Comprehensive Nutrition Care to Prevent Bodyweight Gain and Metabolic Dysfunction Associated with Olanzapine Treatment

Serge Beaulieu, M.D, Ph.D [1,3]., Marilyn Rabin, P.DT [1]., Caryn Roll, P.DT [1]., Isabel Losna, P.DT [1]., Trino Baptista, M.D, Ph.D [1]., Marc-Alain Wolf, M.D [1,3]., Pierre Assalian, M.D [2,3]., Raymond Tempier, M.D MSc FRCPC [2,3]., Gustavo Turecki, M.D, Ph.D [1,3].
Douglas Hospital Research Center [1], McGill University Health Center [2], Dept. of Psychiatry, McGill University [3], 6875 LaSalle Blvd, Verdun, Québec, Canada, H4H1R3 - Fax: (514) 888-4064 - E-mail: rabmar@douglas.mcgill.ca

ABSTRACT

OBJECTIVE: To assess the impact of an intensive nutrition program on bodyweight and serum levels of glucose, insulin and leptin in olanzapine-treated outpatients.

METHOD: Nineteen subjects diagnosed with schizophrenia (DSM-IV) already treated with olanzapine and recruited from our out-patient clinics received 12 individual medical nutrition therapy sessions and 12 group cooking sessions carried out by dietitian/nutritionists during 6 months (Intervention Group, IG). Nine subjects also with schizophrenia, in the control group were weighed monthly (Non-Intervention group, NIG). Bodyweight, glucose and hormones were assessed at baseline and at the end of the study.

RESULTS: Ten subjects in the IG and 6 in the NIG completed the study. The bodyweight change respectively was – 0.7 ± 12.8 and 7.8 ± 8.0 lbs after 6 months. One subject developed diabetes mellitus and 1 abnormal fasting glucose levels in the NIG, whereas glucose levels remained unchanged in the IG. Leptin and insulin levels were numerically elevated in the NIG but the figure did not reach statistical significance.

CONCLUSIONS: A comprehensive nutrition care program at the initial stages of treatment may prevent olanzapine effects on bodyweight and carbohydrate metabolism. This study waits for replication in newly treated olanzapine patients.

INTRODUCTION

Prevention and treatment of excessive bodyweight gain (BWG) and metabolic dysfunction associated with antipsychotic (AP) treatment are important challenges in modern psychopharmacology (1). Agents such as amantadine, nizatidine, metformin, topiramate and orlistat are under active investigation. These drugs are not devoid of relevant side effects, and some are expensive, which makes treatment compliance a difficult issue in many psychiatric patients (1). Therefore, medical nutrition therapy, psycho-educational assistance and guided physical activity must also be used in this special clinical population. Even though some preliminary programs designed to counteract AP-induced BWG have been proposed (2,3), none included extensive nutrition counselling by qualified professional dietitian-nutritionists along with metabolic assessment.

Olanzapine administration has been associated with BWG, and increase in the serum levels of glucose, insulin and leptin (4-6). The purpose of this study was to evaluate whether intensive nutrition care carried out by dietitians might prevent or lessen the impact of olanzapine on BWG and relevant metabolic variables.

METHODS

The study was conducted at Douglas Hospital Research Center, Verdun, Quebec, Canada. The protocol was approved by the Douglas Hospital and MUCH Research Ethics Committees and an informed consent was obtained from each subject. Subsequently, olanzapine-treated patients admitted to the outpatient clinic and willing to participate in the study were randomly assigned to an "Intervention" or to a "Non-Intervention" group. Exclusion criteria included being less than 18 years old; simultaneous treatment with oral contraceptives, hormone replacement therapy, anticonvulsants and any other AP besides olanzapine; abusing alcohol or street drugs (as determined by a urine drug screen) and medical conditions such as end-stage renal disease, diabetes, pancreatitis, liver disease, cancer, anorexia/bulimia, blindness, and thyroid disorder.

Two groups were configured: the first group received nutrition care (intervention group, IG); the second one did not receive any specific nutrition intervention (NIG). The IG participated in 12 individual medical nutrition therapy sessions and 12 group-cooking sessions carried out by the dietitian-nutritionists in charge of this study (MR, CR and IL). Individual sessions lasted 30-60 minutes and were conducted every week for 6 months. Patients in this group were assessed when entering the program, and then at a 6-month interval. Bodyweight, height, body mass index (BMI = bodyweight in kg/height in squared meters) and percentage of body fat assessed by the Tanita Body Composition Analyzer were obtained at each visit, along with a fasting blood sample in order to assess the serum levels of leptin, insulin and glucose.

The NIG was evaluated monthly to determine the BMI without any additional intervention. Blood samples were obtained in a similar way as in the intervention group

Serum leptin and insulin levels were measured by radioimmunoassay with commercial kits from Linco (MO, USA) and ICN (CA, USA) respectively. Inter- and intra-assay variability was < 10% for both hormones. Glucose was assessed with an enzymatic method from Sigma (MO, USA).

Sex distribution was analyzed by the chi-squared test with the Yates' correction for 1 degree of freedom. Since variables were non-normally distributed, bodyweight, percentage of body fat and serum variables within each group were compared with the Wilcoxon Z test for paired samples. Between group comparisons were conducted with the Mann-Whitney U test. Bivariate correlation was conducted with the Spearman test. Data is expressed as mean ± standard deviation. Results were considered significant when p < 0.0 5.

RESULTS

- Detailed food and nutrition assessments revealed a catalogue of unhealthy eating practices both prior to olanzapine treatment and at the start of olanzapine treatment (**Table 1**).

Table 1. Catalogue of unhealthy nutrition and lifestyle practices prior to nutrition intervention

OUT OF 10 PATIENTS	EACH DAY
1	Skipped breakfast
0	Skipped lunch
10	Failed to balance meals with a serving of food from each of the four major food groups
9	Prepared food with additional fat at every meal
0	Ate before going to sleep
0	Ate 0-1 servings of whole grain products
5	Ate 0-1 fruit servings as whole fruit
5	Ate 0-1 vegetable servings
10	Drank 0 cups of milk
10	Ate 0 servings of yogurt
8	Ate 0 servings of cheese
0	Ate 1 serving of alternatives to meat, such as legumes (tofu, chickpeas, lentils, soy beverage, flaxseed or quinoa)
9	Ate 1 serving of fried chicken sausages, cold cuts, poutine or frankfurters
9	Ate candy, chocolate bars, cake, cookies or muffins
3	Drank 1-2 litres of diet or regular cola beverages, koolaid
3	Drank juice instead of eating whole fruit
0	Drank more than 4 cups of coffee
1	Drank too much fluid; more than 2 litres
6	Exercised less than 30 minutes
3	Smoked cigarettes

- Subjects met with the dietitian and received detailed information about:
  1) foods with special health benefits (following Canada's Food Guide to Healthy Eating),
  2) appropriate grain products, vegetables and fruit, milk products, meat and alternatives,
  3) adequate fluid intake,
  4) fat,
  5) portion sizes,
  6) snacks,
  7) dietary fiber,
  8) ideal breakfast time,
  9) meal constituents, and
  10) healthy eating on a restricted budget.
- The group sessions focused on medication and food interaction, perils of dieting and food restriction and how to plan a menu and prepare healthy palatable recipes.
- The results of the first six months of treatment are presented. Twenty-eight patients diagnosed with schizophrenia (DSM-IV) were randomly selected to participate in either the intervention (IG) or non-intervention group (NIG). Ten subjects in the IG and 6 in the NIG completed the study at 6 months.
- Age (years) was similar in both groups: 38.8 ± 10.6 vs. 44.1 ± 8.3, U = 0.9, p = 0.3. Gender distribution was as follows: IG, 4 men and 6 women; NIG, 5 men and 1 women: c2 (1) = 2.5, p = 0.3.
- In both groups, the subjects who dropped out from the study were those who had ceased to be treated with olanzapine and no longer wanted to participate.
- All subjects were receiving olanzapine before entering the study, but both groups (IG and NIG) did not differ in the olanzapine dose (12.8 ± 8.2 vs. 9.3 ± 5, U = 23, p = 0.4) and duration in months of this treatment (11.7 ± 8.1 vs. 14.6 ± 9.7, U = 29, p = 0.9). Subjects in the IG had gained more weight than those in the NIG group before entering the study (Table 4).
- A high variability in BWG was observed during the study:

1) Seven out of 10 subjects in the IG lost BW, whereas 5 out of 6 patients in the NIG gained BW. Collectively, the BW change (lbs.) was - 0.7 (p = 0.33) and + 7.8 (p = 0.075) in the IG and NIG respectively (**Table 2** within subject comparisons).

Change in bodyweight, body fat, glucose, leptin and insulin after Olanzapine administration

		Initial	Final	Δ	z(p)
Bodyweight under olanzapine before starting the program	IG	172.2 ± 36	189.7 ± 52	17.5 ± 20.8	2.1 (0.037)
	NIG	183.5 ± 20.1	191.3 ± 14.8	7.6 ± 22.4	0.9 (0.3)
Bodyweight gain under olanzapine during 6 months of the program	IG	189.7 ± 52	189.0 ± 49.1	-0.7 ± 12.8	0.9 (0.3)
	NIG	191.3 ± 14.8	199.0 ± 15.5	7.8 ± 8.0	1.78 (0.075)

IG = Intervention group; NIG = non-intervention group
Δ = Change between initial and final conditions during the 6-month program;
z = Statistic of the Wilcoxon test for paired samples.

2) In addition, the percentage of body fat significantly increased in the NIG (p = 0.028) and did not change in the IG (p = 0.3) (**Table 3**).

		Initial	Final	Δ	z(p)
Percentage of body fat during 6 months of the program	IG	33.1 ± 8.6	33.1 ± 8.5	1.9 ± 8.3	0.9 (0.3)
	NIG	28.2 ± 10	31.1 ± 10.6	11.6 ± 34.1	2.2 (0.028)

IG = Intervention group; NIG = non-intervention group
Δ = Change between initial and final conditions during the 6-month program;
z = Statistic of the Wilcoxon test for paired samples.

3) At baseline (i.e. at study entry), all subjects had normal fasting glucose levels (< 6.1 mmol/L) which remained in this range in the IG. However, in the NIG, 1 subject developed diabetes mellitus (glucose = 11.2 mmol/L) and one developed abnormal fasting glucose levels (glucose = 6.6 mmol/L) (**Table 4**).

		Initial	Final	Δ	z(p)
Serum glucose levels under olanzapine during 6 months of the program	IG	5.05 ± 0.5	5.01 ± 0.9	-0.004 ± 0.6	0.1 (0.8)
	NIG	5.4 ± 0.35	6.4 ± 2.5	0.9 ± 2.1	0.7 (0.4)

IG = Intervention group; NIG = non-intervention group
Δ = Change between initial and final conditions during the 6-month program;
z = Statistic of the Wilcoxon test for paired samples.

4) Even though plasma leptin and insulin levels numerically increased in the NIG, these results did not reach statistical significance (**Table 5**).

		Initial	Final	Δ	z(p)
Serum leptin levels under olanzapine during 6 months of the program	IG	18.2 ± 11.8	18.9 ± 9.7	1.9 ± 8.3	0.6 (0.5)
	NIG	16.6 ± 18.1	25.5 ± 29.4	11.6 ± 34.1	0.1 (0.8)
Serum insulin levels under olanzapine during 6 months of the program	IG	24.1 ± 11.1	21.9 ± 10.6	-1.6 ± 10.2	0.2 (0.7)
	NIG	29.2 ± 17.3	48.4 ± 58.6	19.2 ± 42.8	0.9 (0.3)

IG = Intervention group; NIG = non-intervention group
Δ = Change between initial and final conditions during the 6-month program;
z = Statistic of the Wilcoxon test for paired samples.

DISCUSSION

- This was an intensive and comprehensive program that contrasts with the study by Nguyen et al. (3) that consisted of educational sessions lasting between 2-5 min at each visit. In our study, individual sessions were 30 min, while the group lessons were 60 min. The favourable outcome seems to be due to the fact that participants made reasonable adjustments to their eating habits with continuous guidance from dietitians specializing in Nutrition Care for Mental Health. **The importance of this study is that it demonstrates that dietitians are key contributors in health promotion and disease prevention in the initial stages of olanzapine treatment (11).**
- **Participants receiving comprehensive nutrition care showed no change in BW and percentage of body fat after 6 months of olanzapine administration.** A high variability in the magnitude of BWG during AP administration has been observed (4), and it is partially related to genetic factors (7). For olanzapine, BWG was estimated by meta-analysis at 8.3 lbs after 10 weeks of treatment (8). A follow-up study of 573 olanzapine-treated patients reported a BWG of 13.8 lbs after 2.54 years of treatment and the BWG reached a plateau after the first 39 weeks of treatment (4). The NIG displayed a BWG of 7.8 lb, which reached marginal statistical significance in the within group comparison (p = 0.07). In addition, the NIG showed a significant increase in body fat. Thus, it appears that this type of nutrition program helps to counteract the tendency of olanzapine to induce BWG.
- A similar trend was observed with the metabolic variables. **Leptin levels, which reflect the degree of BWG and adiposity remained unchanged in the IG, and showed a small increase in the NIG.** Glucose and insulin levels were particularly important in this study, because administration of some atypical APs such as clozapine and olanzapine has been associated with an increased frequency of diabetes mellitus (DM) (6). These serum variables are also an indicator of the degree of insulin resistance, which also plays a prominent role in BW regulation (9).
- **In the NIG, one subject developed Diabetes Mellitus and another showed abnormal fasting glucose levels, whereas glucose levels remained unchanged in the IG.** Both subjects had normal fasting glucose levels before entering the study. While it is not possible to attribute with confidence the positive effects of the nutrition program on carbohydrate metabolism in these olanzapine-treated patients, a large body of data supports the impact of nutrition and physical activity in the prevention or delay of DM in high-risk subjects (10).
- An important limitation of this study is that the patients were receiving olanzapine before starting the program and were already beyond the postulated period of maximal risk for BWG (4). In fact, the subjects in the IG had significantly gained BW before starting the study. Therefore, it may be speculated that they were studied during the plateau of BWG during olanzapine administration. However, the BMI was remarkably similar in both groups at baseline, and the BWG in the IG was close to 0 lbs, contrasting with a numerical increase in the NIG. This suggests a true action of the nutritional intervention, which is also reinforced by the positive effects on carbohydrate metabolism.

REFERENCES

1. Werneke U, Taylor D, Sanders TAB. Options for pharmacological management of obesity in patients treated with atypical antipsychotics. Int Clin Psychopharmacol 2002; 17: 145–160.
2. Aquila R. Management of weight gain in patients with schizophrenia. J Clin Psychiatry 2002;63(suppl 4):33-36.
3. Nguyen CT, Ortiz T, Franklin D, Maguire G. Nutritional education in minimizing weight gain associated with antipsychotic therapy. Department of Psychiatry and Human Behavior, University of California, Irvine. Presented at American Psychiatric Association (APA) May 5-10, 2001 New Orleans.
4. Kinon BJ, Basson BR, Gilmore JA, Tollefson GD: Long-term olanzapine treatment: weight change and weight-rxelated health factors in schizophrenia. J Clin Psychiatry 2001; 62: 92–100.
5. Elkerson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000; 61: 742-749.
6. Henderson DC. Atypical antipsychotic-induced diabetes mellitus. How strong is the evidence? CNS Drugs 2002; 16: 77-89.0
7. Reynolds GP, Zhang ZJ, Zhang XB. Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism. Lancet 2002; 359: 2086-2087.
8. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1686–1896.
9. Baptista T, NG Ying Kin NMK, Beaulieu S, Araujo de Baptista E. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. Pharmacopsychiatry 35: 204-219, 2002.
10. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N Engl J Med 2001; 344: 1343-1350.
11. Psychiatric Disorders. Manual of Clinical Dietetics. American Dietetic Association, Dietitians of Canada, 2000; 46:573-578.

SUPPORTED BY AN INVESTIGATOR-INITIATED TRIAL GRANT FROM ELI-LILLY CANADA TO M.R., S.B. AND MAW.

PRESENTED AT THE FIFTH INTERNATIONAL CONFERENCE ON BIPOLAR DISORDER, PITTSBURGH, PENNSYLVANIA, JUNE 12-14, 2003.