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To: Mackin P, Watkinson HM, Young AH (2005) Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. *Diabetologia* 48:215–221

Received: 17 March 2005 / Accepted: 23 March 2005 / Published online: 3 June 2005
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To the Editor: We read with great interest the recently published paper by Mackin and colleagues on the prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking first-generation antipsychotics (FGAs) or second-generation antipsychotics (SGAs) [1]. In a cross-sectional study, the authors investigated whether FGAs or SGAs induce a greater degree of metabolic dysfunction. Metabolic parameters were determined in 103 diagnostically heterogeneous psychiatric outpatients who had been taking FGAs or SGAs for at least 6 months. The authors conclude that patients taking SGAs are more prone to abnormalities in glucose homeostasis, and furthermore, that prospective studies are needed to explore the precise relationship between antipsychotic drugs, glucose homeostasis, obesity and the metabolic syndrome.

In this article, the authors cite the prospective study of Lindenmayer et al [2], who assessed the effects of clozapine, olanzapine, risperidone and haloperidol on glucose and cholesterol levels in 101 hospitalised patients with schizophrenia or schizoaffective disorder during a randomised double-blind 14-week trial. Lindenmayer et al drew the conclusion that clozapine, olanzapine and haloperidol were associated with an increase in plasma glucose

level. Approximately 14% of the patients under investigation developed abnormally high glucose levels during the course of the study [2].

However, several other prospective studies on antipsychotic-drug-induced dysregulation of glucose homeostasis and weight gain were published before the paper by Mackin et al was accepted by *Diabetologia*. These groups reported the results of prospective studies on weight gain and obesity in patients treated with SGAs (for review see [3, 4]). In addition, the Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes concluded on the basis of these studies that olanzapine and clozapine induce the highest degree of weight gain.

To our knowledge, at least three other prospective studies have been published with respect to glucose metabolism.

In the April 2001 issue of *Human Psychopharmacology*, Chae and Kang examined the effect of clozapine on blood glucose metabolism for 8 weeks as compared with the effect of haloperidol ($n=19$ and $n=15$, respectively) [5]. The clozapine group had a higher degree of impaired glucose tolerance and a longer glycaemia peak delay than the haloperidol group, although these effects were not statistically significant.

In the February 2004 issue of the *American Journal of Psychiatry*, Howes et al reported the results of their prospective study on the impairment of glucose control caused by clozapine, with no change in insulin resistance [6]. Glucose homeostasis was measured in nine female and 11 male patients with schizophrenia before and after clozapine treatment (mean treatment period of 2.5 months). The authors concluded from their study that clozapine impairs glucose control within 4 months of treatment, independently of changes in insulin sensitivity and body mass index.

Finally, our group published an article in the December 2003 issue of the *Journal of Clinical Psychiatry* entitled 'Olanzapine induces insulin resistance: results from a pro-

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spective study'. In this study we investigated glucose homeostasis in patients treated with olanzapine for 8 weeks and in control subjects. The olanzapine-treated patients gained weight, mainly due to an increase in fat mass, and in parallel, leptin levels increased [7]. Olanzapine medication disturbed the glucose homeostasis substantially. The homeostasis model assessment (HOMA) index for beta cell function did not change significantly, but the HOMA index for insulin resistance increased in the olanzapine-treated patients. This study indicated that the disturbances in glucose homeostasis in patients during SGA treatment with olanzapine were mainly due to insulin resistance, while beta cell function remained unaltered [8]. To further explore the pathogenesis of glucose homeostasis dysregulation, we measured the blood levels of several insulin-resistance-inducing factors [9] and of the soluble leptin receptor [10]. As these factors remained unaltered, we concluded that a pathway via the central nervous system, or a direct insulin-resistance-inducing effect of olanzapine in the liver or skeletal muscle cells, might be responsible for alterations in insulin sensitivity.

Taken together, these four studies, published before the paper by Mackin et al was accepted by *Diabetologia*, provide the prospective data on 165 patients treated with olanzapine or clozapine for at least 8 weeks. However, we agree with Mackin et al that large, prospective and long-term studies are needed to explore the precise relationship between antipsychotics, glucose homeostasis, obesity and the metabolic syndrome.

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