Attenuation of Antipsychotic-Induced Weight Gain With Early Behavioral Intervention in Drug-Naive First-Episode Psychosis Patients: A Randomized Controlled Trial

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Background: The purpose of this study was to compare an early behavioral intervention (EBI) with nonstructured standard physical care (routine care intervention [RCI]) in preventing antipsychotic-induced weight gain in drug-naive first-episode psychosis patients.

Method: Sixty-one patients with a DSM-IV–diagnosed psychotic disorder were first randomly assigned to 3 different antipsychotic treatments (risperidone [N = 23], olanzapine [N = 18], and haloperidol [N = 21]) and subsequently randomly assigned to the intervention condition (EBI, N = 35) or RCI (N = 27). EBI was specifically designed to teach strategies to enhance control over factors associated with antipsychotic-induced weight gain and consisted of 8 flexible intervention modules that incorporated behavioral interventions, nutrition, and exercise. In the RCI group, patients were informed about potential weight gain and advised to increase their exercise and limit food intake. Body weight and body mass index were measured at baseline and then weekly for 3 months. In addition to change in weight and body mass index, a third outcome measure was the proportion of patients who had gained more than 7% of their body weight at 3 months. Participating patients were referred between August 2002 and September 2004.

Results: All 61 participants completed the study. Patients in the EBI group gained significantly less weight (mean = 4.1 kg, SD = 4.0) than those allocated to the RCI group (mean = 6.9 kg, SD = 4.5) ($p < .01$) during the 3-month follow-up period. Similar findings were obtained when both groups were compared on treatment-induced change in body mass index, which was significantly less in the EBI group than in the RCI group (1.40 vs. 2.39 kg/m^2) ($p < .01$). Accordingly, significantly fewer patients in the EBI group (N = 11; 39.3%) than in the RCI group (N = 26; 78.8%) ($p < .002$) increased their baseline weight by more than 7%, the cutoff for clinically meaningful weight gain.

Conclusions: EBI was effective in attenuating antipsychotic-induced weight gain in a drug-naive first-episode psychosis cohort. Patients displayed good adherence to this type of preventive intervention.

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Weight gain has been a long-recognized side effect of antipsychotic drugs.[1] According to recent studies, up to 80% of patients receiving antipsychotics suffer significant gain in body weight.[2–4] This antipsychotic side effect has lately become a major concern in the treatment of psychosis since weight gain has been associated with reduced quality of life,[5,6] social stigma,[7] greater morbidity (cardiovascular disease, diabetes mellitus, osteoarthritis, and some types of cancer),[8,9] and mortality.[7,10] Furthermore, fear of weight gain is one of the main factors contributing to poor compliance found in antipsychotic treatment,[11,12] so it may adversely affect clinical outcome.[2,4]

Weight gain usually occurs in the first months of antipsychotic treatment.[2,13,14] The pattern of weight gain over time varies among agents, but it generally appears to be consistent with gradual deceleration.[15–17] As a result, it has been posited that young patients previously unexposed to antipsychotic medication are particularly vulnerable to this antipsychotic side effect.[18,19]

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The mechanisms by which antipsychotic drugs induce weight gain have yet to be fully elucidated. Hypothetical mechanisms of action of these agents, such as serotonin 5-HT_{2C}[20,21] or histamine H_1 receptor antagonism,[22] that modulate appetite and body weight have been implicated. Additionally, lifestyle factors such as poor diet and lack of exercise may also contribute to weight gain.[23] Thus, it has been proposed that antipsychotic treatment might be causing individuals to consume more energy, to expend less energy, or both.[2,24]

Despite this long-recognized side effect of antipsychotic medication, there is a relative dearth of studies of interventions to control weight gain. In accordance with recent guidelines, interventions may include nutritional counseling and initiation of a personal exercise program. Extensive behavioral analysis with appropriate interventions is also broadly recommended.[25,26] There is some preliminary evidence suggesting that psychological interventions may be effective in weight gain control.[27,28] However, there are some limitations in the published studies and questions about their generalizability.[29] Methodological problems include absence of adequate procedures of random allocation, lack of a suitable control group,[30–32] participants and assessors are rarely blind to treatment assignment, and body weight is frequently the only outcome measure reported, with few studies using other relevant measures such as body mass index (BMI) or percentage changes in weight.[33] It is also of note that the interventions were usually tested on chronic samples or in ward settings.[27,34,35] To our knowledge, no randomized controlled trial has been conducted to test psychological weight gain interventions in first-episode psychosis patients.

The present single-blind randomized controlled study was designed to overcome many of the limitations of previously published work. The main aim was to compare an early behavioral intervention (EBI) with nonstructured standard physical care (routine care intervention [RCI]) in preventing antipsychotic weight gain in a first-episode psychosis cohort that had not been previously treated with antipsychotic medication. We hypothesized that EBI would be more effective than standard information and advice in reducing antipsychotic-induced weight gain.

METHOD

Setting and Sample Selection

The study was performed in an integrated clinical and psychosocial program for intervention in nonaffective psychotic disorder, the Cantabria intervention program of first-episode psychosis (PAFIP). The PAFIP was designed to provide comprehensive and multidisciplinary mental health assessment and care and serves a population of 555,000 in the catchment area of the province of Cantabria, Spain. The population of Cantabria is divided between urban (53%) and rural areas (47%). The PAFIP was initiated in February 2001 and has been active since then. It is embedded in the outpatient service at the University Hospital Marqués de Valdecilla. Hospitalization for initial treatment and relapses is available in the only inpatient unit in the region, which is also located at our hospital.

Referrals between August 1, 2002, and September 31, 2004, were considered for participation and were derived from primary care services, emergency services, and mental health professionals. Patients were eligible for the study if they were aged 15 to 60 years; met DSM-IV criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief reactive psychosis, or psychosis not otherwise specified; lived in the catchment area; and provided written informed consent. All patients were experiencing their first episode of psychosis and had not received more than 6 weeks of adequate neuroleptic treatment. Patients with a history of neurologic disease, head injury, mental retardation (DSM-IV criteria), or drug dependence (DSM-IV criteria) were not included in the study.

Study Design and Interventions

The study was designed as a single-blind randomized controlled trial, with research assessors and patients intended to be blind to the intervention status. The staff members performing the assessments were not involved in implementing any aspect of the intervention. However, the single blind for assessors was occasionally difficult to achieve because both intervention groups were treated by different clinicians, a feature that was difficult to conceal from assessors. The DSM-IV research diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version.[36] Patients who met criteria and gave written informed consent were first randomly assigned to one of 3 different antipsychotic treatments (olanzapine, risperidone, or haloperidol) and subsequently randomly assigned to the intervention condition by computer-generated blocks of 4 random numbers. This randomization technique maximizes the likelihood of obtaining comparable groups in small samples and allowed us to compare EBI with RCI during treatment with different individual antipsychotics. The randomization was performed by a member of the team not involved with either the assessments or the treatments.

The study was approved by the ethics committee of University Hospital Marqués de Valdecilla (Santander, Spain). All potential subjects who met intake criteria were given the opportunity to participate. Participants received detailed information about the study, and the 2 interventions were clearly explained. For participants younger than 18 years, consent was also obtained from a parent or guardian. Only patients who were fully competent to give informed consent and who did so were included. Partici-

Table 1. Early Behavioral Intervention Treatment Modules[a]

Engagement and individual assessment (2 sessions)	Individual beliefs about medication, willingness to change or control daily habits, and factors related to weight gain were assessed. Rationale for the intervention was provided, and the preventive framework was emphasized. An individual handbook was introduced that included different sections designed to obtain written information from the client regarding his/her daily habits (ie, self-monitoring records) and to assist the participant in recording important information or practicing skills outside of sessions.
Psychoeducation (2 sessions)	The information provided focused on the roles of eating and activity in weight management. Topics included healthful weight management techniques, such as benefits of healthy nutrition, physical fitness, and available behavioral techniques. A collaborative therapeutic agenda based on previous assessments and clients' goals was developed to guide the future provision of interventions.
Dietary specialized counseling (1 to 4 sessions)	An eating plan based on the Stoplight Diet[38] was developed. Food was classified according to the colors of a stoplight: "Green" (choose as many as you want), "Orange" (eat in limited amounts), and "Red" (think about it before you take it). Participants were encouraged to increase their intake of low-calorie food (ie, vegetables and fruits; Green and Orange foods) and limit the number of foods high in fat and sugar (Red foods).
Exercise program (1 to 4 sessions)	Therapists and patients collaboratively developed individual programs of gradual assignment of exercise. A range of different types of exercise and various levels of intensity was offered, varying from light exercise (increase walking and decrease sedentary activities, particularly time spent watching television or sleeping) to moderate exercise (gym, intense walking, running, etc).
Behavior therapy (1 to 4 sessions)	Motivational counseling techniques; behavior strategies to control frequency of intake, including stimulus control techniques to minimize cues for eating; behavior strategies to enhance control over speed of intake with the aim of developing slower eating habits; and additional behavior strategies such as weight monitoring (ie, weekly weight changes graphic), social assertiveness training for situations involving eating and exercise, stress management, activity scheduling, coping strategies, problem solving, and goal setting.

[a]The early behavioral intervention manual is available from the authors on request.

pation could be withdrawn at any time, and nonparticipation in the research in no way affected access to clinical care.

Pharmacologic Treatment Protocol

Participants were pharmacologically treated according to the PAFIP medication protocol, which was explained to the patient and family by the psychiatrist. At baseline, 96.8% of subjects (N = 59) had not previously received antipsychotic treatment, and 3.2% (N = 2) reported some prior treatment. The mean self-reported duration of prior treatment was 3 weeks (SD = 1.4; range, 2–4 weeks). The patients who were receiving antipsychotics at the first contact underwent a washout period of 3 to 5 days, after which they were randomly assigned to one of the antipsychotic groups. Dose ranges were 5 to 20 mg/day for olanzapine, 3 to 6 mg/day for risperidone, and 3 to 9 mg/day for haloperidol. The initial doses were progressively augmented until therapeutic effects were obtained. The medication doses could be adjusted as clinically indicated within the prescribed range, targeting the lowest effective dose while still enabling patients to receive active treatment. Patients included in the study received mean ± SD doses as follows: 13.1 ± 3.3 mg olanzapine, 4.2 ± 0.9 mg risperidone, and 4.9 ± 1.4 mg haloperidol.

Certain concomitant medications (i.e., lormetazepam and clonazepam) were used in 15 patients (24.5%) for the management of agitation, general behavior disturbances, and/or insomnia. When clinically significant extrapyramidal signs occurred, anticholinergic medication (biperiden at a dose of up to 8 mg/day) was used (N = 21; 34.4%). We did not prophylactically administer antiparkinsonian medications. Antidepressants (sertraline) (N = 1; 1.6%) were permitted in the acute treatment phase if clinically indicated. Compliance was assessed via verbal report from patients and relatives.

Study Interventions

Both interventions, EBI and RCI, were offered for a 3-month period and were undertaken in a community setting. Interventions started when patients reached a minimum clinical stabilization, defined by a global score of less than 5 on the Scale for the Assessment of Positive Symptoms (SAPS),[37] and in any case within 6 weeks of randomization.

Early behavioral intervention. EBI was intended to be a preventive, multi-component, and flexible approach tailored to the needs of this sample. The main aim of the intervention was to learn strategies to enhance control over factors associated with antipsychotic-induced weight gain such as energy intake and activity (energy expended).[2] EBI was conducted according to a manual developed by our group. Treatment comprised 10 to 14 individual sessions completed within the first 3 months of antipsychotic treatment. The structure of the sessions consisted of a weight check, agenda setting, review of self-monitoring records, and setting new homework assignments.

EBI incorporated several modules used on a case-by-case basis with careful consideration of individual relevant issues (Table 1). The following modules were flexibly offered: (1) engagement and assessment, (2) psychoeducation, (3) dietary counseling, (4) exercise program, and (5) behavior therapy. Selection of the intervention strategies to be undertaken during the intervention was based on a collaborative formulation agenda accomplished after initial assessment (Table 2).

Table 2. Characteristics of Early Behavioral Intervention (EBI) and Routine Care Intervention (RCI)[a]

Characteristic	EBI	RCI
Frequency/duration of sessions	Weekly or twice per week/approximately 40 minutes	Weekly/approximately 15 minutes
Estimated average time delay after medication onset	34.5 days	29.5 days
Treatment	Manualized protocol	Nonstructured advice on food intake and exercise
Collaborative therapeutic agenda	Yes	No
Weight monitoring graphic	Yes	No

[a]Advice was provided verbally to the RCI group, whereas in the EBI group psychoeducation included provision of written material.

Three experienced clinical psychologists (M.A.J., C.G.B., and T.P.P.) managed the therapy, and regular supervision was provided by treatment team meetings every 2 weeks. However, no formal measures of treatment fidelity were used. Attendance was used as a measure of patients' treatment compliance.

Routine care intervention. RCI was designed to provide patients with the same physical care that is offered in a comprehensive early psychosis program. Patients allocated to RCI were informed about potential weight gain and advised to increase their exercise and limit food intake. Weight monitoring strategies were also used. Sessions in the RCI group consisted of weight check, provision of nonstructured information about weight gain, and encouragement to limit food intake and/or increase physical activity. A psychiatric nurse (O.M.G.) attached to the project managed this intervention, which was designed to offer a similar frequency of therapist contact as the EBI group.

Assessments

Body weight and BMI were measured before breakfast at baseline and then weekly for 3 months. All weight measures were undertaken by a psychiatric nurse who was blind to the patients' treatment assignment. Clinical assessment instruments undertaken at baseline included the Scale for the Assessment of Positive Symptoms (SAPS),[37] the Scale for the Assessment of Negative Symptoms,[39] the 24-item Hamilton Rating Scale for Depression,[40] and the Calgary Depression Scale.[41] Assessments with the SAPS[37] were also completed weekly during the first 4 weeks and at the 6-week timepoint. Clinical ratings were completed by a psychiatrist (B.C.F.) who was blind to the patients' intervention allocations.

Statistical Analysis

Chi-square and 2-tailed Student t test were used as appropriate. Only 3 patients (4.9%) changed pharmacologic treatment before the completion of the clinical trial. These changes occurred after 9 weeks of antipsychotic treatment. Thus, intention-to-treat analysis was performed. Final statistical analysis included all the patients who completed the study.

Outcome was tested by using 3 criteria: (1) the between-group difference in body weight mean change from baseline during the trial period (difference between baseline and each time point), (2) the between-group difference in BMI mean change from baseline during the study period, and (3) the between-group difference in proportion of patients who had gained more than 7% of their baseline body weight at 3 months. Percentage of weight gain was included as an outcome measure because it has been considered more clinically meaningful and informative than change in body weight.[4,13] In particular, the percentage of patients who gain more than 7% of their baseline body weight has become an accepted metric in the field of psychiatry.[2,42] All p values are 2-tailed at the significance level of .05.

RESULTS

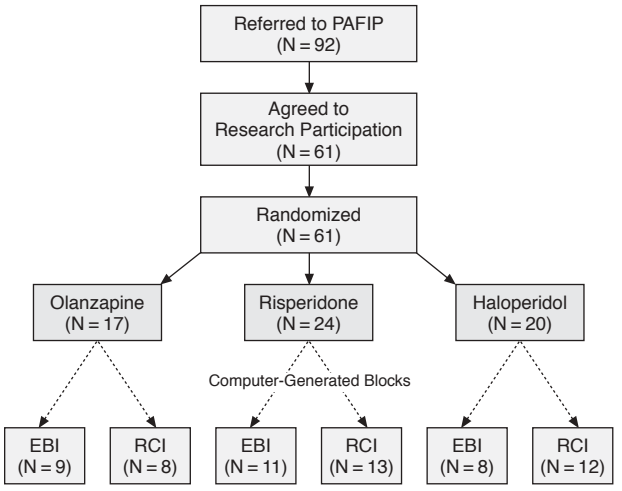
Study Sample

A total of 61 patients were recruited in the study. Initially, patients were randomly allocated to one of 3 antipsychotic treatments: risperidone (N = 24), olanzapine (N = 17), or haloperidol (N = 20). Subsequently, patients assigned to each pharmacologic treatment group were randomly assigned to the EBI group (N = 28) or the RCI group (N = 33) (Figure 1). Fifteen patients were female (24.6%), and mean age at entry was 26.8 (SD = 7.7; median = 24.2; range, 15–44) years. The baseline characteristics of the 2 intervention groups are presented in Table 3. There were no significant differences in demographic or clinical characteristics or weight/BMI values between the patients assigned to the EBI group and those allocated to the RCI group. All of the participants who were randomized completed the 3-month clinical trial protocol. Data were collected for all the patients in at least 5 assessments (baseline, 2-week, 4-week, 8-week, and 3-month).

Outcome Measures

At the endpoint of the study, significant differences between the EBI group and the RCI group in weight gain were found by using the 3 main outcome measures: body weight gain at 3 months, BMI change from baseline at 3 months, and percentage of patients whose weight increased by more than 7% of their initial weight at 3 months. Body weight/BMI changes from baseline in the 2 intervention groups are presented in Table 4.

Figure 1. Randomization of 61 First-Episode Psychosis Patients



Abbreviations: EBI = early behavioral intervention, PAFIP = Cantabria intervention program of first-episode psychosis, RCI = routine care intervention.

Table 3. Baseline Characteristics of 61 Patients Randomized to the Study[a]

Characteristic	EBI (N = 28)	RCI (N = 33)	p Value[b]
Male, N (%)	20 (71.4)	26 (78.8)	.50
Education, y	10.3 (3.4)	10.9 (4.0)	.51
Age, y	26.0 (15.5)	27.5 (8.5)	.43
Weight, kg	70.9 (13.0)	66.5 (13.2)	.20
Height, cm	170.8 (8.2)	170.2 (7.8)	.79
BMI	24.2 (4.0)	22.8 (3.6)	.15
SANS score	7.5 (7.0)	7.1 (5.5)	.81
SAPS score	12.3 (4.0)	12.9 (4.1)	.58
HAM-D score	12.2 (5.2)	12.1 (5.3)	.95
CDS score	1.3 (2.0)	1.6 (2.4)	.58

[a]Data are given as mean (SD) except where indicated otherwise.
[b]The p value for gender was derived using the χ^2 test, and all other p values were derived using the t test.
Abbreviations: BMI = body mass index (kg/m^2), CDS = Calgary Depression Scale, EBI = early behavioral intervention, HAM-D = Hamilton Rating Scale for Depression, RCI = routine care intervention, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

Between-group difference in body weight mean change. Mean body weight gain at 3 months in the EBI group and RCI group is presented in Figure 2. Patients in both groups gained weight during the 13-week trial. Nevertheless, at the end of the study, patients in the EBI group gained significantly less weight (mean = 4.1 kg; SD = 4.0; range, –5.0 to 12.2 kg) than their counterparts in the RCI group (mean = 6.9 kg; SD = 4.5; range, –2.2 to 16.4 kg) (t = –2.62, df = 59, p < .01). When antipsychotic agents were considered separately, there were differences in body weight gain between the EBI group and the RCI group in all 3 pharmacologic treatments. This difference was statistically significant in the olanzapine-treated group (EBI weight gain = 6.6 kg; SD = 2.5; range, 3.2 to 10 kg; RCI weight gain = 9.5 kg; SD = 2.8; range, 5.2 to 14.5 kg) (t = –2.23, df = 15, p < .04) and the risperidone-treated group (EBI weight gain = 3.6 kg; SD = 4.0; range, –3.0 to 12.2 kg; RCI weight gain = 7.8 kg; SD = 3.7; range, 1.9 to 7.8) (t = –2.67, df = 22, p < .01).

Between-group difference in BMI mean change. Treatment-induced change in BMI was significantly less in the EBI group (mean = 1.40 kg/m^2, SD = 1.34) than in the RCI group (mean = 2.39 kg/m^2, SD = 1.53) (t = –2.66, df = 59, p < .01). When mean change in BMI was estimated independently in the 3 different antipsychotic treatments, there were statistically significant differences between EBI and RCI groups receiving olanzapine (EBI mean gain = 2.35 kg/m^2, SD = 0.92; RCI mean gain = 3.35 kg/m^2, SD = 0.89) (t = –2.25, df = 15, p < .03) and risperidone (EBI mean gain = 1.15 kg/m^2, SD = 1.22; RCI mean gain = 2.62 kg/m^2, SD = 1.23) (t = –2.93, df = 22, p < .008).

Between-group difference in percentage of weight gain. The EBI and RCI groups were also compared at the end of the clinical trial on the percentage of weight gain (Figure 3). Fewer patients in the EBI group (N = 11; 39.3%) than in the RCI group (N = 26; 78.8%) increased their initial body weight by more than 7%, the cutoff for clinically significant weight gain,[2,42] which was a significant difference (χ^2 = 9.90, df = 1, p < .002). In the analysis carried out among pharmacologic treatment groups, we obtained similar findings, with significant differences between intervention groups in those receiving olanzapine and risperidone. In the olanzapine treatment group, 100% (8/8) of the patients allocated to the RCI group gained more than 7% of their initial weight compared to 66.7% (6/9) in the EBI group (χ^2 = 3.6, df = 1, p < .05). In the risperidone treatment group, 84.6% (11/13) of the patients in the RCI group gained more than 7% of their initial weight as compared with 27.3% (3/11) in the EBI group (χ^2 = 8.06, df = 1, p < .005).

Pattern of weight gain during the 3 months of follow-up. Mean change in body weight of patients in the EBI group and in the RCI group over the 3-month follow-up clinical trial is presented in Figure 4. It is notable that the between-group difference in changes from baseline had already emerged by the sixth week of the trial for both weight (mean difference = –1.21 kg, SD = 0.85) and BMI (mean difference = –0.43 kg/m^2, SD = 0.29); these differences reached the level of statistical significance by the second month (Table 4), only 3 weeks after the mean time delay before the beginning of EBI, which was estimated as 34.5 days.

DISCUSSION

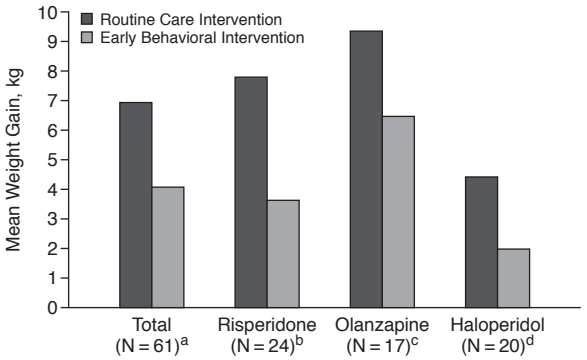
This is the first randomized controlled trial, to the best of our knowledge, that has been conducted to test the

Table 4. Change in Weight and Body Mass Index Over 3 Months for 61 First-Episode Psychosis Patients Randomly Allocated to Either Early Behavioral Intervention (EBI) or Routine Care Intervention (RCI) for Attenuation of Antipsychotic-Induced Weight Gain

	Change From Baseline							
	Weight (kg)				Body Mass Index (kg/m^2)			
Week	EBI (N = 28), Mean (SD)	RCI (N = 33), Mean (SD)	t[a]	p Value[a]	EBI (N = 28), Mean (SD)	RCI (N = 33), Mean (SD)	t[a]	p Value[a]
2	1.45 (3.49)	1.50 (1.64)	–0.07	.93	0.47 (1.16)	0.51 (0.58)	–0.18	.85
4	2.76 (3.29)	2.91 (2.53)	–0.19	.84	0.93 (1.07)	1.01 (0.88)	–0.28	.77
6	3.25 (3.22)	4.47 (3.10)	–1.42	.15	1.11 (1.08)	1.54 (1.08)	–1.49	.14
8	3.43 (3.64)	5.67 (3.85)	–2.21	< .03	1.17 (1.21)	1.97 (1.35)	–2.30	< .02
13	4.10 (3.99)	6.98 (4.50)	–2.62	< .01	1.40 (1.34)	2.39 (1.53)	–2.66	< .01

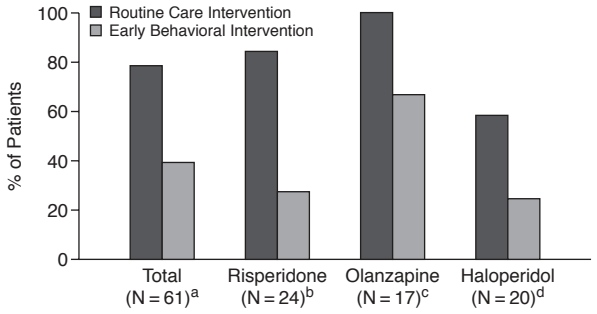
[a]For the between-group differences in change from baseline.

Figure 2. Mean Change in Body Weight of Patients in Early Behavioral Intervention and Routine Care Intervention Groups After 3 Months of Antipsychotic Treatment



Difference between treatment conditions:
[a]t = –2.62, df = 59, p < .01.
[b]t = –2.67, df = 22, p < .01.
[c]t = –2.23, df = 15, p < .04.
[d]t = –1.1, df = 18, p = .28.

Figure 3. Percentage of Patients Who Gained More Than 7% of Their Initial Weight After 3 Months of Antipsychotic Treatment in Early Behavioral Intervention and Routine Care Intervention Groups



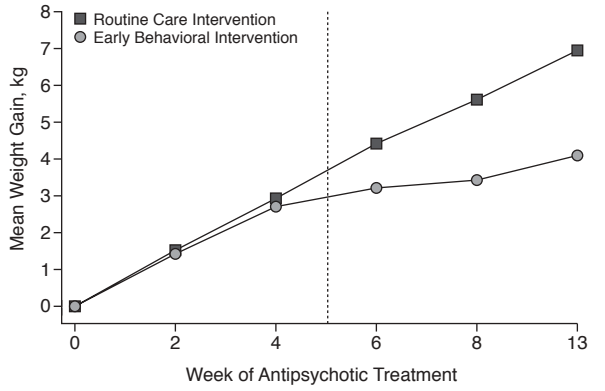
Difference between treatment conditions:
[a]χ^2 = 9.90, df = 1, p < .002.
[b]χ^2 = 8.06, df = 1, p < .005.
[c]χ^2 = 3.6, df = 1, p < .05.
[d]χ^2 = 2.15, df = 1, p = .14.

effectiveness of a specific behavioral intervention designed to prevent antipsychotic-induced weight gain in a first-episode psychosis sample. This study confirms, on the one hand, that antipsychotic treatment is associated with substantial weight gain in patients suffering from psychosis beginning in the first weeks of antipsychotic treatment and shows, on the other hand, that an early behavioral intervention (EBI) is effective in lessening antipsychotic-induced weight gain in a first-episode psychosis cohort that had minimal previous treatment with antipsychotic medication.

Whereas participants in both groups increased their body weight, patients in the EBI group gained significantly less weight (mean = 4.1 kg, SD = 4.0) than those allocated to the RCI group (mean = 6.9 kg, SD = 4.5; p < .01) during the 3 months of follow-up. Similar findings were obtained when both groups were compared on treatment-induced change in BMI, which was significantly less in the EBI group than in the RCI group (1.40 vs. 2.39 kg/m^2; p < .01). Accordingly, significantly fewer patients in the EBI group (N = 11; 39.3%) than in the RCI group (N = 26; 78.8%; p < .002) increased their baseline weight by more than 7%, which has been considered the cutoff for clinically meaningful weight gain.[2,42]

Some previous studies have suggested that behavioral interventions might be effective on weight control in patients taking antipsychotics. Aquila and Emanuel[34] suggested, in a retrospective study of 32 inpatients, that weight gain was controlled over a year by a combination of diet, nutrition, and education. There are also data in outpatient settings suggesting the utility of weight control programs. Wirshing et al.[30] reported in a retrospective analysis of males with schizophrenia some moderation of weight gain. In that study, a stepwise intervention including diet, education, exercise, and group support was tested. Consistent with these findings, Menza et al.[27] have recently shown in a prospective study that a 12-month weight control program focused on nutrition, exercise, and motivation resulted in clinically significant reductions in weight, BMI, and other risk factors for long-term poor health. The sample of this study consisted of patients with schizophrenia treated with atypical antipsychotics.

Figure 4. Mean Change in Body Weight of Patients in Early Behavioral Intervention and Routine Care Intervention Groups During 3 Months of Antipsychotic Treatment[a]



[a]Dashed line indicates mean time delay before the beginning of early behavioral intervention (34.5 days).

More than half of participants (20 of the 31 subjects) completed the program, suggesting that patients with chronic schizophrenia were able to adhere to this type of weight control program. Nevertheless, none of these previous studies have used randomization techniques, so they could not control nonspecific effects and thus allow firm conclusions about the efficacy of the interventions. Furthermore, the studies' samples comprised chronic patients with previous or concomitant treatments.

The present study displays, for the first time, the effectiveness of these interventions in a drug-naive first-episode psychosis cohort when it is feasible to prevent weight gain and its consequences. The intervention was initiated in many cases before the presence of weight gain, so the aim of the intervention was not to produce weight loss in obese patients but to minimize this side effect before it appears. This seems to be a more practical intervention strategy given that, according to a recent review, up to 80% of patients taking antipsychotic medication will end up being overweight.[43,44] It is also noteworthy that young patients displayed a good attitude toward this preventive approach. That 100% follow-up was achieved supports the good adherence of the sample, since there is usually a high correlation between adherence to different aspects of clinical care.[45]

Strengths in the design of the present study included randomized treatment allocation with intention-to-treat analysis. Most of the studies of antipsychotic-induced weight gain use the last-observation-carried-forward technique in preference to intention-to-treat analysis to estimate weight gain over a time period. A recent review suggests that this approach can produce marked underestimates of the magnitude of weight gain and therefore should be avoided.[2] Other methodological strengths of the study include use of assessors who were blind to the patients' assigned treatment group; use of manual-based treatment; comparison of EBI with appropriate physical care, controlling for therapist contact; use of 3 main outcome measures, including BMI and percentage changes; and monitoring of prescribed medication. Finally, the design allowed for assessing differential weight gain among medications.

An obvious limitation of this study is the short duration of the trial. However, EBI was designed to address the critical period of antipsychotic-induced weight gain. In general, the literature indicates that the majority of weight gain occurs during the first 3 months.[4,46–48] In olanzapine treatment, the rate of weight gain appears to be most rapid during the first 12 weeks and trends toward a plateau after approximately 39 weeks of treatment.[18] During these first 3 months, approximately 70% of weight gain occurs.[2,18] With respect to risperidone, it appears that average weight gain reaches a plateau around weeks 8 to 12 and then remains around this level.[13,17,18] Regardless, it remains to be studied whether a longer EBI intervention will be associated with further attenuation in weight gain. In addition, the long-term effect of EBI compared to RCI has to be clarified. Some studies have suggested that energy restriction may lead to short-term weight control, and a regular exercise regimen may be required to maintain the long-term achievements.[49] While this study was not designed to address these long-term issues, the outcomes suggest that these interventions should be explored in longer follow-up studies.

A second limitation is that we could not assess the relative contributions of the different components of the early intervention. EBI adopted a formulation-based approach, so the intervention was performed according to the evaluation of individual weight gain risk factors. Nevertheless, future studies should monitor the balance between caloric intake and caloric expenditure in an attempt to obtain information about the impact of the intervention on lifestyle, regular exercise, and intake to elucidate the effective components of EBI. Another limitation of this study is that we draw no conclusions on whether the particular antipsychotic that patients take affects the attenuation of weight gain achieved with EBI. This issue is of interest since there has been considerable debate on the relative risk of weight gain attributable to various antipsychotics. Nonetheless, this analysis was limited by the sample size and thus had little power to detect differences between drugs. It would require a considerably larger study for the purpose of testing this hypothesis.

Our study has shown promising findings in a relevant, but quite often neglected, problem. According to our results, it is possible to attenuate antipsychotic-induced weight gain in drug-naive young patients by using behavioral techniques. Further challenges include studying the long-term effect and cost-effectiveness of these interven-

tions as well as their impact on other central clinical aspects such as compliance with medication, clinical symptoms, quality of life, and physical health.

Drug names: biperiden (Akineton), clonazepam (Klonopin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), sertraline (Zoloft).

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