Weight Gain While Switching from Polypharmacy to Ziprasidone: A Case Report

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Abstract

Second-generation antipsychotics (SGAs), valproate, and sulpiride are related to significant weight gain and risk of metabolic syndrome (MetS). Among SGAs, olanzapine and clozapine are associated with the highest metabolic risk while ziprasidone is among one of the SGAs with the lowest risk. Several reports suggest that weight loss is observed in switching other antipsychotics to ziprasidone. Here we describe a female patient with chronic paranoid schizophrenia who had an unexpected weight gain and developed MetS during a cross-switch from a polypharmacy of olanzapine, valproate and sulpiride to ziprasidone monotherapy.

Key Words: Ziprasidone, Schizophrenia, Polypharmacy, Weight Gain

Introduction

Second-generation antipsychotics (SGAs), valproate, and sulpiride are associated with risk of significant weight gain (1-3) and metabolic syndrome (MetS) (4). Among SGAs, olanzapine and clozapine are associated with the highest risk of weight gain and MetS, while ziprasidone is one of the SGAs with lower metabolic risk (2, 4). Several reports suggest that weight loss is observed in switching from other antipsychotics to ziprasidone (5-7). We report a patient with schizophrenia having unexpected weight gain while switching from a polypharmacy of olanzapine, valproate, and sulpiride to ziprasidone.

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Case

Ms. P, a 25-year-old Taiwanese woman, has a history of paranoid schizophrenia with onset at age 12, and repetitive hospitalizations due to persistent psychotic symptoms including running conversing auditory hallucinations, persecutory delusions, erotomanic delusions, and impaired social function. She has received psychiatric treatment at our hospital since the onset. She received antipsychotics including olanzapine, zotepine, risperidone, paliperidone, haloperidol, flupenthixol decanoate, amisulpride, sulpiride, aripiprazole, and adjunctive valproate. She was sensitive to extrapyramidal side effects and antipsychotic-induced hyperprolactinemia. From the age of 17 to 24 years, she received a stable regimen of olanzapine 20 mg/day and valproate 700 mg/day with adjunctive anticholinergics, benzodiazepines, and laxatives. At age 24, during psychiatric inpatient treatment, she had acute exacerbation of psychosis and sulpiride 400 mg/day was added. Nevertheless, she still suffered from significant psychotic symptoms (Brief Psychiatric Rating Scale [BPRS] score=53), impaired social function (Personal and Social Performance [PSP] scale=45), hyperprolactinemia (110.8 ng/mL, reference range of 2.8–29.2 ng/mL), and

Table 1 Serial Follow-Ups of Metabolic Profile

	Baseline	Week 4	Week 14	Week 36	1 Year
BW (kgs)	51	55	58.5	59	58
WC (cm)				87	83
QTc (msec)	408		432	425	
Prolactin (ng/dL)	110.8	7.5		36.4	20.3
T-CHOL (mg/dL)	143			136	
TG (mg/dL)	44			53	
LDL-C (mg/dL)	68			67	
HDL-C (mg/dL)	66			62	
Non-HDL-C (mg/dL)	77			74	
Fasting glucose (mg/dL)	93			114	

BW=body weight. WC=waist circumference. QTc=QT (corrected) interval. T-CHOL=total cholesterol. TG=triglyceride. LDL-C=low density lipoprotein-cholesterol. HDL-C=high density lipoprotein-cholesterol. Non-HDL-C=non-high density lipoprotein-cholesterol.

amenorrhea. She felt distressed about her much increased appetite and overeating. After discussion with her, a cross-switch to ziprasidone was decided. She was 149 cm in height and 51 kg in weight, with a body mass index (BMI) of 23.0 kg/m^2 at baseline. All serum lipid profiles and glucose levels were within normal limits.

All inpatients at our psychiatric ward were required to participate in regular psycho-educational group activities, which included a weekly session teaching healthy lifestyle and one-hour exercise on a daily basis. Regular diet was prescribed by psychiatrist and dietician. Low-fat/high-fiber diet was prescribed for her. Snacks were permissible twice daily. The total daily calories were about 2,000 kcal/day.

The doses of ziprasidone were divided in half and taken with food twice daily, gradually titrated up to 240 mg/day in 6 weeks, and tapered to 200 mg/day in Week 33 owing to sedation and stable mental condition. An "off-label" high-dose ziprasidone was prescribed due to the history of treatment resistance and unstable mental condition during the cross-switch. The original psychotropic regimen was gradually tapered. Sulpiride was discontinued on Day 7; valproate was discontinued on Day 13; olanzapine was slowly tapered to avoid withdrawal syndrome and discontinued in Week 14. Adjunctive treatment such as anticholinergics and benzodiazepines were discontinued in the first month. She returned to a regular menstrual cycle with one-month treatment of carbergoline, which was suggested by the consultant gynecologist. Ziprasidone-induced akathisia was managed with propranolol 40 mg/day, which was discontinued in Week 32. Afterwards, she received ziprasidone only. The results of serial follow-ups are shown in Table 1. She had a weight gain of 7.5 kgs, 14.7% of the baseline weight, after cross-switch. There was little difference in the metabolic profile. Her blood pressure was normotensive. She met the International Diabetes Federation definition of MetS, including a fasting glucose over 100 mg/dL and a female waist circumference over 80 cm (8).

Ms. P reported increased anxiety and overeating during the cross-switch period, and had difficulty participating in the psychoeducational and exercise groups, and had better control of her appetite after completion of the switch. She had fair response to ziprasidone, with full remission of positive symptoms (BPRS score=20) and significant improvement in socio-occupational function (PSP scale=65). She was able to participate in shelter work and establish meaningful interpersonal relationships in the rehabilitation psychiatric ward. She complied well with the diet and exercise instructions during this period of time.

Discussion

Weight gain is not only associated with MetS and diabetes mellitus, which lead to cardiovascular diseases and in turn cause significant morbidity and mortality (4), but also with patient dissatisfaction and poor adherence in patients with schizophrenia (9). Weight gain related to SGAs is observed during the first 4–12 weeks of treatment, after which the rate of increase seems to gradually decelerate and finally reaches a plateau (10). Among SGAs, clozapine and olanzapine are associated with the highest risk of developing significant weight gain (i.e., ≥7% of the baseline body weight) and MetS, while amisulpride, aripiprazole, and ziprasidone are associated with the lowest metabolic risk (2, 4). Several open-label trials have demonstrated that there was significant improvement in metabolic profile and weight loss when

switching from either polypharmacy or olanzapine to ziprasidone in both nondiabetic outpatients and diabetic inpatients with schizophrenia (6, 7). However, there was a high premature discontinuation rate (38.5%) when switching to ziprasidone owing to nonresponse, poor tolerability, and underdosing of ziprasidone (6). A high dose of ziprasidone was associated with large improvement of psychotic symptoms in patients with treatment-resistant schizophrenia and affective spectrum disorders (11).

Our patient presented significant unexpected weight gain specifically during cross-switch, and her weight remained in plateau under ziprasidone monotherapy. Environmental factors such as limited ward space and activity and available snacks might be responsible for weight gain. However, she had stayed in our hospital for several years and kept 51 kg in weight under the stable polypharmacy. Furthermore, we had provided dietary intervention, a psychoeducational group, and a daily exercise program. She participated in the ward activity and rehabilitative program more fully after ziprasidone monotherapy. Concomitant significant weight gain and clinical improvement in our case echoed the findings in the CATIE study, in which there was an inverse relationship between change in BMI and change in PANSS scores (12). Clinical response to clozapine in schizophrenia patients was associated with weight gain (13). Sharma et al. (14) proposed that there might be a metabolic threshold for SGAs similar to neuroleptic threshold for first-generation antipsychotics.

The mechanisms of weight gain associated with antipsychotics remain unelucidated. The implicated mechanisms include affinities of histamine H1, α1A adrenergic, 5-HT2C, and 5-HT6 receptors (15) and blockade of dopamine D2, D3, and muscarinic M2, M3 receptors (4). Olanzapine exhibits high antagonistic affinity for D2, H1, five muscarinic receptor subtypes, 5-HT2A, and 5-HT2C receptors (16). Valproate may induce weight gain through dysregulation of hypothalamus, adipokines and insulin resistance (3). Sulpiride may induce weight gain through hyperprolactinemia and dysregulated estradiol production in addition to dopamine D2 blockade (1). Ziprasidone exhibits high antagonistic activity at the D2, 5-HT1D, 5-HT2A, α1 receptors, a high 5-HT2A/D2 ratio, moderate antagonistic activity for H1 and 5-HT2C receptors, and agonist activity at 5-HT1A receptors, and weakly inhibits reuptake of serotonin and norepinephrine (17), and has little effect on the prolactin level (18). The animal models have shown that ziprasidone does not affect food intake (19, 20), and may induce weight loss by increasing resting energy expenditure (20). There may be a dose-response relationship between clozapine and olanzapine serum concentration and metabolic risk, but the data were either controversial or lacked evidence to suggest such relationship for other SGAs (21).

It would be predicted that the cross-switch from a polypharmacy of olanzapine, valproate, and sulpiride to ziprasidone should lead to a more favorable metabolic effect and weight loss based on previous studies (2-6) given the decrease in olanzapine and the new pharmacodynamic profile (i.e., no affinity to muscarinic receptors, absence of valproate-induced metabolic effects, and improvement of hyperprolactinemia). However, it was not the case in our patient. The patient received relatively high-dose ziprasidone (200–240 mg/day), which might be contributory to the weight gain due to its high antagonistic affinity of 5-HT2C and H1 receptors. Sedation from high-dose ziprasidone may lead to a decreased level of activity. However, significant weight gain was not observed in any patient receiving high-dose ziprasidone in one case series (11).

Concomitant significant weight gain and clinical improvement in our case echoed the findings in the CATIE study, in which there was an inverse relationship between change in BMI and change in PANSS scores (12).

Most weight gain occurred during the cross-switch period. The possible explanations are as follows: firstly, the patient received multiple antipsychotics concomitantly and experienced more adverse effects, such as dysregulated appetite and anxiety. Secondly, insufficient symptomatic control may interfere with adherence to diet instruction and participation in the psychoeducational and exercise groups. Thirdly, the patient had been exposed to a low dose of olanzapine for 3 months. In the animal model of chronic olanzapine administration by Shobo et al. (19), there was a trend that the group receiving the lowest dose olanzapine induced more weight gain than the groups receiving placebo and higher doses. Davey et al. (22) found that there was a significant interaction between gender, treatment and time regarding chronic olanzapine treatment in which female rats receiving a low dose of olanzapine experienced weight gain and persistent hyperphagia, and had increased plasma levels of pro-inflammatory interleukins. The weight gain and hyperphagia in our case might be explained by the interaction by gender, treatment and time.

In summary, our case report has the following implications: firstly, significant weight gain can be seen after cross-switch from combined olanzapine, valproate, and sulpiride to ziprasidone. Clinicians should inform patients of such risk before cross-switch. Secondly, clinical monitoring and intervention for weight gain should be implemented during the period of cross-switch.

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