Drug Safety 2006; 29 (6): 550-552
0114-5916/06/0006-0550/$39.95/0

Long-Term Treatment with Atypical Antipsychotics and Risk of Weight Gain

A recent article published in this journal by Gentile[1] showed that atypical antipsychotic treatment of schizophrenia is associated with significant weight gain. Thus, methods to decrease or reverse the weight gain associated with these agents are of interest. Three recent publications (one small study and two case reports) present weight change data indicating weight loss for patients switched from oral olanzapine (Zyprexa®) [1] to fast-dissolution (FD) olanzapine.[2-4] Although the sample size was small (n = 11) and patients were young in two of these papers,[2,4] the findings of these papers merit investigating since patient with schizophrenia faces weight-gain problems and consequences. However, in an earlier study by Kinon et al.,[5] where the majority of patients took olanzapine FD for the study duration, the mean weight gain found was not suggestive of a weight-loss effect with olanzapine FD. This study was an open-label 6-week study of olanzapine FD that started with 85 patients. All patients received olanzapine FD for 1 week and were given the option to remain on olanzapine FD (n = 49) for the remaining time in study or to switch to oral olanzapine (n = 24). The study report lists only mean weight gain (2.96 [SD 3.62] kg) for the whole sample. In the crucial CATIE (Clinical Antipsychotic Trial of Intervention Effectiveness) trial,[6] olanzapine was associated with weight gain even when its effectiveness as an antipsychotic was well appreciated.

Many clinicians are on the trail of a weight-gain stabiliser to improve the global effectiveness of treatment. There are already numerous psychiatrists who have started switching their patients from oral olanzapine to olanzapine FD. Since some of the patients have already shown the possibility of controlling weight, it was suggested that such weight changes due to switching would be recorded in an academic setting, such as the Louis-Hippolyte Lafontaine Hospital, University of Montreal in Canada. Here we present the results collected from 33 patients with schizophrenia who were followed by the Clinical Department of Psychiatry during a period of 4 months after the switch. During this naturalistic study, psychiatrists followed their patients and prescribed treatment as usual. Patients receiving oral olanzapine and wishing to switch to an FD formulation, in this case Zydis®, were asked to document their weight at baseline and 4 months after receiving their first FD dose. The objective weight change data were collected by clinicians. The mean dosage of olanzapine was 13.5 mg/day. Results show that 10 of 33 patients (30%) gained weight; 20 patients lost weight or did not gain any (60%) and 3 patients were not included in the analysis because their prescriptions were changed to another antipsychotic. Four patients gained ≤1kg. One outlier gained 6kg and five gain a mean of 3kg; one lost 14kg and one lost 11kg. The mean of weight loss was 1.24 (SD = 4.08) kg. The mean duration between the beginning of olanzapine treatment and the switch to olanzapine FD was 43.3 months.

The take-home message is firstly that treatment with Zydis® was related to weight stability except in a minority of patients and one outlier. Secondly, the finding of reduced weight with the FD medication must still be considered extremely tentative, although the case could be made that a more definitive trial is now justified. Thirdly, the mechanism through which olanzapine FD produces less weight gain relative to oral olanzapine is unknown. Sixty percent of our patients were able to lose weight or remain stable while receiving a medication that effectively controlled their symptoms. Hypotheses on mechanism are still unclear but may be linked to peripheral serotonin receptors (specifically 5-HT_{2C}). Olanzapine has a high affinity for 5-HT_{2C} receptors.[7] Most of the receptors upon which olanzapine acts are represented in the gastric tract and several of these receptors have been implicated

1 The use of trade names is for product identification purposes only and does not imply endorsement.

in weight gain.[8] Since 5-HT_{2C} receptors in the pylorus are thought to mediate satiety,[2] the antagonism of these receptors by olanzapine can increase appetite. Because of its fast dissolution, olanzapine FD could result in an absorption occurring prior to the level of the pylorus. However, although such receptors are known to exist in rat pylorus, they have yet to be documented in human pylorus.[9] The manufacturer has reported bioequivalence of the two formulations which presumably implies similar kinetics for both the oral and FD formulations including AUC, t_{max} and C_{max}. In any event, rapid dissolution in the mouth does not necessarily mean rapid gastric absorption. Olanzapine is a base (multiple amine groups) and would be ionised in the acid milieu of the stomach and thus not well absorbed, which is in contrast with the alkaline environment of the small intestine. Thus, absorption of newer formulation prior to the level of the pylorus, as postulated, seems unlikely. However, Markowitz et al.[10] recently found that at least some absorption of Zydis® occurs rapidly before the pylorus, both via the regular route and the sublingual route. Further studies using a randomised controlled trial design are necessary to confirm the weight loss observed in these patients. Indeed, the PLATYPUS study is new in the public domain registered at clinicaltrial.gov.

Emmanuel Stip,[1] *Karyne Anselmo*,[2] *Marcel Wolfe*,[1] *Christiane Lessard*[3] and *Pierre Landry*[1]

1 Department of Psychiatry, Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Université de Montréal, Montréal, Québec, Canada

2 Department of Pharmacology, Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Université de Montréal, Montreal, Quebec, Canada

3 Department of Pharmacy, Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Université de Montréal, Montreal, Quebec, Canada

Acknowledgements

The authors have no conflicts of interest that are directly relevant to the content of this letter.

References

1. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain: a literature analysis. Drug Saf 2006; 29 (4): 303-19
2. De Haan L, Van Amelsvoort T, Rosien K, et al. Weight loss after switching from conventional olanzapine tablets to orally disintegrating olanzapine tablets. Psychopharmacology 2004; 175: 389-90
3. Tiedge UA. Vorteile durch Umstellung von der Olanzapin-Filmtablette auf die Schmelztablette. Nervenheilkunde 2005; 3: 232
4. Joseph A. Normalisierung des Kôrpergewichts – Umstellung von Olanzapin-Filmtabletten auf Schmelztabletten. Psychoneuro 2005; 31: 408
5. Kinon BJ, Hill AL, Liu H, et al. Olanzapine orally disintegrating tablets in the treatment of acutely ill non-compliant patients with schizophrenia. Int J Neuropsychopharmacol 2003; 6 (2): 97-102
6. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353 (12): 1209-23
7. Rues VI. Olanzapine: a novel atypical neuroleptic agent. Lancet 1997; 349: 1264-5
8. Rauser L, Savage JE, Meltzer HY, et al. Inverse agonist actions of typical and atypical antipsychotic drugs at the human 5-hydroxytryptamine(2C) receptor. J Pharmacol Exp Ther 2001; 299 (1): 83-9
9. Eberle-Wang K, Braun BT, Simansky KJ. Serotonin contracts the isolated rat pylons via a 5-HT_2-like receptor. Am J Physiol 1994 Jan; 266 (1 Pt 2): R284-91
10. Markowitz JS, DeVane CL, Malcolm RJ, et al. Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. J Clin Pharmacol 2006 Feb; 46 (2): 164-71