Weight change in treatment with olanzapine and a psychoeducational approach

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Abstract

This study assesses the efficacy of an educational and dietary approach in preventing olanzapine-induced weight gain. Eighteen patients affected by schizophrenic disorders were treated with olanzapine and weighed twice-weekly for 24 weeks. A psychoeducational intervention and referral to a nutritionist was introduced from the beginning of olanzapine treatment in 9 patients, and from the 9th week of therapy in 8 patients. Results showed that after 8 weeks of olanzapine treatment, weight gain was contained in the subjects receiving intervention unlike patients without preventive intervention (+0.99 ± 3.34 kg vs. +2.96 ± 3.08 kg; p < .03). At the end of the trial these patients partly shed their gain (−1.77 kg), presenting a final weight which was not significantly different from baseline (+1.19 kg). Subjects receiving the psychoeducational approach from the beginning were significantly heavier than at baseline (+3.4 kg). Poor dietary compliance correlated significantly with an increase in body weight, while higher mean dosages of olanzapine correlated with better weight-gain control.

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Keywords: Weight change; Olanzapine; Psychoeducational approach; Weight control; Schizophrenia

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1. Introduction

People affected by schizophrenia tend to be more obese than non-schizophrenics (Allison & Casey, 2001; Allison, Fontaine et al., 1999) and treatment with antipsychotics often gives rise to an increase in body weight, which is more marked with atypical compounds than with traditional molecules (e.g. clozapine vs. haloperidol). A clinically significant weight gain (≥ 7%) has been demonstrated during short- and long-term treatment with clozapine, olanzapine, risperidone and quetiapine. Increased weight negatively affects patients somatically (risk of hypertension, etc.), psychologically (loss of self-esteem, social withdrawal, etc.) and in terms of compliance with treatment (Osser, Najarian, & Dufresne, 1999; Kurzthaler & Fleischhacker, 2001). Alterations in the metabolism of hormones, as prolactin (Windgassen, Wesselmann, & Schulze Monking, 1996) or thyroid-stimulating hormone, may influence weight change.

The parameters associated with weight gain during therapy with olanzapine are treatment- and patient-related (Blin & Micallef, 2001). Unlike other neuroleptics, olanzapine brings about weight gain in both the short- and long-term, irrespective of dosage (Beasley et al., 1996; Tran et al., 1997).

A relationship has been hypothesised between better clinical outcome and weight gain, although this may not necessarily be an indication of clinical improvement (Kalucy, 1980). Reported patient-related parameters include: age (younger patients gained more weight), gender, cigarette smoking (may influence liability for a lower gain), baseline Body Mass Index (low BMI was a predictor of weight gain; Tollefson et al., 1997), and environment (physical activity).

Clinical management (pharmacological and non-pharmacological) of this side effect is complicated by the lack of clear predictive factors and feasible preventive and therapeutic strategies. Non-pharmacological approaches have yielded contrasting results. Allison and Casey (2001) reviewed non-behavioural treatment of obesity in patients on neuroleptics, demonstrating some positive results. The majority of these studies were, however, conducted in residential or inpatient settings. On retrospective analysis of weight modification during treatment of patients receiving 5 different atypical neuroleptics, Wirshing and colleagues (1999) found that olanzapine-related weight gain was largely reversible with dietary and other behavioural interventions. Ball, Coons, and Buchanan (2001) found that only the male subjects were able to significantly lose weight following a cycle of Weight Watchers meetings and supervised exercise sessions.

The objectives of the study were threefold: first, to assess weight change, in the short-term (8 weeks) and in the medium-term (24 weeks), in patients treated with olanzapine, who had been educated on possible weight gain and referred to a dietician (Group 1: 9 patients). Second, to assess if another group of patients (Group 2: 8 patients), to whom the weight control programme was not proposed during the first 8 weeks, varied their initial weight and whether introducing the programme in the subsequent 16 weeks enabled patients to recover their previous weight status. Third, to see which of the clinical and sociodemographic variables considered was associated with weight gain.

2. Method

2.1. Participants

The participants were twenty subjects affected by schizophrenic-spectrum disorders, with side effects from conventional antipsychotics (C-NL) and, in some cases, unsatisfactory clinical compensation, who
had been in the care of the same psychiatrist (P.S.) for at least one year, at a Mental Health Centre (MHC) in Venice.

2.2. Procedure

After obtaining each patient’s informed consent, the C-NL was fully overlap-switched (Switch 3a) to olanzapine within the first two weeks. In patients receiving depot medication, olanzapine was administered at the next due dose (Switch 3c) (Bazire, 2000). The patients had never previously been treated with atypical antipsychotic medications.

Patients were consecutively recruited and randomly assigned to the two test groups. The patients in group 1 were informed by the attendant psychiatrist that the drug might cause weight gain, even if it was not possible to predict to what extent. In addition, patients were informed that efficacious medication was not available to deal with this side effect and that it was important to pay attention to food intake and to try and boost physical activity.

The patients were weighed in the same conditions (in the morning, wearing underwear) by a nurse from the Mental Health Centre (MHC); blood serum values of TSH, prolactin, glycaemia were evaluated and the following information was collected: variation in body weight in the preceding three months (+ or − at least 3 kg); previous conventional neuroleptic treatment and its duration (< or > two years); compliance with previous treatments; clinical severity (global clinical judgement—GCJ = absence of symptoms or marginally, moderately, markedly, severely, very severely ill); type of extrapyramidal symptoms and their severity (using GCJ assessment criteria); smoking habits.

Patients were assessed by the psychiatrist every 15 days; they were weighed and any problems relating to compliance with medication, diet and any weight gain were discussed, according to the time schedule.

The evolution of clinical conditions and extrapyramidal symptoms was subjectively evaluated by the psychiatrist according to a scale of values (greatly, moderately, slightly improved; no change; slightly, moderately, severely worsened).

Observance of psychiatric appointments throughout the trial, was considered good if the patient attended every appointment, poor if the patient missed up to two appointments, very poor if there was lack of cooperation (lateness, forgetfulness, etc.). Compliance with nutritional check-ups was considered good if the patient had attended every scheduled check-up, poor if they had missed one, very poor if they had not attended any check-ups after the initial one.

Patients were also referred to the nutritionist who examined the patients according to routine procedure: following initial assessment patients were examined after a period 7–9 weeks. Personal and dietary details were noted, with the emphasis on energy intake and energy expenditure, and a nutritional programme and food diary were drawn up. At the check-ups, the difficulties encountered by patients were addressed, the food diary was discussed, any nutritional questions were clarified and physical activity levels were assessed. This procedure (information, training and dietary consultation) was applied to the patients in the second group at the end of week eight.

2.3. Data analysis

Statistical analyses were based on final weight and the relationship between baseline and endpoint. Periodic assessments of body weight and body mass index (BMI; weight (kg)/height m²) were also considered. Body weight and BMI trends were collated with nutritional intervention and account taken of
3. Results

3.1. Sample characteristics

The clinical and therapeutic outcome of all 20 patients at baseline and at the end-point are outlined in Table 1.

Fifteen out of 20 patients were diagnosed with a schizophrenic disorder, according to DSM-IV criteria (paranoid-type in 12 cases and disorganized-type in 3 cases), while the other 5 patients were affected by a schizoaffective disorder. On global clinical judgement, 5 patients were considered “slightly”, 4 “moderately”, 4 “markedly”, and 6 “severely” ill, and one patient was defined “very severely” ill.

The side effects of therapy with conventional antipsychotics (C-NL) were: akathisia (3 patients), tardive dyskinesia (3 patients) and pseudoparkinsonism (14 patients). Three patients were considered “moderately”, 10 “markedly”, 4 “severely” and 3 “very severely” ill from these symptoms.

According to the classifications proposed by the United States National Health Lung and Blood Institute, no patient was underweight (BMI < 18.5), 6 patients presented normal weight (BMI 18.5–24.9), 8 were overweight (BMI 25–29.9), 5 were obese (BMI 30–39.9) and one was severely obese (BMI =/> 40).

In all patients, assessed blood serum values fell within range value.

Right from the early weeks, two subjects (nos. 10 and 15) presented difficulty complying with the therapeutic regimen and treatment was changed. Eighteen patients completed the trial for a duration of 24 weeks: ten in group 1 and eight in group 2. Following preliminary analysis (diagonal Hat matrix values) to identify leverage points (outliers) on the weight variable, patient no. 7 (marked ⬤ in Table 1) was excluded, thereby reducing the number of Group 1 members to nine.

Patient no. 2 took part in the study but declined to give blood samples.

The majority of the subjects were non-smokers; half of them had been taking antipsychotic medication for less than two years and had shown poor compliance with therapeutic programmes prior to this trial. Only two subjects had lost over 3 kg in the months prior to the trial.

After 24 weeks of treatment, on subjective psychiatric evaluation, 13 subjects presented an improvement in clinical picture, status was stationary in one case and had worsened in 3 patients. Extrapyramidal symptoms were moderately or markedly improved in 16 subjects and no change was observed in one patient only.

3.2. Weight changes after 8 weeks

After eight weeks of treatment weight gain was contained in the subjects receiving preventive intervention (group 1), whose weight was not significantly higher than baseline (+0.99 ± 3.34 kg;
3.3. Weight changes from baseline to endpoint (24 weeks)

At the end of the observation period, the whole sample presented a statistically significant increase in body weight (+2.36 ± 4.01 kg; \( t=2.43, df=16, p<.03 \)). However, after the eighth week, the patients in group 2, who were finally informed about the risk of weight gain and referred to a dietician, began to lose weight, containing the increase observed in the first eight weeks. Conversely, group 1 continued to gain weight. At the 24th week, the mean weight of group 1 patients was significantly higher than baseline weight (+2.96 ± 3.08 kg; \( t=2.72, df=7, p<.03 \)).

### Table 1
Clinical and therapeutic issues of the patients

<table>
<thead>
<tr>
<th>Gender/ Age</th>
<th>Diagnosis</th>
<th>Therapy</th>
<th>Start-up weight</th>
<th>BMI</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>F 52</td>
<td>Schizoaffective disor.</td>
<td>6</td>
<td>70</td>
<td>25.71</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>F 37</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>54.2</td>
<td>19.43</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>F 53</td>
<td>Schizophrenia, paranoid type</td>
<td>5</td>
<td>85.1</td>
<td>35.88</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>F 46</td>
<td>Schizophrenia, paranoid type</td>
<td>4</td>
<td>71.2</td>
<td>30.42</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>F** 52</td>
<td>Schizophrenia, disorg. type</td>
<td>4</td>
<td>112.8</td>
<td>42.98</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>M 48</td>
<td>Schizophrenia, paranoid type</td>
<td>6</td>
<td>79.2</td>
<td>28.06</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>F 37</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>72.1</td>
<td>28.16</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>F 68</td>
<td>Schizophrenia, paranoid type</td>
<td>4</td>
<td>67.5</td>
<td>24.50</td>
<td>10</td>
<td>4</td>
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<tr>
<td>M 74</td>
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<td>66.5</td>
<td>21.71</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>M 50</td>
<td>Schizophrenia, paranoid type</td>
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<td>112.2</td>
<td>33.87</td>
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<td>4</td>
</tr>
</tbody>
</table>

Mean (SD) 51.7 (12.4)

M/F 3/7

Group 2

<table>
<thead>
<tr>
<th>Gender/ Age</th>
<th>Diagnosis</th>
<th>Therapy</th>
<th>Start-up weight</th>
<th>BMI</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>F** 24</td>
<td>Schizoaffective disor.</td>
<td>5</td>
<td>79.8</td>
<td>25.91</td>
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<tr>
<td>M 49</td>
<td>Schizoaffective disor.</td>
<td>5</td>
<td>86</td>
<td>28.08</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>F 42</td>
<td>Schizophrenia, disorg. type</td>
<td>6</td>
<td>59</td>
<td>22.48</td>
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<td>2</td>
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<tr>
<td>M 41</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>91.8</td>
<td>29.30</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>M 34</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>103</td>
<td>31.79</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>M** 73</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>74</td>
<td>22.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M 22</td>
<td>Schizophrenia, paranoid type</td>
<td>7</td>
<td>66</td>
<td>23.11</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>M 33</td>
<td>Schizophrenia, paranoid type</td>
<td>4</td>
<td>81.5</td>
<td>28.20</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>M 39</td>
<td>Schizoaffective disor.</td>
<td>5</td>
<td>82.6</td>
<td>29.62</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>M 54</td>
<td>Schizophrenia, disorg. type</td>
<td>8</td>
<td>73</td>
<td>23.84</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean (SD) 39.2 (9.9)

M/F 8/2

**GCJ (Global Clinical Judgement; time 0)=2 (no symptoms), 3 (only marginally ill), 4 (slightly ill) 5 (moderately ill), 6 (markedly ill), 7 (severely ill), 8 ("He/she is among the most severe patients").**

**OIE (Overall improvement at endpoint)=2 (highly improved), 3 (moderately improved), 4 (slightly improved), 5 (no change), 6 (slightly worsened), 7 (moderately worsened).**

**Outlier. ** Drop-out.

Table: Difference between groups.

* Mean age: \( p \) value=.05.

○ Gender ratio: \( p \) value=.04.
(+3.4 ± 4.39 kg; $t=2.32$, $df=8$, $p<.05$). Group 2 partially lost the weight accumulated in the first stage, reaching an endpoint weight that did not significantly differ from baseline (+1.19 ± 3.42 kg; $t=0.98$, $df=7$, $p=0.36$).

Fig. 1 shows the time series trend in mean weight values for the two patient groups, compared at the baseline value, in addition to mean weight and BMI values for the 13 measurements (at time 0 and then every 2 weeks).

Comparison of the mean weight of the two groups at baseline and after the 24 weeks of study did not yield significant differences.

To assess the influence of preventive intervention on weight gain over a similar time period, we compared the weight changes in the two test groups 16 weeks after introduction of the related programme. Thus, for group 1, weights were compared from the first to the ninth weigh-in (from time 0 to the 16th week), and from the fifth to the thirteenth weigh-in (from the 8th to the 24th week) for group 2.

The subjects in group 1 showed a significant increase (3.16 ± 3.59; $t=2.63$, $df=8$, $p<.03$) and those in group 2 a significant decrease (−1.77 ± 1.71; $t=−2.93$, $df=7$, $p<.03$) in mean weight between the two assessments.

3.4. Variables correlated with weight change

Variance analysis based on two models was used to identify any variables that might explain weight variations in the sample as a whole over the 24-week period. The first model considered the following: age, gender, baseline BMI, attitude to smoking, weight loss in the preceding three months, duration of...
previous treatment with antipsychotics and dietary counselling (from baseline to week 8). This model accounted for 40% of the variance, but no variable was statistically significantly correlated.

In addition to dietary counselling (over the two time schedules), the variables used in the second model were clinical severity at baseline, olanzapine dosage, level of overall clinical improvement after 24 weeks and compliance with dietary appointments.

The most influential variables, i.e. the ones presenting significance on variance analysis, were compliance with dietary check-ups and olanzapine dosage. Poor compliance was associated with greater final weight gain (coeff=$+0.31$ $F=21.73$, $<.02$), where a higher olanzapine dosage was associated with a tendency towards weight loss (coeff=$−0.33$ $F=−13.68$, $P<.034$). While not achieving statistical significance, baseline and final clinical outcome influenced weight variation. A more severe clinical picture at baseline (coefficient $−4.05$) and a more marked improvement at the end of the trial (coefficient $−4.79$) were associated with better weight control.

4. Discussion

This sample was small and selected and consisted of patients who were already on medium/long-term antipsychotic medication. However, the majority of these subjects were taking haloperidol and fluphenazine, two of the conventional antipsychotics that induce less weight gain. (Rotatori, Fox, & Wilcks, 1980); none of them had ever taken atypical antipsychotics.

It was decided to use subjective “Global Clinical Judgement” to measure clinical severity at baseline and improvement after treatment for two reasons. First because the main aim of the study was to manage weight gain and second because the use of objective measurement instruments would have been too laborious, considering that the study setting was clinical rather than solely research-oriented.

Dietary intervention followed the routine procedure and, since account had to be taken of the organisational problems typical of local health services, the number of check-ups was rather limited. Furthermore, the nutritionist had no specific psychiatric training, although cooperation with the MHC was constant throughout the trial. Another limitation was the decision to weigh group 2 subjects – who were admitted to the preventive programme from week eight – every two weeks from the start of the trial. The practice of weighing from the start may have been interpreted as interest in and/or concern about body weight, inducing self-control in eating habits and weight, despite the lack of active intervention by the équipe.

Lastly, variations in appetite were not assessed, despite various reports of increased appetite among patients in treatment with olanzapine and other neuroleptics. (Basson et al., 2001; Blin & Micallef, 2001; Eder et al., 2001).

To our knowledge, this is the first longitudinal study incorporated into a busy mental health practice to assess the feasibility and efficacy of a programme to control weight gain resulting from olanzapine. The study design, which had to be adapted to meet the demands of routine clinical practice, seems to support the efficacy and effectiveness of the dietary approach adopted here.

The first noteworthy observation is the marked variability in body weight trends in the various test subjects, confirming the difficulty of predicting response to therapy not only in terms of core psychotic symptoms but also metabolically.

In the initial phase of the study, referring to the first eight weeks of treatment, a mean weight gain of less than one kilogram was observed in the group referred for dietary counselling. These values are lower than
the ones reported in previous studies where dietary intervention was absent. Basson and colleagues (Basson et al., 2001), on assessing the outcomes of two comparative trials on olanzapine and two other neuroleptics, observed a mean weight increase of 2.24 and 2.66 kg, respectively, after 6 weeks of treatment. Beasley and associates (Beasley et al., 1996) found even higher gains, averaging 3.5 kg. In the same time period employed by us, Eder and colleagues (2001) noted that patients gained a mean of 3.3 kg, whereas after 12 weeks of treatment, Osser and associates (1999) observed a mean increment of 5.4 kg. Moreover, in the present trial, patients with no dietary counselling presented a mean weight gain of 2.96 kg in the first eight weeks.

After 24 weeks of treatment, group 1, with dietary counselling from the start of the trial, managed to contain weight gain in the initial phase but continued to increase in weight to the 24th week. A weight gain of 3.4 kg was statistically significant, which is lower than the findings of Tran et al. (1997), who noted a mean weight increase of 4.1 kg, over a period of 28 weeks.

Conversely, group 2 subjects managed to lose part of the weight gained in the first 8 weeks, when no weight-watching programme had been provided.

It cannot be ruled out that the accelerated weight gain in group 1 could be the result of “regression towards the mean”, assuming that the group’s baseline body weight (75 kg) was below that of group 2 (80 kg). However, the mean weight of the two groups did not differ significantly either at the start or at the end of the observation period.

From the two models used to identify the variable that might have influenced better weight control, compliance with dietary appointments appeared to positively influence final weight change. Patient compliance, the good therapeutic relationship it fosters and family cooperation are vital in the outpatient setting. Weight control may be more positive in inpatient or residential settings (Allison, Mentore et al., 1999) simply because it is easier to supervise diet and stimulate physical activities within these contexts (Allison & Casey, 2001). However, since most schizophrenics live at home, any management model must take account of their cooperation. Last but not least, promoting good dietary compliance can only have positive repercussions on patient management as a whole.

Another finding emerging from this trial is the relationship between better weight control and higher dosages of olanzapine, and patients’ baseline (more severe) and endpoint clinical conditions (greater improvement). The relationship between clinical response and weight gain has been variously observed. Some studies have suggested a relationship between clinical efficacy of antipsychotics and weight gain. Kalucy (1980), however, maintained that the excessive weight gain observed in up to 40% of subjects taking antipsychotics is not an indication of clinical improvement. Better clinical response in the patients in this study may be associated with better control of weight gain insofar as it helped improve compliance with the weight-watcher programme.

Data on the sample’s long-term weight behaviour and its long-term weight trend cannot therefore be predicted, particularly in consideration of the reduced frequency of psychiatric appointments (every 3–4 weeks) and termination of the dietary check-ups. A plateau in olanzapine-related weight change has been hypothesized at 10–20 weeks of treatment (Blin & Micallef, 2001); Kinon, Basson, Gilmore, and Tollefson (2001) have suggested that the timepoint beyond which there are no further significant pairwise differences in weight-change data was 39 weeks. The authors observed no significant differences in mean weight change in any of the timepoints between 1 and 3 years of treatment.

This study fails to confirm some data in the literature i.e. the inversely proportional effect of baseline BMI and the limited influence of olanzapine dosage on weight (Basson et al., 2001; Blin & Micallef, 2001;
Kinon et al., 2001). This may be due to the peculiarity of the sample tested by us and/or referral of patients for dietary counselling, which may have altered metabolic profile and hence final outcome.

Having emphasized that a weight-watching approach alters the evolution of weight gain, we can safely urge further research in this direction, with a view to developing an efficacious model with an advantageous cost–benefit ratio. If the weighing of patients and discussion of topics relating to nutrition and perception of body image were to become part of routine psychiatric practice for patients receiving medication capable of altering or transforming the physical self, it might be worthwhile adopting group psychotherapy that incorporates a psychoeducational, as well as cognitive and interpersonal approach.

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References


