

Metabolic Syndrome and Atypical Antipsychotics: A Selective Literature Review

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Abstract

***Aim:** To review the relationship between the metabolic syndrome and atypical antipsychotics.*

***Method:** Selective literature review.*

***Results:** Atypical antipsychotics are effective in the treatment of psychotic disorders and other mental illness. Psychiatric patients have higher rate of physical disorders due to various causes, and metabolic disorders such as diabetes mellitus were described prior to the advent of antipsychotic medication. Atypical (and conventional) antipsychotic drugs are associated with the metabolic syndrome and its components – diabetes mellitus, weight gain, dyslipidaemia and hypertension. Clinical guidelines and consensus statements suggest routine baseline monitoring of patients commenced on these medications, modifying lifestyle factors and treating individual components of the metabolic syndrome.*

***Conclusions:** Increased awareness of risks associated with the metabolic syndrome, and optimal monitoring and management are required to minimize the cardiovascular and other risk factors associated with the syndrome. Further studies specifically focusing on these abnormalities are required (German J Psychiatry 2008; 11: 111-122).*

Keywords: Metabolic syndrome, atypical antipsychotic, physical health, severe mental illness

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Introduction

The second generation antipsychotics have become the cornerstone of treatment of schizophrenia and some other forms of mental illness. However their efficacy in comparison to conventional antipsychotics is being hotly debated and is the subject of much research activity. The meta-analysis by Davis et al. (2003) suggested that some of the atypical antipsychotics (clozapine, amisulpride, risperidone and olanzapine) were more efficacious than conventional neuroleptics, but more recent studies indicate otherwise. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman et al. 2005) indicated that olanzapine was most effective when rates of discontinuation were considered (but was also associated with the most weight gain and dyslipidemia) and the conventional antipsychotic perphenazine was of similar efficacy to quetiapine,

risperidone and ziprasidone. In Phase 2 of the same study, clozapine was found to be more effective than the other atypical antipsychotics (McEvoy et al. 2006). The UK Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CuTLASS) did not reveal any significant advantages of atypicals over the use of conventional antipsychotics (Jones et al. 2006).

Alongside the efficacy debate, recently there has been considerable interest and concern about the metabolic abnormalities associated with atypical antipsychotic use (Consensus Development Conference 2004). The issues being discussed are whether these metabolic abnormalities are seen only with antipsychotic treatment, if there is a difference between atypical and conventional antipsychotics in terms of these side effects, and about the differing metabolic profiles of the various atypical antipsychotics. This selective review will primarily focus on some of the studies examining one or more atypical antipsychotics and one or more components

Table 1: Diagnostic criteria for metabolic syndrome

	NCEP/ATP III Any 3 of 5 criteria	IDF Criterion 1 plus any two of the other four factors
1	Central obesity (Elevated waist circumference) ¹	≥102 cm in men ≥88 cm in women
2	Raised TG level	≥94 cm for Europid ² men ≥80 cm for Europid ² women, with ethnicity specific values for other groups
3	Reduced HDL-C	≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
4	Elevated BP	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
5	Elevated fasting plasma glucose	systolic BP ≥130 or diastolic BP ≥85, or treatment of previously diagnosed hypertension
		≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes

¹Measurement of waist circumference: To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at end of normal expiration (AHA/NHLBI Consensus Statement 2004).

²Europid: white people of European origin, regardless of where they live in the world (Alberti et al. 2005)

of the metabolic syndrome. The other areas which will be briefly reviewed will be the metabolic syndrome and its diagnosis, physical disorders and psychiatry, metabolic concerns preceding the introduction of antipsychotics and management of these side-effects.

Method

This is a selective literature review of studies of antipsychotic medication and components of the metabolic syndrome, including diabetes, weight gain and hyperlipidaemia. Key papers, including case reports and series, cross-sectional surveys, reviews, and both randomized and non-randomized trials were identified by searching clinical databases (MEDLINE, EMBASE, PsycINFO) using Dialog DataStar. Refer-

ences of key papers were hand searched to identify relevant papers.

Metabolic Syndrome: Definition and Diagnosis

The metabolic syndrome is a multi-system disorder, characterized by clustering of abnormalities, which increase the risk of cardiovascular disorders. The abnormalities include those of glucose homeostasis and metabolism, obesity, hyperlipidaemia and hypertension (Blaha & Elasy 2006; Holt et al. 2004; Lieberman 2004; Meyer et al. 2005; Sacks 2004; Toalson et al. 2004). The American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) consensus statement (2004) includes proinflammatory and prothrombotic states as part of the syndrome, though these are not required for diagnosis of metabolic syndrome. According to Alexander et al. (2003), the term metabolic syndrome was first used by German researchers in the late 1970s, who associated it with atherosclerosis. The significance of insulin resistance in the aetiology of the metabolic syndrome was recognized in the late 80s (Reaven 1988). The metabolic syndrome has also been referred to as the Insulin resistance syndrome or syndrome X.

According to the International Diabetes Federation (IDF) definition, criteria for the metabolic syndrome include central obesity, plus any two of the following four factors – raised triglyceride level, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose or previously diagnosed type 2 diabetes. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) defined metabolic syndrome on the basis of easily measured clinical features and laboratory measures (Table 1). Due to their reliance on clinical signs and their validity, these have been adopted by the AHA/NHLBI in their Scientific Statement.

The IDF definition differs from the AHA/NHLBI definition in having Central Obesity as the core feature. An important difference in the definition is that of values for central obesity, which is defined as ≥ 102 cm in men and ≥ 88 cm in women in the NCEP/ATP III definition, while the IDF values are less and (94 cm and 80 cm respectively, with lower values for South Asian men).

Prevalence of Metabolic Syndrome and Associated Disorders

The IDF consensus statement (2006) reports that around 20 to 25% of the world's population has the metabolic syndrome. This is similar to prevalence rates from the United States. Data from 8814 men and women aged 20 years and above from the Third National Health and Nutrition Examination Survey (NHANES III), was used to study the

prevalence of the metabolic syndrome as defined by the NCEP/ATP III criteria (Ford et al. 2002). This study showed the prevalence of the metabolic syndrome to be approximately 22 % (24% when adjusted for age) in the United States, increasing with age, and being almost equal in men and women. The prevalence increased with age, being 6.7% between the ages of 20 and 29 to 43.5% in age groups 60 to 69. A similar finding was reported by Alexander et al. (2003), who used (NHANES III) data to the study the relationship between the metabolic syndrome, hyperglycaemia and age in people older than 50 years of age. This study found the prevalence of metabolic syndrome in people more than 50 years old to be 43.5% (NCEP criteria). Ford & Giles (2003) compared the prevalence of the syndrome using the two definitions (WHO and APT III). They found a prevalence rate of 23.9% using ATP III criteria and a rate of 25.1% using the WHO criteria, with 86.2% of the sample being similarly classified using the two sets of criteria.

Psychiatric Patients and Medical Co-Morbidity

Prior to examining the presence of the metabolic syndrome in patients with mental illness, the physical health of patients with mental disorders needs to be discussed. Risk factors for cardiovascular disorders and rates of physical disorders are increased in the psychiatric population, partly due to low levels of help-seeking (Phelan et al. 2001) and lifestyle factors, such poor diet, reduced of physical activity and smoking. Studies of patients with schizophrenia have reported mortality rate 2 to 3 times, compared to the general population (Lesage et al. 1990; Brown et al. 2000). McCreadie (2003) studied the risk of coronary heart disease (CHD) and stroke, in addition to lifestyle factors in 102 patients with schizophrenia. Seventy per-cent of male patients and 86% of female patients were either overweight or obese, with 2 patients having a BMI above 40 kg/m². The mean 10-year risk of coronary heart disease was increased (9.6%) compared to the general population (6.4%), as was the risk of stroke (4.1%). In 26% of patients, the 10-year risk of CHD was $\geq 15\%$, at which level treatment is advised. Osborn et al. (2006) report raised CHD risk scores in General Practice patients with severe mental illness (SMI). In a cross-sectional survey, Cormac and colleagues (2005) studied the physical health and health risk factors of 248 long-stay psychiatric patients. Thirty six percent of male patients and 75% of female patients were obese, compared to 17% of men and 22% of women in the general population. The mean waist circumference of male patients was 103.1 cm and of female patients was 110.0 cm. Seventy one percent of patients smoked tobacco. Similarly rates of hypertension were increased, as was the prevalence of significant health problems.

The above findings need to be considered in the context of the association between the metabolic syndrome, CHD and diabetes mellitus. It is well recognised that the risk of developing diabetes mellitus and cardiovascular disease is increased in people with metabolic syndrome. Compared to a prevalence rate of 26% in people aged above 50 years and

without hyperglycaemia, 86% of people with diabetes had the syndrome (Alexander et al. 2003). In addition, metabolic syndrome was found to strongly predict the prevalence of coronary heart disease (CHD). In a large family study of 4483 subjects in Sweden and Finland, the prevalence of metabolic syndrome increased with worsening glucose intolerance, with a significant increase in CHD, myocardial infarction (MI), stroke and cardiovascular mortality (Isomaa et al. 2001).

Recently, the role of psychiatrists in the physical healthcare of their patients has been the focus of much attention. Greening (2005) found inadequate recording of physical health parameters and risk factors of 63 patients under the care of a rehabilitation and recovery team and discusses regarding need to routinely monitor physical and lifestyle factors. Dursun et al. (2005) discuss the challenge of including improvement in physical health, alongside that in mental health, in treatment plans, by taking into account both medication-related and lifestyle factors. Tarrant (2006) examined the issue of regular monitoring of metabolic indices in patients prescribed atypical antipsychotic medication in a sector of rural Derbyshire in the UK. In 2004, a total of 60 prescriptions of atypical antipsychotic medication had been issued for 55 patients. The study found significant differences in monitoring between in-patients and out-patients. Though in-patients tended to have regular blood tests as part of the admission process, measurement of blood glucose was not felt to be standard. Out-patient monitoring of blood glucose was described as being 'different and poor', with only 63% of patients who are stable on an atypical antipsychotic having annual random or fasting glucose measurements. The author stresses the need for improved communication between secondary and primary care, with well defined roles for monitoring patients' physical health. Remington (2006) argues that 'regular monitoring is critical for all patients', in view of patients with schizophrenia being at greater risk of Type II Diabetes and of developing insulin resistance. The author suggests an important role for psychiatrists in monitoring both mental and the physical health of patients, and that the current gap between psychiatric and physical care is untenable.

Metabolic Syndrome and Mental Illness

In a population with higher physical morbidity compared to the general population, there has been gradually increasing concern about the contribution of antipsychotic medication to the prevalence of the metabolic syndrome and its components, especially since introduction of the atypical (or second generation) antipsychotic medication. Recent studies have indicated that prevalence of weight gain, glucose intolerance and hyperlipidaemia, and in a few cases, of hypertension, has increased following antipsychotic use, with a number of studies suggesting that atypical antipsychotics fare worse compared to the conventional antipsychotics. But other studies have not demonstrated this association. Using ATP III criteria, the metabolic syndrome was diagnosed in 13

(37%) out of 35 patients with schizophrenia, treated with antipsychotic medication (Heiskanen et al. 2003).

Mackin et al. (2007) report increased prevalence of metabolic syndrome and cardiovascular risk in 90 people treated with antipsychotics, compared to age and gender matched controls. Body mass index (BMI), disorders of lipid and glucose metabolism and risk for cardiovascular disorder were increased in individuals with severe mental illness ('across the diagnostic spectrum') who were treated with antipsychotics, as compared to the controls. In a study of 367 adults treated with second generation antipsychotics, Correll et al. (2006) report that the metabolic syndrome was present in 137 (37.3%) of patients and was significantly associated with the 10-year risk of Coronary Heart disease (CHD) events.

Due to paucity of studies of metabolic syndrome as a whole in the mentally ill, the relationship of individual components of the metabolic syndrome to psychiatric disorders and antipsychotic (especially atypical) medication will be considered in this review.

Diabetes Mellitus and Mental Illness

The issue of antipsychotics contributing to metabolic side effects is complicated by reports of increased prevalence of diabetes mellitus in antipsychotic naïve patients, as first reported before introduction of antipsychotics. Kohen (2004) examined the literature on diabetes mellitus and schizophrenia both before and after the neuroleptic era. The review describes accounts from the period prior to the introduction of phenothiazine antipsychotics, which consistently described impaired blood sugar metabolism, resulting in abnormal 'hyperglycaemic curves' and abnormal glucose tolerance after glucose intake. It also describes interesting accounts suggestive of insulin resistance in patients with schizophrenia, observed when insulin coma therapy was in vogue. Following the introduction of Phenothiazines in 1952, there have been reports associating Phenothiazine treatment with abnormal glucose tolerance and an increased predilection to develop diabetes. Bushe & Holt (2004) reported that people with schizophrenia and other severe mental disorders are at greater risk of developing diabetes or having impaired glucose tolerance. Further they estimate that 15% of patients with schizophrenia may have diabetes while another 15% may have impaired glucose tolerance. It has been suggested that, in addition to sharing environmental risk factors, schizophrenia and type 2 diabetes mellitus may share a genetic link through common susceptibility loci (Gough & O'Donovan 2005). They cite the example of apolipoprotein epsilon 4 allele, which is said to increase the risk of Alzheimer's disease, cardiovascular disease, multiple sclerosis and subarachnoid haemorrhage.

Glucose dysregulation has been demonstrated in antipsychotic-naïve schizophrenia patients. Ryan et al. (2003) examined the prevalence of impaired fasting glucose in 26 first-episode patients with schizophrenia, who were drug-naïve, compared to age-matched healthy controls. More than 15%

of the patients in this cross-sectional study showed impaired fasting glucose and insulin resistance, in addition to higher fasting plasma glucose, insulin and cortisol. It was observed that the waist-to-hip ratio positively correlated with plasma triglyceride level and negatively correlated with HDL cholesterol level.

Similar findings have been reported from studies with larger sample sizes. Data collected by the Schizophrenia Patient Outcomes Research Team (PORT) was used to determine the prevalence and correlates of diabetes in patients with schizophrenia, who were receiving treatment (Dixon et al. 2000). The PORT study used data from Medicaid (n = 6,066) and Medicare (n = 14,182) as well as interview data from the field study (n = 719). Increased prevalence of diabetes was found in the period preceding the use of the atypical antipsychotic medication. The rate of diabetes for persons aged 45-64 in the general population was 6.3%, while the study sample had a lifetime prevalence of 14.9% and current prevalence of 10.8%. Unsurprisingly, the diagnosis of diabetes was associated with greater use of services and cost of care. Elevated prevalence of diabetes mellitus has been found in Bipolar disorder by Cassidy and colleagues (1999), who examined the frequency of diabetes mellitus in bipolar affective disorder patients, compared to the general population (3.4%). The study included 345 patients, selected from an initial cohort of 357 patients and found that the frequency of diabetes mellitus was 9.9% in patients with bipolar affective disorder, while the expected frequency was 3.5%.

Atypical Antipsychotics and Diabetes Mellitus

Atypical antipsychotics were considered a significant breakthrough in the treatment of psychotic disorders, with low frequency or absence of extrapyramidal side-effects. Gradually case reports emerged which pointed to elevated levels of hyperglycaemia and diabetes mellitus associated with use of atypicals. In 1999, Lindenmayer & Patel reported a case of olanzapine-induced diabetic ketoacidosis (DKA), which resolved following discontinuation of olanzapine treatment. The authors discuss the role of olanzapine in suppressing insulin release and in producing a hyperglycaemic response. Tovey et al. (2005) discuss two patients treated with clozapine, who subsequently developed diabetes mellitus, on routine blood testing. Blood sugar level returned to within the normal range after discontinuation of clozapine in one of the patients, but not in the other. The authors discuss the mechanisms by which clozapine may contribute to Insulin resistance – by decreasing uptake of glucose in brain and peripheral tissue as well as by impaired β cell function. They stress the need for baseline measurements prior to and following initiation of treatment with clozapine.

A 'claims based approach', using medical claims data from Medicaid, was adopted to study the incidence of diabetes (as well as hyperlipidaemia and hypertension) in more than 3000 patients with schizophrenia, treated with either clozapine (n

= 552) or conventional antipsychotics (n = 2461) (Lund et al. 2001). There was no significant overall difference in incidence of diabetes, hyperlipidaemia or hypertension between the two groups. However, in patients aged 20 to 34 years who were receiving clozapine, the incidence of both diabetes and hyperlipidaemia was increased. The authors discuss the implications of this finding, in that clozapine may increase the risk of hyperglycaemia by direct physiological effects on insulin secretion or resistance, rather than weight gain alone.

In a five year naturalistic study of 82 patients treated with clozapine (Henderson et al. 2000), weight gain and onset of diabetes were studied at 6 monthly intervals. 36.6% of patients developed diabetes, with 61.7% of the study population experiencing at least one episode of elevated fasting blood glucose. The age of the patients significantly correlated with risk of developing diabetes. All 82 patients in the study gained significant weight over time, this being greatest in the first 12 months, though continuing till 46 months. Serum triglycerides increased significantly as well. The limitations of the study included not being able to examine the role of risk factors such as ethnicity, family history or exercise.

Olanzapine was found to be associated with a significant risk of diabetes compared to risperidone in a large population based nested case-control study. Koro et al. (2002) studied data (between 1987 and 2000) from 3.5 million patients on the United Kingdom based General Practice Research Database. Of the 19,637 patients with schizophrenia, who were eligible for study purposes, 451 developed diabetes during a mean follow up of around 5 years. The risk of developing diabetes was non-significant with the use of risperidone (odds ratio = 1.6, $p = 0.160$), slightly increased with conventional antipsychotics (odds ratio = 1.3, $p = 0.013$) and significantly increased with the use of olanzapine (odds ratio = 4.4, $p = 0.002$). Sernyak et al. (2002) used a national database to study the prevalence of diabetes mellitus in patients receiving atypical and typical antipsychotics over a 4 month period. As the study was cross-sectional in design, a causal relationship could not be explored. However, it was able to establish significant association between antipsychotic treatment and development of diabetes mellitus. Of the 38,632 patients included in the study, 58.6% were being treated with an atypical antipsychotic and 41.4% were being treated with conventional antipsychotics. To avoid the confounding effect of age, subjects were stratified according to age and results analysed. Nearly nine per-cent of subjects who were less than 60 years old and treated with atypical antipsychotic, had a diagnosis of diabetes mellitus. However no significant association was detected at or above the age of 60. The authors suggest that patients who were vulnerable to developing diabetes would have developed the disease before this age, and those who were not vulnerable, would not develop it, in spite of antipsychotic use. There was no significant difference in the diagnosis of diabetes between those receiving atypical or conventional antipsychotics (nearly 19%), when compared across all age groups. 8.75% of patients under the age of 40 receiving an atypical antipsychotic had diabetes mellitus compared to 6.43% of those treated with conventional antipsychotics ($\chi^2=7.24$, $df=1$, $p=0.007$). The odds of being diabetic was increased for clozapine, olanzapine and quetiapine but not for risperidone, when all age

groups were considered. This difference disappeared in patients less than 40 years old, with all the 4 atypical antipsychotics being significant associated with presence of diabetes mellitus.

Lindenmayer et al. (2003) analysed data from a randomized, double-blind trial of clozapine, olanzapine, risperidone and haloperidol in 108 patients with schizophrenia or schizoaffective disorder. Blood glucose levels were significantly increased in patients treated with clozapine and haloperidol after 8 weeks and in patients treated with olanzapine after 14 weeks treatment. However the increases remained within clinically normal ranges and did not correlate with the significant weight gains seen. Clozapine and haloperidol were associated with significant elevation in serum cholesterol.

In another line of investigation, studies were conducted to measure insulin resistance and hyperglycaemia in patients with schizophrenia, treated with antipsychotic medication.

Henderson and colleagues (2005) conducted a cross-sectional study in 36 stable patients with schizophrenia, on treatment with clozapine, olanzapine and risperidone, using frequently sampled intravenous glucose tolerance test. Insulin resistance (IR) was studied by measuring Insulin Sensitivity Index and by using the Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR). Subjects treated with clozapine and olanzapine showed significant IR compared to those treated with risperidone. However, there were no significant differences in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and serum triglyceride levels among the three groups of patients. Newcomer et al. (2002) performed modified oral glucose tolerance tests in patients with schizophrenia, receiving clozapine, olanzapine, risperidone or typical antipsychotics. This study was conducted to determine if antipsychotics contributed to abnormalities in glucose regulation, independent of weight gain or abdominal adiposity. Forty eight patients with schizophrenia and 31 healthy adult controls participated in the study. Compared to subjects on conventional antipsychotics and healthy controls, patients on olanzapine and clozapine had elevated glucose levels at all time points following modified oral GTT. Patients on Risperidone had a similar effect only when compared to untreated healthy controls.

Cavazzoni et al. (2005) performed a retrospective analysis of pooled data from 24 clinical trials from the database of clinical trials involving olanzapine to study treatment emergent diabetes (TED). Based on post-randomisation glucose levels, patients were classified into groups including treatment-emergent diabetes (TED), uncertain glucose tolerance (UGT) or normal glucose tolerance (NGT). TED was identified in 94 (1.4%) of the 5013 patients eligible for inclusion in the study, with 282 (5.7%) of patients identified with UGT. Baseline glucose levels were elevated in 61% of patients who went onto develop TED, as was the prevalence of risk factors for diabetes (such as age, non-white ethnicity, raised BMI, hypertension and glycaemic abnormalities), compared to NGT patients. Interestingly, weight gain was not significantly associated with the risk of developing TED in this group of patients treated with atypical antipsychotics. This industry-sponsored study reported that many patients with

treatment-emergent diabetes may have had pre-existing glycaemic abnormalities or risk factors for Diabetes mellitus.

Pre-clinical studies have indicated differences between antipsychotic in their response to insulin release. Best et al. (2005) studied the effects of clozapine and haloperidol on rat pancreatic β -cells in-vitro. The authors demonstrated the contrasting effects of clozapine and haloperidol on pancreatic β -cell function. Clozapine had no effect on β -cell membrane potential at fasting glucose levels but hyperpolarized the membrane potential, when glucose concentrations were high. In contrast haloperidol depolarized the membrane at both fasting and stimulatory levels of glucose. The effects of these two drugs on electrical activity only partially explained their effect on insulin release. Clozapine inhibited secretion of insulin in response to glucose, which could explain the hyperglycaemia and diabetes associated with it, but did not affect 'basal insulin release'. Interestingly, haloperidol had no effect on insulin release.

Antipsychotics and Weight Gain

Weight gain, especially visceral adiposity, as measured by waist circumference, is one of the key components of the metabolic syndrome and in fact is the main criterion in the IDF definition. Though both Kraepelin and Bleuler have commented on change in weight in psychiatric patients during the course of a psychotic illness (Alison & Casey 2001), significant interest has been evoked with weight gain associated with use of atypical antipsychotic drugs. Drug naive Chinese psychiatric in-patients, meeting DSM-IV criteria for schizophrenia, were studied before and following 10 weeks of antipsychotic treatment, by Zhang et al. (2004). Forty six patients were compared to 38 well matched healthy controls. In addition to physical measurements and biochemical tests, MRI was used to study abdominal subcutaneous fat (SUF) and intra-abdominal fat (IAF). After 10 weeks of treatment, the patient group showed significant increases in SUF and IAF, in plasma leptin levels, plasma glucose and lipid levels. Interestingly no significant difference was found between risperidone and chlorpromazine and no significant correlation was observed between change in BMI and clinical improvement.

Allison et al. (1999) performed a comprehensive review of research literature to estimate and compare the effects of both conventional and atypical antipsychotics on weight gain, using a very thorough search methodology. This was followed by meta-analysis, with the estimated mean weight change calculated using both fixed and random effects models. For patients on standard doses for 10 weeks, the authors calculated point estimates of weight gain for each drug. Weight gain associated with five atypical antipsychotics was examined in the study – ziprasidone(0.04 kg), risperidone(2.10 kg), sertindole(2.92 kg), olanzapine(4.15 kg) and clozapine(4.45 kg). Subjects receiving placebo lost weight in the range of 0.74 kg. Though the two conventional antipsychotics molindone and pimozide were associated with weight loss, the effects were not significant at 10 weeks. The

study indicated that patients may gain more than 5% of initial body weight, with the weight gain becoming more pronounced with time, with the attendant risks for the general physical health of the patient. Almeras et al. (2004) studied anthropometric and metabolic indices associated with atypical antipsychotic treatment, in an open-label, cross sectional, multi-center study. Patients treated with risperidone (n=45) or olanzapine (n = 42) as their 'first and only' antipsychotic were studied. Compared to the reference group, patients treated with the atypical antipsychotics had elevated fasting blood sugar, insulin levels and insulin resistance. The study revealed significant differences between olanzapine and risperidone. Patients treated with olanzapine had a significantly worse metabolic profile compared to those treated with risperidone, with more than a third of the former group exhibiting a 'hypertriglyceridemic waist' (waist circumference ≥ 90 cm, triglycerides ≥ 2.0 mmol/L). Zipursky and colleagues (2005) analysed data from a multi-centre randomized controlled trial of patients with first-episode psychosis, treated with olanzapine or haloperidol. Clinically significant weight gain was defined as $\geq 7\%$ increase in weight (kg) from baseline. In olanzapine-treated patients, the BMI at baseline, 12 weeks, 1 year and 2 years was 23.6, 26, 27 and 27 respectively. In the haloperidol treated patients, BMI at corresponding periods in time was 23.9, 24.8, 25.3 and 25.3. Clinically significant weight gain occurred significantly faster in the olanzapine group compared to the haloperidol group. 36.7% and 40.8% of patients on olanzapine, and 20.5% and 35.9% of haloperidol treated patients were obese or overweight respectively. Subjects from the ethnic minority population demonstrated clinically significant weight gain, independent of treatment group.

Ascher-Svanum and colleagues (2005) argue that weight gain has been considered a prognostic indicator even before the introduction of antipsychotics. They hypothesized that weight gain was a marker of improvement in psychopathology, that weight gain observed with placebo would be associated with clinical improvement and that antipsychotics differing in weight gain liability differed in effectiveness. By using data from randomized controlled trials and meta-analyses, they undertook post hoc analysis and demonstrated that greater weight gain was significantly correlated with better therapeutic response. The authors used data from studies which did not measure weight gain as a primary outcome measure. In a randomized controlled trial examining the efficacy and safety of olanzapine and haloperidol in 263 patients with first-episode psychosis (Lieberman et al. 2003), significant side effects were observed in patients treated with olanzapine. In this group of patients, the mean weight gain was 7.3 kg, with 61.5% of patients gaining more than 7% of their body weight (compared to 22.7% in the haloperidol treated group) and their BMI increasing by 2.39 (compared to 0.88 of patients receiving haloperidol), with these findings being highly significant. Mackin and colleagues (2005) hypothesized that atypical antipsychotics were associated with increased metabolic abnormality compared to conventional antipsychotics. They undertook a cross-sectional study of 106 patients, with the only inclusion criterion being treatment with antipsychotic medication for a minimum of 6 months. All 12 patients (11.6%) receiving atypical antipsychotic had a 'glucose homeostasis' disorder

(either diabetes mellitus or impaired fasting glucose). Though this association was not statistically significant, a trend was identified by the authors. Further sub-group analysis showed BMI and HbA1c of olanzapine treated patients to be lower than quetiapine treated patients.

Aripiprazole is an atypical reported to cause little or no weight gain. McQuade et al. (2004) compared aripiprazole and olanzapine in a 26 week multi-center randomised control trial, especially in terms of significant weight gain. By the end of the trial, 37% of olanzapine-treated patients reported significant weight gain ($p < 0.001$) compared to 14% of patients treated with aripiprazole. Treatment with olanzapine was associated with a worsening of the lipid profile. In a review of weight gain with antipsychotics, Haddad (2005) discusses the issues in interpreting research literature on weight gain. These include the duration of trials, differing outcome measures used, failure to consider baseline BMI and limited information on confounding variables. He suggests that it is important to consider all available information (efficacy, tolerability and patient's previous response if known) before deciding on which antipsychotic to prescribe.

Antipsychotics and Triglycerides

Dyslipidaemia is an important component of the metabolic syndrome, which occurs along with glucose dysregulation and weight gain in patients treated with atypical antipsychotics. Treatment with antipsychotics, both conventional and atypical, have been found to increase the lipid levels in subject selected from the North Finland 1966 Birth Cohort. Of the 5654 (67%) of the 8463 subjects from the original cohort who participated in this study, 45 subjects were receiving antipsychotic treatment. 32 (71%) used typical, 6(13%) used atypical and 7 (16%) both types of antipsychotics. The study found high prevalence of total cholesterol and triglycerides in the 45 subjects treated with antipsychotics as compared to the 5609 who were not, even after adjusting for risk factors for hyperlipidemia. The authors (Saari et al. 2004) suggest that the pathogenesis of hyperlipidemia is related to weight gain, with accumulation of abdominal fat increase release of free fatty acids in the liver and accelerating hepatic triglyceride synthesis as well as very low density lipoprotein (VLDL) release. They further suggest that increased lipids impair glucose metabolism, leading to hyperglycaemia and Type 2 DM.

Sheitman et al. (1999) re-examined the lipid profile of 9 patients with schizophrenia, after initiating treatment with olanzapine. Though they did not observe a change in cholesterol or lipoprotein levels, the level of triglyceride increased from a mean of 170 mg/dl to 240 mg/dl. However in the study by Mackin et al. (2005), fasting cholesterol was raised in 26% of patients, along with elevated fasting triglycerides in 55% of antipsychotic treated patients. In keeping with the theme of raised CHD risk, Menzies (2004) estimated that 67% of his patients had a two-fold or greater risk of a cardiovascular event, on routine biochemical testing.

Case series have played an important role in highlighting the increased prevalence of hyperlipidemia associated with atypical antipsychotic use. A retrospective case series by Meyer (2001) consisted of 14 psychiatric patients, treated with olanzapine or quetiapine, referred for treatment of severe hypertriglyceridemia (defined as fasting triglycerides > 600 mg/dL). On average, it took 9 months for the triglyceride levels to peak. The mean peak triglyceride levels following treatment with atypical antipsychotics was 1459.14 mg/dL from a mean baseline of 211.29 mg/dL. Though BMI and weight increased for all patients from that at baseline, hyperlipidemia was not correlated with weight gain, change in BMI, use of lithium or valproate or previous history of hyperlipidemia. The author discusses regarding the increased risk of pancreatitis and cardiovascular events, especially with triglyceride levels above 1000 mg/dL.

In responding to this paper, Baptista and colleagues (2002) suggest that insulin resistance plays a significant part in development of type 2 DM. They postulate that excess body weight results in insulin resistance, which results in decreased availability of glucose to peripheral tissues. Lipids are mobilized from body stores to meet energy demand and results in hyperlipidemia. The authors stress that causation of hyperlipidemia is multi-factorial, with insulin resistance being an important cause. They designed a 'composed ratio' which included the absolute affinity of antipsychotics for neurotransmitter receptors involved in regulation of food intake. Clozapine and olanzapine had the highest CR. However the author disagrees observing that increase in triglyceride and cholesterol levels did not correlate with BMI, baseline weight, baseline fasting glucose or degree of weight gain (Meyer 2002).

Following case reports of elevated lipids associated with antipsychotic treatment, Koro et al. (2002) explored the association using the General Practice Research Database (GPRD). The GPRD is a computerized database of medical information from around 400 GP surgeries, covering more than 6% of the population. Of the 20,865 patients with a diagnosis of schizophrenia, 18,309 patients were eligible for inclusion in the study, of which 1269 cases of hyperlipidemia were identified. Each eligible case (schizophrenia with hyperlipidemia) was matched with 6 controls (schizophrenia without hyperlipidemia), with 1268 cases matched to 7598 controls. The odds of olanzapine treated patients developing hyperlipidemia was almost five-times (odds ratio = 4.62, 95% CI = 2.44-8.85, $p < 0.001$) compared to patients not prescribed antipsychotics, with odds being 3 times higher (odds ratio = 3.36, CI = 1.77-6.39, $p < 0.001$) when compared to patients treated with conventional antipsychotic medications. Patients treated with risperidone did not show significantly elevated odds of developing hyperlipidemia.

In order to study the effect of antipsychotics on lipid levels, a sub-analysis of data on fasting plasma lipids was conducted by Sramek et al. (2003). The lipid levels were obtained from a randomized study of effect of 6 antipsychotics on QTc interval 'at maximum plasma levels in the presence and absence of metabolic inhibition'. This study reported that ziprasidone was associated with a significant reduction in total cholesterol, triglycerides and total cholesterol/HDL ratio. Though the changes in lipids were not statistically significant

compared to haloperidol, they were significant when compared to olanzapine and risperidone. The limitations included brief duration of the study as well small patient numbers.

Effect of atypical antipsychotic on metabolic profile of psychiatric patients was studied in a community mental health centre in Italy. In a cross sectional survey of 76 patients treated with atypical antipsychotics compared to 36 non-psychiatric controls, Tarricone et al. (2006) compared the prevalence of hyperglycaemia, hypercholesterolaemia and hypertriglyceridaemia. The study found that patients treated with atypical antipsychotics had a significant prevalence of hyperglycaemia ($p = 0.02$) and of hypertriglyceridaemia ($p = 0.007$) compared to controls. The treated group had 8 times higher odds of being diagnosed with hyperglycaemia and 4 times higher odds of being diagnosed with hypertriglyceridaemia. This study was interesting that it did not find any differences between the different atypicals, with all atypicals being associated with adverse metabolic effects. In a retrospective chart review of 208 patients suffering from schizophrenia, schizoaffective or mood disorder treated with an antipsychotic (conventional or atypical), Gupta et al. (2003) found increased prevalence of diabetes (17%), hypertension (29%) and hypertriglyceridemia (44%). The study however did not find significant differences between the antipsychotics. Though this study involved 'real world' patients, confounders such as family history of diabetes were not considered in this cross-sectional study. Patients treated with ziprasidone were not included in this study.

Antipsychotics and Hypertension

As mentioned above, Gupta et al. (2003) reported a prevalence of 29% for hypertension among 208 patients treated with antipsychotic medication. Nevertheless, hypertension is one component of the metabolic syndrome which was not commonly associated with treatment with atypical antipsychotics, in the studies identified by our search and in the literature in general.

Management of the Metabolic Syndrome

Various guidelines, consensus statements and recommendations have been published on the optimal management of the metabolic syndrome. Broadly, these consist of the following components:

1. Baseline monitoring and regular follow up – history, physical examination, blood tests
2. Primary management – 'lifestyle interventions' – weight loss, increased physical activity, smoking cessation, modification of diet

3. Secondary management – treatment of individual components of the syndrome, namely diabetes, obesity, dyslipidaemia and hypertension.

The Consensus Statement on antipsychotic drugs, obesity and diabetes (2004) reiterated the importance of antipsychotic medication in psychiatric treatment. It acknowledges the increased risk of obesity, diabetes and dyslipidaemia following treatment with second-generation (atypical) antipsychotics, with some drugs having a worse metabolic side-effect profile and recommends baseline screening and follow-up on treatment (see box).

The other recommendations include education of patients and carers, and treatment of individual components of metabolic syndrome, as appropriate.

Baseline monitoring

- Personal and family history of obesity, diabetes, dyslipidaemia, hypertension or cardiovascular disease
- Weight, height, BMI
- Waist circumference
- Blood pressure
- Fasting plasma glucose
- Fasting lipid profile

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (2004)

The risk of atherosclerotic cardiovascular disease (ASCVD) is increased 2 fold and the risk of diabetes increased 5 fold by the presence of the metabolic syndrome (Grundy et al. 2005). The Scientific Statement by the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) advises reduction in ASCVD risk factors and lifestyle interventions as the important goals in the management of the metabolic syndrome. The suggestions include smoking cessation and restoration of lipid levels, blood glucose and hypertension to the healthy range. The lifestyle interventions include weight loss, increased physical activity and modification of diet. Further advice on management of individual components of the metabolic syndrome is provided.

The recommendations of the International Diabetes Federation (IDF 2006) are similar to that in the AHA/NHLBI consensus statement. 'Healthy lifestyle promotion' is recommended as the primary management for metabolic syndrome by the IDF, comprising of calorie restriction, increased physical activity and dietary modification. Treatment of individual components of the metabolic syndrome using medication is advised for people not responding to lifestyle interventions. The IDF stresses the need for further studies from around the world to help improve the management of the metabolic syndrome in the future.

Guidelines suggested by Melkersson and colleagues (2004) for management of metabolic adverse effects of antipsychotics complement the above recommendations. These include

using antipsychotic agents with little or no propensity to cause weight gain, diabetes or dyslipidaemia, to use the lowest effective dose, routinely asking for symptoms of diabetes and monitoring for diabetic symptoms and being aware of risk factors such as certain ethnic populations. Interestingly, measuring serum antipsychotic levels is recommended to optimize dose.

The above guidelines/consensus statements largely pertain to the American context, though their recommendations can be extrapolated to other populations. Barnett et al. (2007) address the issue of managing metabolic risk in patients receiving antipsychotic treatment, specifically in the UK psychiatric setting. This review takes a holistic and pragmatic approach, discussing in detail both the initial evaluation and regular monitoring of patients receiving antipsychotic medication. Specifically the recommendations have taken account of practical issues, such as difficulty obtaining informed consent in acutely ill patients. For example, the impracticality of measuring waist circumference and fasting blood glucose/lipids for all patients is explicitly recognised. The authors make real-world recommendations such as using BMI and random blood tests to identify those potentially at risk. These guidelines, on behalf of the British Association for Psychopharmacology (BAP) highlight the need for guidelines tailored to needs of individual populations.

In the absence of treatment directed towards metabolic syndrome as a whole, treatment of individual conditions is the preferred option. Both the consensus statements (IDF and AHA/ NHLBI) provide guidance of optimal treatments for hypertension, diabetes and dyslipidaemia as well as advice on lifestyle risk factors such as obesity, physical inactivity and atherogenic diet. The AHA/NHLBI statement goes further in advising low-dose aspirin therapy/prophylaxis for the prothrombotic state, which has been recognised as part of the syndrome.

Various pharmacological approaches have been tried in the management of antipsychotic-related weight gain and obesity. In a comprehensive review conducted by Werneke and colleagues (2002), eight different medications to treat obesity were studied. These include orlistat, sibutramine, fluoxetine, topiramate, amantadine, nizatidine and cimetidine, and metformin, of which the first two are licensed for treatment of obesity in the UK. The authors discuss underlying receptor mechanisms, including antagonism of serotonergic, dopaminergic, histaminergic and glutaminergic receptors. The other mechanisms involve neuropeptide Y, cholecystokinin and leptin. Both orlistat and sibutramine were effective in double-blind, RCTs, in which subjects in the treatment arm lost 7 – 10 kg in weight, compared to 3 – 6 kg in the controls. Treatment with fluoxetine or topiramate has been associated with dose-related weight loss, though evidence from RCTs is not available. Other drugs such as the noradrenaline reuptake inhibitor reboxetine have been studied as well. In a 6 week double-blind, placebo-controlled, randomized study of two groups of 10 patients each (treated with olanzapine or placebo), patients in both groups gained weight during the trial, but those receiving olanzapine and reboxetine gained significantly less weight (mean=2.5 Kg) compared to patients treated with olanzapine and placebo (mean weight gain of 5.5 Kg). The beneficial effects of small

amounts of weight loss (5% of body weight in obese subjects) or even 1% weight loss in overweight individuals and the resultant reduction in hypertension are stressed by Bushe et al. (2005). In addition to orlistat, topiramate and sibutramine, the authors discuss the significant weight loss associated with use of atomoxetine in a double-blind RCT.

The role of behavioural interventions in management of weight gain both in the general population as well as in those treated with antipsychotics was reviewed by Werneke et al. (2003). In the general population, education, weight monitoring, dietary changes, cognitive strategies and community-based education programmes were found to be effective. One study found energy-restricted diets to be effective in reducing visceral adipose tissue. None of the 13 studies in patients receiving antipsychotics were randomized controlled trials, with apparently insufficient power to detect effect of intervention. Another study found that structured counselling with CBT resulted in reduction BMI from 29.6 to 25.1 kg/m². Werneke and colleagues conclude that, in the absence of robust evidence for weight reduction strategies in psychiatric patients, findings from the general population were being extrapolated to this population. Kwon et al. (2006) compared the efficacy of a weight-management program in 33 patients (with schizophrenia or schizoaffective disorder) taking Olanzapine to 13 patients receiving Olanzapine in the community, but not participating in the program. In the 36 (75%) patients who completed the study, the authors report significant differences in weight ($p = 0.006$) and BMI ($p = 0.007$) between the intervention and control groups. It remains to be seen if the results can be replicated with a larger sample.

Alvarez-Jimenez et al. (2008) included 10 trials involving 482 patients comparing non-pharmacologic management of antipsychotic-induced weight gain with treatment as usual in their meta-analysis. The non-pharmacological interventions studied included both cognitive behaviour therapy (CBT) and nutritional counselling (psychoeducation, diet and exercise). The intervention group showed a statistically significant reduction in weight (weighted mean difference WMD = -2.56 kg) and BMI (WMD = -91 kg/m²) compared to the treatment as usual group.

Conclusion

Atypical antipsychotics play an important role in the management of mental illness, due to their efficacy and due to the low frequency of extrapyramidal and other side effects traditionally associated with conventional antipsychotics. However their use needs to be tempered with the knowledge that these medications can cause significant metabolic abnormalities and the metabolic syndrome in patients treated with these second generation antipsychotics. The different atypical antipsychotic agents differ in their propensity to be associated with or even cause weight gain, diabetes mellitus or dyslipidaemia. The need for studies with more robust methodologies cannot be overemphasized, focusing on metabolic abnormalities of atypical antipsychotics. The plethora of consensus guidelines available to manage the

metabolic syndrome and its components in the mentally ill illustrates that the significance of this issue is being recognised. The management consists of recognizing the syndrome, preventing it in the first place and if it occurs, to treat individual components according to established practice, as well as using antipsychotics least likely to cause these problems. Further epidemiological, pre-clinical and clinical research is required to understand, manage and eventually to prevent these adverse effects.

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