The use of psychiatric drugs and worsening body mass index among inpatients with schizophrenia

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The aim of the present study was to investigate the relationship between 10 psychotropic agents and worsening BMI from overweight to obesity among inpatients with schizophrenia. A total of 138 patients with schizophrenia were recruited in this retrospective study. We included 23 patients with worsening BMI, from overweight ($24 \leq \text{BMI} < 27 \, \text{kg/m}^2$) to obesity (BMI $\geq 27 \, \text{kg/m}^2$), as the case group and 115 patients without a worse BMI as the control group. Data were analyzed to assess the relationships between psychiatric drug use and BMI that worsened from overweight to obesity. Of the 138 patients, 60.9% were men. Their mean age was 47.2 ± 9.7 years, mean age of onset of disease was 32.2 ± 10.4 years, and the mean length of illness 15.0 ± 6.5 years. Valproic acid was found to have a significant impact on the worsening of BMI from overweight to obesity ($P < 0.05$). Age at onset of disease, length of illness, and duration of hospitalization were not associated significantly with worsening of BMI from overweight to obesity. These results call for caution in using valproic acid in schizophrenic inpatients with BMIs indicating overweight or obesity. *Int Clin Psychopharmacol* 29:235–238 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Objective

In the USA, the prevalence of obesity among patients with schizophrenia is greater than 40%, which is 1.5 to two times that in the general population (Allison *et al.*, 1999a). Obesity in schizophrenic patients can cause hypertension, diabetes, stroke, and other associated cardiovascular illnesses (Chwastiak *et al.*, 2009). The average life expectancy of schizophrenic patients is significantly shorter than that of the general population (Capasso *et al.*, 2008). The average life expectancy of male patients with schizophrenia is 18.7 years less than that of the general male population, and the average life expectancy of female patients with schizophrenia is 16.3 years less than that of the general female population (Laursen, 2011). In addition, the mortality rate of schizophrenic patients is increasing (Goff *et al.*, 2005a) and obesity and associated cardiovascular illnesses are considered significant factors in this increased mortality (Goff *et al.*, 2005b).

The mechanisms of weight gain are both pharmacologic and nonpharmacologic (Megna *et al.*, 2011). Nonpharmacologic factors include lifestyle factors (e.g. lack of exercise and smoking) and dietary habits (Megna *et al.*, 2011; Ratliff *et al.*, 2012). Pharmacologic factors include many psychiatric drugs, such as antipsychotic drugs, mood stabilizers, and antidepressants, which can increase obesity in psychiatric patients (Allison *et al.*, 1999b; Ruetsch *et al.*, 2005). Both first-generation (typical) and second-generation (atypical) antipsychotic drugs can cause weight gain (Allison *et al.*, 1999b). Among second-generation antipsychotic drugs, clozapine and olanzapine are considered to have the greatest risk of causing weight gain, whereas risperidone, quetiapine, amisulpride, and zotepine have a modest risk, and ziprasidone and aripiprazole have a low risk (Newcomer, 2005). First-generation antipsychotic drugs, such as thioridazine, mesoridazine, and chlorpromazine, may also cause weight gain (Allison *et al.*, 1999b). Mood stabilizers such as lithium and valproic acid cause marked weight gain, whereas carbamazepine causes moderate weight gain (Zimmermann *et al.*, 2003). Antidepressants, such as imipramine, clomipramine, doxepine, amitriptyline, and nortriptyline, have an obvious, huge impact on weight gain, whereas paroxetine, mirtazapine, and desipramine cause moderate weight gain (Zimmermann *et al.*, 2003).

Predictors of weight gain in schizophrenic patients taking antipsychotic drugs include age, sex, baseline BMI, body weight, and smoking habits. Women, young patients, patients with low baseline BMI and body weight, patients who do not smoke, and those with rapidly changing weight after the initial drug treatment experience more significant weight gain after receiving antipsychotic drugs (Gebhardt *et al.*, 2009; Megna *et al.*, 2011). Studies on whether overweight schizophrenic patients ($24 \leq \text{BMI} < 27 \, \text{kg/m}^2$) progress to obesity (BMI $\geq 27 \, \text{kg/m}^2$) after taking psychiatric drugs have not been carried out previously. The aim of the present study was to investigate the relationships between 10 psychotropic agents and BMI worsening from overweight to obesity among inpatients with schizophrenia.

Methods

Study design

This was a retrospective case–control study carried out at the Tsao-Tun Psychiatric Center in Nantou County, Taiwan, from March 2010 to March 2011. This study was approved by the Institutional Review Board of the Tsao-Tun Psychiatric Center and was carried out in compliance with the Declaration of Helsinki. The inclusion criteria were inpatients who (a) received a diagnosis of schizophrenia on the basis of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision *(DSM-IV-TR)*, and (b) were admitted to chronic wards at the Tsao-Tun Psychiatric Center for more than 2 months.

The exclusion criteria were as follows:

(1) endocrine disorders such as abnormal function of the thyroid, pituitary, or sex glands;
(2) heart diseases such as arrhythmia, myocardial infarction, heart failure, or an installed pacemaker;
(3) immune and allergic diseases such as systemic lupus erythematosus or asthma;
(4) liver or kidney dysfunction: GOT or GPT > 80 IU/l, Cr > 2.5 mg/dl;
(5) pregnant or lactating women;
(6) women less than 6 months postpartum;
(7) physical dysfunction because of a stroke;
(8) involvement in any weight control program within the previous 3 months;
(9) determination by the attending psychiatrist as unsuitable for participation because of flare-ups of psychosis or risk of violence or self-harm.

Data on diagnosis, age, sex, age at onset of disease, length of illness, length of hospitalization, and medical history were obtained from patients' medical records. We followed 138 participants for 1 year. Body height and weight were recorded by the nursing staff before and after the study. All participants were inpatients, and factors related to diet and activity level were better controlled than those in outpatient studies. The 10 psychiatric drugs were independent variables and the three confounding variables were age at onset of disease, duration of illness, and duration of hospitalization. The total number of variables was 13 and the estimated sample size was determined to be no less than 130 (Beth Dawson-Saunders, 1990). Each case was paired with five controls according to their sex, age, and environmental factors (activity level and diet). Of the 138 patients, 23 had a BMI that worsened from overweight ($24 \leq BMI < 27\,kg/m^2$) to obesity (BMI $\geq 27\,kg/m^2$), and they made up the case group, and 115 patients who remained overweight served as the control group. Drugs were seldom switched during the year because treatment emphasized rehabilitation. The exact time point of BMI worsening could not be determined individually; thus, we chose the psychiatric drugs used from January to March, 2011 for further analysis.

Study measures and data collection

Body height was measured to $\pm 0.1\,cm$ with participants barefoot and standing upright. Inpatients received controlled meals from the central kitchen in the hospital. Body weight was measured 2 h after dinner. For this measurement, patients were asked to wear only underwear. The scale precision was calculated as $\pm 0.1\,kg$. The BMI was calculated by dividing weight in kilograms by the square of height in meters. According to the Department of Health, Executive Yuan, Taiwan in 2002 (*http://www.doh.gov.tw*), obesity was defined as BMI $\geq 27\,kg/m^2$ and overweight was defined as $24 \leq BMI < 27\,kg/m^2$.

Statistical analyses

We used descriptive statistics (percentage, quantile, median, mean, SD) to express demographic and clinical characteristics for study participants; categorical variables were expressed as frequency and percentage. Analytical statistics (χ^2-test and logistic regression) were used to assess the relationships between psychiatric drug use and progression from BMI overweight to obesity. Categorical variables were expressed as percentage and continuous variables as quartile, median, mean, and SD. The data were analyzed using the statistical package for the social sciences (SPSS Inc., Chicago, Illinois, USA) version 14.0 for Windows. Differences between groups were considered significant at P value less than 0.05.

Results

Of the 138 inpatients in the study, 60.9% were men. Their mean age was 47.2 ± 9.7 years, mean age at onset of schizophrenia was 32.2 ± 10.4 years, the mean length of illness was 15.0 ± 6.5 years, and the mean length of hospitalization was 4.5 ± 3.0 years.

Four patients (2.9%) were taking amisulpride, 42 (30.4%) were taking clozapine, 10 (7.2%) olanzapine, four (2.9%) were taking quetiapine, 34 (24.6%) were taking risperidone, four (2.9%) were taking thioridazine, 13 (9.4%) were taking zotepine, four (2.9%) were taking lithium, 27 (19.6%) were taking valproic acid, and two (1.4%) were taking trazodone. Seventy-eight patients (56.5%) were taking 1 type of the 10 psychiatric drugs, 27 (19.6%) were taking 2, four (2.9%) were taking 3, and 29 patients (21%) were taking none of these drugs (Table 1).

Table 2 lists the psychiatric drugs taken by the case group and the control group. Table 3 shows the factors related to worsening BMI status. Only the sample sizes for clozapine, risperidone, and valproic acid had sufficient statistical power, and of these, only valproic acid was associated with an increase in BMI from overweight to obesity ($P < 0.05$). No significant differences were found in length of illness, duration of hospitalization, or age at onset of disease.

Table 1   Psychiatric drugs taken by the 138 patients

Drug	N (%)
Amisulpride	
No	134 (97.1)
Yes	4 (2.9)
Trazodone	
No	136 (98.6)
Yes	2 (1.4)
Clozapine	
No	96 (69.6)
Yes	42 (30.4)
Lithium	
No	134 (97.1)
Yes	4 (2.9)
Olanzapine	
No	128 (92.8)
Yes	10 (7.2)
Quetiapine	
No	134 (97.1)
Yes	4 (2.9)
Risperidone	
No	104 (75.4)
Yes	34 (24.6)
Thioridazine	
No	134 (97.1)
Yes	4 (2.9)
Valproic acid	
No	111 (80.4)
Yes	27 (19.6)
Zotepine	
No	125 (90.6)
Yes	13 (9.4)
Total agents (classes)	
0	29 (21.0)
1	78 (56.5)
2	27 (19.6)
3	4 (2.9)

Table 2   Comparison of psychiatric drugs taken by the case group and the control group

	Control group [n (%)]	Case group [n (%)]	$\chi^{2\#}$	P value
Amisulpride			a	1.000
No	111 (82.8)	23 (17.2)		
Yes	4 (100)	0 (0)		
Trazodone			a	0.307
No	114 (83.8)	22 (16.2)		
Yes	1 (50)	1 (50)		
Clozapine			0.554	0.456
No	78 (81.3)	18 (18.8)		
Yes	37 (88.1)	5 (11.9)		
Lithium			a	0.129
No	113 (84.3)	21 (15.7)		
Yes	2 (50)	2 (50)		
Olanzapine			a	0.370
No	108 (84.4)	20 (15.6)		
Yes	7 (70)	3 (30)		
Quetiapine			a	0.522
No	112 (83.6)	22 (16.4)		
Yes	3 (75)	1 (25)		
Risperidone			0.008	0.930
No	86 (82.7)	18 (17.3)		
Yes	29 (85.3)	5 (14.7)		
Thioridazine			a	0.522
No	112 (83.6)	22 (16.4)		
Yes	3 (75)	1 (25)		
Valproic acid			a	<0.05*
No	97 (87.4)	14 (12.6)		
Yes	18 (66.7)	9 (33.3)		
Zotepine			a	0.455
No	105 (84)	20 (16)		
Yes	10 (76.9)	3 (23.1)		
Total agents (classes)			4.416	0.110
0	25 (86.2)	4 (13.8)		
1	68 (87.2)	10 (12.8)		
2 or 3	22 (71)	9 (29)		

aFisher's exact test.
#Yates corrected χ^2.
*$P < 0.05$.

Discussion

Most psychiatrists are well aware of the weight gain and metabolic side effects of second-generation antipsychotic drugs; however, they may not be aware of the similarities in weight gain and the metabolic side effects of valproic acid and lithium. Studies in Taiwan have shown a large prevalence of metabolic disturbances in patients with bipolar disorder (Chang *et al.*, 2009), and that valproic acid was associated with greater plasma insulin and triglyceride levels, greater BMI values, and lower fasting glucose and high-density lipoprotein levels compared with drug-free bipolar patients or healthy controls (Chang *et al.*, 2010a). Two cases of hypothermia have been reported as induced by the combined use of zotepine, valproic acid, and benzodiazepine (Chen *et al.*, 2003a). In addition, non-ketotic hyperosmolar syndrome resulting from cotreatment with olanzapine, lithium, and valproic acid has also been reported in Taiwan (Chen *et al.*, 2003b).

In this study, valproic acid was the only psychiatric drug associated with a significantly worse BMI in inpatients with schizophrenia ($P < 0.05$).

Past studies of valproic acid treatment of children and adolescents have shown valproic acid to be related to increased BMI (Abaci *et al.*, 2009) and metabolic syndrome, including abnormal glucose homeostasis, high

Table 3   Factors assessed in relation to worsening of BMI

Variables	Regression coefficient	SE	Wald statistic	P value	Odds ratio
Length of illness	0.05	0.04	1.54	0.214	1.05
Duration of hospitalization	0.09	0.08	1.52	0.218	1.10
Age at onset of disease	−0.03	0.02	1.38	0.240	0.97

total cholesterol concentration, high triglyceride concentration, and low high-density lipoprotein (Verrotti *et al.*, 2010). In addition, insulin resistance tended to increase during the first year of valproic acid treatment, but decreased subsequently (Masuccio *et al.*, 2010).

There is presently no agreement as to the pathogenetic mechanism by which valproic acid induces weight gain. Recent molecular studies have suggested that the modulation of G protein signaling by valproic acid might occur through its effect on histone acetylation and gene transcription (Beaulieu and Caron, 2005; Martini *et al.*, 2008). Patients with bipolar disorder who were T allele carriers of the GNB3C825T polymorphism had a lower risk for valproic acid-induced

metabolic abnormalities (Chang *et al.*, 2010a, 2010b). The pathogenetic mechanisms are complicated, given the complex nature of the ingestion of nutrients and the consumption of energy. Conceivable pathogenetic mechanisms include dysregulation of the hypothalamic system, hyperinsulinemia and insulin resistance caused by the effect of valproic acid on adipokine levels, and genetic susceptibility. The pathogenetic mechanisms might be multifactorial (Verrotti *et al.*, 2011). This study did not show that clozapine worsened BMI. One possible explanation might be that body weight had reached a plateau before the study. According to Bai *et al.* (2009), body weight reached a plateau at month 42 of clozapine use in chronic patients with schizophrenia.

This study has several limitations. First, the sample sizes for amisulpride, trazodone, lithium, olanzapine, quetiapine, thioridazine, and zotepine were insufficient to reach statistical power. Second, the correlation between dosage of valproic acid and BMI worsening from overweight to obesity remains to be determined. Third, the 1-year follow-up period was relatively short. A potential correlation between the long-term use of these 10 psychotropic agents and BMI worsening could not be determined. Fourth, the mean duration of illness of these inpatients was approximately 15 years; thus, they represented a chronic schizophrenic group. It was also difficult to determine a premorbid BMI and to obtain data on a previous history of psychotropic drug use so that an effect of previous psychiatric drug use on BMI could not be ruled out. Fifth, the present study did not assess whether the patients took nonpsychiatric medications or other compounds that might have caused weight gain during the follow-up period.

Conclusion
There was a significant correlation between the use of valproic acid and BMI worsening from overweight to obesity in schizophrenic inpatients. To prevent this, we suggest caution in the use of valproic acid for schizophrenic patients whose BMI already fulfills the criteria for overweight. More studies with a large sample size are needed to document the long-term effect of valproic acid on BMI worsening.

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Conflicts of interest
There are no conflicts of interest.

References
Abaci A, Saygi M, Yis U, Demir K, Dirik E, Bober E (2009). Metabolic alterations during valproic acid treatment: a prospective study. *Pediatr Neurol* 41:435–439.

Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP, et al. (1999a). The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 60:215–220.

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. (1999b). Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 156:1686–1696.

Bai YM, Chen JY, Chen TT, Lin CY, Chou P, Su TP, et al. (2009). Weight gain with clozapine: 8-year cohort naturalistic study among hospitalized Chinese schizophrenia patients. *Schizophr Res* 108:122–126.

Beaulieu JM, Caron MG (2005). Beta-arrestin goes nuclear. *Cell* 123:755–757.

Beth Dawson-Saunders RGT (1990). *Basic and clinical biostatistics*. Norwalk, Connecticut: Appleton & Lange p215.

Capasso RM, Lineberry TW, Bostwick JM, Decker PA St, Sauver J (2008). Mortality in schizophrenia and schizoaffective disorder: an Olmsted County, Minnesota cohort: 1950–2005. *Schizophr Res* 98:287–294.

Chang HH, Chou CH, Chen PS, Gean PW, Huang HC, Lin CY, et al. (2009). High prevalence of metabolic disturbances in patients with bipolar disorder in Taiwan. *J Affect Disord* 117:124–129.

Chang HH, Yang YK, Gean PW, Huang HC, Chen PS, Lu RB (2010a). The role of valproate in metabolic disturbances in bipolar disorder patients. *J Affect Disord* 124:319–323.

Chang HH, Gean PW, Chou CH, Yang YK, Tsai HC, Lu RB, et al. (2010b). C825T polymorphism of the GNB3 gene on valproate-related metabolic abnormalities in bipolar disorder patients. *J Clin Psychopharmacol* 30:512–517.

Chen KC, Yang YK, Chen PS, Yeh TL, Yang MJ (2003a). Two case studies of hypothermia induced by an increased dosage of zotepine in a combination therapy. *Psychiatry Clin Neurosci* 57:369–371.

Chen PS, Yang YK, Yeh TL, Lo YC, Wang YT (2003b). Nonketotic hyperosmolar syndrome from olanzapine, lithium, and valproic acid cotreatment. *Ann Pharmacother* 37:919–920.

Chwastiak LA, Rosenheck RA, McEvoy JP, Stroup TS, Swartz MS, Davis SM, et al. (2009). The impact of obesity on health care costs among persons with schizophrenia. *Gen Hosp Psychiatry* 31:1–7.

Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, et al. (2009). Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. *J Psychiatr Res* 43:620–626.

Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, et al. (2005a). Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry* 66:183–194.

Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, Daumit GL, et al. (2005b). A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res* 80:45–53.

Laursen TM (2011). Life expectancy in persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 131:101–104.

Martini JS, Raake P, Vinge LE, DeGeorge BR Jr, Chuprun JK, Harris DM, et al. (2008). Uncovering G protein-coupled receptor kinase-5 as a histone deacetylase kinase in the nucleus of cardiomyocytes. *Proc Natl Acad Sci USA* 105:12457–12462.

Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F, et al. (2010). Weight gain and insulin resistance in children treated with valproate: the influence of time. *J Child Neurol* 25:941–947.

Megna JL, Schwartz TL, Siddiqui UA, Herrera Rojas M (2011). Obesity in adults with serious and persistent mental illness: a review of postulated mechanisms and current interventions. *Ann Clin Psychiatry* 23:131–140.

Newcomer JW (2005). Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 19 (Suppl 1):1–93.

Ratliff JC, Palmese LB, Reutenauer EL, Liskov E, Grilo CM, Tek C (2012). The effect of dietary and physical activity pattern on metabolic profile in individuals with schizophrenia: a cross-sectional study. *Compr Psychiatry* 53:1028–1033.

Ruetsch O, Viala A, Bardou H, Martin P, Vacheron MN (2005). Psychotropic drugs induced weight gain: a review of the literature concerning epidemiological data, mechanisms and management [in French]. *Encephale* 31:507–516.

Verrotti A, Manco R, Agostinelli S, Coppola G, Chiarelli F (2010). The metabolic syndrome in overweight epileptic patients treated with valproic acid. *Epilepsia* 51:268–273.

Verrotti A, D'Egidio C, Mohn A, Coppola G, Chiarelli F (2011). Weight gain following treatment with valproic acid: pathogenetic mechanisms and clinical implications. *Obes Rev* 12:e32–e43.

Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmächer T (2003). Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res* 37:193–220.