Reversal of Antipsychotic-Associated Weight Gain

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Background: Given growing concern about weight gain associated with treatment with antipsychotic agents, we performed a retrospective chart review of patients who reversed weight gain associated with antipsychotic treatment to determine the prevalence of reversal and both the course and methods used.

Method: Prevalence of weight gain reversal was determined by surveying clinicians. Of 53 patients who gained ≥ 20 lb (9 kg) during antipsychotic treatment, an initial sample of 12 patients (23%) who subsequently lost ≥ 10 lb (5 kg) was identified. These 12 patients were combined with additional patients, identified by the authors, who met the same criteria for reversal of antipsychotic-associated weight gain to form a total sample of 35 patients. Course and methods of weight loss were determined by reviewing these patients' charts. Information about interventions and both antipsychotic and other medications was collected.

Results: At the point of maximum weight gain, the total sample of 35 patients had gained a mean of 29.36 kg (64.73 lb) over a mean of 33 months. At the point of greatest weight loss (56 months), these patients were a mean of 10.86 kg (23.94 lb) over their baseline weight. The most recent weight for patients (63 months) indicated they were 14.81 kg (32.65 lb) over baseline. The most frequent weight loss interventions were regular dietician visits (42.9% [N = 15]), self-directed diet (28.6% [N = 10]), and weight loss as a treatment goal (25.7% [N = 9]). The least frequent interventions were no intervention (5.7% [N = 2]), psychiatrist addressing weight loss (5.7% [N = 2]), and surgery (2.9% [N = 1]). No significant change in medications prescribed was found.

Conclusion: Some patients who gain weight while taking antipsychotic medications are able to stop gaining and lose weight over time, largely through behavioral interventions. While patients' weight fluctuated, this group sustained a loss of approximately half their initial gain. Dietary interventions appear promising and should be explored further to prevent and reverse weight gain.

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In the pharmacologic treatment of schizophrenia, there is growing concern about weight gain associated with antipsychotic medications. While weight gain has long been recognized as a side effect of antipsychotic agents, it is more rapid and frequent during treatment with novel antipsychotic medications.[1]

While the quality of data varies among studies reporting weight gain in patients treated with antipsychotic agents, there are some consistent trends in the literature. Clozapine and olanzapine are repeatedly associated with the most weight gain,[1–3] perhaps because of their similar receptor binding profiles. In a synthesis of available research data,[1] 10 weeks of treatment was associated with a mean weight gain of 3.99 kg (8.80 lb) among patients prescribed clozapine, followed by olanzapine (3.51 kg [7.74 lb]), thioridazine (3.49 kg [7.69 lb]), chlorpromazine (2.10 kg [4.63 lb]), risperidone (2.00 kg [4.41 lb]), haloperidol (0.48 kg [1.06 lb]), fluphenazine (0.43 kg [0.95 lb]), ziprasidone (0.04 kg [0.09 lb]), and molindone (–0.41 kg [–0.89 lb]). In a systematic review of weight gain related to novel antipsychotics, quetiapine treatment was associated with a similar amount of weight gain as olanzapine and more substantial weight gain than chlorpromazine, haloperidol, and placebo.[4]

Research on the relationship between weight gain and clinical parameters varies in both quality and outcomes. Some studies on the relationship between weight gain and length of treatment indicate that the maximal increase in weight occurs in the first weeks of treatment with various agents, including clozapine, with patients reaching a pla-

teau between 3 and 9 months.[5,6] Other data suggest that while weight gain is greatest in the first year for clozapine-treated patients, it continues at a slower pace for at least 36 months.[7] Data on the link between dose and weight gain are also inconclusive and contradictory. Two studies, for example, suggest that weight gain with risperidone is dose-related,[8,9] while another study shows no such relationship for either risperidone or other antipsychotic agents.[5] Studies indicating that weight gain is more common in persons who are not obese[5] conflict with reports of greater weight gain in patients whose body mass index (BMI) is higher at the outset of treatment.[4] Given the contradictory nature of existing data, it is difficult to discern patterns in weight gain associated with antipsychotic agents.

Blockade of serotonin 2C, α_1-adrenergic, and/or histaminic receptors by antipsychotic agents is believed to distort signals from the gut to the brain, leading to excessive appetite and impaired satiety.[3,10] Excessive caloric consumption presumably then leads to weight gain. The mechanism of action of weight gain associated with conventional antipsychotic agents is less clear. Obesity is associated with greater risk of developing hypertension, type 2 diabetes, coronary heart disease, stroke, death, and reduced quality of life compared with that found in the general population.[11,12]

Relationships between weight gain associated with antipsychotic treatment and long-term health outcomes in patients with severe mental impairment remain poorly understood. There have been recent articles calling for action in addressing this problem.[13,14] They stress the need for an expansion of the limited work done on preventing and reversing antipsychotic-associated weight gain. In our clinical practice, we have noted a number of patients who lost some or all of the weight they had gained during treatment with an antipsychotic medication.

This study is a retrospective analysis to explore the prevalence of reversal of weight gained during antipsychotic treatment and to provide a clinical description of the pattern of weight loss, methods used, and the pharmacology involved.

METHOD

Prevalence Survey

The first step of our study was estimation of the prevalence of reversal of weight gain during antipsychotic treatment by surveying clinical case managers at the Mental Health Center of Greater Manchester (MHC-GM) (Manchester, N.H.). Case managers were first asked to identify patients treated in the past 5 years who gained at least 20 lb (9 kg) after initiation of an antipsychotic agent. Next, they were asked to identify which patients subsequently lost at least 10 lb (5 kg). Only those case managers from departments with patients likely to be prescribed antipsychotic agents were included. All case managers had caseloads of 10 to 30 patients, with daily to no less than monthly contact with their clients.

Chart Review Procedures

The second step was to review the charts of those patients who met criteria for reversal of weight gain. Subjects were not required to provide informed consent, as determined by an institutional review board affiliated with the New Hampshire Department of Behavioral Health, because this study reviewed only preexisting data. There was no contact with patients, and measures were taken to protect their identities. In order to achieve an adequate sample size, the population was supplemented by 23 additional subjects who met the above criteria for reversal of weight gain. These subjects were identified by 2 of the authors (D.L.N., H.W.). This allowed us to review the clinical records of 35 patients with reversal of weight gain. We included patients whose weight increased while taking any antipsychotic medication. Patients were not excluded if they gained weight while taking an antipsychotic agent more than 5 years ago, provided that the weight loss occurred during the last 5 years. We reexamined the data after we excluded patients for whom the period between minimum and current weights was less than 6 months to ensure that we were not overestimating sustained weight loss.

Eighteen of the subjects were men and 17 were women with a mean ± SD age of 43.43 ± 7.97 years. Two patients were Hispanic, 1 was African American, and the remainder were white. Sixteen patients had a DSM-IV chart diagnosis of schizophrenia, 8 had schizoaffective disorder, 7 had bipolar disorder, 2 had major depressive disorder, and 2 had other diagnoses. Mean ± SD length of illness was 12.94 ± 6.20 years. Weights were converted to BMI using an established table to examine the relationship between BMI and weight loss.[15] We categorized BMI on the basis of established criteria.[14] Prior to treatment with the antipsychotic agent that induced weight gain, no patients were considered underweight (BMI < 19), 6 met criteria for normal weight (BMI = 19–24.9), 9 met criteria for being overweight (BMI = 25–29.9), 14 met criteria for being obese (BMI = 30–39.9), and 5 met criteria for being extremely obese (BMI ≥ 40).

The weight of patients at MHC-GM is recorded annually, at the time of any crisis-bed or hospital admission, at sessions with the consulting dietitian, and sporadically at meetings with their treating psychiatrist. A timeline was plotted to examine weight relative to the time at which the antipsychotic medication was prescribed in order to establish that weight gain was associated with initiating treatment with a particular medication and that all subjects met the criteria for reversal of weight gain.

The weight of each patient at 4 landmark timepoints was obtained: baseline (T_1) weight represented the last recorded weight prior to initiation of the antipsychotic

Table 1. Weight Gain and Body Mass Index (BMI) in Patients Taking Antipsychotics at Time of Maximum Weight (T_2), Minimum Weight (T_3), and Current Weight (T_4) Relative to Baseline (T_1)

Variable	T_2[a] (N = 35)	T_3[a] (N = 35)	T_4[a] (N = 35)	Sustained T_4 weight (≥ 6 mo)[b] (N = 11)
Weight gain from baseline, mean ± SD, kg	29.36 ± 13.70	10.86 ± 17.59	14.81 ± 15.12	14.31 ± 13.02
Weight change from baseline, %	33.65	13.45	17.25	14.11
Reversal of weight gain, %	N/A	63.01	49.56	54.93
Time from baseline, mean ± SD, mo	33 ± 28	56 ± 28	63 ± 32	84 ± 21
BMI, mean	41.34	35.06	36.83	39.09

[a]T_1 weight = 92.56 ± 23.89 kg; BMI = 31.56.
[b]T_1 weight = 95.83 ± 15.86 kg; BMI = 33.09.
Abbreviation: N/A = not applicable.

agent associated with weight gain, maximum (T_2) weight represented the highest weight recorded in the chart, minimum (T_3) weight represented the lowest weight recorded in the chart after maximum weight, and current (T_4) weight represented their last recorded weight. The percentage of weight gained was calculated by subtracting the weight at T_1 from the weight at each subsequent point and dividing by the weight at T_1.[16] The number of months from baseline to each of the other points was calculated.

Records were intensively reviewed for the period between T_2 and T_3 to determine interventions used by subjects to reduce weight. Interventions were categorized at the end of data collection by sorting them into what the investigators believed to be natural groupings. Dietary interventions were separated into self-directed, part of a formal program, or resulting from meeting with our consulting dietitian in order to determine which methods were most frequently used. Changes in medications that were considered a medication intervention included a reduction in the amount of antipsychotic, lithium, or valproic acid prescribed; changing the antipsychotic prescribed for a patient; or switching the patient from valproic acid to topiramate. Such interventions were only considered as a weight loss intervention if the progress note specified weight loss as the reason for the change. An analysis of variance (ANOVA) was used to determine if there was a greater magnitude of weight loss associated with the number of interventions used. A p value of .05 was selected to indicate statistically significant differences.

The prescribed antipsychotic medication and dose were recorded at each point (T_1–T_4) to determine if weight reduction was associated with an alteration in medication or dose. The prescription of medications other than antipsychotics that are commonly associated with weight gain or loss was also recorded. McNemar tests were used to compare the number of patients on each medication before and after the weight loss period. This test was selected because we were examining dichotomous data on the same group of subjects at 2 points in time.[17] Chlorpromazine equivalent doses were calculated to determine if dose was related to the magnitude of weight loss.[18] A t test was used to determine whether there was a significant difference in chlorpromazine equivalent doses of medication at T_2 and T_3.

Patients' Global Assessment of Functioning (GAF)[19] score and Mental Health Statistical Improvement Project (MHSIP)[20] data were rated quarterly by the treating clinician beginning in the mid-1990s as a part of routine clinical care. We recorded these ratings for the months during which each patient was at T_2 and T_3 weights. MHSIP data included information about residential status (alone, with others/family, mental health–supported housing) and employment status (competitive, sheltered, no activity). A t test was used to compare GAF scores at T_2 and T_3. Only patients with available ratings at both time periods were included in these analyses. McNemar tests were used to determine if the number of patients in each residential and employment category changed between T_2 and T_3. An ANOVA was used to determine if magnitude of weight loss was associated with work status or residential status.

RESULTS

Thirteen (29%) of 45 available case managers completed the prevalence survey. It identified 53 patients who gained ≥ 20 lb (9 kg) during treatment with an antipsychotic medication. Twelve patients (23%) met the criteria for reversal of weight gain. No other data were gathered on the 41 patients who did not lose weight.

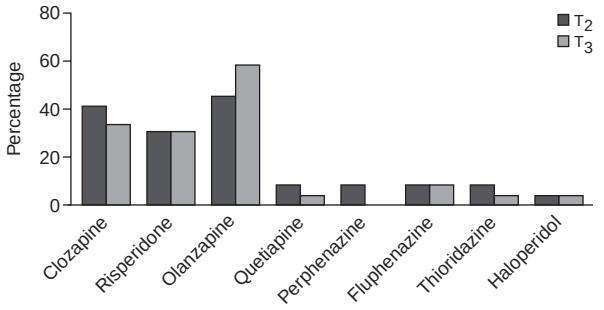
Table 1 illustrates the pattern of weight gain and loss relative to baseline among the 35 patients in the chart review portion of the study who reversed their weight gain (12 patients from the prevalence survey supplemented by 23 additional patients identified by authors). On average, this group gained about one third of their previous body mass, then lost two thirds of their original gain, and sustained a loss of one half of their original gain over the course of approximately 5 years. There were no significant differences in the magnitude of weight loss based on gender, diagnosis, ethnicity, or BMI at baseline in this group. Eleven patients had a T_4 weight available at least 6 months after T_3. The mean ± SD duration from T_3 to T_4 for this subgroup was 21 ± 14 months compared with 7 ± 12 months for the entire group studied. The mean increase in

Table 2. Frequency of Weight Loss Interventions in Patients Taking Antipsychotics (N = 35)[a]

Intervention	N	%
Dietitian visit ≥ once/mo for 1 y	15	42.9
Self-directed diet	10	28.6
Weight loss as a goal on treatment plan	9	25.7
Dietitian visit < once/mo for any length of time	7	20.0
Medication intervention	6	17.1
Exercise	6	17.1
Medical illness	4	11.4
Clinic, group, or meeting	3	8.6
No intervention noted	2	5.7
Psychiatrist recommended weight loss	2	5.7
Surgery	1	2.9

[a]Data on weight loss interventions were available for only 33 patients, but percentages are based on total N.

Figure 1. Percentage of Patients Taking Antipsychotic Medications at Time of Maximum Weight (T_2) and Minimum Weight (T_3)[a]



[a]There were no significant differences in the frequency with which any 1 medication was prescribed between the 2 periods.

weight from T_3 to T_4 (i.e., the weight they regained) was 9.48 kg (20.90 lb) for these 11 patients compared with 3.84 kg (8.47 lb) for the entire group.

The frequency with which interventions were used by patients during their weight loss process is summarized in Table 2. We were able to identify interventions for all but 2 patients. Of the remaining 33 patients, 15 (46%) used 1 intervention to lose weight, 9 (27%) used 2 interventions, 7 (21%) used 3 interventions, and 2 (6%) used 4 interventions. The mean number of interventions used by patients was 1.77. Patients who used 3 interventions lost significantly more weight (37.13 kg [81.86 lb]) than patients who used 2 interventions (12.55 kg [27.67 lb]; $F = 2.92$, $p = .043$). Twenty-seven patients (82%) utilized some form of dietary change, whether it was self-directed, part of a formal group, or through the dietitian, and 6 (18%) followed some form of exercise regimen. Six patients (18%) used only nonbehavioral interventions (surgery, illness, or medications). Because many patients used multiple methods to lose weight, we were unable to analyze statistically if any 1 method was associated with a greater magnitude of weight loss.

Table 3. MHSIP Data and GAF Scores at Time of Maximum Weight (T_2) and Minimum Weight (T_3)

Item	T_2	T_3	p Value
Residential status, N (%)			
Lives alone	13 (38.2)	11 (34.4)	.625
Lives with others/family	7 (20.6)	6 (18.8)	1.000
Mental health–supported housing	14 (41.2)	15 (46.9)	.250
Employment status, N (%)			
Competitive	7 (20.6)	14 (43.8)	.016
Sheltered	15 (44.1)	10 (31.3)	.344
No activity	12 (35.3)	8 (25.0)	.549
GAF score, mean[a]	47.2	45.4	

[a]$t = 1.600$, $df = 24$, p = NS.
Abbreviations: GAF = Global Assessment of Functioning, MHSIP = Mental Health Statistical Improvement Project.

Our review revealed that 18 (54.5%) of 33 patients for whom we had complete T_2 and T_3 data had a change in antipsychotic medications between these 2 points. However, there were no significant differences in the proportion of patients treated with each antipsychotic medication at T_2 compared with T_3 (Figure 1). There was also no difference in the chlorpromazine equivalent dose at T_2 (1077 mg) and T_3 (1146 mg) ($t = 0.910$, p = NS). Concomitant medications associated with influences on weight that were prescribed for this group of 35 patients were lithium, valproic acid, and topiramate. There were no significant differences in the number of patients prescribed each of these medications between T_2 and T_3.

Table 3 reports the MHSIP data and GAF scores for patients at T_2 and T_3. No significant differences were found between T_2 and T_3 in terms of GAF scores or the magnitude of weight lost based on work or residential status; however, there was a statistically significant increase in the number of patients competitively employed at T_3.

DISCUSSION

The data indicate that approximately one quarter of patients who experience weight gain associated with antipsychotic treatment may eventually be able to reverse the process. We found no evidence of an impact of gender or other demographic variables on the magnitude of weight loss. The majority of patients in this group used behavioral interventions to assist them in losing weight. There is some evidence that use of multiple weight loss interventions is more effective.

The most common intervention was consulting with a dietician. The dietician typically asked patients to log their food consumption and then directed them to eliminate 1 or 2 high calorie foods from their diet. In addition to the methods used by patients to lose weight, the trend toward higher rates of employment between T_2 and T_3 suggests that increased activity could have contributed to weight loss. The mean rate of competitive employment among all severely mentally impaired patients at this

community mental health center between 1999 and 2001 was 33.7%, indicating that those patients who reversed their weight gain were involved in a similar level of competitive employment as their peers. The fact that nearly half of the patients sampled lived in mental health–supported housing indicates that even patients whose level of functioning is such that they require additional support to live in the community are able to reverse weight gain with support. Supported housing did not control dietary intake but did offer patients assistance in making healthy choices when grocery shopping.

Patients continued treatment with various antipsychotic agents in the same proportions and doses, indicating that the weight loss in this sample was primarily due to behavioral interventions. We were unable to find evidence for a pattern of changes in type or dose of antipsychotic or other medication prescribed that might account for the observed weight loss. Taken as a whole, these data suggest that dietary interventions may be a key to helping people with severe mental illness to manage medication-induced weight changes, ideally in combination with several other behavioral interventions.

The pattern of weight change seen in this study has several implications. The mean increase of nearly 34% in body weight over 33 months suggests that the reversal of weight gain is associated with above average initial weight gain. Furthermore, these data indicate that reversal of weight gain is a long-term phenomenon. Patients in this study sustained weight gain for nearly 3 years on average before beginning reversal. This finding is consistent with previous studies of the longitudinal course of weight gain.[6] We did not examine the pattern between T_1 and T_2 to determine whether the weight gain reached a plateau at some point prior to 3 years.

Weight loss in this group occurred between 3 and 5 years after initial weight gain, with substantial variability. The mechanism of reversal of weight gain is unknown. It could be due to accommodation of biological mechanisms that caused the initial weight gain. Alternatively, it could also be the product of an improved ability to maintain a diet and/or exercise regimen secondary to cumulative improvement in negative symptoms and cognitive impairments associated with long-term treatment with second-generation antipsychotics. The statistically significant increase in competitive work from T_2 to T_3 in this group is consistent with the hypothesis that these patients had reached a point of higher functioning in their treatment, resulting in improvement in a number of areas (diet, work). Further research is needed to determine mechanisms of action for reversal of weight gain.

While patients did lose some of the weight that they gained, most did not return to their T_1 weight, and many regained some of their initial weight loss. The mean loss of weight from T_2 to T_3 was 18.5 kg (40.8 lb) or 15.17% of the maximum weight. While it cannot be ignored that the mean BMI remained in the obese range, literature on weight loss supports the goal of a 5% to 15% reduction in initial body weight.[15] Additionally, the maintenance of 55% of the weight loss over nearly 2 years among those patients with long-term follow-up indicates considerable capacity to maintain weight loss. In the general population, one third of any weight loss is generally regained within a year.[15] Nonetheless, further research is needed to develop interventions that may help people with severe mental impairment go further in achieving improvements in body size and physical fitness.

There are a number of limitations to this study. The survey method of assessing prevalence of weight changes may have underestimated actual cases. We have few data on the group of patients who failed to reverse weight gain associated with antipsychotic treatment. Therefore, we could not evaluate those factors that differentiate patients who reversed weight gain from those who did not. It is unclear whether those who did not lose weight ever attempted to do so or if they tried similar interventions. The group who did not lose weight may not have been taking the antipsychotic medication for a sufficient duration to complete a weight reversal cycle or may have achieved less symptomatic improvement. Additionally, we did not evaluate patients who did not gain weight on antipsychotic agents. Therefore, we have no data on whether dietary interventions are effective early in treatment to prevent weight gain. Finally, we have no data on the health consequences of weight gain and loss in this sample. It remains unclear whether the health consequences of weight gain/loss associated with antipsychotic treatment are adequately reflected in the literature on obesity in the general population.

Further research is needed to understand the implications of weight change among people with severe mental impairment, to identify interventions to prevent weight gain among patients treated with antipsychotic medications, and to assist those who have already gained weight to reduce their weight and maximize their physical fitness. This study suggests that dietary interventions, multiple behavioral methods, and time may all be important contributors to reversal of weight gain. Controlled trials of these interventions are needed to clearly identify effective clinical approaches to prevention and management of weight gain associated with antipsychotic treatment.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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