

# WEIGHT CHANGES IN PATIENTS TREATED WITH ANTIPSYCHOTICS: ONE YEAR OBSERVATIONAL STUDY

L. DIMA<sup>1</sup> D. VASILE<sup>2</sup> V.VOICU<sup>2</sup>

**Abstract:** *The risk of inducing weight gain is heterogeneous among antipsychotics. The aim of the present study was to compare the weight changes in patients treated with haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole over one year follow-up. The study was designed as one year prospective observational study on 131 patients with schizophrenia or related disorders treated with one of the mentioned antipsychotics. Weight changes were significantly higher at 12 months after inclusion in the group treated with olanzapine than in the groups treated with haloperidol, risperidone and aripiprazole. The variability of data within individual antipsychotic groups reinforces the need of identifying the factors determining it, beyond the antipsychotic, by further studies.*

**Key words:** *weight change, overweight, antipsychotics, haloperidol, olanzapine, risperidone, quetiapine, aripiprazole.*

## 1. Introduction

Schizophrenia, one of the most devastating psychiatric disorders, is not exclusively a problem of mental health, but also a problem of public health. It has been shown that people with schizophrenia have an average lifespan of about 15 years less than the general population [1] and that mortality in these patients is increasing in recent decades [2]. While previously it was thought that excess mortality results mainly from the high rate of suicide, suicide is presently occurring at lower rates (5%) and the main cause for excess mortality seems to be cardiovascular complications [3]. Multiple factors might

be involved, from increased incidence of risk factors (smoking, obesity, diabetes, poor diet, and sedentary lifestyle) to poor accessibility to health care. Data from CATIE trial [4] revealed that the percentage of common diseases such as hypertension, diabetes, or dyslipidemia, which are appropriately treated, is reduced in patients with schizophrenia. Second generation antipsychotics are associated with an increased risk of weight gain, hyperglycaemia, and lipids changes, although the propensity for metabolic side effects differs between individual compounds. Excess weight is associated with reduced quality of life [5], medication non-adherence [6], [7], as well as with

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<sup>1</sup> Faculty of Medicine, *Transilvania* University of Braşov.

<sup>2</sup> University of Medicine and Pharmacy „Carol Davila” Bucharest Faculty of Medicine, Department of Clinical Pharmacology, Toxicology and Psychopharmacology

increased risk for impaired glucose tolerance, dyslipidemia, and hypertension [8]. However, the relationship between weight gain in patients treated with atypical antipsychotics and increased mortality in people with schizophrenia has not been established yet [9,10], but other factors apart from antipsychotic liability for metabolic effects might be involved [3,8]. The risk of inducing weight gain is heterogeneous among antipsychotics. Even more, it has been found that the weight changes are very different among patients treated with the same antipsychotic [11]. A better understanding of differences among antipsychotics in their risk of inducing weight changes through data from clinical trials, observational studies together with elucidation of molecular mechanisms involved in this side effect would allow a better management of treated patients.

In this context, the aim of the present study was to compare the weight changes in patients treated with haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole over one year follow-up.

## 2. Material and Method

The study was designed as a one year observational study, in routine clinical settings. The study sample consisted of 131 patients hospitalized in the Clinical Emergency Central Military Hospital “Dr. Carol Davila”, Bucharest from February 2009 to May 2010 for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or brief psychotic disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. The choice of the antipsychotic was made by the treating physician.

The main outcome variables, the weight and the Body Mass Index (BMI), were registered at inclusion, at discharge, at 6 and 12 months. Socio-

demographic and clinical characteristics were registered. Percentages of patients with more than 7% increase of weight from baseline (considered clinically significant), as well as percentages of patients with BMI equal or higher than 25kg/m<sup>2</sup> were calculated at each evaluation.

Selected patients gave written informed consent for anonymous data processing and analysis.

## 3. Statistical Analysis

Univariate analysis of variance (ANOVA) with last significant difference post hoc tests for continuous variables and chi-square tests for dichotomous variables were used to compare baseline demographic and clinical characteristics between treatment groups. Mean increase of weight from baseline was compared between groups, at each evaluation, by analysis of variance ANOVA. In cases where the analysis of variance revealed differences between groups to be significant or close to the level of statistical significance, the differences between pairs of antipsychotics were assessed by post hoc analysis with Least Significant Difference (LSD) test. At 12 months of follow-up, the mean weights adjusted for the inclusion weights were compared between groups by analysis of covariance (ANCOVA) and post hoc Bonferroni test. The level of statistical significance was considered for  $p$  lower than 0.05.

## 4. Results

The mean weight at baseline was highest in the group treated with haloperidol (77.27 kg, standard deviation (SD) 17) and lowest in the group treated with risperidone (69.43 kg, SD 15.06), but without statistically significant differences between treatment groups. There were no statistically

significant differences either for the mean BMI, or for percentages of overweight patients within groups. The percentages of overweight patients were higher than 50% in all the five groups (Table 1).

*Weight changes in treated groups over the 12 months of follow-up*

Table 1

	<i>Haloperi dol</i> (N=19)	<i>Olanzapi ne</i> (N=31)	<i>Risperi done</i> (N=28)	<i>Quetia pine</i> (N=33)	<i>Aripipr azol</i> (N=20)	<i>Total</i>	<i>p</i>
<b>Mean dose [mg/day]</b>	7,89 (5,44)	14,52 (4,35)	4,93 (1,15)	366,67 (145,1)	11,38 (3,76)		
<b>Age</b>	42,32 (11,47)	39,13 (12,88)	41,43 (10,98)	43,88 (15,16)	38,95 (14,92)	41,25 (13,21)	NS
<b>Male</b>	10/19 (53%)	19/31 (61%)	8/28 (29%)	11/33 (33%)	8/20 (40%)	56/131 (43%)	NS
<b>Antipsychotic naïve at inclusion At inclusion</b>	2/19 (11%)	11/31 (35%)	7/28 (25%)	8/33 (24%)	3/20 (15%)	31/131 (24%)	NS
<b>Weight [kg] (mean, SD)</b>	77,26 (17)	75 (15,15)	69,43 (15,06)	75,85 (18,67)	72,7 (16,17)	74 (16,48)	0,475
<b>BMI:≥25kg/m<sup>2</sup> [%]</b>	11/19 (58%)	17/31 (55%)	16/28 (57%)	17/33 (52%)	11/20 (55%)	72/131 (55%)	0,991
<b>BMI [kg/m<sup>2</sup>]</b>	25,88 (5,6)	25,53 (4,75)	24,87 (4,74)	25,94 (5,73)	25,24 (4,55)	25,5 (5,05)	0,935
<b>At 6 months</b>							
<b>Weight change [kg] (mean, SD)</b>	1,42 (2,09)	3,65 (5,44)	1,33 (2,8)	1,47 (2,3)	1,05 (2,68)	1,89 (3,54)	0,034
<b>BMI [kg/m<sup>2</sup>]</b>	26,39 (5,37)	26,83(4,5 2)	25,32 (4,95)	26,54 (5,68)	25,61 (4,19)	26,19 (4,96)	0,777
<b>Adjusted weight*[kg] (mean,SE)</b>	75,7 (0,75)	77,77 (0,59)	75,04 (0,64)	75,7 (0,58)	75,02 (0,73)		0,012
<b>At 12 months</b>							
<b>Weight change [kg] (mean, SD)</b>	1,68 (2,43)	5,3 (4,16)	2,93 (5,6)	3,24 (5,04)	1,26 (2,51)	3,13 (4,53)	0,014
<b>More than 7% weight change</b>	4/19 (21%)	14/31 (45%)	8/28 (29%)	10/33 (30%)	3/20 (15%)	39/131 (30%)	0,147
<b>BMI[kg/m<sup>2</sup>]</b>	26,49 (5,26)	27,5 (4,51)	25,91 (5,54)	27,14 (5,85)	25,62 (4,53)	26,64 (5,19)	0,665
<b>BMI:≥25kg/m<sup>2</sup> [%]</b>	11/19 (58%)	22/31 (71%)	15/28 (54%)	19/33 (58%)	10/20 (50%)	77/131 (59%)	0,559
<b>Adjusted weight**[kg] (mean,SE)</b>	75,80 (0,99)	79,29 (0,78)	76,59 (0,83)	77,29 (0,75)	75,14 (0,99)		0,01

The mean weight increased in all treatment groups at 6 months and 12 months. At both assessments increase was maximal in the group treated with olanzapine. The mean increase in olanzapine-treated group was 5.3 kg at 12

months, followed by the group treated with quetiapine (3.24 kg), risperidone (2.93 kg) and lower in the groups treated with haloperidol (1.68 kg) and aripiprazole (1.26 kg). The increase was significantly higher in the group treated with olanzapine compared to groups treated with aripiprazole ( $p = 0.002$ ), haloperidol ( $p = 0.006$ ), and risperidone ( $p = 0.043$ ) and at the limit of statistical significance compared to the group treated with quetiapine ( $p = 0.065$ ). At 12 months, the mean weight adjusted for inclusion value (ANCOVA estimates) was significantly higher in the group treated with olanzapine versus aripiprazole ( $p = 0.001$ ), haloperidol ( $p = 0.006$ ) and risperidone ( $p = 0.02$ ) treated groups. The adjusted mean in the group treated with quetiapine was lower than that in the olanzapine group and higher than in the group treated with aripiprazole, but the differences did not reach the statistical significance ( $p = 0.066$ , and  $p = 0.086$ , respectively). The percentage of overweight patients increased at 12 months from 55% to 71% in the group treated with olanzapine, from 52% to 58% in the quetiapine group, remained unchanged in the group treated with haloperidol (58%) and slightly decreased in the groups treated with risperidone (from 57% to 54%) and aripiprazole (from 55% to 50%). The differences between groups were not statistically significant. Proportion of patients whose weight gain from baseline to 12 months was clinically significant (more than 7% increase) was 45% in the group treated with olanzapine, 30% in the group treated with quetiapine 29% in the treated with risperidone, 21% in the group treated with haloperidol and 15% in aripiprazole-treated group. The differences were not found statistically significant (Chi Square = 6.3135,  $df = 4$ , significance = 0.1769).

## 5. Discussion

Antipsychotics hierarchy based on the average increase in weight at 12 months in the present study is consistent with most literature data according to which the maximum risk to induce weight gain is associated with clozapine and olanzapine, followed by quetiapine and risperidone, which in turn have a higher risk than with higher risk than aripiprazole [12,13]. Systematic reviews of clinical trials also showed that the proportion of patients with clinically significant weight gain (greater than or equal to 7% of initial weight) is higher in patients treated with olanzapine compared to patients treated with other atypical antipsychotics [14]. This finding appears also in our study (45% of patients treated with olanzapine compared to 15-30% of patients in the other groups), although with no statistical significance. Our study results revealed that in some treatment groups, for example in case of aripiprazole, the number of overweight patients decreased over the 12 months, although the average weight change per group increased slightly. This observation, together with that of high standard deviation values, higher than the correspondent means, illustrates the large variability of the results within the groups. This has been also reported in studies conducted under controlled conditions and has no well defined explanation [14]. Neither the mechanisms of antipsychotic-induced weight gain are elucidated [11], [15]. Complex interplay between factors involved in regulating energy metabolism and feeding behaviour, effects of disease in patients treated with antipsychotics (such as agitation or apathy, anhedonia, depression) and various pharmacodynamic effects of medication, plus the involvement of covariates such as demographic characteristics, previously

treatment co-medication and pharmacokinetic interactions [16], diet, physical activity level, or the patient's constitution and genetic factors make it difficult to delimit the role of each. It has been shown that antipsychotic induced weight gain is more pronounced in antipsychotic naive patients, compared to those chronically treated [15]. This could have influenced the results in our study, as the overall percentage of drug-naive patients was of only 24%, slightly higher in olanzapine treated group (35%) and lower in the haloperidol (11%) and aripiprazole (15%) groups, although the differences between groups were not statistically significant. Aripiprazole was generally found to have low propensity for metabolic effects and to be poorly correlated with weight gain [17-19]. Even more, it might be correlated with weight loss and improved lipid profile [20].

The heterogeneity of antipsychotic effects on weight results from complex drug-genetic-environmental factors interactions, resulting in alterations of the relationship between peptides and hormones that regulate feeding behaviour and energy metabolism, yet insufficiently understood. A special place has been recently occupied by genetic studies, which offer the promise of explaining the variation in risk associated with an individual antipsychotic, from one patient to another [11]. Clarifying these aspects by future studies could allow anticipating the response and therefore finding individual strategies of prevention and management of treated patients.

## 6. Conclusion

In the present 12 months follow-up study in patients with schizophrenia and related disorders, weight changes were significantly higher in the group treated with olanzapine than in the groups treated

with haloperidol, risperidone and aripiprazole. The results should be interpreted with caution, given the limits characteristic for an observational study design. The variability of data within antipsychotic groups reinforces the need of identifying the factors determining it, beyond the antipsychotic, by further studies. Identification of high risk patients could lead to individualized treatment strategies and better health outcomes.

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