Effects of Patient Demographics, Risperidone Dosage, and Clinical Outcome on Body Weight in Acutely Exacerbated Schizophrenia

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Background: Predictors for risperidone-related weight gain remain unclear. This study aimed to identify clinical factors influencing body weight in risperidone-treated patients.

Method: One hundred forty-six newly hospitalized DSM-IV schizophrenia patients with acute exacerbation entered this prospective, 6-week, repeated-measures trial. The mean ± SD risperidone dose was 4.3 ± 1.4 mg/day at week 6. Efficacy, body weight, and tolerability were measured biweekly. Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE). For determining the impacts of possible prognostic factors on body weight, we utilized generalized estimating equation methods to control for other variables and the within-subject dependence over repeated assessments.

Results: After the effects of other factors (including baseline body weight) were adjusted, every 1-week increase in treatment duration raised body weight by 0.442 kg ($p < .0001$). Increasing baseline body weight by 1 kg reduced weight gain by 0.022 kg ($p < .0001$). Every 1-year increment in age decreased body weight by 0.052 kg ($p < .001$). Undifferentiated subtype predicted higher weight by around 0.9 kg than other subtypes ($p < .05$). Each 1-mg/day increment in risperidone dosage heightened body weight by 0.084 kg ($p = .015$). Responders (those with PANSS total-score reduction ≥ 20%) also had higher weight by 0.513 kg on average ($p = .007$). Specifically, every 1-point diminution in score in PANSS total, PANSS positive, PANSS negative, PANSS cognitive, and NOSIE increased body weight, on average, by 0.029 kg, 0.057 kg, 0.079 kg, 0.079 kg, and 0.035 kg, respectively ($p \leq .009$). Other variables did not have significant influences.

Conclusion: The results suggest that lower initial body weight, younger age, undifferentiated subtype, higher dosage, and treatment response (for positive, negative, and cognitive symptoms and social functioning) are associated with greater weight gain in acutely ill patients treated with risperidone. Further studies with longer observation and in other populations are needed.

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The problem of weight gain with atypical antipsychotics has become the focal point of clinical interest.[1–4] It has been speculated that weight gain may result from improved mental status, which allows the patient to eat and feel better.[5] On the other hand, concerns are growing about the health implications of excess weight gain as well as its potential impact on patients' self-esteem and, consequently, on compliance.[1,2] Among atypicals, clozapine and olanzapine produce the most weight gain; risperidone produces intermediate weight increase.[2,3,6] Although theories regarding action of these agents on receptors (such as serotonin 5-HT_{2C}[7] and histamine H_1[8] receptors) and on leptin levels[9] have been proposed, the exact mechanism for the weight gain remains to be elucidated.[9] Moreover, clinical factors governing weight change induced by these novel agents have not been fully defined.

In clozapine-treated patients, lower baseline body weight was indicated to be related with maximum weight gain.[10,11] Young age also predicted greater weight gain in a retrospective chart review[11] for patients receiving clozapine or other antipsychotics. Gender did not alter clozapine-associated weight change.[12] Dosage[13] and efficacy[14,15] of clozapine were associated with weight increase, but results from existing studies were inconsistent.[3,10,12,16,17] Of note, most of these studies were limited by small sample sizes.[12–14,16] For patients receiving olanzapine in multicenter trials,[4,18,19] low baseline body mass index (BMI) and better clinical outcome were predictive of greater weight gain. Dosage of olanzapine was not a significant predictor.[18] Age and gender effects varied between olanzapine studies.[4,17]

Risperidone differs from clozapine and olanzapine in pharmacologic profile.[20,21] Since its introduction in the United States in 1994, risperidone has been widely prescribed for the treatment of chronic,[2] acutely exacerbated,[22] and first-episode[23] schizophrenia. To date, data concerning predictors for risperidone-induced weight gain have been scanty and controversial. In several small studies[24–26] for children, adolescents, or patients with mental retardation, age, gender, baseline weight and BMI, and risperidone dosage did not affect weight change. In the phase III study[27] for chronic schizophrenia, a positive correlation between risperidone doses (2, 6, 10, 16 mg/day) and weight gain was revealed. In another multicenter study[28] comparing risperidone and olanzapine treatment in chronic patients, lower baseline BMI, young age, and better clinical response significantly increased weight gain after 6-week treatment; but dosage and gender had no influence.[4] The contribution of either drug in these analyses, however, was not shown.[4] In addition, the mean ± SD modal dose (7.2 ± 2.7 mg/day) of risperidone in the study[4,28] may be higher than currently recommended ones.[22,29,30] Finally, risperidone-related weight gain was reported to be higher in acutely symptomatic patients than in chronic subjects.[11] Therefore, the effects of drug dosage and other variables on risperidone-induced weight change deserve further study, particularly in other populations such as acutely ill schizophrenics.

The present study, utilizing rigorous statistics to control for confounding factors and effects of repeated clinical measurements, analyzed the influences of drug doses, clinical manifestations (including positive, negative, and cognitive symptoms and social functioning), and thorough patient demographic variables on body weight of 146 inpatients who received risperidone monotherapy for acutely exacerbated schizophrenia.

METHOD

This prospective, open-label, and repeated-measures study was conducted in the inpatient unit of the China Medical College Hospital, Taichung, Taiwan. The protocol was approved by the facility's institutional review board.

Subjects

All newly hospitalized schizophrenic patients with acute exacerbation were screened and evaluated by experienced psychiatrists. Chinese patients in Taiwan entered into this study if they (1) were physically healthy and had all laboratory parameters within normal limits, (2) were aged 18 to 60 years, (3) satisfied DSM-IV criteria for schizophrenia, (4) had a minimum baseline total score of 60 on the Positive and Negative Syndrome Scale (PANSS),[31] (5) had no DSM-IV diagnosis of substance (including alcohol) abuse, (6) were nonsmokers, (7) had not received depot antipsychotics for the preceding 6 months, (8) had never received atypical antipsychotics before, and (9) gave written informed consent and were competent to do so.

Study Design

The whole study was divided into 2 stages. During the washout stage, the subjects were placed on a placebo for 7 days, which could be shortened to a minimum of 1 day for patients with extremely emergent psychotic symptoms. During the active treatment stage, risperidone was gradually titrated to the target dose 6 mg/day (or lower, in case of intolerance) within 1 week. From day 8 to day 42, the dosage remained the same as that used on day 7, or could be reduced on day 14 or day 28 after the drug-safety evaluation (see "Clinical Assessments" below). This dosing strategy was based upon our recent work.[22] Lorazepam was allowed as needed for insomnia (p.o.) or agitation (i.m.), and benztropine, for extrapyramidal side effects (EPS). No other centrally acting drugs (including anticonvulsants) or cytochrome P450 inducers (or inhibitors) that might interfere with risperidone's metabolism[32–34] were permitted.

Clinical Assessments

Efficacy, body weight, and drug safety were assessed on day 0, day 14, day 28, and day 42. The main efficacy instruments were the PANSS (and its positive, negative, and cognitive[35] subscales) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE).[36] The cognitive subscale consists of 5 items in the PANSS: conceptual disorganization, difficulty in abstract thinking, mannerism and posturing, disorientation, and lack of judgment and insight.[35] This subscale has been used in the pilot D-serine trials.[37,38] The NOSIE captures patient's social functioning and his/her activities of daily living. This scale thus complements the PANSS (that focuses more on psychopathology) and has been useful in the clozapine trial conducted by Kane et al.[39] Drug safety was evaluated by means of routine physical and neurologic examinations, laboratory tests, the Extrapyramidal Symptom Rating Scale (ESRS),[40] and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale.[41] The ESRS was designed to evaluate 3 types of EPS: parkinsonism, dystonia, and dyskinesia. Other side effect profiles were determined by the UKU scale. An experienced research psychiatrist (H.-Y. L.) administered all psychopathology and side effect rating instruments.

Statistical Analyses

The purpose of this study was to evaluate correlates of risperidone-related weight change in acutely ill schizophrenic patients. We collected body weight as the response value. Potential prognostic factors were baseline patient demographic variables, treatment duration (weeks 0–6), risperidone dosage, and clinical outcome. Baseline patient

demographics included body weight, BMI (body weight [kg] divided by body height [m^2]), sex, age, duration of education, age at onset, duration of illness, schizophrenia subtypes, number of previous hospitalizations, and hospitalization duration. Clinical outcome included treatment response (PANSS total-score reduction ≥ 20%) and scores in PANSS total, PANSS positive subscale, PANSS negative subscale, PANSS cognitive subscale, and NOSIE.

To evaluate the influences of the prognostic factors on the response values and to control for all other potential confounding variables, the multiple linear regression model was one of the appropriate methods. Importantly, a basic requirement for conventional multiple linear regression is that the collected data should be independent. In other words, each subject should provide one and only one record in the data set. For repeated-measures studies (such as the current one), the longitudinal follow-up data obtained from the same subject, however, are intra-individually related and violate the "independent" requirement. To adjust this within-subject dependence effect, Liang and Zeger[42] set up a statistical method named generalized estimating equation (GEE) for multiple linear regression in repeated-measures studies. In the current study, we thus conducted the GEE analysis utilizing the "PROC GENMOD" procedure under the SAS/STAT V8.1 system.[43] Statistical significance was defined as $p < .05$.

RESULTS

Patient Disposition, Characteristics, and Weight Change

One hundred forty-six patients completed at least the assessments on day 0 and on day 14 (the first posttreatment visit) and were thus eligible for data analysis. The numbers of patients active on days 28 and 42 were 136 and 117, respectively. The reasons for premature discontinuation were concurrent somatic illness (N = 4), sufficient response (N = 16), poor response (N = 5), and noncompliance (N = 4).

The demographic data of all subjects at baseline were as follows: male:female ratio = 85:61, mean ± SD age = 33.3 ± 9.5 years, duration of education = 10.8 ± 3.1 years, age at illness onset = 24.3 ± 8.1 years, duration of illness = 107.8 ± 88.2 months, number of previous hospitalizations = 1.7 ± 2.4, and total duration of previous hospitalizations = 32.1 ± 97.5 weeks. The distribution of schizophrenia subtypes was 96 paranoid, 19 disorganized, and 31 undifferentiated.

The mean ± SD body weight rose gradually: 60.8 ± 11.8 kg at baseline, 62.1 ± 12.0 on day 14, 62.9 ± 12.2 on day 28, and 63.9 ± 11.8 on day 42.

Drug Dosing, Efficacy, and Safety

The mean ± SD risperidone doses were rather stable: 4.4 ± 1.5 mg/day on day 14, 4.4 ± 1.4 mg/day on day 28, and 4.3 ± 1.4 mg/day on day 42. Twenty-two (15%) subjects received i.m. lorazepam injections for agitation during the trial. The doses of p.o. lorazepam and benztropine were quite low: 0.8 ± 1.0 mg/day and 0.5 ± 0.9 mg/day, respectively, within the last 2 weeks of the trial.

The mean PANSS total scores declined during the 6-week period: 89.7 ± 15.6 at baseline, 76.7 ± 16.2 on day 14, 70.6 ± 16.7 on day 28, and 68.2 ± 15.9 on day 42. The mean scores of the PANSS positive subscales revealed a similar trend: 23.4 ± 4.4, 19.0 ± 4.9, 17.1 ± 5.0, and 16.2 ± 4.9 at the 4 visits; and so did the mean scores of the PANSS negative: 26.6 ± 6.0, 24.0 ± 6.2, 22.6 ± 6.4, and 22.1 ± 6.2, respectively. The mean PANSS cognitive scores were 14.1 ± 4.4, 12.2 ± 4.1, 11.3 ± 4.1, and 10.7 ± 3.7, respectively; and the mean NOSIE scores were 72.5 ± 14.0, 63.3 ± 12.8, 59.3 ± 12.2, and 58.2 ± 12.3.

Since our dosing strategy was to reduce side effects (excluding weight change) as possible, adverse events in the subjects were minimal (if any), short-lived, and resolved spontaneously or after dose reduction. No clinically significant and relevant abnormal laboratory test results were recorded. No patients withdrew from the trial due to adverse reactions.

Table 1. Effects of Treatment Duration, Baseline Body Weight, Age, Diagnosis Subtype, and Risperidone Dosage on Body Weight (kg) in 146 Patients With Acutely Exacerbated Schizophrenia[a]

Parameter	Estimated Coefficient	Standard Error of the Estimated Coefficient	p Value
Treatment duration (1-wk increment)	0.4418	0.0511	< .0001
Baseline body weight (1-kg increment)	0.9779	0.0105	< .0001
Age (1-y increment)	–0.0520	0.0156	.0009
Sex (male vs female)	0.4404	0.2729	.1065
Paranoid vs undifferentiated subtype	–0.9236	0.3671	.0119
Disorganized vs undifferentiated subtype	–0.9434	0.4064	.0203
Dose (1-mg increment)	0.0839	0.0344	.0148

[a]Multiple linear regression analysis with the generalized estimating equation method[42] under the SAS/STAT V8.1 System.[43]

Predictors of Weight Change

Analyses were performed to explore the impacts of various factors on body weight after controlling for other variables by the GEE method's multiple linear regression. Table 1 shows the effects of treatment duration, baseline patient-related variables, and risperidone dosage. Every 1-week increase in treatment duration significantly raised body weight by 0.442 kg. A 1-kg increment in baseline body weight was associated with a 0.978-kg increase in posttreatment body weight; that is, increasing baseline body weight by 1 kg could significantly reduce weight gain by 0.022 (i.e., 1 – 0.978) kg. Every 1-year increment in patient's age decreased body weight by 0.052 kg. Male

Table 2. Effects of Treatment Response (PANSS Total-Score Reduction ≥ 20%), PANSS Total Score, PANSS Positive Score, PANSS Negative Score, PANSS Cognitive Score, and NOSIE Score on Body Weight (kg) After Controlling for Treatment Duration, Risperidone Dosage, Baseline Body Weight, and Other Patient-Related Variables in 146 Patients With Acutely Exacerbated Schizophrenia[a]

Parameter	Estimated Coefficient	Standard Error of the Estimated Coefficient	p Value
Treatment response vs poor response	0.5128	0.1909	.0072
PANSS[b]			
Total	–0.0293	0.0069	< .0001
Positive	–0.0571	0.0218	.0089
Negative	–0.0792	0.0226	.0005
Cognitive	–0.0785	0.0262	.0027
NOSIE[b]	–0.0351	0.0081	< .0001

[a]Multiple linear regression analysis with the generalized estimating equation method[42] under the SAS/STAT V8.1 System.[43]
[b]1-point increment in score.
Abbreviations: NOSIE = Nurses' Observation Scale for Inpatient Evaluation, PANSS = Positive and Negative Syndrome Scale.

patients, compared with female, tended to gain more weight by a mean of 0.440 kg; however, the difference did not reach statistical significance. Compared with paranoid or disorganized subtype, undifferentiated subtype was predictive of higher weight by more than 0.9 kg. Finally, each 1-mg/day increment in risperidone dosage heightened body weight by 0.084 kg. Other variables (duration of education, age at the onset of psychosis, duration of illness, number and duration of prior hospitalizations, and baseline BMI) did not have significant influences on body weight. Table 2 presents the relationships between clinical improvements and body weight after adjusting the effects of those variables in Table 1. As shown, responders (those with PANSS total-score reduction ≥ 20%) were 0.513 kg heavier than poor responders. Moreover, every 1-point reduction in score in PANSS total, PANSS positive, PANSS negative, PANSS cognitive, and NOSIE significantly raised body weight by 0.029 kg, 0.057 kg, 0.079 kg, 0.079 kg, and 0.035 kg, respectively.

DISCUSSION

The weakness of this study is evident. Since this was an open, uncontrolled trial for newly admitted, acutely ill patients, effects of hospitalization had to be considered.[11] Inpatient treatment may lead to reduced activity. Besides, meals are served regularly, and food intake is controlled by the staff. Accordingly, the mean weight gain (around 3 kg) in the present study is higher than that in most of the studies enrolling chronic patients on risperidone (see references 44 and 45 for review). Additionally, nonwhite patients were reported to gain more weight than white individuals.[4] This cross-ethnicity difference, if reconfirmed by more evidence, may also contribute to the rather marked weight gain in our Chinese patients.

This study also presented several strengths. First, it recruited a large cohort of subjects and utilized novel statistics (GEE methods) to control for the effects of repeated measurements and other potential confounding factors. Second, owing to our dosing strategy[22] (see "Study Design" above), drug side effects (excluding weight change) were at most minimal and thus unlikely to interfere considerably with efficacy assessment. Our patients then received a mean ± SD final dose of 4.3 ± 1.4 mg/day, which is comparable to that recommended.[22,29,30] At this dose regimen, patients who received higher doses gained more body weight.

The majority[4,10,12,14,15] of previous studies on antipsychotic-related weight gain considered treatment response as a whole. Of note, risperidone or other atypicals appear effective against both positive and negative symptoms,[21,27,39,46] certain cognitive impairments,[47] and social dysfunction[48] in schizophrenia patients. To our knowledge, this is the first study demonstrating correlations of body weight versus clinical improvement in all of these dimensions in antipsychotic-treated patients. Bustillo et al.[16] have tried to find a potential relationship between body weight and positive and negative symptoms in 33 patients receiving clozapine. A negative result was revealed, perhaps partly due to the small sample size.

In an earlier study[11] including patients on risperidone (N = 15), clozapine (N = 29), zotepine (N = 19), or classical antipsychotics, the relationships of diagnosis subtypes with body weight were insignificant. In the present study, undifferentiated subtype (N = 31) predicted higher weight than disorganized (N = 19) or paranoid type (N = 96) in patients receiving risperidone. Currently, the number of disorganized or catatonic patients is lower than that decades ago.[49] In accordance, there were rather few disorganized or undifferentiated patients (and no catatonic ones) in our population. Larger studies (thus with more disorganized and undifferentiated patients) may be needed to substantiate the influences of diagnosis subtypes on body weight.

Although baseline BMI did not significantly affect body weight in our patients, lower baseline body weight and young age were associated with larger weight gain. These results lend support to the findings of the Basson et al. study,[4] which took into account both olanzapine- and risperidone-treated patients. Consistent with other trials,[4,17] this study did not find a significant gender difference in risperidone-related weight gain. A retrospective study[11] involving various antipsychotics found that first-episode subjects had a higher risk of weight gain during treatment. The current study focusing on risperidone, however, failed to demonstrate a correlation of body weight versus number or duration of prior hospitalizations after controlling for confounding factors. Three other variables (duration of education, age at the onset of psychosis, and duration of illness) did not significantly impact the body weight of our patients either.

The present study suggests that lower baseline body weight, younger age, undifferentiated subtype, higher risperidone dosage, and treatment response (for positive, negative, and cognitive symptoms and social functioning) are all related with greater body weight in patients with acutely exacerbated schizophrenia. These short-term findings, however, are just preliminary; whether they can be extrapolated to long-term observations requires clarification. Better-designed studies in other populations and with longer duration are warranted.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal).

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