

# Antipsychotic-Induced Weight Gain: A Review of the Literature

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With the availability of the so-called novel antipsychotic agents, extrapyramidal symptoms are becoming increasingly problematic for patients with schizophrenia, and simultaneously, a new symptom is emerging as a preeminent concern. This side effect is weight gain and its metabolic concomitants. This article reviews what is currently known about antipsychotic-induced weight gain, describes the magnitude of the problem, briefly touches on mechanisms of action, and addresses the correlation of interindividual variations in magnitude of weight gain. In addition, we address questions about the effects of weight gain on compliance and whether or not there is a correlation between weight gain and therapeutic efficacy. Finally, we address medical consequences of weight gain and review the literature supporting various treatment options for antipsychotic-induced weight gain. As will be seen, this is an area of research in its infancy, and much work remains to be done.

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Schizophrenia is a severe and disabling illness estimated to affect approximately 1% of the adult population worldwide.<sup>1</sup> Obesity, although perhaps less devastating at the individual level, is a serious medical condition and affects over 40 million adults in the United States and many more worldwide.<sup>2</sup> It is currently estimated that over 22% of the U.S. adult population is obese and over 50% is overweight.<sup>3</sup> In both the United States and virtually every developed and developing country worldwide, the prevalence of obesity is rising.<sup>2,3</sup>

Given this background, 2 points become apparent: first, continued development of safe and effective treatments for schizophrenia is essential. Second, any practice that has the potential to further exacerbate problems of obesity warrants serious scrutiny.

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The so-called "novel" or "atypical" antipsychotic agents are changing the face of schizophrenia treatment. When chlorpromazine initially emerged as a treatment for schizophrenia, a revolution in the field of psychiatry occurred with marked improvements in many patients. However, these improvements often came at the price of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).<sup>4</sup> When the newer antipsychotics became available, clozapine being the first,<sup>5,6</sup> the risk of EPS and TD fell dramatically, but an old problem became exacerbated. The first generation of antipsychotic agents were known to cause an increase in body weight. However, the newer agents seem to far outstrip their predecessors with respect to this potential. Thus, as concerns about EPS and TD have diminished, concerns about weight and the consequences thereof have increased dramatically in the area of schizophrenia treatment. In this article, we will review what we know about the causes, consequences, and treatment of antipsychotic-induced weight gain. As will be seen, apart from the magnitude of the problem, we currently know very little, and much work remains to be done in this clinically important and scientifically interesting area.

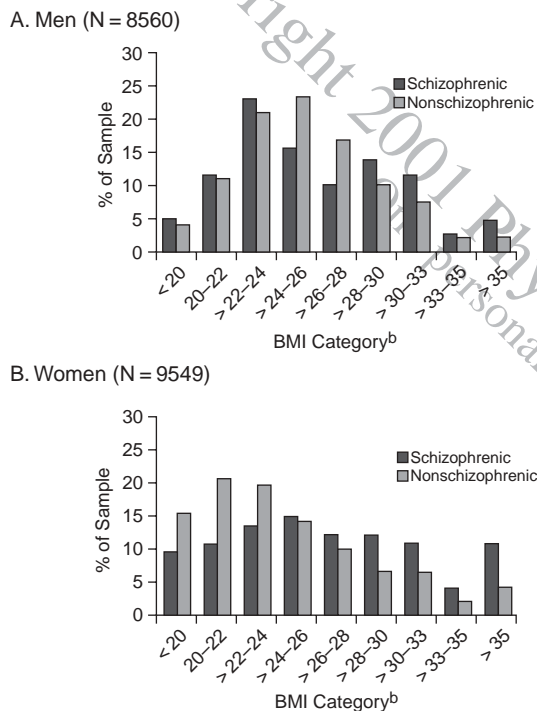
## HISTORICAL OVERVIEW

Changes in weight during psychosis have been noted for the past century. Kraepelin wrote, "The taking of food fluctuates from complete refusal to the greatest voracity . . . Sometimes, in quite short periods, very considerable differences in the body weight are noticed. . . ." <sup>7(p87)</sup> Bleuler observed, "In acute forms of the illness the patient's weight in particular is often subject to irregular and wide variations for which there is no known explanation. Most of our

Table 1. Prior Studies of Obesity Prevalence Among People With Schizophrenia<sup>a</sup>

Study	Sample	Criterion	Finding
Hutton <sup>10</sup>	72 male veterans in a psychiatric day treatment program	≥ 120% above ideal body weight	Approximately 40% obese
Silverstone et al <sup>11</sup>	226 outpatients with chronic schizophrenia	BMI ≥ 30	31% of the males and 37% of the females were obese, 3 times the prevalence of the general British population at that time
Kendrick <sup>12</sup>	101 long-term mentally ill adults	BMI ≥ 30	26% were obese
Stedman and Welham <sup>13</sup>	51 long-term female inpatients receiving psychotropic drugs	BMI ≥ 30	62% were overweight and/or obese
Centorrino et al <sup>14</sup>	44 chronically psychotic outpatients treated with clozapine for 2.2 years	BMI ≥ 30	55% were obese

<sup>a</sup>Abbreviation: BMI = body mass index.

Figure 1. Age-Adjusted Body Mass Index (BMI) Distributions: 1989 NHIS Sample<sup>a</sup>

<sup>a</sup>Adapted with permission from Allison et al.<sup>16</sup> Abbreviation: NHIS = National Health Interview Survey.

<sup>b</sup>A BMI > 27 constitutes obesity.

hospitalized patients, however, differ very little from the healthy in respect to weight variations, except that in chronic conditions the fluctuations appear to be wider and more frequent.”<sup>8(p161)</sup> Both authors noted that food intake and weight often decreased as psychosis worsened, but eating and weight returned to normal or increased when an acute psychotic episode receded. However, as chlorpromazine became widely available in the 1950s, a new pattern of sustained increased weight was commonly observed. As early as 1958, Planansky stated, “It is clear that the introduction of tranquilizing treatment on a mass scale has brought an entirely new problem into the wards of mental hospitals—obesity on a mass scale.”<sup>9(p301)</sup> Planansky’s

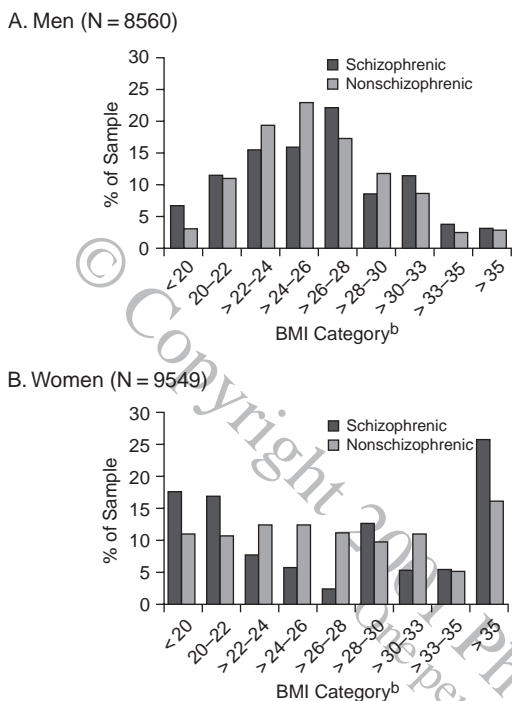
observation was not an isolated one. Concerns have continued over the decades and are now a major area of focus for research in the treatment of schizophrenia.

### MAGNITUDE OF THE PROBLEM

#### The Distribution of Relative Body Weight Among People With Schizophrenia

Before describing the magnitude of weight gain induced by antipsychotic agents, it may be helpful to comment on the prevalence of overweight and obesity among individuals with schizophrenia. Were the overwhelming majority of individuals with schizophrenia underweight, then a moderate weight gain might be benign. In contrast, if the prevalence of overweight and obesity is anywhere near as high among individuals with schizophrenia as it is among the general population, then even mild degrees of weight gain are quite troubling. Table 1 provides a summary of some older studies estimating the prevalence of overweight or obesity among individuals with schizophrenia. As can be seen, the prevalence is quite high, suggesting marked cause for concern with respect to this issue. However, the studies listed in Table 1 are limited in that they are based on relatively small samples, the measurements of height and weight may be weak, and the samples may not be representative. In addition, because obesity rates change over time,<sup>15</sup> they may not represent the current situation. To provide an update, Allison et al.<sup>16</sup> conducted a study comparing individuals who stated that they had been diagnosed with schizophrenia to individuals who stated that they had not been diagnosed with schizophrenia from the 1989 National Health Interview Survey. These individuals also reported their height and weight. This survey provided a large, nationally representative sample of the U.S. civilian, noninstitutionalized population. Because it is based only on noninstitutionalized subjects who are able to respond to an interview, it probably does not include many, if any, acutely ill individuals with schizophrenia. Figure 1 displays the results of this comparison. As can be seen, in general, the schizophrenic population is as or more obese than the nonschizophrenic population. In fact, in the case of women, there appears to be a relatively

**Figure 2. Age-Adjusted Body Mass Index (BMI) Distributions: NHANES-III Samples (1988–1994)<sup>a</sup>**



<sup>a</sup>Adapted with permission from Allison et al.<sup>16</sup> Abbreviation: NHANES-III = the third National Health and Nutrition Examination Survey.

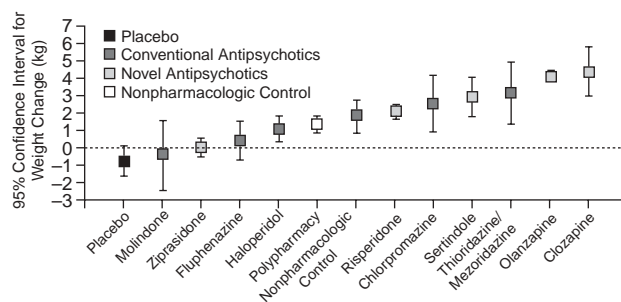
<sup>b</sup>A BMI > 27 constitutes obesity.

marked excess of overweight and obesity among individuals with schizophrenia.

One limitation of these data is that they are based on self-reported height and weight. Self-reported height and weight are highly correlated with measured height and weight but are known to have some biases.<sup>17</sup> Therefore, Allison et al.<sup>16</sup> also studied subjects from the third National Health and Nutrition Examination Survey (NHANES-III), which meticulously measured heights and weights of a representative sample of a U.S. civilian noninstitutionalized population between 1988 and 1994. Data from the NHANES-III were compared with data on over 2000 individuals with schizophrenia who had their heights and weights measured upon entry into randomized clinical trials testing the safety and efficacy of novel antipsychotic agents. These data are displayed in Figure 2. As can be seen, among women with schizophrenia there is again a tendency toward greater overweight and obesity than among those without schizophrenia. Among men the results are somewhat less pronounced, but it does appear that there is a substantial degree of obesity and overweight among men with schizophrenia and, among those that are acutely ill, perhaps some excess of underweight.

Overall, the information we have about overweight and obesity among individuals with schizophrenia suggests

**Figure 3. Meta-Analysis of Antipsychotics and Weight Gain: Estimate at 10 Weeks<sup>a</sup>**



<sup>a</sup>Adapted with permission from Allison et al.<sup>29</sup>

that weight is a substantial problem and is likely to be impairing the health of these individuals, especially because many of the adverse effects of overweight and obesity (e.g., diabetes, dyslipidemias, hypertension) are conditions for which individuals with schizophrenia tend to be underdiagnosed and undertreated.<sup>18–21</sup>

### MAGNITUDE AND TIME COURSE OF WEIGHT GAIN

A large number of studies describe weight gain among individuals taking various antipsychotic agents.<sup>10,22–28</sup> Perhaps the most comprehensive review to date was a meta-analysis recently reported by Allison et al.<sup>29</sup> This meta-analysis included over 80 studies and over 30,000 patient measurements. The results are displayed in Figure 3. As can be seen, weight gain varies substantially from drug to drug, but virtually all antipsychotic agents produce some degree of weight gain. The 2 agents associated with the highest weight gain (clozapine and olanzapine) appeared to produce between 4 and 4.5 kg of weight gain at 10 weeks of treatment on the standard dose. Weight gains were estimated at 10 weeks because, across all drugs, this time period is the one for which the most data were available. For some drugs, it appears that weight gain continues to increase over time<sup>28,30</sup> with the point of asymptote being directly related to the initial degree of weight gain. This finding is consistent with the idea that each antipsychotic agent may induce a relatively fixed degree of increased energy intake and/or decreased energy expenditure within each individual and that the individual therefore continues to gain weight until a new energetic equilibrium is reached at a “settling point.”<sup>31</sup>

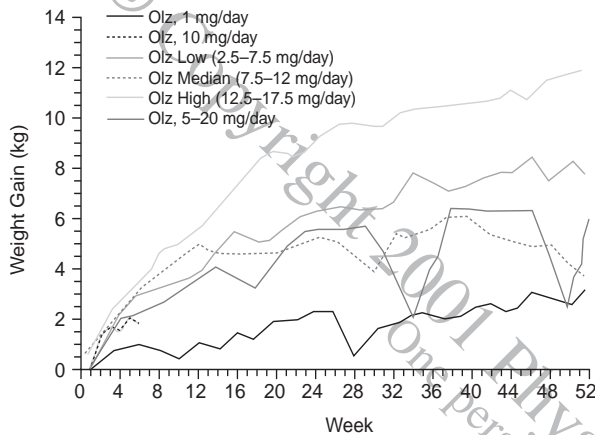
Another way of quantifying the magnitude of weight gain is by looking at the percentage of patients who gain more than a certain amount of weight. For reasons that are obscure to the current authors, a metric that has become popular in the field of psychiatry is the percentage of patients that gain more than 7% of their baseline body weight. Such information is generally included in the package insert of new drugs. Table 2 tabulates such infor-

**Table 2. Percentage of Patients With  $\geq 7\%$  Increase in Body Weight<sup>a</sup>**

Drug	Increase With Drug	Increase With Placebo
Ziprasidone	9.8	4.0
Risperidone	18.0	9.0
Quetiapine	25.0	4.0
Olanzapine	29.0	3.0

<sup>a</sup>Data from Tandon et al.<sup>32</sup>

**Figure 4. Pattern of Weight Gain With Olanzapine Treatment<sup>a</sup>**



<sup>a</sup>Adapted with permission from Nemeroff.<sup>33</sup>

mation.<sup>32</sup> As can be seen, the percentage of patients who gain more than 7% of their body weight is quite large for certain drugs, and the relative ordering of drugs with respect to this percentage is fairly consistent with the relative ordering of drugs based on their potential to induce mean weight gain at 10 weeks as portrayed in Figure 3.

Finally, the time course of weight gain among individuals can be of interest. Although somewhat more limited information is available on this topic, the pattern of weight gain over time generally appears to be consistent with gradual deceleration. Figure 4 describes the weight gain with different doses of olanzapine.<sup>33</sup> As can be seen, during the first year of treatment, body weight tends to increase but seems to largely plateau or asymptote by 1 year. What is striking about this figure is the magnitude of the weight gain at 1 year for the dosage labeled "olanzapine high (12.5–17.5 mg/day)." This category was meant to characterize typical conditions of use in which psychiatrists were allowed to titrate the dose for a patient within a given range. As can be seen, under these circumstances patients gained, on average, 12 kg. For most patients this is a clinically meaningful degree of weight gain that may be associated with alterations in carbohydrate and lipid metabolism. The data also imply that the weight gain is generally not dose dependent within the therapeutic dose range of 5 to 20 mg/day. Thus, lowering the dose of olanzapine is not likely to reduce the weight gain, but may put

the patient at risk for a relapse of psychosis. Another olanzapine data set that reported average weight changes across the average doses prescribed over a few years noted similar findings with weight reaching a plateau of 7 to 8 kg at approximately 40 weeks of treatment.<sup>34</sup>

Much less data about the time course of weight gain are available for risperidone and quetiapine. By combining a few studies that varied in duration from 8 to 52 weeks, it appears that average weight gain with risperidone reaches a plateau of 2 to 3 kg around weeks 8 to 12 and then remains around this level.<sup>35–37</sup> Data regarding quetiapine are more variable. Short-term studies suggest a weight gain of about 3 kg,<sup>29</sup> but other reports span a range of 2 to 5.6 kg over long-term treatment.<sup>38</sup> Ziprasidone was associated with no or minimal weight gain in patients studied for up to 1 year.<sup>39</sup> Since the majority of data are presented as mean figures, weight changes for individual patients may vary considerably from the averages.

## MECHANISMS OF ACTION

The topic of mechanisms of action can be addressed rather succinctly because, frankly, we know very little. At the level of energetics, we know that in order to gain weight individuals must take in more energy than they expend over some period of time. Thus, we know that antipsychotic agents must be causing individuals to consume more energy, to expend less energy, or both. The current authors are aware of no quality data at present that would allow estimation of the extent to which individuals taking antipsychotic agents increase their energy intake and/or decrease their energy expenditure. However, we can extrapolate from theory to suggest that it is unlikely that decreases in energy expenditure alone could account for the magnitude of weight gain being observed.<sup>31</sup> This is consistent with clinical anecdotes that some individuals taking antipsychotic agents become ravenous. Nevertheless, despite these anecdotes, when averaged over an extended period of time the degree of increased energy intake required to produce, for example, a 4.5-kg weight gain over a 10-week interval is not that large. Consider the following: From overfeeding studies, we know that gaining 1 g of body weight for the typical human during overfeeding requires approximately 8.08 kilocalories (kcal) of energy intake above energy expenditure.<sup>40</sup> Therefore, gaining 4.5 kg of body weight would require taking in an excess of approximately 36,360 kcal. If these kilocalories were dispersed evenly over 10 weeks, this would amount to approximately 520 extra kcal per day above energy expenditure. It should be noted that a typical large muffin sold in New York City may have as many as 900 kcal. Therefore, individuals could gain 4.5 kg over a 10-week period by eating approximately 3/4 of a large, New York City muffin every day above and beyond the amount of food they needed to maintain their current body

**Table 3. Known Olanzapine Receptor Activity (direct or indirect)<sup>a</sup>**

Receptor	Study
GABA <sub>A</sub> receptors in the hippocampus and the temporal cortex	Farnbach-Pralong et al <sup>42</sup>
5-HT <sub>2A</sub>	Bymaster et al, <sup>43</sup> Kapur et al, <sup>44</sup> Schotte et al <sup>45</sup>
5-HT <sub>2C</sub>	Bymaster et al, <sup>43</sup> Schotte et al <sup>45</sup>
5-HT <sub>2B</sub>	Wainscott et al <sup>46</sup>
5-HT <sub>3</sub>	Bymaster et al, <sup>43</sup> Schotte et al <sup>45</sup>
5-HT <sub>6</sub>	Roth et al <sup>47</sup>
D <sub>1</sub>	Bymaster et al, <sup>43</sup> Schotte et al <sup>45</sup>
D <sub>2</sub>	Bymaster et al, <sup>43</sup> Kapur et al, <sup>44</sup> Schotte et al <sup>45</sup>
D <sub>3</sub>	Schotte et al <sup>45</sup>
D <sub>4</sub>	Bymaster et al <sup>43</sup>
M <sub>1</sub> muscarinic	Bymaster et al <sup>43</sup>
M <sub>2</sub> muscarinic	Bymaster et al <sup>43</sup>
M <sub>3</sub> muscarinic	Bymaster et al <sup>43</sup>
M <sub>4</sub> muscarinic	Bymaster et al <sup>43</sup>
M <sub>5</sub> muscarinic	Bymaster et al <sup>43</sup>
α <sub>1</sub> adrenergic	Bymaster et al <sup>43</sup>
α <sub>2</sub> adrenergic	Bymaster et al <sup>43</sup>
Histamine (H <sub>1</sub> )	Bymaster et al, <sup>43</sup> Schotte et al <sup>45</sup>
NMDA subtype of glutamate receptor	Farber et al <sup>48</sup>

<sup>a</sup>Abbreviations: GABA =  $\gamma$ -aminobutyric acid, NMDA = *N*-methyl-D-aspartate.

weight. Of course these numbers are approximate, but they give a sense that, at least averaged over time, an individual may not need to be ravenous to gain substantial weight while taking antipsychotic agents. However, it is also possible that individuals may eat quite modestly for several consecutive days and then, for reasons that are not understood, have bursts of ravenous binge eating, which could account for the weight gain equally well. Further research is necessary to disentangle these possibilities.

With respect to the neuropharmacology, these plausible mechanisms of action are reviewed in more detail by Zorn and Casey in this supplement.<sup>41</sup> However, we briefly point out that disentangling the specific neuropharmacologic or neuroendocrinologic mechanisms of action will be extremely difficult. For example, olanzapine is known to have activity (either direct or indirect) at at least 19 different receptor sites as indicated in Table 3. Other drugs may be active at still other receptor sites (e.g., clozapine at  $\delta$ -opioid receptors),<sup>49</sup> may have reuptake inhibition properties,<sup>50</sup> and may affect hormonal levels such as prolactin.<sup>51</sup> This is an extremely exciting area, and much research remains to be done to explore mechanism of action.

One tool that would be extremely useful in helping to elucidate mechanism of action would be an experimental model of antipsychotic-induced weight gain. Typically, a rodent, most often a rat, would be used for such purposes. However, currently, conditions under which rodents will reliably gain weight with antipsychotic-induced agents that produce weight gain in humans have not been defined. Although some studies<sup>52-55</sup> do show weight gain with

administration of antipsychotic agents in rats, many studies show no weight gain or even weight loss.<sup>52,56,57</sup> The current authors have research underway to isolate the set of circumstances under which the rat can reliably be used as a model of antipsychotic-induced weight gain and, thereby, serve as a tool for mechanistic studies.

## INTERINDIVIDUAL VARIATIONS

Isolating the factors that are correlated with interindividual variations in the weight-gain response to antipsychotic drugs would be useful. There is clearly marked heterogeneity in this response, and understanding the correlates thereof might point the way toward understanding mechanism of action. In addition, being able to identify individuals at high risk of gaining weight prior to the initiation of treatment might put clinicians in a better position to choose the optimal treatment for each patient and/or provide preventive counseling or treatment to reduce the likelihood of excessive weight gain.

Unfortunately, we do not have a great deal of information on the correlates of degree of weight gain. In rodents, there is some evidence that females gain more weight than do males.<sup>52,53,55</sup> However, there is yet to be a thorough examination of this issue in humans.

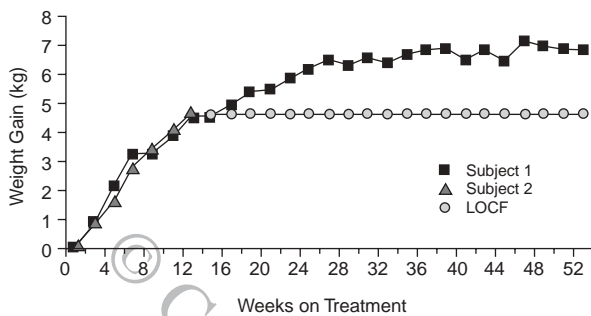
From a pharmacogenetic point of view,<sup>58</sup> it would be very interesting and useful to know what polymorphisms are associated with magnitude of weight gain. The genes coding the receptor proteins with which these drugs interact are obvious candidates for study. To the current authors' knowledge, only one published study has examined whether polymorphisms of a particular gene are correlated with the weight gain response in humans. Rietschel et al.<sup>59</sup> studied 152 patients treated with clozapine. They compared weight gain among individuals who did and did not possess the Cys23Ser polymorphism of the 5-HT<sub>2C</sub> receptor. They stated "a weight gain of at least 5% was found in 25% of our patients, and 14.5% gained at least 10%. Our findings, however, do not support a possible association with the mutation."<sup>59(p2002)</sup> Thus, little literature has been published on this topic, and at this time no evidence implicates an association between any particular genetic polymorphism and weight-gain response.

Finally, much has been made about the fact that baseline body mass index (BMI) is inversely correlated with the degree of weight gain on antipsychotic agents. Although this is true, it may be largely artifactual as we address in the subsequent section on methodological issues.

## METHODOLOGICAL ISSUES

Although there are many intriguing and important methodological issues in this area of research, we highlight only 2 here. The first issue relates to the method used to estimate the magnitude of weight gain induced by

Figure 5. Hypothetical Last-Observation-Carried-Forward (LOCF) Data



particular antipsychotic agents in longitudinal treatment studies. A typical study might assign “N” individuals to receive a particular drug. Those “N” individuals are then followed over time, and weight may be measured at repeated (e.g., weekly or monthly) intervals. Subjects may be followed for a period of 6 to 12 months or longer. During this period, some individuals will drop out of the study for a variety of reasons. The question then becomes how does one estimate the weight gain for individuals at, for example, 12 months when some of the individuals under study have dropped out prior to 12 months and, therefore, provide no data on body weight at the 12-month timepoint? Several approaches to this dilemma exist. One could analyze data only from those individuals who complete the study, one could use approaches such as multiple imputation,<sup>60</sup> or one could use the last-observation-carried-forward (LOCF) technique.<sup>61</sup> LOCF is one of the most common approaches taken. Unfortunately, in this case it can produce marked underestimates of the magnitude of weight gain and therefore should be avoided (Figure 5).

The reason that LOCF can produce marked underestimates is because weight gain tends to increase over time; by carrying an individual’s weight at one timepoint forward to a subsequent timepoint, one is holding the trajectory of his or her weight gain flat when, in fact, it would have likely increased had the individual remained in the study and on drug treatment. Therefore, to the extent that one wishes to estimate weight gains at time *t* among individuals who take the drug until time *t*, LOCF is an inappropriate technique. Readers should therefore be very skeptical of presentations of degree of weight gain in which the LOCF technique is used. Such presentations are likely to underestimate the actual magnitude of weight gain.

A second methodological issue is the role of regression to the mean in interpreting the correlation between baseline BMI and degree of subsequent weight gain while taking an antipsychotic drug. As was stated earlier, several studies have shown that baseline BMI is inversely correlated with the degree of subsequent weight gain. That is, the thinnest individuals gain the most and the heaviest

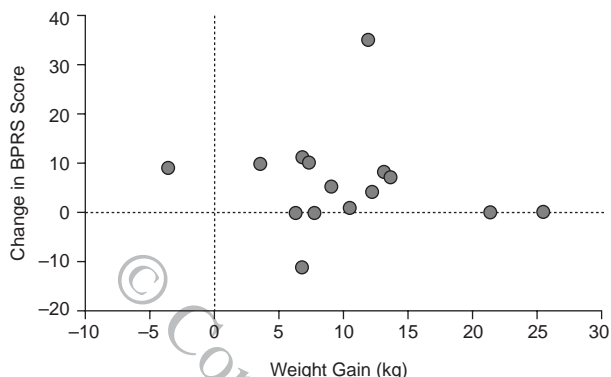
individuals gain the least. However, to go from this observation to state that a particular drug causes greater weight gain among thin than among overweight individuals would be inappropriate, because such an effect can be due solely to regression to the mean. That is, even among groups of untreated individuals whose weight, on average, remains constant, some individuals will gain weight and some individuals will lose weight over time. Individuals who start out with lower body weight are more likely to gain weight over time, and individuals who start out with higher body weight are more likely to lose weight over time. This is the essence of regression to the mean. Thus, until and unless someone shows that there is an interaction between baseline BMI and group assignment in a randomized clinical trial, it is inappropriate to state that antipsychotic drugs cause more weight gain among thinner individuals than among heavier individuals.

### WEIGHT GAIN, COMPLIANCE, AND EFFICACY

Questions about the association between degree of weight gain with both compliance with medication and therapeutic efficacy are also of interest. With respect to degree of weight gain and compliance, substantial anecdotal information suggests that weight gain is a major cause of noncompliance. However, quantitative data are more difficult to find. In a mailed survey to relatives of people with schizophrenia, Angermeyer and Matschinger<sup>62</sup> found that relatives rated weight gain as the second most troubling side effect for patients, second only to sedation and preceding EPS. Some similar data from individuals with schizophrenia are beginning to appear.<sup>63</sup> However, these have yet to be carefully documented with data from randomized clinical trials showing that individuals receiving antipsychotic drugs who gain more weight are less compliant with medication and/or more likely to drop out than individuals who gain less weight. Evaluation of such data is an important area for future research.

The question of whether greater weight gain is associated with greater therapeutic efficacy (within any given drug) is an important question. If the answer to this question was strongly affirmative, it might suggest that the mechanisms of action for therapeutic efficacy and weight gain are so tightly linked, if not identical, that there is little that can be done about weight gain without compromising therapeutic efficacy. Indeed, ability to produce weight gain in an animal model might then be taken as an indicator of a drug’s potential as a future antipsychotic agent. Although it is frequently claimed that degree of weight gain is positively correlated with degree of therapeutic efficacy, we find the literature unconvincing on this point. Consider the letter by Gupta et al.<sup>64</sup> and the data contained therein. We have extracted and plotted those data in Figure 6. As can be seen, there is no obvious relationship between magnitude of weight gain and degree of therapeutic efficacy.

Figure 6. Weight Gain Versus Therapeutic Efficacy<sup>a</sup>



<sup>a</sup>Data from Gupta et al.<sup>64</sup> Abbreviation: BPRS = Brief Psychiatric Rating Scale. Pearson correlation coefficient,  $r = -0.112$  ( $p = .692$ ); Kendall's  $\tau = -0.149$  ( $p = .452$ ); Spearman's  $\rho = -0.227$  ( $p = .415$ )

Indeed, statistical analyses of these data indicate no statistically significant correlation (Pearson correlation coefficient,  $r = -0.112$ ;  $p = .692$ ). It is also important when evaluating data on the correlation between weight gain and efficacy to control for duration of treatment. Typically, the longer a patient is treated with an antipsychotic agent, the more weight they will gain. At the same time, patients who are not doing well on treatment with a particular agent will generally discontinue treatment; therefore, duration of treatment will also be positively correlated with degree of therapeutic efficacy. This alone can introduce a spurious correlation between degree of weight gain and therapeutic efficacy. Therefore, it is essential to ask whether duration of treatment has been controlled for when presented with data indicating any correlation between weight gain and efficacy. At this time, we are aware of no clear and compelling body of data for any given drug showing that greater weight gain is correlated with greater efficacy after controlling for duration of treatment.

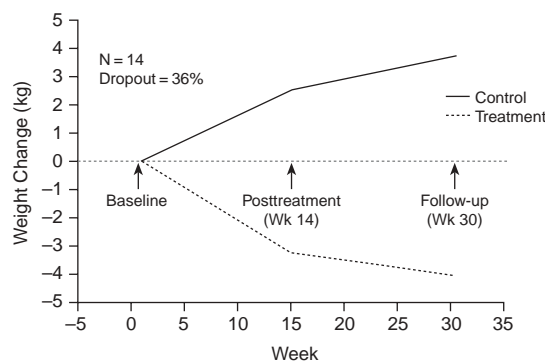
### TREATMENT OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

Treatment of antipsychotic-induced weight gain has generally taken 1 of 2 approaches, behavioral treatment or pharmacologic treatment. Most of these studies are small studies of somewhat low-to-moderate quality. Table 4 summarizes some of the reports of behavioral treatment of obesity among individuals taking antipsychotic agents. As can be seen, some of these studies have reported positive results. This may be because the very essence of behavioral treatment is the concept that to the extent that one can control the environment, one can achieve at least partial control over behaviors such as eating and activity. Because many of these studies were conducted in inpatient or residential settings, the investigators were often able to achieve good environmental control and, therefore, weight

Table 4. Behavioral Treatment of Obesity in Psychiatric Inpatients

Study	Finding
Knox <sup>65</sup>	74 overweight psychiatric inpatients. Over 6–34 months, 70% lost weight and 18% attained an ideal weight
Allyon <sup>66</sup>	One hospitalized schizophrenic patient lost 32 kg (28% of original body weight) over 14-month period
Bernard <sup>67</sup>	One “severely obese” schizophrenic patient with metabolic/endocrine disturbances lost 46 kg (20% of initial body weight) over 6-month period
Harmatz and Lapuc <sup>68</sup>	Diet only (N = 7): no weight loss. Group therapy (N = 7): $\approx 2.5\%$ weight loss after 6 weeks of treatment, but regained $\approx 1\%$ at 4-week follow-up. Behavior modification (N = 7): $\approx 4\%$ weight loss at 6 weeks, plus further 3% loss at 4-week follow-up

Figure 7. Behavioral Treatment of Obesity: Psychotic Patients in Residential Setting<sup>a</sup>



<sup>a</sup>Adapted with permission from Rotatori et al.<sup>69</sup>

loss. Figure 7 portrays results from one of the strongest studies by Rotatori et al.<sup>69</sup> Although the study is clearly short term in nature, the results are positive.

With respect to pharmacologic treatment, there are also few data. Table 5 summarizes the pharmacologic treatment reports from the published literature. As can be seen, the results are somewhat mixed, with some studies indicating positive results and others indicating results that are best described as neutral to modest. However, it should be noted that none of these studies has used the 2 newest antiobesity agents currently available, namely, sibutramine and orlistat.<sup>75</sup> These 2 drugs may have greater potential for treating this population. This may be especially true for orlistat, a lipase inhibitor that partially blocks the intestinal absorption of lipid. Because orlistat is not centrally acting and indeed largely unabsorbed, concerns about exacerbation of a patient's psychotic symptoms would be minimal. Nevertheless, until careful clinical trials are conducted with these agents among individuals taking antipsychotic drugs, it is difficult to recommend them and make definitive statements about them.

The issue of exacerbation of psychotic symptoms through the use of antiobesity agents is an important one. Numerous case reports exist in the literature of individuals

Table 5. Pharmacologic Treatment of Obesity Among Psychotic Individuals

Drug	N	Weight Results	Side Effects	Study
Amantadine	10	100% lost; mean = 5.5%	Trivial	Correa et al <sup>70</sup>
Fenfluramine	4	2 lost	1 patient	Kolakowska et al <sup>71</sup>
D-Fenfluramine	16	-5.4 kg (fenfluramine) -2.8 kg (placebo)	Typical of "normals"	Goodall et al <sup>72</sup>
Chlorphentermine or phenmetrazine	30	none	Trivial	Sletten et al <sup>73</sup>
D-Fenfluramine	3	Overeating eliminated	None	Svacina et al <sup>74</sup>

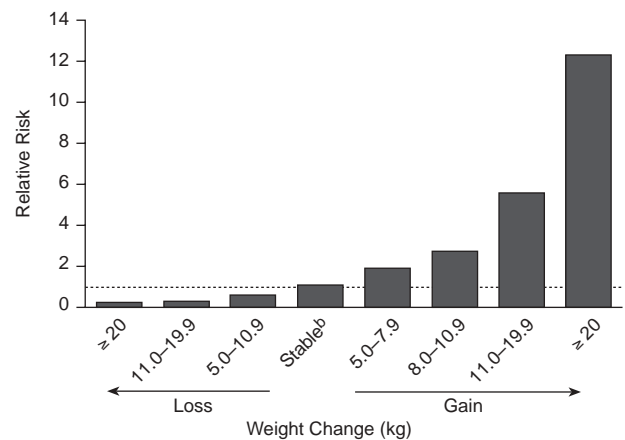
Table 6. Case Reports of Psychosis Associated With Fenfluramine and/or Phentermine

One 32-year-old woman with no psychiatric history taking phentermine, 30–60 mg/day (Cleare <sup>76</sup> )
One 22-year-old woman with no psychiatric history taking phentermine, 30–90 mg/day (Devan <sup>77</sup> )
Three women, 2 with psychiatric history, on fenfluramine, 60–80 mg/day (Shannon et al <sup>78</sup> )
One 50-year-old woman with psychiatric history, on fenfluramine, 20 mg tid, and phentermine, 30 mg qid (Bagri and Reddy <sup>79</sup> )

with and without histories of psychosis experiencing psychotic symptoms subsequent to taking antiobesity agents. In some cases, causality was strongly implicated by demonstration that the symptoms could be repeatedly induced by reintroduction of the drug and alleviated by withdrawal of the drug. This finding is not unexpected given that antiobesity agents currently available that act on appetite suppression, at the most simplistic level, up-regulate the same neurotransmitter systems that antipsychotic agents down-regulate. Table 6 summarizes the literature of cases of antiobesity drug-induced psychotic reactions. These cases highlight the importance of conducting careful clinical trials of antiobesity agents in the population of individuals with schizophrenia to establish not only efficacy but safety as well. Until such trials are conducted, we cannot recommend widespread use.

### CONSEQUENCES OF WEIGHT GAIN

The psychosocial consequences of weight gain are all too familiar to many of us. They include a sense of demoralization, inability to control one's own behavior, physical discomfort, and being the target of substantial social stigma.<sup>80,81</sup> However, obesity is a serious medical condition as well as a condition with serious psychosocial consequences. Obesity is associated with an increased risk of dyslipidemia, hypertension, type 2 diabetes mellitus, cardiovascular disease, osteoarthritis, and numerous other diseases.<sup>82,83</sup> In addition, obesity is associated with an increased rate of mortality.<sup>84,85</sup> It is well documented that weight gain increases the risk of many diseases. For example, Figure 8 shows the increased risk of type 2 diabetes mellitus<sup>86</sup> with weight gain that is similar in magnitude to the amount of weight individuals gain with antipsychotic agents. From these data, we might project that individuals

Figure 8. Relative Risk of Clinical Type 2 Diabetes Mellitus as a Function of Weight Gain<sup>a</sup>

<sup>a</sup>Adapted with permission from Colditz et al.<sup>86</sup> Fourteen-year follow-up of the 1976 Nurses' Health Study cohort. Total N = 114,281 with 2204 new cases of non-insulin-dependent diabetes mellitus. Weight change = (weight in 1986) - (weight at age 18). Relative risk adjusted for age and body mass index at age 18 years.

<sup>b</sup>Stable: ≤ 4.9 kg loss to ≤ 4.9 kg gain.

gaining weight on treatment with antipsychotic agents would have increased risk of a variety of conditions. Allison et al. (K. R. Fontaine, Ph.D.; M. Heo, Ph.D.; E. P. Harrigan, M.D.; et al., manuscript submitted) have conducted detailed analyses using the Framingham heart study to model the increased risk of hypertension, diabetes, and earlier mortality that would result as a function of a weight gain of similar magnitude to that induced by antipsychotic drugs. These modeling studies strongly support the concept that weight gain induced by antipsychotic agents would be associated with substantial adverse events including increased mortality rate.

Going beyond modeling data, we can look at observed data on patients taking antipsychotic agents. Unfortunately, careful documentation of rates of illnesses such as diabetes, heart disease, dyslipidemia, and so on among patients gaining various degrees of weight through various antipsychotic agents has not been conducted. However, an emerging body of data in case reports suggests that there is an increase in the incidence of such outcomes with antipsychotic agents that increase body weight.<sup>87-92</sup> This seems to be especially true for diabetes. Currently it is



conjectured that certain antipsychotic agents such as olanzapine and clozapine may have an independent effect of increasing risk of diabetes above and beyond their effect on body weight. However, at this stage, this effect is largely speculative.

Finally, one of the strongest demonstrations of the deleterious effects of antipsychotic-induced weight gain comes from a recent study<sup>93</sup> in which individuals who had gained weight while taking certain novel antipsychotics were switched to ziprasidone, a novel antipsychotic agent that does not cause weight gain. On average, these subjects lost weight and had corresponding improvements in serum lipids and serum measures indicative of better glucose tolerance. These findings suggest that choice of the right antipsychotic agent for the patient is an important one and that weight gain and metabolic factors should be considered in that decision.

### CONCLUSION

In conclusion, the marked propensity of certain novel antipsychotic agents to produce weight gain and corresponding alterations in other metabolic factors is of substantial clinical importance and scientific interest. Clinicians should be aware of these problems and use this information in guiding their clinical decision making. Researchers have much work ahead of them in helping to understand the causes, effects, and treatment of antipsychotic-induced weight gain.

*Drug names:* amantadine (Symmetrel and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), orlistat (Xenical), quetiapine (Seroquel), risperidone (Risperdal), sibutramine (Meridia).

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