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Reply to Ebenbichler *et al*

Reply: 'Second Generation Antipsychotic Drugs: Is There a Common Mechanism in the Development of Obesity?'

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Sir

We would like to thank Dr Ebenbichler and co-workers for their comments and express common interest in a multidisciplinary hypothesis regarding the effects of second generation antipsychotic (SGA) drugs. Even though a unifying mechanism and primary sites of action have not yet been defined, their observations open up an excellent opportunity for a more global perspective. Given the complexity of the pathogenesis of type II diabetes, it is challenging to understand the role that SGAs play in the progression to insulin resistance and diabetes (O'Neill, 2005). This topic has been intensely debated in the literature and considerable evidence points to a variety of adverse physiological effects, including dyslipidemia (Meyer and Koro, 2004), hyperglycemia (Mackin *et al*, 2005), and increased leptin levels (Zhang *et al*, 2004). The mechanisms underlying the association of SGA medication with increased prevalence of weight gain and diabetes are multifactorial (Nasrallah, 2003). Certainly, the studies carried out by our laboratory showing a direct and differential effect of antipsychotic agents in adipocytes help to elucidate how cell enlargement may occur and ultimately play a role in body fat distribution and obesity that is seen with the use of SGAs. In addition, other studies focusing on different organs have reported evidence of adverse effects of the drugs (Schwenkreis and Assion, 2004; Horacek *et al*, 2006; Richards *et al*, 2006). Moreover, second-generation antipsychotic agents vary significantly in their risk for diabetes and their effects on glucose and lipid metabolism (Newcomer, 2005). More importantly yet, this risk may be correlated with drug concentration in blood (or plasma, or serum), and levels reached at the site of therapeutic and/or toxic effect (s) (Medori *et al*, 2006).

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The comments of Dr Ebenbichler and co-workers are constructive and support the body of evidence behind the incidence of diabetes in schizophrenic patients on SGAs. Furthermore, the reports of Ebenbichler and co-workers on insulin signaling pathways in muscle (Engl *et al*, 2005) may create additional hypothesis-driven research directed toward understanding molecular mechanisms that promote poor cellular response in insulin target tissues. Conversely, attention should also be given to neuroendocrine aspects of schizophrenia when it comes to carbohydrate abnormalities. Neuroendocrine dysfunction has been documented in those subjects (Tandon and Halbreich, 2003), particularly hypercortisolemia, which increases the risk for comorbid diabetes even before treatment with SGAs is initiated. This might be a condition where plasma concentrations of SGAs would be critical to activate malfunctioning of insulin-target tissues. To make matters even more complex, genetic polymorphism has been implicated in the SGA-induced weight gain (Reynolds *et al*, 2005). Therefore, the association between these polymorphisms and the symptom responses to antipsychotic treatment and side effects of such treatment, notably weight gain, should be further investigated as well, and related to the presumed functionality of these polymorphisms. Such studies clearly demonstrate the potential of pharmacogenetics in optimizing treatment for the individual patient.

DISCLOSURE/CONFLICT OF INTEREST

We disclose that there are no conflicts of interest for any of the authors relating to this submission.

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