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COMMENTARY

Mind the mortality gap: the importance of metabolic function in mental illnesses

Oliver D. Howes · Katherine Beck

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It has become increasingly apparent that severe mental illnesses are associated with physical ill health as well. This is important: people with major mental illness die, on average, two decades earlier than the general population (Tiihonen et al. 2009) and physical illnesses, such as heart disease, are major contributors to this premature mortality (Mottillo et al. 2010; Saha et al. 2007).

One underlying mechanism that could contribute to this increased risk of heart disease is altered metabolic function and the development of the metabolic syndrome—the combination of obesity, glucodysregulation, dyslipidaemia, and hypertension (Mannucci et al. 2008). Over the last year or so, a number of papers in *Psychopharmacology* have examined the effects of psychotropic drugs on metabolic function and other aspects of physical health (Yan et al. 2013; Amrami-Weizman et al. 2013; Vieweg et al. 2013; Konopaske et al. 2013; Joshi et al. 2013; Santarelli et al. 2013; Kiyatkin 2013; Ou et al. 2013; Ogasa et al. 2013; Davey et al. 2012; Jassim et al. 2012; Kim et al. 2013). Three papers in this issue extend this to address aspects of metabolic function in patients with mental disorders (Amrami-Weizman et al. 2013; Sagud et al. 2013; Hu et al. 2013). The first finding, little remarked upon by Sagud et al. in their paper (Sagud et al. 2013), is that metabolic syndrome is common in major depressive disorder: seen in about one third of patients in comparison to about one fifth of the general population (Beltran-Sanchez et al. 2013). This is so common as to suggest we should routinely be evaluating this in our patients with major depression. Sagud et al. also found that treatment resistance was common in major depression. However, they did not find a difference in prevalence of metabolic syndrome between patients who had responded to treatment and those who had not.

O. D. Howes (✉) · K. Beck
Institute of Psychiatry and Clinical Sciences Centre, London, UK
e-mail: oliver.howes@kcl.ac.uk

One common factor that could contribute to the high prevalence of metabolic syndrome in both the resistant and responder patient groups is treatment with psychotropic medication. Among psychotropic drugs, antipsychotics have been particularly linked to metabolic dysregulation (Howes et al. 2004a; Nielsen et al. 2010). Significant alterations in glucose homeostasis, and even diabetic ketoacidosis, can occur soon after starting an antipsychotic (Guenette et al. 2013; Howes et al. 2004b), and there have even been fatal cases of diabetic ketoacidosis associated with antipsychotic treatment (Guenette et al. 2013). Clearly, it is important to understand the impact of these drugs on metabolic function, and how to alleviate their effects.

In this month's issue of *Psychopharmacology*, Hu et al. report the effects of two antipsychotics, paliperidone and olanzapine, on metabolic indices and other components of the metabolic syndrome (Hu et al. 2013). One aspect of their patient sample that distinguishes it from other studies is that the patient group did not show metabolic risk factors when entering the study. Despite this, treatment with antipsychotic drugs was associated with significant increases in a range of metabolic indicators over the course of the 12-week trial. Hu et al. did not find major differences between the two drugs, although there is a hint that some indices, notably fasting glucose and low density lipoprotein, changed more with olanzapine than paliperidone. Larger samples will be needed to determine if there are differences and whether these are of a magnitude that is clinically significant. Nevertheless, clinicians are left with "Hobson's choice" given that both drugs were associated with alterations in a range of metabolic parameters.

In this context, the study by Amran-Weizman et al. (2013) is to be welcomed as it offers clinicians an additional strategy. Here, they show that the addition of reboxetine reduces the risk of at least some of the metabolic complications associated with olanzapine treatment. This extends their earlier finding that reboxetine reduced weight gain and appetite stimulation

associated with olanzapine treatment (Poyurovsky et al. 2007) to demonstrate improvements in triglyceride and leptin levels as well. These are important benefits if they are maintained. The study lasted 6 weeks, which, while standard for a clinical trial, is short in terms of clinical practice so it will be important to evaluate the benefits of this approach over longer periods. Another recent study found that the combination of reboxetine and betahistine, reduced olanzapine associated weight gain more than the addition of reboxetine alone (Poyurovsky et al. 2013). While this combination was well tolerated in the study, clinicians and patients will, of course, want to know if the additional benefit out-weighs the risk of other side-effects.

Doctors typically take an oath to "first do no harm". The studies published in this issue will help psychiatrists abide by this, highlighting as they do the impact of metabolic dysregulation in our patients, the potential of our treatments to contribute to this, and by providing strategies to counteract these effects. This is important if we are to reduce the mortality gap between our patients and the general population.

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