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# Early prediction of olanzapine-induced weight gain for schizophrenia patients

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ABSTRACT

The aim of this study was to determine whether weight changes at week 2 or other factors predicted weight gain at week 6 for schizophrenia patients receiving olanzapine. This study was the secondary analysis of a six-week trial for 94 patients receiving olanzapine (5 mg/d) plus trifluoperazine (5 mg/d), or olanzapine (10 mg/d) alone. Patients were included in analysis only if they had completed the 6-week trial (per protocol analysis). Weight gain was defined as a 7% or greater increase of the patient's baseline weight. The receiver operating characteristic curve was employed to determine the optimal cutoff points of statistically significant predictors. Eleven of the 67 patients completing the 6-week trial were classified as weight gainers. Weight change at week 2 was the statistically significant predictor for ultimate weight gain at week 6. A weight change of 1.0 kg at week 2 appeared to be the optimal cutoff point, with a sensitivity of 0.92, a specificity of 0.75, and an AUC of 0.85. Using weight change at week 2 to predict weight gain at week 6 is favorable in terms of both specificity and sensitivity. Weight change of 1.0 kg or more at 2 weeks is a reliable predictor.

## 1. Introduction

Obesity is prevalent among schizophrenia patients (Dickerson et al., 2006), and many antipsychotics used to treat schizophrenia may also result in weight gain (Allison et al., 1999b). For example, weight gain associated with olanzapine is commonly reported (Allison et al., 1999b; Duggan et al., 2005). Weight gain can lead to various medical complications such as diabetes mellitus, dyslipidemia, cardiovascular disease, and osteoarthritis (Bellanger and Bray, 2005; Huxley et al., 2010; Kawachi, 1999; Newcomer and Haupt, 2006). In addition, weight gain induced by antipsychotics may contribute to low self-esteem, medication nonadherence and subsequent relapse (Allison et al., 1999a). Psychiatrists need to balance the risk of weight gain against the benefit of symptomatic control. Therefore, reliable information about the risk for weight gain is required for patients receiving antipsychotics.

The mechanism of weight gain during treatment with olanzapine is not fully understood, and is likely to be multifactorial (Albaugh et al., 2006). In studies on the prediction of weight gain for patients taking antipsychotics, risk factors already identified include male gender, nonwhite ethnicity, first-episode psychosis, increased appetite, better clinical response, lower baseline body mass index (BMI), younger age, and gene polymorphism (Basson et al., 2001; Kinon et al., 2005; Ou et al., 2013; Ujike et al., 2008). Increased appetite is most likely a result of the antipsychotic medication, probably because antipsychotic medication is an antagonist of serotonergic 5-HT2c receptors, histaminergic H1-receptors, and dopamine receptors (Bak et al., 2014; Starrenburg and Bogers, 2009). However, to date, few of these risk factors have led to the development of a clinically useful decision-making tool.

Three industry-sponsored studies have reported that early weight increase during the course of olanzapine treatment may predict substantial weight gain following long-term use (Kinon et al., 2005; Lipkovich et al., 2006, 2008). A recent meta-analysis study (Musil et al., 2015) has concluded that weight increase is common during the first weeks of treatment. These findings indicate that early prediction of weight gain and, consequently, the timely implementation of weight management strategies is of great benefit. Consensus guidelines emphasize the importance of appropriate baseline screening and measuring of body weight, beginning in the initial weeks of treatment for patients taking olanzapine (American Diabetes Association, 2004; De Hert et al., 2009).

We recently conducted a six-week, randomized, double-blind study to compare the efficacy and safety of low-dose olanzapine (5 mg/d) plus low-dose trifluoperazine (5 mg/d) versus full-dose olanzapine (10 mg) in the acute treatment of schizophrenia (Lin et al., 2017). One of the

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findings was that no significantly different changes in body weight occurred at weeks 1, 2, 3, 4, and 6 between the two groups after treatment. The explanation for this is that weight change due to olanzapine is not dose-related within a range of 5–20 mg/day (Kinon et al., 2001), whereas weight increase due to trifluoperazine is unusual (Stahl, 2014). Therefore, possible weight change induced by trifluoperazine may be minimal if patients receive 5 mg daily of trifluoperazine plus 5 mg daily of olanzapine for short-term treatment. The aim of the study was to determine whether weight change, percentage of weight change, and/or BMI change at weeks 1 or 2 predicted weight gain at week 6 for schizophrenia patients receiving olanzapine treatment, and therefore to determine which predictor was most powerful and user-friendly.

## 2. Methods

### 2.1. Ethics

The study was the secondary analysis of a clinical trial, conducted from January 2012 to February 2016, as documented elsewhere (Lin et al., 2017). This study was approved by the Kai-Syuan Psychiatric Hospital's institutional review board (IRB) and conducted in accordance with Good Clinical Practice procedures, the Declaration of Helsinki, and national legal requirements (Taiwan's Human Subjects Research Act). This study was registered on Clinicaltrials.gov (Identifier number: NCT02704962).

### 2.2. Patients, study design, procedures, and body weight assessment

As previously described in detail (Lin et al., 2017), all newly hospitalized schizophrenia patients for acute treatment were evaluated by trained and board-certified psychiatrists. Inpatients were enrolled into this study if they: 1) were physically healthy and had all laboratory parameters within normal limits, 2) were aged between 18 and 55 years, 3) satisfied DSM-IV (APA, 2000) criteria for schizophrenia, 4) had a baseline Clinical Global Impression-Severity of Illness Scale (CGI-S) (Guy, 1976) ≥4, 5) had no DSM-IV diagnosis of substance abuse or dependence (including alcohol) in the past 6 months, 6) had not received depot antipsychotics during the preceding three months, and 7) had not taken olanzapine for at least 4 weeks before participating in the trial. Patients excluded from this study were: 1) those with histories of serious adverse reactions to olanzapine or trifluoperazine, 2) those with histories of tardive dyskinesia or neuroleptic malignant syndrome, 3) female subjects who were pregnant or at risk of pregnancy or lactation, and 4) those diagnosed with treatment-resistant schizophrenia (Kane et al., 1988), or having previously received clozapine or electroconvulsive therapy. Written informed consent was obtained from every patient and his or her legal guardian.

After a washout period of at least 3 days, patients were randomly assigned to a 1:1 ratio of 5 mg/day of olanzapine plus 5 mg/day of trifluoperazine, or 10 mg/day of olanzapine alone for 6 weeks. Patient adherence and safety were closely monitored by the research staff. Benzodiazepine was allowed as needed for insomnia or agitation. Biperiden, up to 6 mg/day, was also allowed to treat motor side effects, but prophylactic use of biperiden was prohibited. No other psychotropic agents were permitted during the study.

Symptom severity was rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). At weeks 0, 1, 2, 3, 4, and 6 (or upon early termination), body weight (kg) was measured in the morning after emptying the bladder and before breakfast, using a high-quality, calibrated digital scale, with the patient wearing indoor clothing but no shoes.

### 2.3. Statistical analyses

Patients were included in the analysis only if they had completed the 6-week trial (per protocol analysis). Weight gain was defined as a 7% or greater increase of the baseline weight (kg) to endpoint. Weight gainers and non-weight gainers were compared in terms of sex, age, age at onset, baseline PANSS, baseline weight (kg), baseline BMI (kg/m$^2$), weight change at week 1 (kg), percentage of weight change at week 1, BMI change at week 1, weight change at week 2 (kg), percentage of weight change at week 2, and BMI change at week 2. Age at onset was regarded as the age at which the first psychotic symptoms occurred.

Each statistically significant predictor at weeks 1 and 2 from the univariate analysis was separately entered into a receiver operating characteristic (ROC) analysis for determining which one was a powerful and user-friendly predictor. The ROC curve was used to determine the optimal cutoff point of predictor between the weight gainers and non-weight gainers, maximizing both the sensitivity and specificity of the predictor(s) so that false positive and false negative rates could be minimized. The area under the ROC curve (AUC) is a measure of the overall discriminative power. In practice, an AUC ≥ 0.8 indicates a good discriminative capacity (Weinstein and Fineberg, 1980).

All data were processed by SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Pearson $\chi^2$ test was used to compare categorical variables; independent *t*-test for continuous variables. All tests were two-tailed, and significance was defined as an alpha of less than 0.05.

## 3. Results

### 3.1. Patient characteristics

A total of 94 newly hospitalized schizophrenia patients with acute exacerbation were randomly assigned for treatment with olanzapine plus trifluoperazine ($N$ = 47) or olanzapine alone ($N$ = 47). No antipsychotic-naive or first episode schizophrenia patients were enrolled. Twenty-seven of the 94 patients dropped out early from the study. One patient withdrew from the trial after 2 weeks of treatment due to a weight increase of 5.5 kg. Sixty-seven patients who completed the 6-week trial were enrolled in the analysis. The mean age of the patients was 39.4 (SD = 8.5) years, and 47.8% ($N$ = 32) were males. The mean PANSS score of 95.0 (SD = 16.5) at baseline reflected a fairly severely symptomatic population (Table 1).

Eleven of the 67 patients (16.4%) were classified as weight gainers. There were no between-group differences in terms of sex, age, age at onset, baseline PANSS, baseline weight, and baseline BMI (Table 1). Table 2 lists the mean body weight, mean BMI, mean weight change, mean percentage of weight change, and mean BMI change of the two groups at each assessment.

### 3.2. Early prediction of weight gain

Weight change at week 1, percentage of weight change at week 1, and BMI change at week 1 were significant predictors of weight gainers at week 1. Similarly, weight change at week 2, percentage of weight change at week 2, and BMI change at week 2 were also significant predictors of weight gainers at week 2 (Table 1). ROC analysis was employed to determine the optimal cutoff point and AUC of each significant predictor. Table 3 shows the cutoff point, sensitivity, specificity, predictive power, and AUC of each predictor at weeks 1 and 2. At week 1, all the AUCs provided by weight change (0.75), percentage of weight change (0.75), and BMI change (0.75) were less than 0.8. At week 2, a weight change of 1.0 kg appeared to be the optimal cutoff point for predicting weight gainers, with a sensitivity of 0.92, a specificity of 0.75, a predictive power of 0.88, and an AUC of 0.85. A weight change of 1.23% appeared to be the optimal cutoff point for predicting weight gain, with a sensitivity of 0.91, a specificity of 0.70, a predictive power of 0.81, and an AUC of 0.84. A BMI change of 0.36 appeared to be the optimal cutoff point for predicting weight gain, with a sensitivity of 0.91, a specificity of 0.75, a predictive power of 0.83, and an AUC of 0.85. ROC curves of weight change at weeks 1 and 2 are illustrated in Fig. 1.