Weight Gain Associated With Neuroleptic Medication: A Review

by Josephine M. Stanton

Abstract

In this article we review the empirical literature on weight gain associated with neuroleptic drug use. Weight gain, which appears to be associated with an increase in appetite, is variable but likely to be larger initially and then plateau. Clozapine and low-potency phenothiazines are associated with the largest gains and molindone with weight loss, but the mechanism is not known. Amantadine and fenfluramine may reverse weight gain to some degree. Dietary fat seems to play an important role in obesity, and research is needed to increase the data base and elucidate possible mechanisms. Studies are also needed to evaluate preventive strategies and to determine which drugs are least likely to produce weight gain as well as which drugs could be added to a neuroleptic regimen to control weight.

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Weight gain has been a documented side effect of antipsychotic drug use for over 30 years (Mefferd et al. 1958; Planansky 1958), but it receives little attention in spite of its clinical importance in the management of chronic schizophrenia (Kalucy 1980; Silverstone et al. 1988). The multimillion dollar diet industry is testament to the lengths to which psychiatrically healthy people will go to avoid obesity. While the health risks of excess weight are the same for both healthy people and those with mental illness, obesity may be more of an impediment to those whose social skills are often poor.

This article reviews the clinical and research findings documented in the literature on weight gain as a side effect of neuroleptic medication. The areas covered are the clinical features of weight gain, differences among the available medications, proposed mechanisms, and pharmacological treatments. Some recent findings concerning energy intake and energy expenditure are also presented, and directions for research are suggested.

Clinical Features

Most of the published data about the clinical features of weight gain are from early naturalistic and often retrospective studies. The exception is the prospective study by Johnson and Breen (1979). However, many of the early findings have been replicated in the recently published reports of patients who gain weight on clozapine.

Appetite. Although use of neuroleptic medication is associated with an increase in appetite (Mefferd et al. 1958; Bernstein 1987; Brady 1989), it is not clear what form this increase takes. In discussions of weight gain associated with antidepressants and lithium, "carbohydrate craving" is often reported (Berken et al. 1984; Bernstein 1987; Brady 1989; Goodwin and Jamison 1990). This is not the case in the literature about weight gain associated with neuroleptic medication.

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Calorie Intake. It has been demonstrated in strictly controlled inpatient situations that reduced calorie intake can lead to weight loss in patients on neuroleptic medication (Sletten et al. 1967*a*; Klein et al. 1972).

Timeframe. Most weight gain occurs early in treatment, and while it continues in some people, it is more likely to plateau after 1 to 2 years (Klett and Caffey 1960; Amdisen 1964). Lamberti et al. (1992) recorded stable weights in patients established on standard antipsychotics. Clozapine-associated weight gain also appears to be greatest in the first weeks of treatment (Leadbetter et al. 1992).

Amount. The amount of weight gained varies considerably. Amdisen (1964) reports an average weight gain on chlorpromazine of 16.4 lb in the first 12 months, increasing to 25.2 lb by 18 months. Leadbetter et al. (1992), in reviewing the literature on clozapine, cite average gains of 9 to 27 lb. Cohen et al. (1990*b*) describe individual cases where weight change on clozapine varied from no gain to an increase of 69 lb over up to 9 months.

Reversibility. Weight gain is probably reversible. This seems to be accepted in the literature (Kalucy 1980; Speight 1987), and there are records of reversibility of weight gain in at least some patients (Ayd 1959; Amdisen 1964; Gordon and Groth 1964).

Fat Distribution. Stedham and Welham (1993) looked at the fat distribution of 51 female, chronic inpatients on psychotropic drugs. Most were obese and their weight gain distributed more centrally than expected, that is, their waist-to-hip ratio was increased. Excess fat in this part of the body is important because most health morbidity related to obesity is more strongly associated with waist-to-hip ratio than with other obesity indicators (Hartz et al. 1984; Lapidus et al. 1984; Larsson et al. 1984; Lanska et al. 1985).

Dose-Response Relationship. Amdisen (1964) found a significant dose-response relationship only at the highest dose levels of chlorpromazine. Johnson and Breen (1979), in a prospective study of 132 patients with schizophrenia on depot antipsychotic medication, found no significant correlation between dose and weight change. Only between the highest and the lowest doses was there any trend indicating a dose-response relationship. Kalucy (1980) reports that significant weight gain can be seen on low doses of phenothiazines.

Correlation With Clinical Efficacy. Leadbetter et al. (1992) found weight gain on clozapine tended to be greatest in patients who had the best clinical response. This was observed in several early studies (Planansky 1958; Planansky and Heilizer 1959; Klett and Caffey 1960; Holden and Holden 1970; Singh et al. 1970).

Predictive Factors. Little is known about which patients are at most risk of weight gain. Vendsborg et al. (1976) found that patients on lithium who were overweight at the start of therapy were more likely to gain weight than those who started at normal weight. It is not known if this is also the case with neuroleptic medication.

Thus, while psychiatrists can warn patients on neuroleptics to expect an increase in appetite, they can also reassure them that weight gain is likely to plateau, may be reversible once medication is stopped, and may be prevented by dietary control.

Differential Drug Effects

This is an important topic for the clinician when choosing an agent for a patient who is concerned about weight gain. Data on which to base such decisions are limited.

Low-Potency Phenothiazines. In the early research, chlorpromazine was associated with more weight gain than other neuroleptics (Klett and Caffey 1960; Amdisen 1964). Branchey et al. (1978), in a double-blind, crossover trial with geriatric patients, found significantly more weight gain over 8 weeks on thioridazine than on fluphenazine.

Haloperidol. Haloperidol is thought to be associated with less weight gain than other agents (Bernstein 1987; Brady 1989). Some small prospective, double-blind, randomized clinical trials found statistically nonsignificant trends for less weight gain on haloperidol decanoate than on fluphenazine decanoate or pipothiazine palmitate (Wistedt et al. 1984; Bechelli et al. 1985; Cookson et al. 1986). (Pipothiazine, not currently available in the United States, is a piperidine-substituted phenothiazine with properties similar to chlorpromazine's.) Cookson (1991) describes a randomized, double-blind trial in 181 patients comparing haloperidol decanoate and fluphenazine decanoate over 1 year. The data on weight gain are not yet published, but no significant difference was

found between the two medications (personal communication, 1993). McLaren et al. (1992) reported no significant differences in weight gain in a trial comparing bromperidol decanoate and fluphenazine decanoate. (Bromperidol, not currently available in the United States, is a butyrophenone with properties similar to haloperidol's.)

Weight Loss. Several early studies documented weight loss associated with molindone (e.g., Gallant and Bishop 1968; Freeman and Frederick 1969; Gardos and Cole 1977). This finding was challenged by Parent et al. (1986) but confirmed by Dufresne et al. (1993) in a randomized, double-blind controlled trial. McCreadie et al. (1982) compared weekly pimozide with fluphenazine decanoate and found considerable weight loss, an average of 11 lb in 9 months, in the pimozide group. The study was small and had a dropout rate of almost 40 percent.

Other Drugs. In a retrospective chart review, Doss (1979) found less weight gain with loxapine than with thiothixene, fluphenazine, haloperidol, or thioridazine. Clozapine appears to be associated with considerable weight gain, even in patients already established on other antipsychotics (Cohen et al. 1990*b*; Lamberti et al. 1992; Leadbetter et al. 1992). Early studies of remoxipride suggest that it may be associated with less weight gain than thioridazine (McCreadie et al. 1988), and both weight gain and weight loss have been recorded (Holm et al. 1993).

In summary, it appears that the clinician has limited data on which to base a choice of drugs. While there appears to be no difference between haloperidol decanoate and fluphenazine decanoate, the studies of the other drugs have methodological limitations. Few of the trials are randomized and controlled, sample sizes are small with many dropouts, and no attention has been paid to ensuring equivalent dosages. If all else is equal, the low-potency phenothiazines and clozapine are probably best avoided for the patient who is concerned about weight gain. There is some indication that pimozide and loxapine, if clinically appropriate on other grounds, may be preferable. Molindone stands out because it is repeatedly associated with weight loss.

Mechanisms

The mechanism of weight gain associated with neuroleptic medication is poorly understood, but several possibilities have been suggested.

Sedative Effects. Sedative effects could lead to less activity and less calorie utilization. This would be consistent with the low-potency drugs being associated with more weight gain because they are more sedating than other antipsychotics. On the other hand, considerable weight gain has been recorded in patients whose activity level has increased secondary to improvement in psychomotor retardation (Leadbetter et al. 1992). Gopalaswamy and Morgan (1981) found no correlation between level of physical activity and patients' weight. This explanation also does not account for the observed increase in appetite associated with use of neuroleptic medication (Mefferd et al. 1958; Bernstein 1987; Brady 1989).

Thirst. Anticholinergic activity is said to contribute to weight gain because increased thirst leads to increased intake of caloric drinks (Bernstein 1987; Brady 1989). So far, this has not been documented.

Resetting Controls. Kalucy (1980) observed that weight gain eventually plateaus and suggested that the mechanism involved may be the resetting of controls that tend to contain weight gain. However, a stable, continuous increase in appetite will not lead to endless weight gain. As the amount of fat tissue increases so does blood volume, connective tissue, muscle, internal organ size, and so on. This increase in fat-free mass results in a higher metabolic rate (Ravussin and Swinburn 1992). Thus, with no change in physical activity, a steady increase in calorie intake will produce an increase in weight to a plateau at which the additional calories are needed to maintain the status quo. This explanation is consistent with neuroleptic-associated weight gain being merely a result of appetite increase resulting in an early weight gain that plateaus out.

Neurotransmitters. Most of the research in this area has focused on the serotonergic system (Silverstone and Goodall 1986). Drugs that enhance serotonergic transmission have been shown to decrease carbohydrate intake in humans and animals (Wurtman and Wurtman 1981). Neuroleptics block serotonergic transmission, which is a presumed mechanism for the stimulation of weight gain. The low-potency antipsychotics, chlorpromazine, thioridazine, and mesoridazine all have a greater affinity for serotonergic receptors than the other antipsychotics (Bernstein

1987), as does clozapine (Coward 1992). Fluoxetine, a highly selective serotonergic reuptake inhibitor, is associated with a small, but significant, weight loss (Benfield et al. 1986; Ferguson 1986). High-carbohydrate diets stimulate serotonin synthesis (Wurtman 1986).

Similar arguments can be made for the importance of the catecholaminergic and histaminergic systems in weight gain. Association of highly specific dopamine antagonists such as benzamides with weight gain indicate that it may be directly mediated by dopamine (Cookson 1991).

Metabolism. The mechanism for weight gain associated with neuroleptic medication may be related to the balance of fat and carbohydrate oxidation. Flatt (1989) has demonstrated that weight gain in rats given steroids is caused by increased oxidation of carbohydrate rather than fat. The result is increased appetite and increased fat storage.

In summary, there is considerable speculation as to the mechanism of weight gain associated with neuroleptic medication. There is little empirical evidence for the role of sedation, thirst, or resetting of controls. Evidence indicates that serotonergic transmission and serotonergic blockade may play an important role in mediating weight gain by increasing the oxidation of carbohydrate rather than fat.

Pharmacological Treatments

In general, polypharmacy is best avoided. Further, patients generally do not like taking a second medication to mitigate the side effects of the first. There has, however, been some interesting research in this area.

Amphetamine Derivatives. Sletten et al. (1967*b*) found that amphetamine derivatives did not cause weight loss in patients on chlorpromazine. This may be because the anorectic effect of these drugs is via adrenergic receptors, which are blocked by chlorpromazine. Silverstone et al. (1980) found that pimozide, a much more selective agent than chlorpromazine, had no effect on dextroamphetamine-induced anorexia.

Fenfluramine. Fenfluramine, an anorectic, stimulates the release and decreases the reuptake of serotonin, which causes an increase in postsynaptic activity. While fenfluramine may display some amphetamine-like properties at high doses (60–120 mg/day), it has no psychostimulant effect at normal doses and can have a mild depressant effect on the central nervous system. Potential for abuse is small, but abrupt cessation can cause severe depression (Reynolds 1989). Also, fenfluramine does not appear to exacerbate psychotic illness (Shore et al. 1985; Stahl et al. 1985; Kolakowska et al. 1987; Marshall et al. 1989). Concern has been raised about the neurotoxicity of fenfluramine in laboratory animals (Schuster et al. 1986). However, this problem has been documented only at large weight-corrected doses and has not been reliably replicated or associated with functional losses. Neither have long-lasting neurological effects been documented in obese patients or autistic children (Aman and Kern 1989).

Goodall et al. (1988) reported on a 12-week double-blind trial of *d*-fenfluramine. Patients on depot neuroleptics experienced significant weight loss without deterioration in mental state. One would expect fenfluramine to be most effective with the more selective antipsychotics. These agents have less antiserotonergic activity, so they would be less likely to antagonize fenfluramine's action. But there are no data to support this theory.

Tryptophan. Cohen et al. (1990*a*) report that daily administration of 1–3 g of L-tryptophan (a serotonin precursor) to patients on clozapine has no effect on weight gain. Recent reports on an association of tryptophan with eosinophilia myalgic syndrome make it an even less attractive alternative (Wright 1991).

Amantadine. Most of the literature on antipsychotics and amantadine describes its use with extrapyramidal side effects. Correa et al. (1987) studied the effect of amantadine on neuroendocrine side effects of neuroleptics in 10 patients in an open-label study with an ABA reversal design. All patients lost weight while on amantadine. However, there is a risk of worsening psychotic illness with amantadine (Hausner 1980; Nestelbaum et al. 1986; Rego and Giller 1989; Wilcox and Tsuang 1990), so it probably will not be used much in the future.

In summary it appears that fenfluramine, prescribed concurrently with neuroleptics, can induce significant weight loss without adverse effects. Amantadine may be useful in some patients but it may worsen psychosis. Both medications would have to be used long term.

Energy Intake and Expenditure

Dietary Composition. Weight gain is caused by an imbalance

between energy intake and expenditure. Recent studies in clinical nutrition have produced interesting results by separating components of energy intake and storage.

Alcohol cannot be stored and all kilojoules must be oxidized (Lands and Zakhari 1991). Carbohydrate is stored but in small amounts, only about 1 kg. Carbohydrate stores are strictly controlled (Ravussin and Swinburn 1992), but changes in weight due to fluctuation in glycogen stores can be larger than 1 kg because glycogen is stored with 2 to 4 times its own weight in water (Olsson and Saltin 1970; Acheson et al. 1988).

Dietary carbohydrate ordinarily is not converted to fat, but in conditions of massive carbohydrate overfeeding, de novo, inefficient fat synthesis does occur (Acheson et al. 1987, 1988). Acheson et al. (1988) recorded a 35 percent increase in energy expenditure in their subjects when massive carbohydrate overfeeding (about 5,000 kcal a day; 85% carbohydrate for several days after glycogen stores were saturated) was used to induce de novo fat synthesis. They estimated that about 25 percent of the energy of the glucose channeled into de novo lipogenesis was needed for the metabolic process.

In contrast, dietary fat is easily converted to body fat stores, and the capacity for storage is very large. Studies of food intake are also consistent with the signal role of dietary fat in obesity (Dreon et al. 1988; Romieu et al. 1988; Miller et al. 1990). Miller (1990), in a review of mainly animal evidence, concludes that "diet composition may be just as important as diet energy content in promoting obesity" (p. 283). Experimental studies in humans have failed to show that the proportion of dietary fat affects obesity when energy intake is controlled (Alford et al. 1990; Rumpler et al. 1991). However, the amount of fat in the diet does affect obesity when food intake is unrestricted (Lissner et al. 1987).

The role of dietary fat in satiety appears to be minimal. Flatt (1988) argued that levels of glycogen stores are an obvious way for the body to sense low energy stores and stimulate appetite. Duncan et al. (1983) found that people fed fewer calories per volume of intake ate for longer periods, felt more satiated, and ate fewer calories.

Lissner et al. (1987) fed volunteers three diets consisting of apparently similar foods in which fat contributed 15 to 20 percent, 30 to 35 percent, or 45 to 50 percent of the total calories. Subjects ate freely from the food available on their diets. Mean daily calorie intake correlated with the dietary fat level, that is, 2,087 kcal on the low-fat diet, 2,352 kcal on the medium-fat diet, and 2,714 kcal on the high-fat diet. The average weight changes over the 2-week period on each diet corresponded, that is, a 0.4 kg loss on the low-fat diet, 0.03 kg loss on the medium-fat diet, and 0.32 kg gain on the high-fat diet. Thus, subjects did not compensate in intake volume for the reduced fat content of their diets.

When Lissner et al. (1987) compared these results with earlier studies that replaced the sucrose content of food (Pokiros et al. 1977, 1982), they concluded that compensation for loss of calorie density was much less when fat was decreased than when sucrose content was replaced. This finding has obvious applications for anyone concerned with weight gain. By reducing dietary fat one should be able to reduce the diet's, energy content with minimal loss in satiety. Decreasing fat intake may be particularly effective in people on neuroleptic medication who experience an artificial increase in appetite.

Energy Expenditure. Most energy expenditure is accounted for by resting metabolic rate, food processing, and exercise (Calles-Escandon and Horton 1992). The only one of these under voluntary control is exercise. Data from clinical trials looking at exercise as a means of treating obesity are disappointing (Bray 1990). King and Tribble (1991) suggest that exercise may be most effective in treating obesity when programs are intensive and continue over a long period. Exercise also appears to be more effective in men than in women. Type of adipose tissue may also be important. Individuals with hypercellular obesity, that is, normal numbers of enlarged fat cells, may be more likely to lose weight with exercise training than those with normocellular obesity, that is, an increased number of normal sized fat cells (Gwinup 1975; Bjorntop 1989). The nature of adipose tissue in weight gain associated with neuroleptic medication is not known.

Several studies have found regular exercise to be an important correlate of weight loss maintenance (Colvin and Ohlson 1983; Hoiberg et al. 1984; Marston and Criss 1984). Pavlou et al. (1989), in a randomized, controlled trial that added exercise to a calorie-restricted diet, found little difference in weight loss between exercise and nonexercise groups but striking differences in maintenance

over up to 3 years.

Exercise may also affect energy expenditure by increasing the resting metabolic rate. There is considerable debate in the literature about the persistence of the temporary increase that follows exercise and whether it interacts with the thermal effect of food (Calles-Escandon and Horton 1992).

In summary, recent nutrition research indicates the importance of dietary composition. Dietary carbohydrate is less readily and less efficiently converted to body fat than is dietary fat. Dietary carbohydrate may also have a special role in satiety. Evidence indicates that the major role of exercise in managing obesity is weight loss maintenance.

Directions for Research

Increasing Data Base. Recording patient weights and heights in all clinical drug trials and in general use of neuroleptic medications could generate a great deal of prospective information on weight gain with little extra expenditure. These records could be a source of further data on the time course, variability, reversibility, and predictive factors of weight gain associated with neuroleptic medication. Further study is warranted on the distribution and nature of the adipose tissue and the number and size of fat cells. Correlates of weight gain such as improvement in clinical response, other neuroendocrine side effects, prolactin level, and other biochemical measures should be assessed prospectively. Assessment of diet on and off neuroleptic medications could answer many important research questions, but constructing such a study would pose considerable ethical and practical problems.

Prevention. Sletten et al. (1967*a*) and Klein et al. (1972) reported that patients on neuroleptic medication lost weight by decreasing their calorie intake, but these studies were done under controlled situations in a hospital. Simple preventive strategies such as encouraging patients to eat less and exercise more are often recommended in the literature but have not been tested. It is hypothesized that reducing dietary fat would be of particular benefit and this possibility should be tested.

If patients on neuroleptic medication experience carbohydrate craving, it may help to encourage them to choose sweetened food high in carbohydrate, which might satisfy their craving with a much lower energy intake, rather than food such as chocolate and pastries.

Mechanisms. Documentation of the nature of appetite increases and the food choices associated with starting neuroleptic medication would be of interest. If the carbohydrate craving associated with antidepressants and lithium were not found with neuroleptic medication, it might indicate that neuroleptics have a different mechanism. It would also be of interest to know the relationship between increased appetite and weight gain, that is, whether all or some of those who do not gain weight also experience increased appetite. The effect of various neuroleptic medications on the ratio of fat and carbohydrate oxidation might also be measured.

Drug Effects. Large controlled, double-blind clinical trials are needed to establish which neuroleptics are least likely to be associated with weight gain. Earlier studies indicate that molindone, pimozide, and loxapine may be worth investigating. The effect of anticholinergic medications, commonly used with neuroleptics to control extrapyramidal side effects, should be assessed. Ideally, a study of this type would use a randomized, double-blind, prospective design. However, since no data have been published in this area, a preliminary naturalistic but prospective study might generate hypotheses to be evaluated more formally.

More clinical trials of fenfluramine should be done with patients concerned about their weight gain. Subjects would have to be compliant and reliable with their medication use and able to give informed consent. Accounts of exacerbation of psychotic illness in patients on amantadine make research on this drug more problematic.

Conclusions

Weight gain associated with neuroleptic use is a poorly studied and probably a poorly managed problem. More systematic study is needed of the phenomenon and its prevention and treatment. Neuroleptic use generates enough other distressing or conspicuous side effects to impede compliance without affecting body image as well. There seems little doubt that controlling weight gain could improve compliance and patients' physical health, and also increase social acceptance of the mentally ill.

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