrenia treated with clozapine experienced a significant increase in appetite and 4 of these patients gained 22 to 44 lb within the first 2 months of treatment. Several years later, Leadbetter et al.⁷ conducted an open-label trial to determine the prevalence and clinical relevance of weight gain during clozapine treatment. In this study, 21 institutionalized patients with schizophrenia who had not responded to other antipsychotic drugs or who were experiencing intolerable adverse effects were weighed weekly for 12 weeks before and 16 weeks after starting clozapine therapy. Overall, patients gained an average of 13.9 lb (approximately 9% over their baseline body weight) by week 16. Eight (38%) of the 21 patients gained more than 10% of their initial body weight, 6 (29%) gained between 5% and 10% of their initial body weight, 4 (19%) gained less than 5% of their initial body weight, and 3 (14%) lost weight (a loss of 3 to 10 lb). Thus 67% of patients experienced moderate-to-marked gains in weight after being treated with clozapine for 16 weeks.

Similar findings were reported by Lamberti et al.¹¹ In a retrospective chart review, the authors assessed changes in the weight of 36 institutionalized patients with chronic schizophrenia who were switched from a conventional neuroleptic to clozapine. They reviewed patients' weight during the 6 months before clozapine treatment (when patients were being treated with a conventional neuroleptic) and during the 6 months after switching to clozapine. Each patient was weighed monthly during the 1-year study period. At the start of the study, patients weighed, on average, about 15 lb more than their ideal body weight, but their weight had remained stable (even though they were overweight) during the 6 months preceding clozapine therapy. After starting clozapine therapy, patients gained a substantial amount of weight (mean = 16.9 lb). Unlike Leadbetter et al.,⁷ Lamberti et al.¹¹ reported that the amount of weight gained during treatment with clozapine was inversely correlated with improvements in BPRS scores. However, this correlation did not reach statistical significance.

Umbricht et al.,⁸ in a retrospective chart review of 82 patients with chronic schizophrenia treated with clozapine for up to 90 months, found that weight gain was greatest during the first 12 months of treatment but continued at a slower rate for at least 36 months. After that, weight tended to plateau, even with continued treatment. In this study, the only predictor of weight gain was the patient's weight at baseline. Patients who were underweight at the start of treatment tended to gain significantly more weight than those who were overweight or at their ideal weight. As in the Lamberti et al. study,¹¹ weight gain was not correlated with clinical improvement (as measured by BPRS total scores) at weeks 6 or 12.

Significant weight gain early in the course of clozapine treatment and initial body weight as a predictor of weight gain were also reported by Hummer et al.¹² In this study, 81 outpatients with treatment-resistant psychosis who were being treated with clozapine for the first time were weighed weekly for the first 18 weeks of treatment, then monthly thereafter. At 1 year, 36% of patients had gained more than 10% of their initial body weight, with most of the weight gain occurring within the first 12 weeks of treatment. Patients at highest risk for weight gain were those who were underweight at the start of treatment.

Bustillo et al.⁹ conducted a double-blind trial to determine whether clozapine causes more weight gain than haloperidol and whether weight gain is related to clinical improvement. In this study, 39 outpatients were randomly assigned to treatment with clozapine or haloperidol for 10 weeks. At the end of the study period, patients in the clozapine group had gained a mean of 11.7 lb, while those in the haloperidol group had gained a mean of 1.5 lb. Overall, patients treated with clozapine gained 7% of their initial body weight but those given haloperidol gained only 1% of initial body weight. Among patients who were followed up for 1 year, 58% of those receiving clozapine gained at least 10% more than their baseline body weight and 21% gained at least 20%. The authors reported that changes in scores on the BPRS positive symptom subscale and the Scale for Assessment of Negative Symptoms did not correlate with weight gain, again supporting the idea that weight gain may not be related to a drug's efficacy.

Although weight gain clearly is a problem with clozapine, this drug is indicated for use only in patients who have not responded to other antipsychotic medications and, consequently, changing the medication is not an alternative. Thus, of more concern to clinicians is the potential for weight gain associated with more widely used newer antipsychotics, principally risperidone and olanzapine. My colleagues and I conducted a retrospective study of 100 patients with schizophrenia who were treated with risperidone or olanzapine for the first time (i.e., patients had not been previously exposed to either drug, although they had been treated with conventional neuroleptics) (R. Ganguli, M.D., J. S. Brar, M.D., M.P.H., Z. Ayrton, M.S.,

unpublished data, 1998). Body weight and BMI were measured during the initial hospitalization and approximately 4 months later (but only in patients who had continued taking risperidone or olanzapine).

Both the risperidone and olanzapine groups were well matched with regard to age, sex, race, and duration of treatment. The mean duration of treatment for patients in the risperidone group was 125.3 ± 11.7 days and in the olanzapine group, 115.5 ± 19.1 days. At the end of the follow-up period, patients in the risperidone group had lost about 2 lb while those in the olanzapine group had gained nearly 5 lb, a statistically significant increase (Table 1). No statistically significant change in BMI was seen in the risperidone group, but the BMI increased significantly in the olanzapine group. No significant differences were seen in weight change or BMI between male and female patients. However, we did find that none of the patients in the risperidone group who were classified as not obese at the start of treatment became obese after treatment, while 1 man and 3 women classified as not obese in the olanzapine group were considered obese by the end of treatment. This change in obesity status occurred within only 4 months after starting olanzapine treatment.

Other researchers have also found that olanzapine, which is pharmacologically similar to clozapine, causes more weight gain than does risperidone and most other antipsychotic medications. Nemeroff¹³ reported a 26-lb increase in body weight after 1 year in patients receiving 15 ± 2.5 mg/day of olanzapine. In a meta-analysis of 78 studies published between 1966 and 1997, Allison et al.¹⁴ reported that mean weight gain after 10 weeks of treatment in patients given clozapine or olanzapine was 9.8 lb and 9.1 lb, respectively. In contrast, weight gain at 10 weeks with risperidone was only 4.6 lb and with haloperidol, 2.3 lb. The newer antipsychotic ziprasidone was the least likely to cause weight gain, averaging only a 1.9 lb increase at 10 weeks. (Insufficient data were available to evaluate quetiapine.) Of all the antipsychotic drugs studied by Allison et al., only molindone was associated with weight loss.

MOLINDONE

As early as 1973, researchers were reporting weight loss, or at least no weight gain, in patients treated with molindone. Gallant et al.,¹⁵ for example, in a double-blind comparison of molindone and trifluoperazine in 24 patients with schizophrenia, found that patients given molindone did not gain weight while those treated with trifluoperazine gained a mean of 4.4 lb. In an open-label study by the same authors,¹⁵ clinical improvement occurred in nearly all of 30 schizophrenic patients treated with molindone and was accompanied by "remarkably consistent weight loss" (mean = 9.9 lb).

In a small study in which molindone was compared with chlorpromazine and placebo,¹⁶ 4 patients treated with

Table 1. Body Weight and Body Mass Index at Baseline and 4-Month Follow-Up in Patients Treated with Risperidone or Olanzapine^a

Measure	Baseline		Follow-Up		p Value
	Mean	SD	Mean	SD	
Body weight, lb					
Risperidone	182.8	45.2	180.8	43.8	NS
Olanzapine	186.8	55.0	191.6	55.2	< .001
Body mass index, kg/m ²					
Risperidone	29.6	9.4	29.5	9.1	NS
Olanzapine	29.5	7.4	30.3	7.5	< .001

^aGanguli R, Brar JS, Ayrton Z. Unpublished data, 1998.

molindone and 5 patients given placebo lost at least 8.8 lb, while 4 patients receiving chlorpromazine gained 11 lb or more. In a similarly small trial conducted by Gardos and Cole,¹⁷ 9 patients with chronic schizophrenia were switched from their usual antipsychotic (chlorpromazine, thioridazine, mesoridazine, fluphenazine, thiothixene, or haloperidol) to molindone for 3 months. At the end of the treatment period, all patients had lost weight, a mean of 16.7 lb (range, 2.0 to 37.0 lb). The mean loss was 8.5% of initial body weight, and weight loss occurred in both patients who were underweight and those who were overweight at baseline. Most weight loss occurred in the first month of treatment, but weight loss continued slowly after that, and even after patients resumed treatment with their usual antipsychotic. In a more recent 8-week, randomized, double-blind trial, Heikkinen et al.¹⁸ compared the efficacy and safety of molindone with that of chlorpromazine in 45 acutely psychotic patients. They found that both drugs were equally effective, as measured by decreases in BPRS scores. No significant changes in weight or BMI occurred in the chlorpromazine group. In the molindone group, patients lost a significant amount of weight (mean = 4.8 lb), with a corresponding significant decrease in BMI. The authors reported that weight loss with molindone did not appear to be related to extrapyramidal symptoms, such as akathisia or hyperkinesia. However, systematic ratings of these symptoms were not included in the published results.

CONCLUSION

Nearly 40 years ago, researchers were reporting that excessive weight gain was a problem associated with use of antipsychotic drugs and one that could decrease compliance and increase health risks.¹ Today, we are still confronted with the issue of weight gain in our patients treated with some antipsychotics for schizophrenia and other psychotic disorders. Losing weight is such a difficult task, even for patients without mental illness, that preventing or minimizing weight gain in the first place is the best means of managing this problem. Patients beginning maintenance therapy should be informed of the possibility of significant weight gain at the start of treatment, and nutri-

tional assessment and counseling should be a routine part of patient management.

As Allison et al.¹⁴ have shown, the risk of weight gain varies substantially among antipsychotic agents. Thus, one means of preventing weight gain is to select the drug with the least potential for weight gain that also effectively controls a patient's symptoms. In this regard, among the atypical agents, risperidone has an advantage over clozapine and olanzapine, which tend to cause considerable weight gain.

Drug names: chlorthalidone (Librium and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), loxapine (Loxitane), mesoridazine (Serentil), molindone (Moban), olanzapine (Zyprexa), phenobarbital (Nembutal and others), promazine (Sparine), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trifluoperazine (Stelazine and others).

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