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Association Between Weight Gain and Remission Status at 3 Months in First-Episode Schizophrenia

To the Editors:

Weight gain is a well-known and unwanted adverse effect of antipsychotic medication in people with schizophrenia associated with numerous metabolic disorders. Interestingly, findings from several studies as early as the 1950s[1,2] have shown weight gain to be associated with symptom improvement. This has brought forth the concept of the "metabolic threshold," which states that metabolic abnormalities have some role in the clinical efficacy of antipsychotics.[3]

A recent review examined 15 studies on the association between weight gain and clinical improvement.[4] Although most studies reported an association, a key limitation identified was the absence of truly clinically significant improvement such as remission.[5] Furthermore, 2 studies, which explored symptom dimensions individually, found the most significant associations with changes in general psychopathology, rather than key symptom constructs of schizophrenia, namely, positive and negative symptoms.[6,7] Finally, publication bias was possible—14 of the 15 reviewed studies reported a positive association between weight gain and symptomatic improvement. In this study, we examined the relationship between clinically significant weight gain and symptomatic remission in individuals with first-episode schizophrenia. In line with evidence from previous research, we hypothesized that weight gain would be associated with remission.

Participants were recruited from a naturalistic study on first-episode psychosis conducted at the Institute of Mental Health, Singapore. Inclusion criteria were the following: a *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder; experiencing their first psychotic episode; and, having less than 4 weeks of antipsychotic treatment prior to study entry. Height and weight were measured at recruitment and at a 3-month follow-up. Antipsychotic prescription information was obtained at 3 months and doses were converted into total daily chlorpromazine equivalents.[8] Diagnosis was ascertained using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision*, and psychopathology was rated on the Positive and Negative Syndrome Scale (PANSS). Remission status was defined at 3 months using the proposed criteria by Andreasen et al.[5] Clinically significant weight gain was defined as a 7% or more increase from baseline to 3 months. Descriptive statistics compared baseline and follow-up characteristics of remitters and nonremitters. Statistical analyses were performed using the χ^2 test for categorical variables, the Student t test for normally distributed continuous variables, and the Mann-Whitney U test for nonnormally distributed continuous variables. The χ^2 test was also used to calculate the odds ratio and confidence interval of weight gain compared with remission. The formula by Leucht et al[9] was used to calculate the relative (percentage) change in PANSS from baseline to 3 months; this included the total score and the scores for positive symptom, negative symptom, and general pathophysiology subscales. Spearman ρ was used to examine correlation between change in PANSS scores and weight gain.

Thirty-one participants were included in this study; 21 (67.7%) achieved symptomatic remission at 3 months. There were no significant differences in demographics, baseline symptom severity, and treatment between nonremitters and remitters (Table 1). Weight gain was not significantly different between nonremitters and remitters (5.3% vs 8.9%, respectively; $P = 0.291$); furthermore, the presence of clinically significant weight gain was not significantly associated with remission (odds ratio, 2.12; confidence interval, 0.43–10.52). Weight gain was inversely correlated with change in general psychopathology subscale ($r = -0.363$, $P = 0.044$), and change in total PANSS score ($r = -0.419$, $P = 0.019$), but not with positive ($r = -0.261$, $P = 0.157$) and negative ($r = 0.251$, $p = 0.197$) subscales.

DISCUSSION

We found that weight gain was associated with symptomatic improvement, specifically in general psychopathology. This finding supports the trends observed in previous studies.[6,7] However, we found no significant difference between weight gain and remission status at 3 months.

Our findings seem to be incongruent with other studies, which report that weight gain is correlated with symptom improvement; we propose several explanations for this.[1,10,11] Although our results showed an improvement in both total PANSS and general psychopathology scores, there was no improvement in positive and negative symptom scores, which predominantly define remission status; 2 other studies showed similar correlations of weight gain and improvement in general symptoms.[6,7] Conversely, most other investigations have reported symptom improvement as a whole and not as separate symptom dimensions. Therefore, overall symptom improvement could have been attributed to an improvement in general symptoms in most of these studies, which would not truly be indicative of an improvement in schizophrenia symptoms. More work could be conducted to precisely characterize symptom improvement, differentiating clinically significant and schizophrenia-specific improvement (positive and negative symptoms) from nonspecific improvement (general symptoms).

We also raise the issue of publication bias. In other studies, the clinical significance of weight gain that showed a positive finding has been reported to be small, with most reports demonstrating correlational significance. This raises concerns regarding publication bias as only 1 of the 15 reviewed studies reported no association between weight gain and clinical improvement. Our findings lend support to this single report, and going forward, we suggest that findings from future studies, regardless of statistical significance, be encouraged to address this issue.[12]

Our third point relates to the definition of metabolic threshold, which states that symptomatic improvement necessitates preceding metabolic changes, including weight gain and obesity. However, and as discussed previously, the improvement in general symptomatology is not specific to schizophrenia. The relationship between weight gain and symptomatic improvement is complex; for example, adherence has been shown to be a key predictor of symptomatic improvement.[13,14] Accordingly, weight gain might be an indicator of adherence, which, in fact, may be the determinant in clinical outcome.[15] The metabolic threshold also fails to explain why antipsychotics with vastly dissimilar metabolic profiles effect similar degrees of symptomatic improvement. Aripiprazole, amisulpride, and haloperidol are examples of weight-neutral antipsychotics, which are comparably efficacious and yet confer only little or no weight gain.[10,16] Such a discrepancy refutes the metabolic threshold.

TABLE 1. Characteristics of Study Sample

	Total	Nonremission* (n = 10)	Remission* (n = 21)	$p^{\dagger}$
Sex, n (%)				0.901
Male	15 (48.3)	5 (50)	10 (47.6)	
Female	16 (51.6)	5 (50)	11 (52.3)	
Age at recruitment, mean (SD), y	30.7 (8.6)	33.7 (11.3)	29.3 (6.9)	0.374
Ethnicity, n (%)				0.540
Chinese	19 (61.2)	6 (60)	13 (61.9)	
Malay	10 (32.2)	4 (40)	6 (28.5)	
Indian	2 (6.4)	0 (0)	2 (9.5)	
Diagnosis, n (%)				0.322
Schizophrenia	23 (74.1)	9 (90)	14 (66.6)	
Schizophreniform disorder	3 (9.6)	0 (0)	3 (14.2)	
Schizoaffective disorder	5 (16.1)	1 (10)	4 (19)	
Duration of untreated psychosis, median (range), wk	51.4 (1039)	47.1 (1038)	51.4 (258)	0.687
Antipsychotic type at 3 mo, n (%)				
Typical	6 (19.3)	2 (20)	4 (19)	
Haloperidol		2 (20)	3 (16)	
Fluphenazine		0 (0)	1 (3)	
Atypical	23 (74.1)	7 (70)	16 (76)	
Risperidone		5 (50)	14 (66.5)	
Olanzapine		1 (10)	2 (9.5)	0.849
Quetiapine		1 (10)		
Typical and atypical	2 (6.4)	1 (10)	1 (5)	
Olanzapine and haloperidol		1 (10)	0 (0)	
Olanzapine and depot flupenthixol decanoate			1 (5)	
Antipsychotic dose at 3 mo, CPZeq,[‡] median (range), mg	150 (1125)	150 (475)	113 (1125)	0.164
Baseline PANSS score, mean (SD)				
Total	67.9 (13.3)	68.6 (15.7)	67.6 (12.4)	0.859
Positive symptoms	17.8 (6)	16.6 (5.6)	18.4 (6.2)	0.424
Negative symptoms	16.5 (6.3)	18.9 (6.4)	15.3 (6.0)	0.156
General psychopathology	33.5 (6.9)	33.1 (6.5)	33.8 (7.3)	0.795
BMI at baseline,[§] mean (SD)	22.7 (5.4)	24.5 (6.9)	21.8 (4.5)	0.191
≥7% weight gain at 3 mo, n (%)				0.452
No	18 (58.1)	7 (70)	11 (52.4)	
Yes	13 (41.9)	3 (30)	10 (47.6)	

*Remission status at 3 mo.

[†]*P* value comparing remission and nonremission groups at 3 mo.

[‡]Chlorpromazine equivalent (mg)

[§]Body mass index.

More importantly, regardless of remission status, our study showed that a sizeable proportion of individuals with first-episode schizophrenia developed clinically significant weight gain for a 3-month period. This change has the potential to effect subsequent morbidity and mortality.[17] Therefore, it is crucial that clinicians take steps to prevent and manage the metabolic abnormalities associated with schizophrenia and not perceive weight gain as a "necessary evil" in improving symptoms.

The strengths of this study include the use of a validated clinical outcome (ie, remission) to determine clinical improvement.[5] The naturalistic setting of the study is also a strength because findings can be generalized to real-world clinical settings, but the heterogeneity of antipsychotic prescriptions might have confounded the study findings. Limitations include the short 3-month duration of follow-up, which could have restricted the amount of weight gain. In the literature, the minimum time frame required before a clinically significant weight gain occurs ranges from 3 weeks to 6–12 months of antipsychotic treatment.[12,18] Therefore, it is plausible that with a longer follow-up duration, a greater proportion of our sample might have achieved clinically significant weight gain. The possibility of a type 2 error with the small study sample size also cannot be excluded. Finally, physical activity and dietary intake were not assessed, which could have had significant effects on weight gain.

In conclusion, although our study found a significant association between weight gain and clinical improvement, there was no significant difference in weight gain and remission status at 3 months. We urge that future studies employ clinically relevant outcome criteria such as remission and/or specific symptom domains, to derive more meaningful interpretations of weight gain. Finally, regardless of the place of metabolic threshold, it is imperative that morbidity and mortality secondary to metabolic disorders remain as key clinical concerns.

AUTHOR DISCLOSURE INFORMATION

This study was funded by the Singapore National Healthcare Group Small Innovative Grant I (SIG/08016). Dr Lee is further supported by the Singapore Ministry of Health's National Medical Research Council under its Transition Award (Grant Number NMRC/TA/002/2012). Dr Remington has received research support, consulting fees, or speaker's fees from the Canadian Diabetes Association, the Canadian Institutes of Health Research, Laboratorios Farmacéuticos Rovi, Medicure, Neurocrine Biosciences, Novartis Canada, Research Hospital Fund-Canada Foundation for Innovation, and the Schizophrenia Society of Ontario.

Oh and See have no financial interests to declare.

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Comparison of Treatment Retention Between Risperidone Long-Acting Injection and First-Generation Long-Acting Injections in Patients With Schizophrenia for 5 Years

To the Editors:

Schizophrenia is a chronic disease that requires long-term management with antipsychotics; however, an important barrier to the success of long-term treatment is drug noncompliance, which increases the risk of recurrence and hospitalization.[1] On the other hand, effectiveness is taken into account when integrating the parameters of efficacy, safety, and tolerability from the point of view of patients and psychiatrists. Continuation rate can be used as an alternative parameter to effectiveness.[2] Against this background, a recent effectiveness study reaffirmed that reliable treatment continuation afforded by long-acting injections (LAIs) is effective at preventing rehospitalization.[3] However, there have been no naturalistic reports in Japan clarifying the treatment retention using risperidone long-acting injection (RLAI) or first-generation antipsychotics (FGA) LAIs for 5 years. We retrospectively investigated the treatment retention using RLAI or FGA LAIs for 5 years in clinical setting.

This was a retrospective cohort study involving patients who were administered RLAI, fluphenazine decanoate, or haloperidol decanoate between September 2005 and July 2014 on an inpatient or an outpatient basis at the psychiatry department of Fukui Kinen Hospital or Tanzawa Hospital. All subjects had been diagnosed with schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. The treating psychiatrists judged whether treatment with LAIs should be continued on the basis of patient's response. Patients who were taking other oral antipsychotics, mood stabilizers, benzodiazepines, and anticholinergics were included. To evaluate treatment continuation or discontinuation rates, we retrospectively reviewed patient records from initiation of treatment to the latest visit day in July 2014. Treatment continuation was defined as continuation of LAIs until the latest visit day in July 2014. We counted the time (weeks) until discontinuation of treatment because of all causes until the latest visit day in July 2014.

The treatment continuation rate was estimated using a Kaplan-Meier survival analysis. The treatment groups were compared using a Cox proportional hazard model. The significance level was less than 0.05. All analyses were performed using Stat View by Abacus Concepts.

Of the 400 patients, 219 received RLAI, 67 received fluphenazine decanoate, and 114 received haloperidol decanoate. There were no significant differences between RLAI, fluphenazine decanoate, and haloperidol decanoate in sex (male/female) (103/116 [47%/53%], 33/34 [49%/51%], and 55/59 [48%/52%]), mean subject age (42.5 ± 14.8 years, 42.3 ± 14.7 years, and 43.0 ± 13.9 years), and mean duration of illness (18.0 ± 11.3 years, 16.0 ± 12.0 years, and 17.3 ± 11.2 years). The average dose of RLAI, fluphenazine decanoate, and haloperidol decanoate was 42.7 ± 11.2 mg (12.5–50), 26.6 ± 20.9 mg (6.25–150), and 97.0 ± 47.3 mg (12.5–200), respectively. The continuation rate results are shown in Figure 1. The reasons for discontinuation of RLAI were patient's decision (n = 52), insufficient efficacy (n = 30), side effects (n = 13), transfer to another hospital (n = 30), death (n = 2), and unknown (n = 4). On the other hand, the reasons for discontinuation of fluphenazine decanoate and haloperidol decanoate were patient's decision (n = 20, n = 31), insufficient efficacy (n = 12, n = 21), side effects (n = 14, n = 25), transfer to another hospital (n = 5, n = 5), and unknown (n = 3, n = 2). Because the reason for transfer to another hospital was not related to the symptoms of the patient, these discontinuation cases were omitted from the analysis. The time until RLAI discontinuation owing to any reason was longer than that with fluphenazine decanoate (hazard ratio [HR] (95% CI), 0.37 (0.24–0.55); $P < 0.001$) and haloperidol decanoate (hazard ratio [HR] (95% CI),