Metabolic Side Effects and Management

1. The metabolic syndrome, syndrome X or the insulin Resistance Syndrome

These terms refer to a syndrome consisting of central obesity as indicated by excessive visceral fat, plasma lipid abnormalities, glucose dysregulation, and high blood pressure. People with the metabolic syndrome are at increased risk of coronary heart disease, other diseases related to plaque buildups in artery walls (e.g., stroke and peripheral vascular disease) and type 2 diabetes. The syndrome as a whole is more of a risk factor for these adverse outcomes than any one element. The criteria for diagnosing the metabolic syndrome proposed by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) are the most current and widely used but are not universally accepted. The consist of : waist line greater than 40 inches for a male, 35 inches for a female; triglycerides =/>150 mg/dl; HDL-cholesterol =/<40 mg/dl for a male or 50 mg/dl for a female; fasting blood sugar =/> 110 mg/dl; and blood pressure =/>130/85.

The metabolic syndrome has become increasingly common in the United States and other developed countries due to diet and limited exercise. Its estimated that about 20–25 percent of US adults have it. The syndrome is closely associated with a generalized metabolic disorder called insulin resistance, in which the body cannot use insulin efficiently. This is why the metabolic syndrome is also called the insulin resistance syndrome (Reaven 2003; Cheal et al. 2004). The Adult Treatment Panel III (ATP III) has published criteria for diagnosing the metabolic syndrome, a cluster of closely related abnormalities related to insulin resistance that increase cardiovascular disease risk. Using steady-state plasma glucose (SSPG) concentration in the top tertile as a measure of insulin resistant, insulin resistance and the presence of the metabolic syndrome as defined by the criteria given above were significantly associated in 443 healthy volunteers ($P < 0.001$). However, the sensitivity and positive predictive value of the metabolic syndrome criteria was only 46% (69 of 149) and 76% (69 of 91), respectively. Being overweight, with high triglycerides, low HDL cholesterol, or elevated blood pressure, most often resulted in a diagnosis of the metabolic syndrome. Thus, the ATP III criteria do not provide the most sensitive approach to identifying insulin-resistant individuals. The individual components vary both in terms of their utility in making a diagnosis of the metabolic syndrome and their relationship to insulin resistance, with the obesity and lipid criteria being most useful. Antipsychotic drug treatment may increase the frequency and severity of the metabolic syndrome.

A Consensus Conference to evaluate the effect of antipsychotic drugs on obesity and diabetes, cause and consequence of the metabolic syndrome, was held in the US in 2004. (ADA et al 2004) Experts in the field from the American Diabetes and American Psychiatric Association concluded that the risk of weight gain was greatest for clozapine and olanzapine, intermediate for risperidone and quetiapine, and lowest for aripiprazole and ziprasidone. They did not evaluate amisulpride but there is evidence that it causes little or no weight gain. They also concluded that the risk of diabetes and lipid abnormalities parallels the risk for weight gain.

Hemoglobin A1c measures a form of hemoglobin that is sensitive to excessive glucose levels. Levels above 6.0 are indicative of insulin resistance and type 2 diabetes. It may be useful to monitor this measure in patients who are unable or unwilling to provide a fasting blood glucose specimen.

Patients who manifest the metabolic syndrome should have consultations with internists if possible to receive counseling about the risk of diabetes mellitus and cardiovascular damage. The Consensus Conference (ADA et al 2004) recommended that switching to another atypical less likely to cause insulin resistance, e.g. aripiprazole, risperidone and ziprasidone "should be considered" unless they have failed to respond to these agents. Our view is that a switch under such circumstances would ordinarily be indicated.

Weight gain: general information

Upper body fat, characterised by visceral fat deposition and measured by waist to hip ratio or waist measurement alone may lead to insulin resistance, high triglycerides and low HDL (Lapidus et al, 1984; Larsson et al, 1984) . Patients with schizophrenia have significantly higher waist to hip ratios and over three times as much visceral fat as age, sex, and lifestyle matched controls (Thakore et al 2002).

The prevalence of overweight and obesity in individuals with schizophrenia ranges from 26% to 62% (Hutton, 1994; Kendrick, 1996; Stedman et al, 1993; Centorrino et al,1994). Obesity rates change over time so these may not be representative of the current situation. Using data from the 1989 US National Health Survey Allison and colleagues (1999a) found comparable rates of overweight or obesity in non-institutionalized males with and without a diagnosis of schizophrenia but females with a diagnosis of schizophrenia were more likely to be overweight or obese). The National Health and Nutrition Survey (NHANES-III) reported rates of overweight and obesity markedly greater in females with a diagnosis of schizophrenia (Allison et al, 1999a).

Virtually all antipsychotic agents produce weight gain (Allison, et al 2001). The extent of weight gain may increase the risk of weight-related medical comorbidity. A meta-analysis of 81 studies, of at least 10 weeks duration concluded that weight gain was greatest for the atypical agents clozapine and olanzapine, moderate with risperidone, and modest for ziprasidone (Allison et al, 1999b). There was insufficient data for quetiapine. The low potency typical antipsychotic agents had a higher weight gain liability than high potency agents. The evidence to date indicates that amisulpride, aripiprazole, risperidone, and ziprasidone are least likely to cause the metabolic syndrome but they may do so in vulnerable individuals, so all individuals receiving these medications will need periodic checking. Those receiving olanzapine, quetiapine and clozapine will need more frequent monitoring.

Compliance with prescribed antipsychotic medication is low and weight gain contributes to psychotropic non-compliance (Fenton et al,1997). Behavioural interventions to improve diet and increase physical activity are the primary means to promote and maintain weight loss (Yanovski et al, 2002). Patients level of awareness of their obesity does not correlate with their level of concern. This disconnect between

awareness and concern may impact on the ability of individuals to implement lifestyle programs for weight management (Meyer et al, 2002).

A number of drugs including orlistat, sibutramine, topiramate and nizatidine, have been trialed in a nominal number of patients to manage weight gain (Werneke et al, 2002). Most of these trials involved concomitant dietary restrictions. Many appetite-affecting drugs have undesirable side effects or potential interactions with psychotropic medications. The current evidence does not support the routine use of pharmacological interventions for overweight patients on antipsychotics, although selected individuals may benefit.

Recommendations:

Baseline height, weight and waist-hip measurements should be performed for all patients prescribed antipsychotic agents. Weight and waist-hip ratios should be monitored at 3-month intervals during treatment.

Patients should have access to education and programs to modify lifestyle to limit weight gain.

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2. Dyslipidaemia: General Information

Changes in lipid profiles have been associated with atypical antipsychotics. Clozapine and olanzapine have been associated with greater increases in serum triglyceride levels than risperidone, aripiprazole, and ziprasidone (McIntyre et al, 2001; Henderson, 2001; Henderson, 2000; Atmaca et al, 2003; Wirshing et al, 2002; Baptista et al,2002; Meyer, 2002). An elevated triglyceride/HDL ratio is a particularly useful measure of the insulin resistance syndrome and by itself is an excellent predictor of insulin resistance. Ratios =/> 3.5 are abnormal and predictive of 2-3 fold greater risk of cardiovascular disease or higher (Jeppsen et al. 2003) Elevations in serum cholesterol levels were noted in patients taking clozapine and olanzapine, however the mean changes were within normal limits (Lindenmayer, 2003).

Weight gain weakly predicts increases in serum triglycerides with some atypical antipsychotic drugs. If the patient does not gain weight, lipid increases may still occur. The use of lipid lowering drugs has been reported to have varying effects in patients taking clozapine (Henderson 2001). Lifestyle changes are of benefit in reducing weight and improving diet.

Recommendations:

Fasting serum lipid concentrations should be monitored at commencement of antipsychotic treatment and at regular intervals (6 monthly) during treatment. Patients with a family history of lipid disorders should be monitored more closely when prescribed clozapine or olanzapine. In patients who are not treatment resistant and who have elevated triglyceride/HDL ratios, switching from olanzapine to aripiprazole, risperidone or ziprasidone may be beneficial with regard to metabolic side effects.

Behavioural changes to promote healthy diet and exercise should be encouraged in all patients with schizophrenia.

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3. Impaired GlucoseTolerance/Insulin resistance: general information

Diabetes is more common in patients with schizophrenia (Lean et al,2003; Mukherjee et al, 1989). A study of patients in the US Veterans Administration health care system found that the rate of diabetes was 6.2 – 8.7% (Sernyak et al, 2002) compared with 1.1% of males aged 20-39 years without schizophrenia (Harris et al, 1998). Most of these patients had already been exposed to antipsychotic medication so this may be an overestimate.

Clozapine and olanzapine have been implicated in most reports of new-onset diabetes (Mahmoud et al, 2001; Koller et al, 2001; Leibzeit et al, 2001; Mir et al, 2001; Koller et al, 2002; Henderson et al, 2000). At least 36% of patients commenced on clozapine and followed up for 5 years, were subsequently diagnosed and treated for diabetes (Henderson et al, 2000). This association is not dose-related. The risk of developing diabetes with olanzapine is significantly greater than for risperidone (Koro et al, 2002). Blood glucose levels returned to pre-treatment levels when the antipsychotic agent was discontinued and were observed to re-emerge when rechallenged. The mechanism is unclear but with clozapine it may be related to drug-induced insulin resistance and increased insulin secretion. Weight gain is a risk factor for the development of diabetes but was not present all reported cases. The absence of a family history of diabetes does not exempt patients from treatment-emergent hyperglycaemia or ketoacidosis.

Hyperglycaemia can cause or contribute to long-term medical complications including peripheral neuropathies, retinopathy, and nephropathy as well as cardiovascular and cerebrovascular disease (Newcomer et al, 2002). There is a progressive relationship between hyperglycaemia and the risk of a cardiovascular event such as myocardial infarction or stroke, beginning with glucose levels below threshold for diabetes.

Recommendations:

Patients prescribed atypical antipsychotic agents should have their blood glucose levels monitored regularly (6-12mths) or more frequently depending on presentation of clinical risk factors. Monitoring glycosylated haemoglobin (HbA_{1C}) may be useful where fasting blood glucose levels are difficult to obtain. However, it is less sensitive for lower levels of hyperglycaemia. Rising HbA_{1C} levels should lead to more definitive tests such as oral glucose tolerance testing.

Patients may require a change to an antipsychotic agent with lower potential to produce hyperglycaemia, eg switch from olanzapine to aripiprazole, risperidone, or ziprasidone or possibly amisulpride.

Treatment resistant patients on clozapine who become diabetic and who have responded well to clozapine should probably stay on it and receive long-term concomitant treatment for diabetes.

Behavioural changes to improve diet and exercise should be implemented.

Physicians should be aware that patients with schizophrenia may need special assistance and training in monitoring their own blood glucose status and attending followup.

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