Graylands Hospital Drug Bulletin

Metabolic Syndrome and Antipsychotics

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Metabolic Syndrome – definition

Metabolic syndrome is a cluster of interrelated risk factors for developing cardiovascular disease (CVD) and type 2 diabetes and is associated with increased morbidity and mortality.[1, 2] The definition of metabolic syndrome differs depending on the source of information. The Adult Treatment Panel III (ATP-III) and the International Diabetes Federation (IDF) are two commonly used diagnostic sources[3] (Table 1). For a person to be defined as having metabolic syndrome, they must have central obesity plus any two of the other four factors.[1, 2]

Table 1:Diagnostic criteria of Metabolic Syndrome[1, 2]

Criteria	ATP-III	IDF
Waist Circumference (cm)		
Men	≥102	≥94 (≥90 for Asian men)
Women	≥88	≥80 (same for Asian women)
Blood Pressure (mmHg)	≥130/85	≥130/85
High-Density Lipoprotein (mmol/L)		
Men	<1.03	<1.03
Women	<1.30	<1.30
Fasting blood triglyceride level (mmol/L)	≥1.7	≥1.7
Fasting blood glucose level (mmol/L)	≥6.1	≥5.6

Although body mass index (BMI) and weight gain can aid clinicians to monitor the development of metabolic syndrome, waist circumference is a better predictor of CVD and diabetes risk as it correlates strongly with insulin resistance and is not affected by muscle mass.[4, 5] Obesity, particularly central obesity, is the primary risk factor for metabolic syndrome.[5]

Prevalence in mental illness

There is increasing focus on metabolic syndrome in patients with a mental illness. Patients with severe and persistent mental illness are twice as likely to develop metabolic syndrome than the general population.[3, 6] Up to 50% of patients with schizophrenia may be affected by metabolic syndrome.[7] A Graylands Hospital audit in 2008 found the prevalence of metabolic syndrome was almost double that of the general population.[8]

The impact of metabolic syndrome is of major concern as it can lead to increased morbidity and mortality, poorer quality of life and result in non-compliance with medications.[9] Several lifestyle factors associated with metabolic syndrome and CVD are common among patients with mental illness. These include sedentary lifestyle, unhealthy diet, smoking and substance misuse.[3] In addition to this, many medications prescribed to treat mental illnesses, such as antipsychotics, have metabolic and cardiovascular adverse effects that contribute to a patient's comorbidities.[6, 10-12] Young people experiencing their first episode of psychosis are particularly at risk of rapid and significant weight gain if treated with antipsychotics.[13]

First generation compared to second generation antipsychotics

First generation antipsychotics are associated with a lower incidence of metabolic syndrome compared to second generation antipsychotics, though significant weight changes can occur with both.[9] A comparison of weight gain in commonly used antipsychotics is outlined in Table 2. Clozapine and olanzapine produce the most weight gain, while aripiprazole and ziprasidone produce the least.

Table 2: Summary of weight gain with antipsychotics[4, 7, 14]

	Weight Gain
First Generation Antipsychotics	
Chlorpromazine	++
Zuclopenthixol	++
Flupenthixol	++
Haloperidol	+
Trifluoperazine	+
Fluphenazine	+/-
Second Generation Antipsychotics	
Clozapine	+++
Olanzapine	+++
Risperidone	++
Paliperidone	++
Quetiapine	++
Amisulpride	+
Aripiprazole	+/-
Ziprasidone	+/-

+=increased effect; -=no effect

Mechanism of antipsychotic induced metabolic syndrome

Many of the elements of metabolic syndrome are driven by weight gain.[15] This weight gain is a complex side effect of antipsychotics, with several causal mechanisms.[16]

Patients taking antipsychotics have a reduced rate of resting energy expenditure, which can result in weight gain if strategies, such as increased physical activity, are not introduced.[16]

Two receptors are also associated with weight gain, the serotonin 2C (5-HT_{2C}) and histamine 1 (H1) receptors. Antagonism of 5-HT_{2C} by antipsychotics increases food intake despite satiety. H1 receptor blockade increases appetite.[16] Clozapine and olanzapine have the greatest affinity for these receptors, which could be the reason for their higher propensity to cause weight gain.[16]

Pharmacogenetics can also affect weight gain. Patients with a lower BMI are at highest risk of weight gain. Early and rapid weight gain appear to be predictors for long-term weight gain.[16]

The exact mechanism of antipsychotic-induced hyperglycaemia is unknown. It may be caused by drug-induced insulin resistance from associated weight gain, changes in body fat distribution, or direct effects on insulin-sensitive target tissues.[10]

Hypertriglyceridaemia is associated with insulin resistance. Elevated fasting triglyceride (TG) levels are a sensitive marker, and a TG to High-Density Lipoprotein (HDL) ratio greater than 3 can be used to predict insulin resistance.[5]

Management

There is no current international or national consensus on management of metabolic syndrome.[17]

Patients should be educated and counselled, where possible, on metabolic syndrome as it is avoidable.

Choice of antipsychotic

Optimal treatment of psychosis is a priority in patients with schizophrenia. However, other factors should be considered when choosing an antipsychotic agent. These include nature of the illness, medical comorbidities, effectiveness of the medication and potential for extra-pyramidal and metabolic side effects.[16] If metabolic syndrome is likely, benefits of continuing treatment with an antipsychotic medication should be balanced against the patient's cardiovascular and diabetic risk.[10]

Switching to an antipsychotic, such as ziprasidone or aripiprazole, with a low propensity to cause metabolic syndrome can be effective in reversing the side effects caused by the previous antipsychotic.[16] However, other factors may prevent this change and each case should be evaluated individually.

Obesity and weight gain

Serious mental illness, medication effects, poor nutrition, lack of impulse control and lack of exercise can all contribute to weight gain in patients with mental illness.[10]

Weight loss of as little as 5% body weight can significantly reduce morbidity and mortality.[13]

Adjunctive treatments with other medications to treat weight gain have been studied, though these indications are not approved in Australia. Topiramate and sibutramine have both been associated with weight loss in patients taking antipsychotics[18], though data is limited and many patients discontinued treatment due to adverse effects.[6] Sibutramine and topiramate must be used with caution due to reports of psychosis and mood changes.[19, 20]

Metformin has produced weight loss during randomised clinical trials,[21, 22] though it is unclear whether this is due to insulin sensitisation or gastrointestinal side effects that reduce appetite.[6]

Medications that counteract hyperprolactinaemia, such as amantadine and bromocriptine, have also shown some success in a limited number of clinical trials.[23]

These pharmacological treatments remain experimental due to insufficient evidence to support their use in general practice.[6]

Diabetes

It is estimated that the rate of type 2 diabetes in patients with schizophrenia is approximately double that of the general population.[7] Fasting blood glucose (FBG) should be tested at baseline regardless of risk factors or symptoms present. Ongoing regular FBG testing is also recommended (see Table 4). Weight gain is a risk factor for diabetes, but occurrence of diabetes is not always related to weight gain.[7]

Hyperlipidaemia

Hyperlipidaemia is a major risk factor for CVD and is commonly found in association with diabetes.[7] Fasting levels of total cholesterol, low-density lipoproteins, TG and HDL should be obtained prior to and during antipsychotic treatment (Table 4).[6, 7]

If hyperlipidaemia is evident, therapeutic lifestyle changes and possibly pharmacotherapy should be initiated to achieve target levels. Lifestyle changes consist of a low fat and high fibre diet, increased physical activity and weight management. Drug therapies recommended include statins, fibrates, bile acid binding resins and fish oil. These should be initiated after 3 months of lifestyle changes if

targets have not been achieved.[6] Medical and family history, as well as smoking status should be considered when evaluating hyperlipidaemia.

Hypertension

Blood pressure (BP) should be monitored in all patients with mental illness due to the increased risk of CVD.[7] Non-pharmacological management, including weight loss, smoking cessation, increase in exercise and a low-salt diet (<4g/day) is first line treatment.[24] If these interventions do not produce goal BP (Table 3), antihypertensive therapy should be initiated. [24, 25] Reference ranges are different for Aboriginal and Torres Strait Islander populations.[24]

Table 3: Heart Foundation's target blood pressure for adults[24]

Patient Groups	Target BP (mmHg)
People with proteinuria >1g/day (with or without diabetes)	<125/75
People with associated condition/s or end-organ damage • Coronary Heart Disease • Diabetes • Chronic kidney disease • Proteinuria (>300mg/day) • Transient Ischaemic Attack/Stroke	<130/80
People with no associated conditions	<140/90 or lower if tolerated

Antihypertensive drug treatment should be initiated immediately if systolic BP >180mmHg and/or diastolic BP>110mmHg.[24]

Behavioural strategies

The main behavioural strategies used for antipsychotic-induced metabolic syndrome are cognitive behavioural therapy, behavioural therapy, nutritional intervention or a combination of these.[16] Group educational sessions on nutrition and exercise have resulted in moderate success in small clinical trials.[6] Interventions specifically targeting eating habits, and weekly sessions consisting of weight monitoring and nutrition discussion also produced weight loss.[6] Weight loss appears to be correlated with the number of sessions attended.[6]

Monitoring

Routine monitoring of patients with schizophrenia allows for early detection of metabolic side effects. Table 4, adapted from the American Diabetes Association, details specific recommendations for evaluation and monitoring. Currently there is no consensus on frequency and recommended tests to be performed.

Ongoing monitoring for 6 months is recommended when switching antipsychotic agents. Closer monitoring is also recommended in patients whose weight is still increasing. It can be carried out less frequently once weight has stabilised.[7]

Waist circumference is the preferred measurement of central obesity (Table 1), but is not always practical in the mental health setting. BMI is therefore an accepted measurement for obesity, but waist circumference should be measured when possible. A BMI ≥25 is considered overweight, and ≥30 is obese.[26]

Summary

Initial testing for metabolic syndrome in mental health patients should be done regardless of risk factors. Whilst antipsychotics, particularly clozapine and olanzapine, increase the risk of developing diabetes and CVD, severe mental illness itself is a contributing factor.[7]

In patients who develop signs of metabolic syndrome, clinicians must choose between switching to an antipsychotic with fewer metabolic adverse effects, or continuing antipsychotic therapy and treating the side effects with adjunctive treatment.[6]

Patients receiving antipsychotic treatment usually require long-term therapy, therefore initial diagnosis and management is important to reduce the morbidity and mortality associated with metabolic syndrome.

Table 4: Recommendations for initial evaluation and monitoring in patients with schizophrenia[9, 27]

	Initial Visit	4 weeks	8 weeks	12 weeks	6 monthly	Annually
Personal/Family history	X					X
Height/weight (BMI)* or Waist Circumference	X	X	X	X	X	
Blood Pressure	X			X	X	
Fasting blood glucose	X	X**	X**	X	X	
Fasting lipid profile	X			X	X	

*: BMI should be used unless trained staff are able to measure waist circumference. Use same method for all visits.
**: Finger prick tests can be carried out at 4 and 8 weeks to identify early cases. Formal laboratory tests can then be carried out when necessary.

Prolactin Elevation with Antipsychotics

Prolactin

Antipsychotics increase prolactin levels due to blockade of dopamine receptors in the hypothalamus.[1] Dopamine inhibits the release of prolactin, therefore all antipsychotics increase the level of prolactin to some degree, but not always above the normal range.[2] Persistent prolactin elevation can cause a number of adverse effects[2] (Table 1). High prolactin levels reduce the concentration of oestrogen and testosterone in the body, which account for many of the adverse effects. Prevalence in women appears to be higher than in men.[3] Pituitary tumours, stress and pregnancy are other causes of increased prolactin which may need investigation.[4]

Table 1: Adverse effects of hyperprolactinaemia[2, 3]

Hyperprolactinaemia can cause:

- Sexual dysfunction – decreased libido, decreased arousal, anorgasmia
- Reduced bone mineral density
- Galactorrhoea
- Menstrual disturbances
- Reduced fertility
- Breast growth
- Hypogonadism
- Possible increased risk of breast cancer

Monitoring

Careful questioning by the clinician is recommended to ensure ongoing monitoring of sexual dysfunction and menstruation.[5] Prolactin should be measured at baseline, after 6 months and then yearly.[2] Sexual dysfunction, in particular, is a common cause of medication non-compliance.[6]

Management

Reducing the dose of antipsychotic or switching to a non-prolactin-elevating antipsychotic is often first line of treatment.[2, 7] A list of antipsychotics and their effects on prolactin are shown in Table 2.

If prolactin elevation is mild (<1000mIU/L), the level should continue to be monitored.[5] If it continues for greater than 3 months (accompanied by symptoms of hyperprolactinaemia) or the prolactin level is >1000mIU/L, consideration should be given to reducing the dose or switching antipsychotic.[5] Aripiprazole and ziprasidone appear to have the least effect on prolactin levels.[8]

It is important to differentiate between depression, negative symptoms of schizophrenia and elevated prolactin, as all of these can cause similar symptoms such as decreased libido and reduced sexual activity.[8]

Fertility may return in female patients once prolactin has normalised, therefore patients should be advised to use contraception, if required. The effects of hyperprolactinaemia and male fertility has not been investigated systematically.[8]

Table 2: Prolactin elevation with antipsychotics[2]

	Prolactin Elevation
First Generation antipsychotics	
Chlorpromazine	+++
Flupenthixol	+++
Fluphenazine	+++
Haloperidol	+++
Zuclopenthixol	+++
Second Generation antipsychotics	
Risperidone	+++
Paliperidone	+++
Amisulpride	+++
Olanzapine	+
Ziprasidone	+/-
Aripiprazole	-
Quetiapine	-
Clozapine	-

+= increased effect; -= no effect

Treatments

Sildenafil

Sildenafil may be effective for male patients experiencing erectile dysfunction due to antipsychotic use. Response rates appear to be similar to use in the general population.[9]

Dopamine agonists

Dopamine agonists such as amantadine can improve symptoms of hyperprolactinaemia, though worsening of psychiatric symptoms may occur.[8]

Oral Contraceptive

Combined oral contraceptives in premenopausal women can reduce the symptoms of oestrogen deficiency, such as amenorrhoea.[10] This treatment, however, increases the risk of thromboembolism and breast cancer.[10]

Precautions

People under 25 years should avoid prolactin elevation, as peak bone mineral density has not been reached.[5] As hyperprolactinaemia may be associated with breast cancer, and possibly prostate cancer, caution is required in these patients.[5]

Conclusion

Patients on prolactin-elevating antipsychotics should be routinely monitored for signs of hyperprolactinaemia. It is also important to consider the patient's response to treatment before reducing the dose or switching antipsychotic.

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References available on request

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