Schizophrenia, antipsychotics and metabolic disease

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There are two issues at the forefront of both clinical concern and research approaches in the treatment of schizophrenia. One reflects a major inadequacy of antipsychotic drugs, namely their lack of efficacy in improving the negative features and cognitive deficits in the disease, and is being addressed primarily by the search for, and development of, new pharmacotherapies. The other problem, the topic of a ‘Perspective’ article in this issue, is that a substantial proportion of people with schizophrenia suffer from a variety of metabolic problems, from overweight and obesity to cardiovascular disease and diabetes (see pp. 357).

These symptoms are, of course, not unique to schizophrenia sufferers, they are common and increasing problems in both the developed and under-developed worlds and which reflect rapid changes in dietary and other lifestyle factors. Nevertheless several studies show obesity, hyperlipidemia and diabetes to be more common in schizophrenia than in control groups, problems that inevitably contribute to lower life expectancy in these patients. These symptoms are increasingly described as components of the ‘metabolic syndrome’, a useful, if arbitrarily and variably defined, concept identifying a set of risk factors for chronic metabolic and cardiovascular disease.

The essential question here relates to the cause, or causes, of these metabolic disturbances in patients with schizophrenia. Some attempt was made to address this in a recent supplement in this journal sponsored by Lilly, the manufacturers of olanzapine, as well as in many hundreds of other research reports and reviews in the past few years. Despite a huge body of valuable research work, attempts at obtaining a clear understanding of the causes, incidence and consequences of the metabolic syndrome in schizophrenia remain confounded by instances of misinterpretation, special pleading and inappropriate extrapolation.

Clearly there is much at stake; in 2005, Lilly made a settlement of over US$690 million in respect of claims for damages from users of olanzapine who developed diabetes-related conditions, and it is conceivable that there may be further claims against this or other pharmaceutical companies in respect of the metabolic consequences of antipsychotic drug treatment.

We can get an understanding of the problem by starting with some clear facts. That some antipsychotic drugs can cause weight gain is undisputed; this side effect has been observed in patients receiving antipsychotic treatment since the introduction of chlorpromazine half a century ago. There is now adequate evidence that there are significant differences between drugs in the extent of this weight gain. Thus olanzapine and clozapine are the worst offenders, while aripiprazole, ziprasidone and some of the typical antipsychotics show little weight gain above placebo levels; the effects of other antipsychotic drugs lie between these two extremes. It is worth remembering that most reports and metanalyses of antipsychotic-induced weight gain use data from clinical trials in which subjects have typically received many years of prior treatment with antipsychotic drugs that may already have induced weight gain. Thus such reports are likely to underestimate the true effect of individual drugs on body weight, and this is becoming apparent in some recent studies of initially drug-naïve individuals.

It is well established that, in the general population, increases in body weight are associated with increased risk of type II diabetes. Whether or not the evidence for antipsychotic-induced diabetes is convincing, it would seem that the weight gain following antipsychotic treatment is inevitably going to increase the likelihood of eventual diabetes in patients with schizophrenia. To argue otherwise would be to suggest that patients with schizophrenia receiving antipsychotic treatment are in some way protected against this consequence of weight gain. Thus such reports are likely to underestimate the true effect of individual drugs on body weight, and this is becoming apparent in some recent studies of initially drug-naïve individuals.

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Rather than being protected from the development of diabetes, there are suggestions that patients with schizophrenia may be at increased risk, independent of drug-induced weight gain. However,
the evidence here is somewhat inconsistent. Case-control studies of drug-naïve patients with a first episode of psychosis in their mid-twenties provide no indication of an increase in glucose intolerance or other indicators of the metabolic syndrome (e.g., Zhang et al., 2004). On the other hand, there is an increased frequency of diabetes in relatives of patients with schizophrenia, and there is now a substantial literature, mainly of case reports, of diabetes associated with certain antipsychotic drugs, sometimes independent of weight gain and reversible on drug withdrawal. An experimental study showed that patients receiving olanzapine or clozapine had impaired glucose regulation, in comparison with those receiving typical antipsychotics and independent of adiposity (Newcomer et al., 2002), a finding consistent with some laboratory studies suggesting that these same drugs can impair pancreatic beta-cell function.

Interestingly, there is a substantial literature relating stress and the metabolic syndrome (Björntorp, 2001), providing a possible explanation why older drug-free patients, or those poorly responding to antipsychotic treatment, may also have increased liability to abdominal obesity and glucose intolerance. This could well reflect the effects on glucose metabolism of years of chronic stress associated with inadequately treated disease. It should not be forgotten that there are other lifestyle risk factors for diabetes that are increased in patients with schizophrenia. One of these is cigarette smoking; notwithstanding the protective effect that it may have on the development of obesity, smoking is itself an independent risk factor for the development of diabetes (Wannamethee et al., 2001).

It would seem that the occurrence of metabolic illness in schizophrenia provides a further economic and social burden and, since it may represent an avoidable component of the morbidity associated with psychiatric disease, a quantitative pharmacoeconomic investigation of the problem would be very worthwhile. We should, however, not assume that an increased risk of metabolic disease is an inevitable consequence of schizophrenia and/or its drug treatment. There are ways in which the risks can be modified in addition to considering the pros and cons of switching to a different antipsychotic. The lifestyle recommended for all of us, including regular exercise, a healthy diet and giving up smoking, should be particularly valuable, although perhaps particularly difficult, for the patient with schizophrenia. Thus, while monitoring the problem is important, it has little value without intervention, for which Barnett et al. provide some valuable guidance in their ‘Perspective’ article.

References