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Discussion paper

Considering metformin in cardiometabolic protection in psychosis

A 20% reduction in life expectancy is testament to the disproportionate burden of cardiovascular morbidity and mortality in psychiatric populations. Cardiovascular disease largely explains the mortality gap between those with schizophrenia and the general population, a gap that continues to widen (1). Lifestyle factors such as poor nutrition, obesity, cigarette smoking, substance abuse and sedentariness contribute to a complex set of cardiovascular risks. However, cardiometabolic disturbances and weight gain occur within weeks of first exposure to antipsychotic medications (2), a particular concern as psychotic disorders typically commence in youth at a vulnerable developmental phase and with a lifetime ahead. By the time this population reach their late 30s, rates of diabetes (10.2%) and prediabetes (37%) indicate that early weight gain and its attendant insulin resistance effect a biological path from normal glucose metabolism to disease (3). For young people with early psychosis, this means that not only can early weight gain influence a path towards obesity-related medical disorders, but it may limit ability to engage in healthy physical activities as basic as walking, as well as damaging self-worth and confidence to participate in active physical pursuits (4).

In tackling or preventing cardiometabolic risk, a lifestyle programme to prevent weight gain at initiation of antipsychotic treatment is primary and fundamental. A multipronged approach is required, including healthy eating strategies, supervised caloric restriction for those gaining weight and sedentariness-reducing strategies. Another potential tool in our armamentarium is metformin, first line in treating type 2 diabetes mellitus and with established efficacy in euglycaemic disorders such as polycystic ovary syndrome. Twelve RCTs and three meta-analyses demonstrate that metformin alone or with lifestyle intervention can attenuate weight gain in normoglycaemic patients with psychosis commencing or receiving antipsychotic medications (5). The weight benefit translated to clinically meaningful improvements in cardiometabolic risk factors. The utility of these studies to influence practice is limited by low statistical power and relatively short study length. Nevertheless, in four adequately powered studies, metformin consistently improved weight and metabolic parameters for a variety of antipsychotics applicable to general psychiatric practice (5). These benefits were evident in the critical early phase following antipsychotic initiation in drug-naïve, first-episode psychosis patients, regardless of the antipsychotic used. The review also observed that metformin plus lifestyle intervention was significantly more effective than metformin or lifestyle intervention alone: compared with placebo, metformin plus lifestyle gave a net weight reduction of 7.8 kg in as short a period as 12 weeks.

The utility of metformin as a safe and cheap treatment for preventing diabetes in at-risk obese populations without psychiatric disease is established. In our view, patients with psychosis constitute another important at-risk group, similar to those with prediabetes: in particular, those on antipsychotic medications with significant weight gain and acquisition of cardiometabolic risk factors. Just as in the non-psychiatric at-risk population, metformin is not a solitary panacea. Early lifestyle intervention is an opportunity to modify the long-term health trajectory of a generation of at-risk psychiatric patients and should be primary. However, metformin addition increases the effectiveness of lifestyle intervention, at least in the short term. We suggest that metformin in concert with a structured, supervised lifestyle programme could be considered in the severely mentally ill when antipsychotic agents are initiated or in antipsychotic recipients who are overweight, obese or have elevated cardiometabolic risk factors. A precipitous rise in body weight, waist circumference or fasting glucose can be viewed similarly to an obese non-psychiatric patient with impaired glucose tolerance, where lifestyle and metformin intervention are considered acceptable. Furthermore, obesity has a disproportionately greater impact on the psychiatric patient's ability to exercise and their self-confidence to participate in physical activities (4). Taken alongside their greater likelihood of co-occurring hyperlipidaemia and tobacco smoking, then perhaps this psychiatric population should be considered at even greater cardiovascular risk and hence with a stronger justification for early intervention, than their equivalent obese non-psychiatric population.

We believe the opportunity exists for medical practitioners to actively engage in cardiometabolic protection of people with schizophrenia, perhaps some of our most vulnerable patients. Early, pro-active intervention with lifestyle strategies and, where necessary, metformin may offer a primary preventative strategy in antipsychotic recipients. Actively protecting cardiometabolic health could be an efficient way to reduce clinical, social and economic burden in the psychiatric population. Is it time to extend the early intervention paradigm for treating first-episode psychosis to encompass the body as well as the mind?

Declarations of interest

JC has received an unrestricted educational grant from Janssen-Cilag and speaker honoraria from Pfizer, Astra-Zeneca and Janssen-Cilag. KS serves on an advisory board for sitagliptin for Merck Sharpe and Dohme and has received honoraria for educational seminars from Janssen-Cilag and Merck and an unrestricted educational grant from Janssen-Cilag. DS is currently a member of two Guideline Development Groups (GDG) for NICE: (i) NICE guidance for children and young people affected by psychosis and schizophrenia and (ii) NICE guidance for adults with psychosis and schizophrenia. The views expressed are not those of GDG, NCCMH or NICE. NM and HN have no relevant declarations.

Please see editorial comment to this paper by D. Taylor: Acta Psychiatr Scand 2012;126:233–234.

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