ORIGINAL ARTICLE

Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine

Manejo do ganho de peso em pacientes portadores de esquizofrenia durante o tratamento com olanzapina em associação com nizatidina

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Abstract

Objective: *Weight gain is associated with treatment with many psychotropic agents. Nizatidine, H2 receptor antagonist, has been proposed to have weight-reducing effects. This was a 12-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of nizatidine in reducing/limiting weight gain in patients with schizophrenia who have been under treatment with olanzapine.* ***Method:*** *Patients receiving olanzapine (2 to 6 months) and weight gain ≥ 5% of their body weight during olanzapine treatment were randomly assigned to receive nizatidine 600 mg or placebo for up to 12 weeks. Change in psychopathology was assessed using Brief Psychiatric Rating Scale scores from baseline to endpoint. Safety was assessed using the Safety Assessed Software, assessment of glucose and lipid blood levels, and treatment-emergent adverse events.* ***Results:*** *Out of 54 patients enrolled in this analysis, 45 completed the protocol. The mean weight change prior randomization was 7.6 kg and 7.3 kg for those randomized to placebo and nizatidine, respectively (p = 0.828). Patients receiving placebo and nizatidine had a mean weight gain of 12.3% (0.7 kg) and 12% (1.1 kg) from baseline to endpoint, respectively (p = 0.9). Patients from both groups experienced a statistically significant decrease on the Brief Psychiatric Rating Scale mean score from baseline to endpoint. Treatment-emergent adverse events were reported by 18.5% and 25.9% on the placebo and nizatidine group, respectively. There were no statistically significant differences in glucose and lipid blood levels from baseline to endpoint and between groups.* ***Conclusions:*** *The concomitant use of olanzapine with nizatidine was not effective in controlling weight gain in patients who had previously gained weight during treatment with olanzapine when compared to placebo.*

Descriptors*: Schizophrenia; Antipsychotics agents; Weight gain; Clozapine; Nizatidine*

Resumo

Objetivo: *Ganho de peso está associado ao tratamento com inúmeros psicotrópicos. O uso de nizatidina, um antagonista H2, pode estar associado à redução de peso. Este foi um ensaio clínico aleatorizado, duplo-cego, controlado com placebo, de 12 semanas, desenhado para avaliar a eficácia da nizatidina em reduzir/limitar o ganho de peso em pacientes com esquizofrenia recebendo olanzapina.* ***Método:*** *Pacientes recebendo olanzapina (entre dois e seis meses) e com ganho de peso ≥ que 5% desde o inicio do tratamento foram aleatorizados para receber nizatidina 600 mg ou placebo. Alterações psicopatológicas foram avaliadas usando-se a* Brief Psychiatric Rating Scale *total. A segurança foi avaliada por meio da pontuação na* Safety Assessed Software*, avaliação dos valores de glicemia e lipídios e a incidência de eventos adversos decorrentes do tratamento.* ***Resultados:*** *Dos 54 pacientes incluídos na análise, 45 completaram o protocolo. A alteração média de peso antes da aleatorização foi de 7,6 kg e 7,3 kg nos pacientes aleatorizados para placebo e nizatidina, respectivamente (p = 0,828). Pacientes recebendo placebo e nizatidina tiveram, respectivamente, ganho médio de peso de 12,3% (7 kg) e 12% (1,1 kg) ao longo do estudo (p = 0,9). Ambos os grupos apresentaram diminuição estatisticamente significativa na pontuação média da* Brief Psychiatric Rating Scale*. Eventos adversos emergentes do tratamento foram relatados por 18,5% e 25,9% dos pacientes recebendo placebo e nizatidina, respectivamente. Não houve diferença estatisticamente significativa nos níveis glicêmicos e lipídicos do início ao final do estudo ou entre os grupos de tratamento.* ***Conclusões:*** *Comparado ao placebo, o uso concomitante de olanzapina e nizatidina não foi eficaz em controlar o peso em pacientes com ganho prévio de peso durante o tratamento com olanzapina.*

Descritores*: Esquizofrenia; Agentes antipsicóticos; Ganho de peso; Clozapina; Nizatidina*

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Introduction

According to the mental health supplement of the National Health Interview Survey,[1] body mass index (BMI) distribution of schizophrenic individuals is generally similar to or higher than that of the general population, and weight changes in schizophrenic patients were well documented even in the pre-antipsychotic drug era.[2] The reported prevalence of overweight and obesity in patients with schizophrenia has been found to range from 40% to 62%,[3-7] and obesity is a complicating factor in many medical illnesses commonly seen in patients with schizophrenia.[8-9] Atypical antipsychotics are associated with superior tolerability, compliance, and relapse prevention and have led to improved treatment for patients with serious mental illness.[10] However, novel antipsychotics apparently produce an even greater weight gain when compared to typical agents.[11-13] A recent meta-analysis of over 80 studies on weight change during antipsychotic treatment showed a mean weight gain after 10 weeks of treatment of 9.8 lb (4.45 kg) with clozapine, 9.1 lb (4.15 kg) with olanzapine, and 4.6 lb (2.10 kg) with risperidone compared to 2.4 lb (1.08 kg) with the typical antipsychotic haloperidol.[11] Many theories (including increased food intake[14-15] have been advanced to explain the antipsychotic-related weight gain in schizophrenia.[16-17] Recently, serotonin, dopamine, and histamine receptor blockade has been implicated.[18-19] In this manuscript, it is of particular interest the role of histamine in the regulation of appetite and satiety as it is well known that atypical antipsychotics have a much greater affinity to the H-1 receptor when compared to typical medications.[20] This fact is consistent with the hypothesis that effects on histamine may contribute to atypical antipsychotic-treatment associated weight gain. Cimetidine, an H-2 receptor antagonist, has been reported to reduce weight in overweighed healthy subjects,[21] and also in overweighed type 2 diabetes mellitus patients,[22] although this finding has not been unequivocal.[23-24] Gastrointestinal regulatory peptides, such as cholecystokinin, have been proposed to mediate the satiety signal from gut to brain. In normal subjects, cimetidine increased the basal cholecystokinin and may be one mechanism by which it reduces the appetite. A report by Sacchetti et al. described a patient with repeated episodes of weight gain during olanzapine treatment who experienced weight reduction after 4 to 5 weeks of therapy with nizatidine (150 mg BID), an H-2 antagonist.[25] In a 16-week double-blind trial, Cavazzoni et al. reported significantly less weight gain at weeks 3 and 4 with olanzapine+nizatidine 300 mg BID compared to olanzapine+placebo, although no statistical difference between groups was seen at 16 weeks.[26] In that study, nizatidine was well-tolerated and did not adversely affect clinical outcomes. In an open-label study, Lopez-Mato et al. described that ranitidine also prevented or corrected weight gain in patients receiving olanzapine.[27]

The studies by Cavazzoni et al. and Lopez-Mato et al. showed that H2 antagonists may prevent or reduce weight gain when initiated concomitantly with olanzapine treatment.[26-27] During the treatment with olanzapine, approximately 25% of schizophrenic patients has a decrease in body weight or gain no weight.[28] In those individuals, a pharmacological approach to control weight gain is certainly not recommended. According to a review by Kinon et al., approximately 48% of olanzapine-treated patients gain less than 7%.[28] For these patients, behavioral and dietary changes may suffice to manage their body weight changes and no pharmacological approaches would be necessary.[28] The purpose of the present study was to evaluate whether the use of an H2 antagonist in schizophrenic patients who have already gained weight could promote stabilization or reduction in body weight. Additionally, patients were considered responders if remained in therapy for 6 weeks or more and had no weight gain or a weight gain ≤ 3% since started using nizatidine (baseline). Non-responders were defined as any patients who failed to remain at least 6 weeks in the study and had gained > 3% since starting treatment with nizatidine. Possible effects of nizatidine on psychopathology and safety parameters were also assessed.

Method

1. Sample

Outpatient subjects (male or female, 18 to 65 years of age) met DSM-IV[29] diagnostic criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. After a complete description of the study to the subjects, written informed consent was obtained. In order to be eligible to participate in this protocol, patients had to be in treatment with olanzapine (5 to 20 mg/day) for no less than 2 months and no more than 6 months, had a record of their body weight when initiated on olanzapine, had gained ≥ 5% since initiated the treatment with olanzapine, and had a total BPRS score < 45. Patients were excluded if they had any known physical illness that could affect body weight and composition, were currently participating in a formal weight loss program, or had a body mass index (BMI) ≥ 40 kg/m^2 or weight ≥ 114 kg. Patients with a diagnosis of diabetes mellitus could be enrolled provided their condition was under control and if they were in treatment for DM for at least 6 months. The study protocol was approved by Hospital Mario Kroëff Ethical Review Board on the 28th November 2002.

2. Study design

This was a randomized, double-blind, 12-week placebo-controlled trial. After a complete description of the study to the subjects, written informed consent was obtained. After baseline assessments, all eligible patients were randomized to receive placebo (PBO) or 300 mg nizatidine BID (NIZ). This study had a total of 4 follow-up interviews and assessments were performed in a monthly basis. Figure 1 shows the study design.

3. Assessments

Patients were weighed at each visit. All investigators were given detailed instruction at study start-up on uniform and consistent weight measurements. Psychopathology was assessed using the total score of the 18-item Brief Psychiatric Rating Scale (BPRS; each item rated from 1 to 7).[30] Safety parameters were assessed by treatment-emergent adverse events, routine laboratory analytes, and extrapyramidal symptoms (EPS), measured by the total score of the Simpson–Angus Scale.[31] Treatment-emergent adverse events were considered those that worsened or were described for the first time after initiating the treatment with nizatidine.

4. Statistical analysis

A mixed-effects model for repeated measures analysis of variance (ANOVA) was used to analyze the primary outcome measure (i.e. mean changes in total body weight from baseline to endpoint) and other continuous data. When the distribution was not normal, it was used the Mann-Whitney non-parametric test. For the comparison between responders and non-

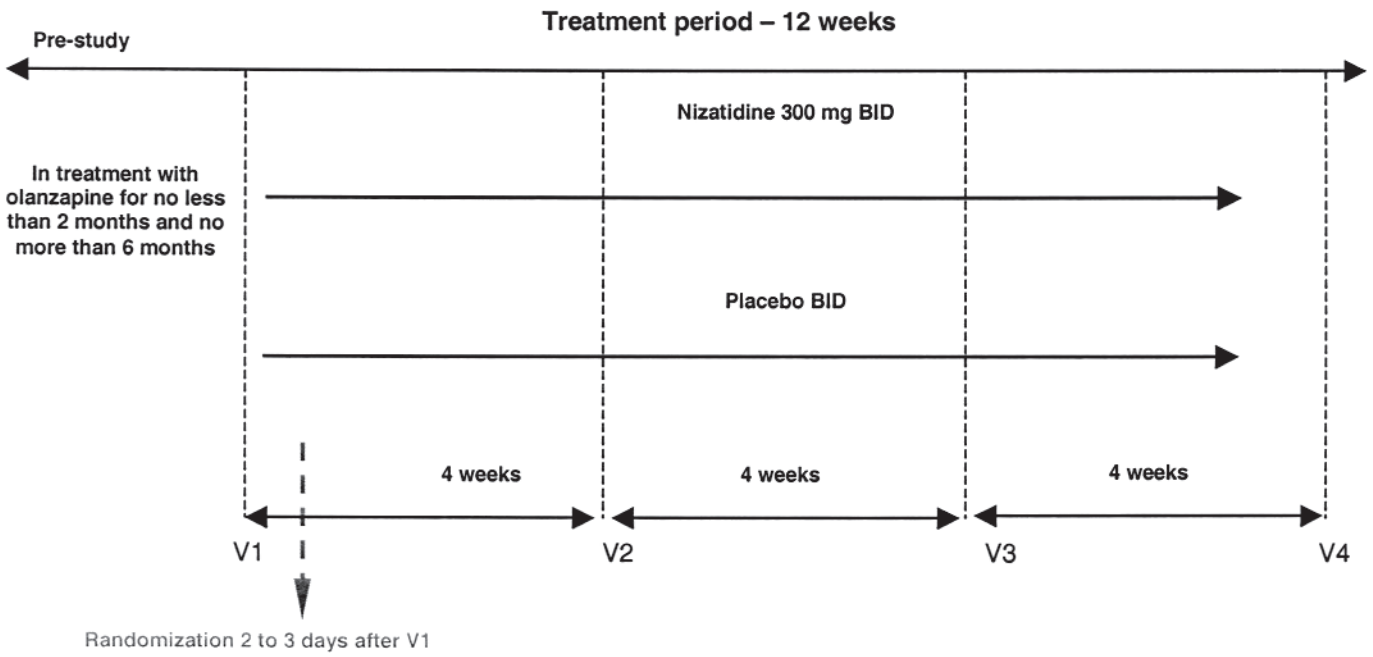

Figure 1 - Study design

responders, it was used the chi-square test. Results are expressed as the mean ± standard deviation (SD), unless otherwise stated. Statistical significance was set at $p \leq 5$.

Results

1. Sociodemographic and clinical characteristics

A total of 54 patients were included in this analysis; 27 patients were randomized to receive nizatidine 300 mg BID and 27 to receive placebo, in association with their usual treatment with olanzapine (5-20 mg/day). Forty-five patients completed the treatment with no statistical difference between completers in both groups ($p = 0.39$). Age at first episode, number of previous episodes and hospitalizations during the last 6 months were assessed and groups were comparable regarding those clinical characteristics at baseline (Table 1). Additionally, the groups did not differ in terms of socio-demographic characteristics (Table 1). Out of the total sample, 59.3% (n = 32) were male and the mean age was 35.2 (SD ± 12.2).

Patients had to have an increase of at least 5% in their body weight from the time they initiated on olanzapine and were randomized. There was no statistical difference in the mean percentage of weight gain before randomization to PBO or NIZ (PBO = 12.3%, NIZ = 12%) ($p = 0.829$). Table 2 shows body weight mean values before and during the study. The mean duration on olanzapine treatment, before being randomized to nizatidine or placebo, was 2.9 months for both groups. Among the 54 patients included in the analysis, none had a previous diagnosis of diabetes and none developed DM during the 12-week period of the study.

There were no statistical or clinical significant differences between genders. From the baseline assessment females had a 12.5% increase in body weight after the beginning of olanzapine treatment and males 11.9%, with BMC of 26.0 and 26.3 for females and males, respectively.

2. Effect on weight

Both groups did not significantly differ with respect to amount of weight gain at endpoint: patients receiving NIZ had a mean weight gain of 1.1 kg and those randomized to PBO gained 0.7 kg ($p = 0.9$). Figure 2 shows the change in body weight between groups. Multiples comparisons along treatment visits,

Table 1 - Sociodemographic and clinical characteristics at baseline for both treatment groups

		Placebo	Nizatidine	Total	P-value
Mean age (SD) – years		34.9 (12.2)	35.5 (12.4)	35.2 (12.2)	0.45
Gender (n/%)	Female	13 (48.1%)	9 (33.3%)	22 (40.7%)	0.27
	Male	14 (51.9%)	18 (66.7%)	32 (59.3%)	
Ethnicity (n/%)	White	16 (59.3%)	20 (74.1%)	36 (66.7%)	0.45
	Black/ mulatto	9 (33.3%)	5 (18.5%)	14 (25.9%)	
	Other	2 (7.4%)	2 (7.4%)	4 (7.4%)	
Body weight when initiating treatment with olanzapine (kg; SD)		64.3 (12.2)	64.8 kg (13.4)	64.5 (12.7)	0.76
Mean time between time initiating on OLZ and baseline (months)		2.9 (1.1)	2.9 (1.2)	2.9 (1.1)	0.67
Age at first episode (years; SD)		24.9 (8.4)	22.3 (6.4)	23.6 (7.5)	0.21
Mean number of previous episodes (SD)		4.7 (5.0)	3.2 (4.3)	4.0 (4.7)	0.12
Hospitalization during the last 6 months	Yes	15 (55.6%)	9 (33.3%)	24 (44.4%)	0.23
	No	12 (44.4%)	18 (66.7%)	30 (55.6%)	

Table 2 - Body weight measures at different points during the treatment with olanzapine

	Mean body weight when initiating treatment with olanzapine	Mean weight change between initiating treatment with olanzapine and visit 1	Mean weight change in patients with ≤ 2 months of treatment with olanzapine and visit 1	Mean weight change in patients with > 2 months of treatment with olanzapine and visit 1	% of weight change since initiating treatment with olanzapine and visit 1
PBO	64.8 kg (SD ± 13.4)	7.6kg (SD ± 3.7)	6.5 (SD ± 3.5)	8.7 (SD ± 3.8)	12.3% (SD ± 6.9%)
NIZ	64.3kg (SD ± 12.2)	7.3 kg (SD ± 4.0)	6.8 (SD ± 3.8)	7.8 (SD ± 4.2)	12% (SD ± 7.5%)
p-value NIZ vs. PBO	0.76	0.828	0.76	0.76	0.829

regardless of treatment groups, showed that body weight at endpoint was statistically, although not clinically (< 5%), higher when compared to baseline (V1 *versus* V4: p = 0.002); however, body weight at endpoint was significantly lower when compared to those at Visits 2 and 3 (V2 *versus* V4: p = 0.003, and V3 *versus* V4: p = 0.001).

3. Responders and non-responders

53.8% (n = 28) were considered responders, i.e., remained in therapy for at least 6 weeks and had no weight gain or had weight gain ≤ 3% since started using nizatidine (baseline). There was no statistical difference in the rates of responders for nizatidine 57.7% and placebo 50% (p = 0.58). Females had a lower responder rate (39.3%), when compared to males (60.7%), but this difference was not statistically significant (p = 0.63)

4. Effect on psychopathology and safety

Significant improvement on the BPRS total scores was observed in both treatment groups from baseline to endpoint (p < 0.001 for both groups). However, the BPRS score was not significantly different between groups at endpoint (PBO: 23.7 ± 9.9; NIZ: 24.2 ± 8.5; p = 0.12). Figure 3 shows the changes in BPRS total score from baseline to endpoint in both groups. Decreases in BPRS total score were seen as early as week 4 (V1- NIZ: 27.5; PBO: 23.9 vs. V2 - NIZ: 25.4; PBO: 21.8; p = 0.006)

All patients showed a statistically significant improvement on the Simpson–Angus Scale from baseline to endpoint (p < 0.001). There were no statistically significant differences between groups at endpoint (PBO: 1.4 ± 2.8; NIZ: 0.6 ± 1.3; p = 0.51). There were no significant differences in treatment-emergent adverse events reported between groups (NIZ: 25.9% *versus* PBO: 18.5%; p = 0.5), and only 3 patients (1 NIZ; 2 PBO) discontinued the study due to an adverse event. Headache, somnolence, and hypersomnia were the only treatment-emergent adverse events reported by more than 2 patients. There were no significant differences between groups on any of the measured laboratory analyses (Table 3).

Discussion

The appropriate selection of APs ought to be based on drug efficacy and risk factors in clinical daily practice. Although more efficacious in a number of clinical outcomes, treatment with atypical antipsychotics may be associated with weight gain.[11-13] Thus, patients should be informed of that adverse event in order to avoid excessive weight gain. Nutritional advice must be given and regular physical exercise recommended. Many studies have shown that behavioral, pharmacological or a combination of both methods turned out to be efficacious in preventing weight gain.[13,26,32]

At present, there is no standardized pharmacological treatment for antipsychotic-related body weight gain. Some studies have assessed the effects of agents such as amantadine, orlistat,

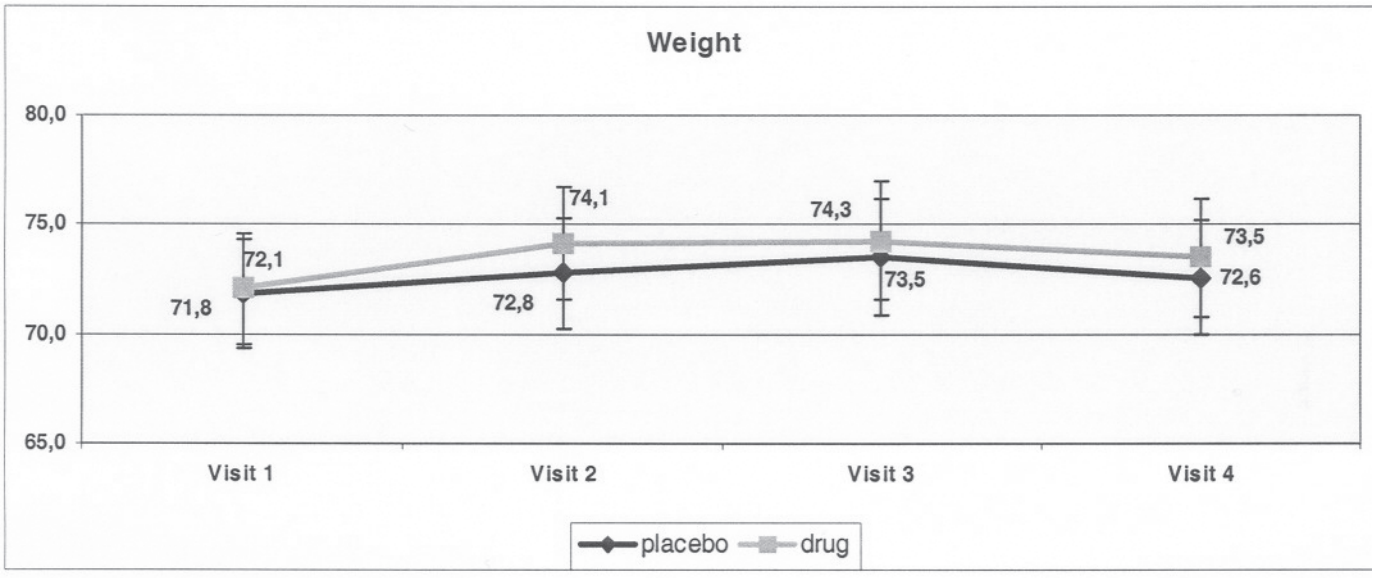

Figure 2 - Body weight changes from baseline to endpoint in patients receiving nizatidine or placebo

Table 3 - Laboratory analytes between treatment groups and from baseline to endpoint

	V1 (week 0)	V4 (week 12)	p-value NIZ vs. PBO	p-value V1 vs. V4
Glicemia			0.414	0.606
PBO	83.3 (10.2)	84.6 (14.7)		
NIZ	85.4 (12.0)	87.1 (14.5)		
Cholesterol total			0.241	0.630
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46)		
HDL			0.8	0.9
PBO	49.2 (9.4)	46.5 (12.7)		
NIZ	48.7 (13.4)	45.8 (10.6)		
LDL			0.34	0.77
PBO	191.3 (36.8)	180.3 (34.1)		
NIZ	195.5 (47.0)	198.8 (46.0)		
Triglycerides			0.38	0.28
PBO	148.2 (71.0)	152.7 (75.1)		
NIZ	168.4 (120.0)	179.4 (112.7)		

metformin, nizatidine, and topiramate as pharmacological alternatives to manage this adverse event.[26,33-37] Treating weight gain with pharmacological agents in psychiatric patients must be done with caution as some drugs used to this purpose may exacerbate the psychiatric condition, once their primary site of action is the central nervous system.[12] Thus, the use of a medication to manage weight gain in psychiatric patients without central activity would be of particular interest.[12]

Previous studies showed that H2 antagonists might be related to weight loss in humans.[21-22,25-27] Causing weight loss by a mechanism that is yet to be defined, H2 antagonists are more likely to have their the primary site of action outside the central nervous system, as H-2 antagonists as a class are very hydrophilic and cross the blood–brain barrier to a limited extent.[38] Due to their peripheral site of action, H2 antagonists were used in some studies to manage weight gain in schizophrenic patients on olanzapine. Among those studies two are of most interest due to their design and methodology.[26-27]

Cavazzoni et al. compared two different doses of nizatidine (300 mg QD and 300 mg BID) with placebo to manage weight gain in patients initiating treatment with olanzapine.[26] At weeks 3 and 4, patients treated with nizatidine 300 mg BID reported significantly less weight gain compared to placebo; however, no significant difference between the treatment groups was seen at 16 weeks. The authors suggested that nizatidine 300 mg BID may have a potential effect, albeit transient and possibly dose-related. The authors hypothesized a rebound phenomenon of weight recovery, a decrease in compliance over time, and interindividual variability as possible reasons for the apparent lack of persistent effect of nizatidine in controlling weight gain.

Lopez-Mato et al. evaluated the efficacy of different doses of ranitidine in preventing or reducing weight gain in schizophrenic patients treated with olanzapine in an open-label trial.[27] According to their results, the use of ranitidine prevented or corrected weight gain in 59.6% of the patients receiving olanzapine. Patients not receiving ranitidine exhibited an average weight gain of 3.4 kilograms (SD: -2.5 to +16 kg), and an increase of 1.19 kg/m^2 in their BMI. Patients treated with ranitidine 300 mg/day gained 0.9 kilogram (SD: -4 and +10.6 kg), with an increase of 0.34 kg/m^2 in their BMI. For patients on the highest dose of ranitidine (600 mg), the weight gain curve trended towards normalization. They lost 1.6 kilogram and 0.6 points in their BMI, in average. Additionally, they lost up to –15 kilograms and gained less weight (up to 7 kilograms) when compared to those receiving a lower dose of ranitidine or placebo. Contrary to the study of nizatidine by Cavazzoni et al. the effect of weight control with ranitidine was sustained along all the study period.[26]

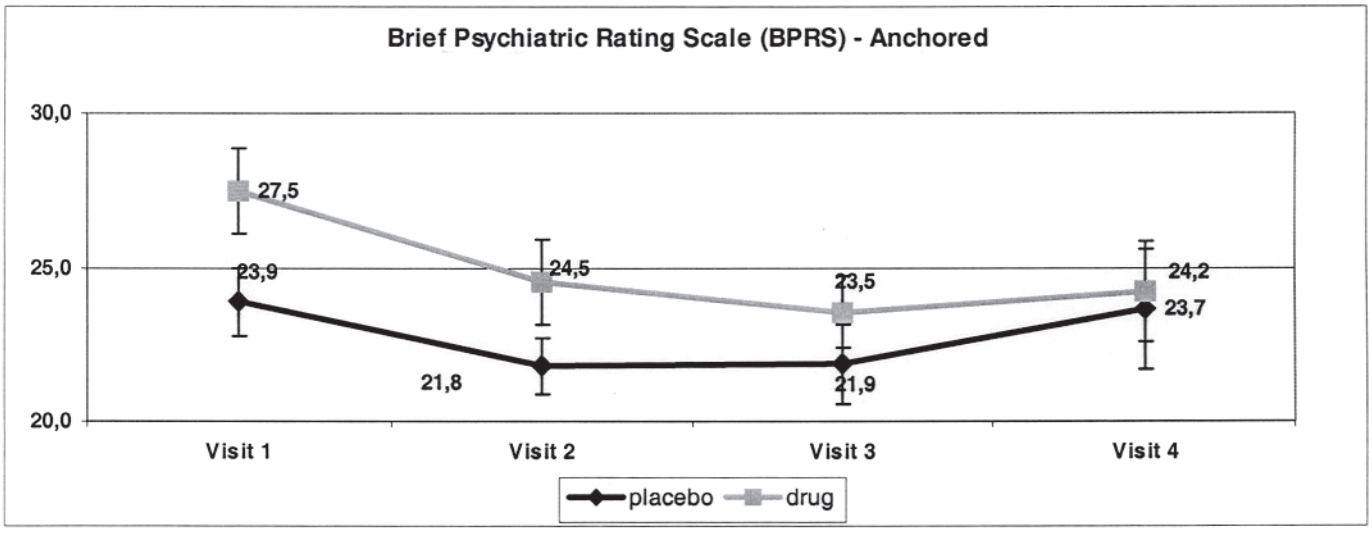

Figure 3 - Changes in BPRS total score from baseline to endpoint according to treatment groups

Our study had the main objective of assessing whether an H2 antagonist, nizatidine, could be of help for patients with schizophrenia or related disorders that had already had substantial weight gain (≥ 5%) with olanzapine. If so, it would avoid unnecessary use of this pharmacological strategy to a significant part of patients who, during the course of their treatment with olanzapine, did not present weight gain nor had a weight gain that could be managed by behavioral and/or dietary strategies.[28]

We demonstrated that nizatidine when administered to olanzapine-treated patients with previous weight gain did not differ from placebo in the amount of weight control. It could be hypothesized that the greater increases in body weight occurred most likely during the first months after initiating treatment with olanzapine (pre-study). Patients randomized to nizatidine gained on average 6.8 kg and those randomized to placebo, 6.5 kg, during that study period. Although continuing gaining weight, this increase was substantially lower (NIZ: 1.1kg and PBO: 0.7 kg) when compared to the initial phase of treatment with olanzapine. Those results are in accordance with previously published data, showing that the rate of weight gain appears to be more intense during the first 12 weeks of olanzapine treatment, occurring less rapidly in subsequent weeks, and plateauing around the 39th week.[28] That might be one explanation why nizatidine did not differ from placebo in controlling weight as most patients could already be in or close to the plateau phase.

Another concern related to the use of atypical antipsychotics is the potentially increased risk of treatment-emergent diabetes. Contrary to weight gain, that has been reported with some atypicals more than others (e.g., clozapine, olanzapine), recent reviews show that the potentially increased risk of DM appears to be a class-wide occurrence among the new generation antipsychotics.[13,39] In our study, blood glucose and lipids levels did not differ from baseline to endpoint and between patients in the two treatment groups during the 12 weeks of the study duration.

There are consistent data suggesting that the main driver when choosing an antipsychotic treatment must be the drug efficacy.[13,39] Although treated as a homogeneous group, effectiveness is different from one drug to another. For instance, in a recent meta-analysis, Davis et al. described that only clozapine, amisulpride, risperidone, and olanzapine were more efficacious than typicals, while other atypicals were not. After considering the drug's efficacy, medication's risk profile must also be considered.[10]

According to measures in the levels of psychopathology, extrapyramidal symptoms, laboratory analytes, and reports of treatment-emergent adverse events assessed during the study, nizatidine did not interfere with the efficacy and/or safety of olanzapine. This study did not have the intention to determine the efficacy or safety of olanzapine. Patients' levels of psychopathology were followed-up in the trial by using BPRS. Patients included in this study were not in an acute phase due to the inclusion criterion of a score on the total BPRS < 20. Despite this low score at baseline, it is interesting to note that patients using olanzapine continued to show a slight, yet statistically significant, decrease in their level of psychopathology during the 12 weeks of the study duration. Furthermore, extrapyramidal symptoms also decreased in intensity, according to score at Simpson-Angus Scale.

1. Study limitations

This study has some limitations that must be considered. It could be argued that this sample size is not large enough to detect differences between treatment groups. However, this may not be the main reason for these negative findings. There is some limitation in the design of the study. Before entering the study, patients were receiving olanzapine according to their physicians' discretion, as they were not in a controlled trial. Thus, the exact doses and compliance to the antipsychotic treatment might have substantially diverged among patients. Furthermore, patients in this study gained on average 7 kg after starting taking Olanzapine and before entering the trial. One could hypothesize that if nizatidine was delivered earlier before weight gain, during the first weeks of treatment, results might have favored this intervention.

Finally, only body weight at the time olanzapine was initiated was a required measure to be enrolled in this study, yet no requirement was made regarding metabolic parameters. Any conclusion about changes in those analyses must be taken very cautiously. The same caution must be observed regarding conclusions on psychopathology and extrapyramidal symptoms, as the study was not designed for purposes of efficacy and/or safety.

Conclusions

Our results showed that, when patients had already gained substantial weight with olanzapine treatment, the concomitant use of nizatidine did not differ from placebo in controlling weight gain. Olanzapine shows a remarkable efficacy in improving psychopathology in schizophrenic patients; however, some patients may experience significant weight gain. Innumerous studies show that weight gain can be adequately and successfully managed with behavioral and/or pharmacological approaches. The relatively rapid onset of weight gain with olanzapine suggests the importance of early intervention for weight gain mitigation. Proactive interventions to deal with this adverse event, regardless of the nature of the intervention, may result in weight stabilization/loss. Furthermore, appropriate attention to this issue can improve the quality of life for patients treated with antipsychotic drugs, and decrease morbidity and mortality due to weight-related disorders.

References

1. Center for Diseases Control (CDC). National Health Interview Surveys (NHIS). U.S. Department of Health and Human Services (USDHHS): [cited 15 Jan 2006]1989. CD-ROM. Series 1993;10(3). Available at: http://cdc.gov/nchs/about/major/nhisquest_data_related_1969_1996.htm .
2. Post F. Body-weight changes in psychiatric illness: a critical survey of the literature. *J Psychosom Res*. 1956;1(3):219-26.
3. Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, Weiden PJ, Cheskin LJ. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry*. 1999;60(4):215-20.
4. Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. *Br J Psychol*. 1988;153:214-7.
5. Stedman T, Welham J. The distribution of adipose tissue in female inpatients receiving psychotropic drugs. *Br J Psychiatry*. 1993;162:249-50.
6. Kendrick T. Cardiovascular and respiratory risk factors and symptoms among general practice patients with long-term mental illness. *Br J Psychiatry*. 1996;169(6):733-9.
7. Centorrino F, Baldessarini RJ, Kando JC, Frankenburg FR, Vopicelli SA, Flood JG. Clozapine and metabolites: concentrations in serum and clinical findings during treatment of chronically psychotic patients. *J Clin Psychopharmacol*. 1994;14(2):119-25.

8. Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC. Novel antipsychotics and new onset diabetes. *Biol Psychiatry*. 1998;44(8):778-83.
9. Masand PS, Blackburn GL, Ganguli R, Goldman LS, Gorman J, Greenberg I, Kawachi I, Perkins DO, Sach CS. Weight gain associated with the use of antipsychotic medications. *J Clin Psychiatry Audiograph Series*. 1999;2.
10. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry*. 2003;60(6):553-64.
11. 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(11):1686-96.
12. Green AI, Patel JK, Goisman RM, Allison DB, Blackburn G. Weight gain from novel antipsychotic drugs: need for action. *Gen Hosp Psychiatry*. 2000;22(4):224-35.
13. Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE, Davis JM, Kane JM, Lieberman JA, Schooler NR, Covell N, Stroup S, Weissman EM, Wirshing DA, Hall CS, Pogach L, Pi-Sunyer X, Bigger JT Jr, Friedman A, Kleinberg D, Yevich SJ, Davis B, Shon S. Physical health monitoring of patients with schizophrenia. *Am J Psychiatry*. 2004;161(8):1334-49.
14. Bromel T, Blum WF, Ziegler A, Schulz E, Bender M, Fleischhaker C, Remschmidt H, Krieg JC, Hebebrand J. Serum leptin levels increase rapidly after initiation of clozapine therapy. *Mol Psychiatry*. 1998;3(1):76-80.
15. Robinson RG, McHugh PR, Folstein MF. Measurement of appetite disturbances in psychiatric disorders. *J Psychiatr Res*. 1975;12(1):59-68.
16. Doss FW. The effect of antipsychotic drugs on body weight: a retrospective review. *J Clin Psychiatry*. 1979;40(12):528-30.
17. Stanton JM. Weight gain associated with neuroleptic medication: a review. *Schizophr Bull*. 1995;21(3):463-72.
18. Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, Mintz J, Marder SR. Novel antipsychotics: comparison of weight gain liabilities. *J Clin Psychiatry*. 1999;60(6):358-63.
19. Cookson JC. Side effects during long-term treatment with a depot antipsychotic medication. *Clin Neuropharm*. 1991;14(Suppl 2):S24-S32.
20. Bymaster FP, Hemrick-Luecke SK, Perry KW, Fuller RW. Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. *Psychopharmacology* (Berlin). 1996;124(1-2):87-94.
21. Stoa-Birketvedt G. Effect of cimetidine suspension on appetite and weight in overweight subjects. *BMJ*. 1993;306(6885):1091-3.
22. Stoa-Birketvedt G, Paus PN, Ganss R, Ingebretsen OC, Florholmen J. Cimetidine reduces weight and improves metabolic control in overweight patients with type 2 diabetes. *Int J Obes Relat Metab Disord.* 1998 ;22(11):1041-5.
23. Andersen T, Hojby Rasmussen M. Cimetidine and obesity: conflicting evidence. *Int J Obes Relat Metab Disord*. 1999;23(5):550-1.
24. Birketvedt GS, Thom E, Bernersen B, Florholmen J. Combination of diet, exercise and intermittent treatment of cimetidine on body weight and maintenance of weight loss. A 42 months follow-up study. *Med Sci Monit*. 2000;6(4):699-703.
25. Sacchetti E, Guarneri L, Bravi D. H(2) antagonist nizatidine may control olanzapine-associated weight gain in schizophrenic patients. *Biol Psychiatry*. 2000;48(2):167-8.
26. Cavazzoni P, Tanaka Y, Roychowdhury SM, Breier A, Allison DB. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13(2):81-5.
27. Lopez-Mato A, Rovner J, Illa G, Vieitez A, Boullosa O. Randomized, open label study on the use of ranitidine at different doses for the management of weight gain associated with olanzapine administration. *Vertex*. 2003;14(52):85-96.
28. Kinon BJ, Basson BR, Gilmore JA, Tollefson GD. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. *J Clin Psychiatry*. 2001;62(2):92-100.
29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association; 1994.
30. Woerner M, Mannuzza S, Kane J. Anchoring the BPRS: an aid to improve reliability. *Psychopharmachol Bull*. 1988;24(1):112-7.
31. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11-9.
32. Vreeland B, Minsky S, Menza M, Rigassio Radler D, Roemheld-Hamm B, Stern R. A program for managing weight gain associated with atypical antipsychotics. *Psychiatr Serv.* 2003;54(8):1155-7.
33. Deberdt W, Winokur A, Cavazzoni PA, Trzaskoma QN, Carlson CD, Bymaster FP, Wiener K, Floris M Breier A. Amantadine for weight gain associated with olanzapine treatment. *Eur Neuropsychopharmacol*. 2005;15(1):13-21.
34. Baptista T, Kin NM, Beaulieu S, de Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. *Pharmacopsychiatry*. 2002;35(6):205-19.
35. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry*. 2002;159(4):655-7.
36. Atmaca M, Kuloglu M, Tezcan E, Ustundag B, Kilic N. Nizatidine for the treatment of patients with quetiapine-induced weight gain. *Hum Psychopharmacol*. 2004;19(1):37-40.
37. Vieta E, Sanchez-Moreno J, Goikolea JM, Colom F, Martinez-Aran A, Benabarre A, Corbella B, Torrent C, Comes M, Reinares M, Brugue E. Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. *J Clin Psychopharmacol*. 2004;24(4):374-8.
38. Brunton LL. Agents for control of gastric acidity and treatment of peptic ulcers. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 8th ed. New York/St. Louis/San Francisco: McGraw-Hill Inc. p. 897-913.
39. Expert Group. 'Schizophrenia and Diabetes 2003' Expert Consensus Meeting, Dublin, 3-4 October 2003: consensus summary. *Br J Psychiatry Suppl*. 2004;47:S112-4.