


## Metabolic Syndrome in Patients with Severe Mental Illness Undergoing Psychiatric Rehabilitation Receiving High Dose Antipsychotic Medication

Bapu V. Ravindranath

### ABSTRACT

**Background:** To review evidence of chronic antipsychotic medication and the association with metabolic syndrome in mentally ill patients. This evidence was used to analyse a cohort of patients with severe mental illness and to deduce a correlation between the prevalence of metabolic syndrome and their dose regimens. **Materials and Methods:** Twenty-four male patients undergoing Psychiatric rehabilitation underwent a review of current medication and assessment of risk factors for metabolic syndrome. Assessment criteria was based upon National Cholesterol Education Programme expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (NCEP ATP III) criteria, incorporating waist circumference, raised triglycerides, reduced high density lipoprotein, raised blood pressure and fasting blood glucose. PubMed, Nature and Science Direct databases have been used to compile the medical and scientific background on metabolic syndrome and antipsychotic medication and the effect on patients particularly on high dose. **Results:** Out of 24 patients, 10 patients (41.7%) were receiving high dose antipsychotics (HDA) and four were on maximum dosage limits of 100%. 8.3% (2/24) patients were receiving only one first generation antipsychotics (FGA), 37.5% (9/24) patients were receiving only one second generation antipsychotic (SGA), 45.8% patients (11/24) were receiving two or more SGA only, and only one patient was receiving two or more FGA. One patient was receiving a combination of FGA and SGA. PRN ("as needed") therapy was not included in this study as their usage was limited. Clozapine was mostly prescribed in these patients (10/24, 41.6%). Four out of the 24 patients refused blood tests therefore were excluded from the following results. In the patients evaluated, 55% (11/20) had confirmed metabolic syndrome. In these patients with metabolic syndrome, 45.4% (5/11) were on HDA and 27.3% (3/11) were on maximum British National Formulary (BNF) limits of 100% of dosage. Four out of the nine remaining patients not diagnosed with metabolic syndrome were on HDA. **Conclusions:** Evidence supports the association between antipsychotic medication and metabolic syndrome. The data extrapolated from this cohort of mentally ill patients demonstrates that there is an increase in risk factors for metabolic syndrome and weight gain in the majority of patients on antipsychotic medication. The data however does not support any further predisposition to metabolic syndrome in these patients taking HDA. It also cannot be assumed antipsychotic medication is independently associated with the prevalence of these abnormalities.

**Key words:** Antipsychotics, metabolic syndrome, high-dose antipsychotics

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### INTRODUCTION

#### Clinical background - metabolic syndrome and antipsychotic drug interactions

The risk of adverse side effects, particularly metabolic syndrome, has been shown to support the monitoring of patients on antipsychotic therapy with severe mental illness.<sup>[1]</sup> Some of these patients have been

Consultant Psychiatrist, Rathbone Low Secure Unit, Liverpool, UK

**Address for correspondence:** Dr. Bapu V. Ravindranath  
5 Childwall Lane, Liverpool L25 1PL, UK E-mail: [bapu.ravindranath@gmail.com](mailto:bapu.ravindranath@gmail.com)

shown to develop hyperlipidaemia and hypertension which can cause cardiovascular disease, glucose intolerance and diabetes mellitus type II, with a reduced life expectancy by 20% compared to the general population.<sup>[2,3]</sup> Sedentary lifestyle, smoking, a lack of dietary awareness and infrequent physical exercise also are likely contributors.<sup>[4]</sup> Genetic factors leading to insulin resistance<sup>[5]</sup> can also contribute to the patients' predisposition to metabolic disorder, and currently there is debate as to whether these disorders are part of the disease process itself through increase of stress factors and inflammatory responses.<sup>[6]</sup> It remains controversial as to whether pharmacokinetic variations within individuals results in variability in response to treatment.<sup>[7]</sup> Up to 50% of patients with schizophrenia may develop metabolic syndrome.<sup>[8]</sup> It remains possible that all factors in some way contribute to the predisposition of metabolic syndrome in these patients, however, antipsychotic drugs are thought to be the main causal factor in the development of metabolic syndrome.<sup>[1,5,9,10]</sup>

Metabolic syndrome is usually classed under the National Cholesterol Education Programme expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (NCEP-ATP III) criteria or the International Diabetes Federation (IDF) guidelines [Table 1].<sup>[11]</sup> These criteria include increased waist circumference, hypertriglyceridemia, reduced high density lipoproteins (HDL) levels, increased blood pressure and increased fasting blood glucose.

Weight gain, predominantly central, is the most noticeable sign of metabolic syndrome<sup>[12]</sup> which the clinician should view as the red flag for further complications such as hypertension, cardiovascular disease (CVD) and a predisposition to diabetes mellitus type II.<sup>[13,14]</sup> Weight gain can be distressing for the patient and can cause further deterioration in compliance.<sup>[9]</sup> Patients have been shown to develop diabetic ketoacidosis without weight

gain (a metabolic syndrome risk factor), particularly in the early course of treatment, hence monitoring patients in the absence of weight gain.<sup>[15]</sup>

The Consensus Development Conference<sup>[16]</sup> recommends the monitoring of all patients on antipsychotic drugs.

Guidelines for screening for hyperglycaemia in patients treated with antipsychotic medication include HbA1c every 3-6 months to monitor glycaemic control.<sup>[17]</sup>

Studies have shown that non treated schizophrenic patients had higher amounts of central visceral adiposity compared to control patients, whom subsequently have demonstrated to be at higher risk of diabetes mellitus type II, dyslipidaemia and cardiovascular complications.<sup>[16,17]</sup> Cardiovascular risk management with people with severe mental illness include risk assessment and review of antipsychotic medication.

Recent evidence has also queried the role of hypothalamic-pituitary adrenal (HPA) -axis dysregulation in patients with both schizophrenia and metabolic syndrome.<sup>[18]</sup> The role of HPA axis disruption may play an integral part on plasma cortisol levels, which is likely to disrupt metabolism. Cortisol plays a role in stress modulation, and hypercortisolemia has been demonstrated in patients with schizophrenia.<sup>[19]</sup>

Clinical presentation of severe characteristics of central obesity that can be a sign of metabolic syndrome include central obesity, high blood pressure, high triglycerides, low HDL-cholesterol and Insulin resistance [Figure 1].

In a population of 86 patients with schizophrenia, 50% responded positively to dexamethasone suppression<sup>[20]</sup> - part of the screening test for Cushing's syndrome. There are many pathophysiological similarities between metabolic syndrome and Cushing's syndrome, and efforts are being made into looking at glucocorticoids excess in both syndromes.<sup>[21,22]</sup>

**Table 1: ATP III and IDF definitions of metabolic syndrome comparing the ATP III and IDF definitions of metabolic syndrome**

ATP III definition	IDF definition
Waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women	Waist circumference ≥94 cm for European men and ≥80 cm with ethnicity specific values for other groups
Triglycerides ≥150 mg/dL (1.7mmol/L)*	Plus any two of the following criteria
HDL cholesterol <40 mg/dL (1.3mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women*	Raised TG level: ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
Blood pressure ≥130/≥85 mm Hg*	Reduced HDL cholesterol: <-40 mg/dL (1.03 mmol/L**) in males and <-50mg/dL (1.29 mmol/L**) in females, or specific treatment for this lipid abnormality
Fasting glucose ≥100 mg/dL**	Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension
	Raised fasting plasma glucose ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

\*Or drug treatment; \*\*These values have been updated from those originally presented to ensure consistency with ATP III cut-points #Fasting Glucose criteria changed from ≥110 mg/dL to ≥100 mg/dL in AHA statement 1n 2005; AHA - American Heart Foundation; ATP III - Adult Treatment Panel; IDF - International Diabetes Federation

Disruption of this axis adjusts cortisol levels which impact upon stress management and weight control.<sup>[23]</sup>

Evidence has also pointed to clinical depression playing an integral part in weight gain, over-eating, and both a lack of energy and motivation, which again could be associated with the development of metabolic syndrome.<sup>[22,23]</sup>

These factors support the theory of the development of metabolic syndrome in the absence of antipsychotic medication; however, the literature heavily supports the contribution of antipsychotics in causing syndrome. Treatment with antipsychotic medication, particularly the newer second generation “atypical” antipsychotics [Table 2], has been claimed to be associated with weight gain, impaired glucose metabolism, hypertension, and diabetes.<sup>[24]</sup>

Atypical antipsychotics have revolutionised the treatment of negative symptoms of mental illness; however, their usage is impeded by these side effects. Since the introduction of atypical antipsychotics nearly 20 years ago, there has been a 0.7% per year higher rate of diabetes type II in patients with schizophrenia compared the general population.<sup>[24]</sup> Older patients receiving antipsychotics, in particular second generation antipsychotics (SGAs) are more at risk of metabolic syndrome.<sup>[25]</sup>

Although antipsychotics usage has been associated



**Figure 1:** Central obesity that can be a sign of metabolic syndrome

**Table 2: Typical first generation antipsychotics vs atypical second generation antipsychotics**

First generation “typical” antipsychotics	Second generation “atypical” antipsychotics
Chlorpromazine	Clozapine
Fluphenazine	Olanzapine
Haloperidol	Quetiapine
Mesoridazine	Asenapine
Perphenazine	Sulpiride
Thioridazine	Amisulpiride
Trifluoperazine	Aripiprazole
	Melperone
	Risperidone

with the metabolic syndrome an exact mechanism of action has not been elucidated. However, strong evidence suggests interaction with the 5HT2c receptors, histamine-1 receptors and dopamine D2 receptor.<sup>[26]</sup> Typical antipsychotics work in a different manner to atypical antipsychotics, and there is variability in the antagonism for different receptors. Typical antipsychotics such as Haloperidol are thought to work more selectively on dopamine receptors in the mesolimbic and mesofrontal systems in the brain.<sup>[27,28]</sup>

Histamine-1 and 5HT2c receptor activation is thought to contribute to the adverse side effects such as weight gain, reduced satiety and sedation.<sup>[29]</sup> Typical and atypical antipsychotics show varying responses depending on their binding affinity and antagonism at these sites. Clozapine and Olanzapine have been shown to cause a higher increase in weight gain than typical, first generation antipsychotics.<sup>[30]</sup> Binding affinity of Haloperidol (FGA) and Clozapine, Olanzapine and Risperidone (SGA) and their antagonism at specific receptor sites is significant. Lower binding affinity proceeds greater side effect profile as the lower the drugs antagonism, the higher response of activation at these receptor sites. This suggests why Haloperidol, with a high binding affinity on H1 and 5HT 2D receptors, as opposed to Clozapine which has a lower binding affinity, will produce less side effect profile of weight gain, sedation, and satiety blockade. Clozapine, on the other hand, will have a greater side effect profile.<sup>[31]</sup> Both first generation (typical) and second generation (atypical) antipsychotics have been shown to cause varying degrees of weight gain.<sup>[32]</sup>

The risk and extent of weight gain is “high” with Clozapine, Olanzapine, “moderate” with Chlorpromazine, Quetiapine, Risperidone and “low” with Amisulpride, Aripiprazole, Haloperidol and Trifluoperazine.

There is now evidence to suggest the role of genetic polymorphisms, particularly the 5HT2c receptor subtype, in patients susceptible to metabolic syndrome on SGAs.<sup>[32]</sup> An interaction between 5HT2c receptor polymorphisms and leptin promoter regions has been shown to account for 30% of the variance of drug-induced weight gain.<sup>[33]</sup> These genetic influences may be mediated by effects on leptin secretion which may contribute to weight gain and therefore the patients’ risk of developing metabolic syndrome.

Further receptors; particularly histamine-1, may also play an integral part in drug-induced weight gain.<sup>[34]</sup> Recent evidence has suggested a role in hypothalamic AMP-kinase (AMPK) phosphorylation, which regulates appetite and leptin metabolism through the action of

histamine-1 receptor. Atypical antipsychotics have been shown to be a potent stimulator of arcuate and Para ventricular hypothalamic AMPK. This in turn has been linked to the regulation of food intake, reversing the action of leptin, leading to increased appetite and decrease fat breakdown.<sup>[35]</sup> These studies do not demonstrate ethnic variability; however they do demonstrate the importance of genetic polymorphisms between patients. This could potentially predict pharmacogenetic outcomes in those with both schizophrenia and induced weight gain. This could lead to genetic counselling methods in the future for patients susceptible to metabolic syndrome.

### High-dose antipsychotic usage

SGAs have licensed dose ranges which are relatively narrow,<sup>[36]</sup> and close monitoring of patients on these antipsychotics for adverse reactions is of great importance.

Evidence links antipsychotic usage with development of metabolic syndrome, but data linking increases in dosage to prevalence of this syndrome is lacking.

HDA refer to those prescribed over and above the British National Formulary (BNF) limit recommendations or Summary of Product Characteristics.<sup>[28]</sup> These may include monotherapy, or combined antipsychotic polypharmacy which can be calculated by converting the dose of each drug into a percentage of the BNF limitation, and then adding these together. A cumulative dose of more than 100% is deemed high.<sup>[37]</sup> [Refer to Antipsychotic Dosage Ready Reckoner, Prescribing Observatory for Mental Health (POMH) UK].

BNF guidelines state high doses should be recommended for emergencies, acute therapy or those patients with continual psychosis who are intolerant to the lower dosages of medication.<sup>[38]</sup>

Several studies support the link between antipsychotic usage and metabolic syndrome,<sup>[10,31]</sup> in particular the CATIE (Analysis of the Clinical Antipsychotic Trials of Intervention Effectiveness) trial.<sup>[39]</sup> This was a landmark 18-month randomised controlled trial involving 1493 patients with schizophrenia, identifying long term effects of antipsychotic therapy (5 SGA and 2 FGA), and in particular metabolic changes. The results demonstrated Olanzapine, a widely used SGA, caused the greatest weight gain, increase in glucose and lipid metabolism and the highest discontinuation rate.

Dose-response relationships of antipsychotics have been evaluated and there is conflicting evidence as to whether or not there is therapeutic benefit in increasing the dosage of antipsychotics.<sup>[37,38]</sup>

Although studies have suggested risk factors for metabolic syndrome such as sedentary lifestyle, smoking, metabolic biochemical disturbances and depression, evidence suggests a link between usage of antipsychotics and this syndrome.

The aim of this study is to evaluate this evidence and use it to support any findings from the study group database to confirm this association and to also find if increasing the dosage increases the risk of metabolic syndrome.

## MATERIALS AND METHODS

A cohort of patients received high dose antipsychotic medication due to treatment resistance to standard dose of medication. This was a clinical decision by the treating team.

Twenty four adult male mentally ill patients admitted into an intense rehabilitation programme were assessed for their antipsychotic medication risk factors for metabolic syndrome. These included weight changes from baseline on admission, and factors of assessment (using the IDF criteria and ATP III criteria), incorporating waist circumference (>40 inches), raised triglycerides (>1.7 mmol/L), reduced HDL cholesterol (<1.03 mmol/L), raised blood pressure (>130/85 mm hg) and Fasting Blood Glucose (>5.6 mmol/L) and/or diagnosis of Diabetes Mellitus type II. This cross sectional study aimed to identify those patients on high dose antipsychotic, and deduce any correlation with metabolic syndrome in these patients. The type of antipsychotic was also evaluated; whether typical, atypical or a combination of medication. Weight differences from baseline on admission were also evaluated in these patients [Figure 2], however, waist circumference is a more reliable parameter of diagnosis of metabolic syndrome as it rules out muscle mass and can directly measure central obesity [Figure 3]. Patients with an increase of weight gain of 7% or more from baseline on admission were also red flagged, and their average monthly weight change was calculated. Unfortunately, patient data from baseline on admission

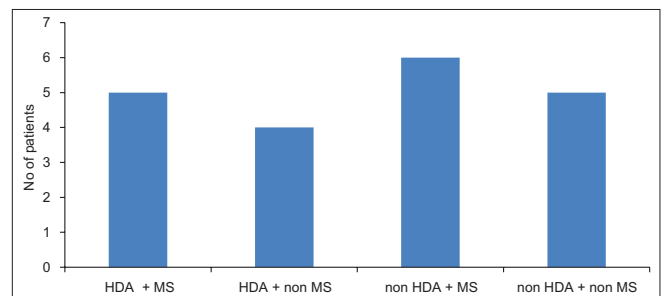


Figure 2: Weight gain from base line

until their current time in rehabilitation could only be recorded and pre-admission information was limited.

## RESULTS

The mean age of the 24 patients included in this study was 39.5 years of who were all male. 22 patients suffered with schizophrenia, one patient suffered with bipolar disorder, and the other patient suffered with depression with psychosis. All the patients were receiving antipsychotic medication; Ten patients (41.7%) were on HDA (above 100% of therapy according to the BNF upper limits prescribing guidelines); four patients were on maximum dosage limits of 100%. 8.3% (2/24) patients were receiving only one FGA, 37.5% (9/24) patients were receiving only one SGA, 45.8% patients (11/24) were receiving two or more SGA only, and only one patient was receiving two or more FGA. One patient was receiving a combination of FGA and SGA [Figure 4]. PRN (“as needed”) therapy was not included in this study as their usage was limited. Clozapine was mostly prescribed in these patients (41.6%) [Figure 5]. Amisulpride was prescribed in 29.1% of these patients, Risperidone in 20.8%, Olanzapine in 16.7% and Quetiapine in 12.5%.

In the patients evaluated, 55% (11/20) had confirmed metabolic syndrome. These patients met both the IDF and ATP III Criteria for metabolic syndrome [Figure 5]. In these patients with metabolic syndrome, 45.4% (5/11) were on HDA and 27.3% (3/11) were on maximum BNF limits of 100% of dosage. Four of the nine remaining patients not diagnosed with metabolic syndrome were on HDA. Four out of 24 patients refused blood tests therefore were excluded from the results.

## DISCUSSION

Following the assessment of twenty four (24) male patients suffering from a lifetime illness of schizophrenia, bipolar affective disorder and paranoia, eleven (11) of the twenty (20) patients (exclusion criteria = four, 4) had confirmed metabolic syndrome, and of these patients (45.4%) were on HDA. Patients without metabolic syndrome were verging on diagnosis. Most patients were on two (2) SGAs, the most common being Clozapine. FGA were prescribed as routine medication in only four (4) patients. Most FGAs were prescribed as PRN (“as needed”) therapy which was not included in this study due to its low requirement. There was no significant difference in waist circumference between antipsychotics [Figure 6]. Clozapine showed a slight rise in FBG and Risperidone showed a dramatic increase in blood pressure compared to other medication. There was no correlation between

HDA and increase in weight. In those patients with confirmed metabolic syndrome, two (2) had new onset diabetes. Patients without metabolic syndrome had no diagnosis of diabetes.

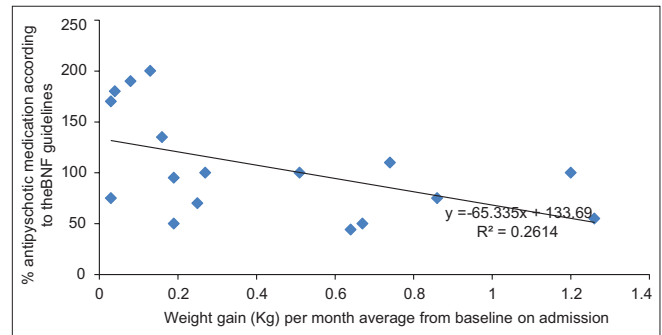


Figure 3: Waist circumference

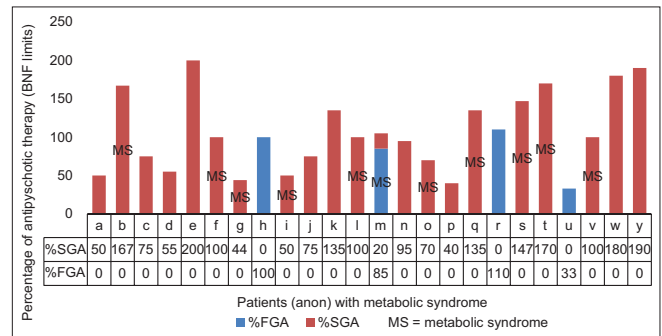


Figure 4: BNF prescribing limits, %

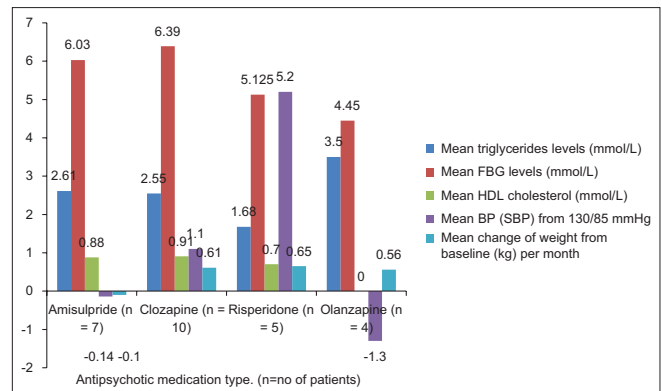


Figure 5: Metabolic parameters

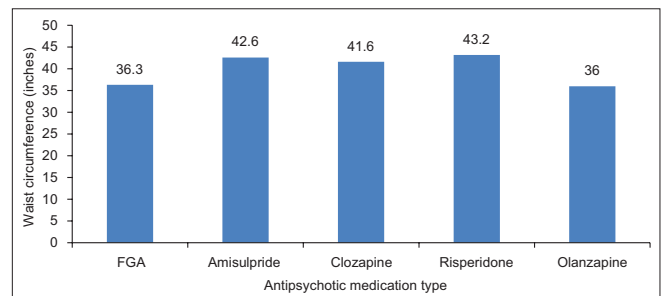


Figure 6: High dose antipsychotics

Confounders in this study have been acknowledged therefore it is difficult to place a firm conclusion. These include a small sample size, with four (4) patients in the exclusion criteria (refusing blood tests), and variation in age. However clinically it is uncommon to have a large number of cohorts receiving a high dose of antipsychotics. The limitations of the study also include a retrospective design and cross sectional survey. Increase in age however was not a significant predictor of metabolic syndrome in these patients. These patients were admitted at different periods and it was difficult to accurately record baseline weight, blood results, blood pressure and waist circumference. It was also difficult to accurately record pre-admission assessments in relation to previous medication, lifestyle habits and genetic predisposition to family history of diabetes and CVD. Ethnic origin was also taken into account; however the majority of patients were white (22/24).

It was clear from the measurements from baseline on admission that nearly all the patients were overweight and/or had put considerable weight on during their rehabilitation. However, muscle mass may contribute to this weight and therefore waist circumference was used as a more accurate parameter for metabolic syndrome.

Blood pressure was relatively controlled in most patients. Due to limited access to patient records, it was difficult to establish any antihypertensive treatment the patient may have previously been on, or any existing CVD. It is also important to question any interaction with antipsychotics, antidepressants or anxiolytics on reducing patient's blood pressure and therefore adjusting their readings. Therefore an ambulatory 24 hour blood pressure reading would have been more accurate.

A pre-admission assessment was carried out to find out when the patient was first diagnosed with the illness. These patients have likely to have been on a medley of antipsychotic medication for many years and therefore may have established weight gain and metabolic syndrome before admission. However, there was no accurate data confirming if the patient was previously on HDA, nor if the patient had metabolic syndrome pre-admission.

The rehabilitation centre provides excellent facilities for these patients such as dietary and exercise modifications, and continual screening for diabetes and CVD. Subjective assessment on calorie intake and exercise was carried out on these patients however were difficult to quantify the results.

This study reviewed previous evidence based around associations between mentally ill patients

on antipsychotic medication and risk of metabolic syndrome. This evidence was used to support data taken from a cohort of patients to analyse their medication dosage, their medication type, and whether these patients had metabolic syndrome. The data however does not support any further predisposition to metabolic syndrome in these patients taking HDA. It also cannot be assumed antipsychotic medication is independently associated with the prevalence of these abnormalities, especially due to confounders within the study method.

## CONCLUSION

Evidence has proved a strong link between patients who are mentally ill and metabolic syndrome. This review has highlighted main concerns that predispose these patients to metabolic syndrome, particularly antipsychotic medication, which can increase their health risks to secondary complications such as diabetes and CVD, increasing morbidity and mortality. It can also be established that other factors such as sedentary lifestyle, poor diet and exercise, genetic influences and biochemical changes from the illness itself could also contribute to the development of metabolic syndrome, leading to the importance of patient management.

Metabolic syndrome can be reversed and therefore patients should be educated and counselled on the importance of diet change and exercise as a first line prevention.

Patients on HDA should be monitored closely. Although evidence remains limited on increase risk factors predisposing the patient to metabolic syndrome, other adverse reactions such as EPS and QT syndrome are detrimental on these patients' lives. Evidence questioning the therapeutic benefit of HDA also remains controversial therefore further research in this field would be of clinical importance.

### To the future

There is currently research into Histamine-1 receptor antagonists in treating patients with antipsychotic induced weight gain. Genetic counselling also may provide a means of assessing individual risk of these consequences. This would be valuable in informing treatment decisions for practitioner and patient in the future. On going screening for diabetes and CVD, and monitoring patients carefully on antipsychotic medication, particularly at high doses and/or on SGAs is crucial. Switching these patients to lower risk medication is an option. It is a question of risk/benefit management and psychosis should be the main priority for the treatment of these patients, especially when it becomes a chronic burden to their daily living. Further

prospective studies in the future to find out if there is a clear correlation between HDA and its predisposition to causing metabolic syndrome in these patients would be valuable.

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