

Weight Gain in Asian Patients on Second-generation Antipsychotics

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Abstract

Introduction: There is increasing evidence that second-generation antipsychotics are associated with weight gain. However almost all available literature has been for Caucasian populations. **Materials and Methods:** A health quality improvement project was undertaken at the Institute of Mental Health/Woodbridge Hospital to monitor patients who were started on second-generation antipsychotics. This 2-year survey of 266 patients on second-generation antipsychotics closely tracked weight gain and other physical and biochemical parameters. **Results:** Of the 222 patients regularly monitored, 78.4% had weight gain (mean weight gain 1.9 kg, maximum weight gain 20.1 kg). Weight gain group liability was highest for clozapine (72.4%), followed by olanzapine (66.7%) and risperidone (65%). Most of the weight gain occurred in the first 4 weeks of treatment and 95.9% of those who gained weight had done so in the first 6 months. The maximum weight gain was seen at 12 weeks for risperidone and 8 weeks for clozapine, quetiapine and olanzapine; the latter having another peak at 6 months. **Conclusion:** The survey confirms that weight gain is also a problem for Asian patients treated with second-generation antipsychotics. It reinforces the need for the regular monitoring of patients and the need for psychoeducation and advice on diet and a healthy lifestyle.

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Introduction

Weight gain is a serious side-effect with antipsychotic medication use. There is increasing evidence that with certain second-generation antipsychotics (SGA) weight gain liability is greater than with the high potency first-generation antipsychotics (FGA).¹ A meta-analysis of 81 studies of at least 10 weeks' duration showed that with the SGAs, clozapine and olanzapine produced the greatest weight gain (3.99 kg and 3.51 kg, respectively), with a moderate increase with risperidone (2 kg) and minimal for ziprasidone (0.04 kg). Unfortunately, there was no data on quetiapine and aripiprazole at the time of that analysis.² Research with SGAs since then has continued to show that the greatest weight gain is still with clozapine and olanzapine; risperidone and quetiapine are associated with intermediate levels of weight gain and ziprasidone and aripiprazole with the least weight gain.³

Most international studies have been in Caucasian populations. Asians (mainly Chinese) are frequently mentioned collectively with Hispanics and Afro-Americans

as "minority ethnic groups" in these studies. In a PubMed search for publications in the last 10 years, there were only 7 studies which specifically noted the weight gain in Asian patients on atypical anti-psychotics.⁴⁻¹⁰ In a small sample of 28 olanzapine and risperidone matched pairs of Chinese schizophrenia patients in Hong Kong, treatment with olanzapine was associated with significantly greater weight gain.⁶ In a larger naturalistic study in 3 Asian countries (Korea, Taiwan and Malaysia) which examined clinical outcomes in schizophrenia patients receiving monotherapy with either olanzapine, risperidone or typical anti-psychotics, mean weight increase was greater for olanzapine treated patients.⁷ A 6-week study on drug-naïve first-episode schizophrenia patients in India revealed the greatest weight gain was with olanzapine (5.1 kg) followed by risperidone (4.1 kg).¹⁰

This prospective follow-up of Asian patients treated in a tertiary psychiatric hospital in Singapore, an island state in Southeast Asia, establishes the extent of the problem amongst an Asian cohort treated with a wide range of SGAs.

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Materials and Methods

All patients newly started on second-generation antipsychotics in a 2-year period from September 2005 to August 2007 were followed-up under a Health Quality Improvement Project funded by the Ministry of Health, Singapore. These were outpatients with schizophrenia or schizoaffective disorder (DSM-IV TR criteria) who had been prescribed any of the 6 SGAs approved by the US Food and Drug Administration (clozapine, olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone). Their weight was recorded at baseline and subsequently at 4 weeks, 8 weeks, 12 weeks, 6 months, 9 months, 12 months, 18 months and 24 months. The weight was taken at the start of the consultation with the psychiatrist.

In addition, patients' heights were taken at the first visit and waist and hip circumferences were measured at regular intervals. The body mass index (BMI) and waist-to-hip ratio (WHR) was calculated at baseline before starting the SGA. The BMI or Quetelet's Index (derived from weight, height,² measured in kg/m²) is the recommended standard for relative weight which is commonly used as a gauge for body fat and to define overweight and obesity.¹¹ It is highly correlated with body fat percentage. Following the World Health Organization (WHO) guidelines, the Ministry of Health, Singapore, issued new BMI cut-off points as triggers for public health interventions and research. In these, a BMI of 18.5 to 22.9 is "low risk to moderate risk" (optimal range), 23 to 27.4 is moderate to high risk and 27.5 and above is high to very high risk.¹²

Clinic staff were trained to take the hip and waist measurements using the guidelines from WHO. Waist circumference was measured midway between the lower rib margin and the iliac crest and hip circumference was measured at the level of the widest circumference. Ethnic-specific values for waist circumference provided by the International Diabetes Federation were used.¹³ This gives the range for South Asians and Chinese (male ≥ 90 cm, female ≥ 80 cm).

All statistical analyses were done using the Statistical Package for the Social Sciences, version 13 (SPSS) software. Descriptive statistics were presented as mean (SD) and n (%). Linear regression was performed to determine the rate of weight increase over time for all subjects and sub-grouped by medications. Statistical significance was set at $P < 0.05$.

Results

Demographics

During the study period, 266 outpatients were started on SGAs. There were 175 women (65.8%) and 91 men (34.2%). The racial distribution closely mirrored the population distribution in the country; 213 were of Chinese ethnicity

(80.1%), 29 were Malays (10.9%), 16 were Indians (6%) and 8 (3%) belonged to other ethnicities. The mean ($\pm$ SD) age was 42.2 years (± 14.4) (range, 19 to 88) (Table 1). The SGA use was as follows: risperidone (163 patients, 61.3%), olanzapine (45 patients, 16.9%), clozapine (29 patients, 10.9%), quetiapine (25 patients, 9.4%), aripiprazole (3 patients, 1.1%) and ziprasidone (1 patient, 0.4%).

Table 1. Demographic Profile of Patients on Second-generation Antipsychotics

		No. of patients	%
Gender	Male	91	34.2
	Female	175	65.8
Race	Chinese	213	80.1
	Malay	29	10.9
	Indian	16	6.0
	Others	8	3.0
Age group (y)	<20	13	4.9
	21-30	46	17.3
	31-40	68	25.05
	41-50	72	27.1
	51-60	44	16.6
	61-70	9	3.3
	>70	14	5.3

The mean baseline BMI was 23.08 (minimum 13.0, maximum 39.9, mode 24). Baseline BMI measurements revealed that 135 patients (50.8%) were in the normal range, 89 (33.5%) were in the moderately obese range and 42 (15.8%) in the obese range. Similarly, for the WHR, 144 patients (54.1%) were in the normal range and 122 patients (45.9%) were in the unhealthy range. Of the 122 patients in the latter group, 73 patients (59.8%) also had moderate or high BMIs.

For 44 patients (16.5%), there were no repeat weight measures for various reasons such as follow-up default and medication non-compliance. Of the 222 patients for whom there was regular monitoring, 48 patients (21.6%) had no weight gain and 174 (78.4%) had a mean weight gain of 1.9 kg with a maximum recorded at 20.1 kg.

The weight increase was mainly for those on risperidone (103 patients, 60.5%), olanzapine (30 patients, 17.6%), clozapine (21 patients, 11.6%), quetiapine (14 patients, 8.2%), aripiprazole (2 patients, 1.2%) and ziprasidone (1 patient, 0.6%). Weight gain liability was in the following order: clozapine (72.4%), olanzapine (66.7%), risperidone (65%), quetiapine (56%) and aripiprazole (66.6%) (Table 2).

Most of the weight increase occurred in the first 4 weeks in 82 patients (47.1%) and almost all those who had gained

Table 2. Patients on Second-generation Antipsychotics with Weight Gain

	Name of drugs	No. of Patients	%	No. of patients with weight increase	%
1	Risperidone	163	61.3	103	60.5
2	Olanzapine	45	16.9	30	17.6
3	Clozapine	29	10.9	21	11.6
4	Quetiapine	25	9.4	14	8.2
5	Aripiprazole	3	1.1	2	1.2
6	Ziprasidone	1	4	1	0.6
	Total	266	100	171	100

weight had done so by 6 months (167 patients, 95.9%). Other patients showed weight gain by 9 months (2 patients), 12 months (2 patients) and 18 months (2 patients) and 1 patient by 24 months.

The mean weight gain at 4 weeks was 2.03 kg (± 1.73), at 8 weeks was 3.74 kg (± 3.36), with the maximum weight gain at 12 weeks at 3.89 kg (± 4.14), and then tailing down thereafter to 3.41 kg (± 2.62) at 6 months, 1.00 kg (± 0.42) at 9 months, 1.15 kg (± 1.48) at 12 months and 1.40 kg (± 0.28) at 18 months. Using linear regression, the most significant weight gain was in the first 12 weeks; rate of increase was 0.26 kg (95% CI, 0.119 to 0.410; $P < 0.001$).

The maximum weight gain was seen at 12 weeks for risperidone but earlier at 8 weeks for clozapine (after which it tapers off), olanzapine (which also has a second peak at 6 months) and quetiapine (which showed a decrease thereafter). At 12 weeks, the rate of increase with risperidone was 0.37 kg/week (95% CI, 0.1888 to 0.556). For clozapine and olanzapine at 8 weeks it was 2.62 kg/week (95% CI, -0.203 to 5.445) and 2.78 kg/week (95% CI, -0.452 to 6.005).

Amongst the 266 patients who were started on SGAs, 23 patients (8.6%) had hypertension, 14 patients (5.3%) already had a history of diabetes, 14 (5.3%) had hyperlipidaemia, 3 (1.1%) had stroke, 1 had ischaemic heart disease and 6 (2.3%) were smokers. Eleven of the 14 diabetic patients had weight gain.

Discussion

The prevalence of overweight among Singapore adults increased between 1985 and 1998 and the proportion of obese adults aged 18 to 69 years old was 6.9% in 2004.¹⁴ Obesity was more prevalent among females (7.3%) compared with males (6.4%) and Malays had the highest proportion of obese adults (19.1%) followed by Indians (13.4%) and Chinese (4.2%). Global trends in obesity prevalence similarly showed little change from 1960 to 1980, then a marked increase to 28% in men and 34% in

females in 2000 in the US and 10% to 20% of men and 10% to 25% of women in Europe in 2002.¹⁵

The main concern about weight gain is the risk of obesity which contributes to the development of other metabolic risk factors such as hypertension, type 2 diabetes and dyslipidaemia and the metabolic syndrome. Patients with schizophrenia have poor health and unhealthy lifestyles. Studies have shown that they are twice as likely to die of cardiovascular disease compared to the general population because of higher rates of obesity.^{16,17} Recent research has estimated that while clozapine may decrease suicidal behaviour in 492 of 100,000 schizophrenia patients over a 10-year period, the weight gain induced by clozapine would be expected to result in 416 additional deaths.¹⁸

There is consistent evidence that SGAs associated with more weight gain such as clozapine and olanzapine are associated with an increased risk of diabetes, hyperglycaemia and dyslipidaemia.³ Higher risk is also associated with female gender, overweight patients and those on treatment for up to a year.¹⁹

“Clinically significant” weight gain is commonly defined as a $\geq 7\%$ increase in body weight from baseline.²⁰ Pharmaceutical companies use this definition on their product labels and report weight gain of 29% for olanzapine, 23% for quetiapine, 18% for risperidone, 10% for ziprasidone and 8% for aripiprazole. Wirshing et al²¹ in reviewing 8 antipsychotic efficacy studies during a period of 6 years involving 92 male patients with schizophrenia found that weight gain plateaued at 20 weeks with olanzapine and clozapine versus 10 weeks with risperidone and sertindole.

The exact mechanisms by which antipsychotic medications cause weight gain is poorly understood although genetic, environmental and neurobiological mechanisms have been implicated.²² The correlation between histamine receptors and weight gain is supported by the high rates of weight gain with olanzapine which has the highest affinity for histamine receptors. Those with the lowest affinities, ziprasidone and aripiprazole have the lowest risk of weight gain. Other neurotransmitter systems thought to be involved include serotonin antagonism at 5HT_{2c} receptors and dopamine antagonism.²³ Studies in mice have shown that serotonin receptor 5-HT_{2c} blockade is associated with increased appetite and obesity. However recent work by Wirshing does not support the finding.²¹ γ -aminobutyric acid (GABA) is reported to promote weight gain and decrease glutamatergic function which causes weight loss. In animal studies, agonists at the glutamate N-methyl D-aspartate (NMDA) receptor stimulate feeding behaviour. It is hypothesised that anti-psychotics that alter the GABA-glutamate balance may cause weight gain.²⁴

Changes in hormonal levels may affect the sensitivity of satiety centres in the hypothalamus. Anti-psychotics

(FGAs and risperidone) which elevate prolactin levels may directly promote weight gain by decreasing insulin sensitivity or indirectly affecting androgen/oestrogen ratios which lead to weight dysregulation.²⁴ The adipocyte-derived hormone leptin has been associated with body weight and a recent study in a Chinese population showed a significant relationship between the 3 leptin G/A genotypes and mean BMI gain particularly in male schizophrenia patients on long-term clozapine.⁴

There are limitations associated with this project. While it is a prospective review, it was basically a safety and clinical quality improvement initiative. We did not design the project to evaluate the risk of increased weight that is specifically attributable to the SGAs. There was no attempt to control patients in terms of prior anti-psychotic treatment which would have contributed to the higher baseline weight. History of prior FGA treatment and use of other medications such as mood stabilisers and the type, dosage and length of treatment would have been useful in the analysis. A research study would have analysed only the 135 patients whose BMI were in the normal range at baseline and there would have been stricter attempts at monitoring without loss of repeat weight measures for 44 patients.

Neither was there a detailed study of lifestyle and dietary habits which also contribute to weight gain. In addition as it was a naturalistic project, there was no attempt to control which SGA was chosen; the doses of SGA used and the rate of titration was entirely a clinical decision left to the individual psychiatrists. The project also overshadows a compelling possibility that psychiatric patients such as normal Singapore adults may also be facing an increasing prevalence of overweight and obesity irrespective of antipsychotic treatment. Nonetheless, the project has served to highlight and give credence to the clinical view that Asian patients also experience weight gain with SGAs. Hence, caution is needed with SGA use with careful decision-making and patient consultation. Local patients need to be advised on the risks of weight gain; comprehensive psychoeducation and regular monitoring are imperative for all patients started on SGAs.

Conclusion

The SGAs are recognisably the most effective treatment for schizophrenia at present. However, as clinicians we must try to achieve the most favourable risk-benefit ratio for patients. Treatment with SGAs produces a range of increases in mean body weight particularly in the first 6 months. The highest risk of weight gain was seen with clozapine and olanzapine. This is consistent with findings in Western populations and warrants close monitoring for metabolic adverse events in other ethnic groups.

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