

# DRUG BULLETIN

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## Metabolic Disturbances with Antipsychotic Medication

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- ✦ Increasing clinical experience with atypical antipsychotics has demonstrated an association between these medications and metabolic disturbances, including hyperglycaemia, diabetes mellitus, weight gain and dyslipidaemia.
- ✦ The term metabolic syndrome describes the incidence of a number of interrelated metabolic disturbances occurring in one patient and is becoming increasingly recognised as a major adverse effect on patients' health.
- ✦ Patients with schizophrenia are at a higher risk of comorbid physical illness, therefore prevention and early intervention for metabolic disturbances are particularly important.

### DIABETES

It appears that the prevalence of insulin resistance and diabetes is higher amongst patients with schizophrenia than the general population<sup>1,2</sup> and insulin resistance was reported in patients with schizophrenia before the widespread use of antipsychotic medications<sup>3,4</sup>.

Some reviews have failed to find consistent evidence for the increased risk of diabetes in patients taking antipsychotic medications<sup>3,5</sup>. However when looking at the volume of published information, a trend towards an increased risk appears to have emerged.

#### Typical Antipsychotics

From the mid 1950's, reports of hyperglycaemia, glucosuria and deterioration in diabetic control emerged with the use of phenothiazine antipsychotics<sup>6</sup>. While phenothiazine treatment continued to be associated with glucose regulation abnormalities, higher-potency typical antipsychotics such as haloperidol, did not appear to be associated at the same

magnitude<sup>6</sup>. A report published in 1968 found the prevalence of diabetes in psychiatric in-patients had increased from 4.2% in 1954 to 17.2% in 1966, most likely due to the introduction of phenothiazine antipsychotics<sup>7</sup>. A more recent publication found that the prevalence of diabetes in patients taking a typical antipsychotic was 18.64%<sup>8</sup>.

#### Atypical Antipsychotics

The introduction of atypical antipsychotics was associated with a further increase in the prevalence of diabetes amongst psychiatric patients, with reports varying from 10-50%<sup>8</sup>. Investigations of over 20,000 outpatients in the United States found the prevalence of diabetes amongst patients taking atypical antipsychotics was 18.84%, which was not significantly different from the prevalence of those taking typical antipsychotics<sup>8</sup>.

Various case reports, surveys and reviews can be found in the literature that attempt to establish the incidence of diabetes or impaired glucose tolerance with different atypical antipsychotic agents. There have been reports with clozapine, olanzapine, risperidone and

quetiapine, some of which are described in a previous Graylands Drug Bulletin<sup>9</sup>.

The American Diabetes Association, in collaboration with a number of other associations, found the atypical antipsychotics, clozapine and olanzapine appear to be associated with the greatest risk for developing diabetes<sup>10</sup>. Results for risperidone and quetiapine are discrepant and at this stage, aripiprazole does not appear to have an effect<sup>10</sup>.

Unfortunately amisulpride is not available in the US, so was not reviewed, however, another literature review did not find any data concerning amisulpride and diabetes risk<sup>11</sup>.

### Possible Mechanisms of Antipsychotic-Induced Hyperglycaemia

The mechanisms for the apparent increased risk of diabetes in patients taking antipsychotic medications, are not clear. Weight gain, which can be precipitated by antipsychotic medication, increases the risk of diabetes. Diabetes can however occur in patients who do not gain weight and one study found that the risk of diabetes whilst being treated with clozapine, was independent of weight gain<sup>12</sup>.

Hypotheses of other possible mechanisms include disturbance of glucose metabolism, aggravation of existing insulin resistance or insulin resistance due to a direct effect on insulin-sensitive target tissues<sup>6,10,13</sup>.

### Diagnosis and Treatment Recommendations

For the diagnosis of diabetes, venous blood samples should be used, as opposed to blood glucose meters<sup>14</sup>. For patients with symptoms of diabetes (eg. thirst, polyuria, recurrent infections), a fasting venous plasma glucose level of  $\geq 7.0$  mmol/L or random level of  $\geq 11.1$  mmol/L, is diagnostic. For asymptomatic patients, if these levels are obtained, a confirmatory test should be performed on a separate day.

For patients who have repeat abnormal tests of fasting venous plasma glucose levels 5.6 to 6.9 mmol/L or random levels of 5.6 to 11

mmol/L, an oral glucose tolerance test should be performed.

Interpretation of oral glucose tolerance test*	
Venous plasma glucose level	
<b>Diabetes</b>	
fasting	$\geq 7$ mmol/L
2-hour	$\geq 11.1$ mmol/L
<b>Impaired Glucose Tolerance</b>	
fasting	$< 7$ mmol/L
2-hour	7.8-11.1 mmol/L

\* Adapted from the Therapeutic Guidelines: Endocrinology V3 2004

Consistent advice should be provided on diet, exercise and smoking. Diabetes medication may need to be instituted. Metformin is usually the medication of first choice in obese patients with type 2 diabetes, however, each patient should be assessed individually.

The Therapeutic Guidelines: Endocrinology 2004 and the Diabetes, Psychotic Disorders and Antipsychotic Therapy: Consensus Statement 2004 (which can be viewed at [www.psychiatry.unimelb.edu.au/open/diabetes\\_consensus](http://www.psychiatry.unimelb.edu.au/open/diabetes_consensus)) contain guidance on appropriate drug therapy for type 2 diabetes<sup>14,15</sup>.

## WEIGHT GAIN

There is some support for the possibility that schizophrenia may in itself promote obesity<sup>16</sup>. However, antipsychotic medications have been widely recognised as a cause of weight gain. Weight gain can reduce medication compliance and it contributes to medical comorbidity.

### Typical and Atypical Antipsychotics

Weight gain due to typical antipsychotic medications was noticed soon after their introduction in the 1950s. From the studies available, it appears that all typical antipsychotics have the potential to cause weight gain. However of the products currently available in Australia, chlorpromazine may cause the most weight gain<sup>17,18</sup>.

Of the atypical antipsychotics, clozapine and olanzapine have been associated with the most weight gain, then risperidone and quetiapine, with aripiprazole and amisulpride having the least potential for weight gain<sup>10,18,19</sup>.

## Possible Mechanisms of Antipsychotic-Induced Weight Gain

The main rationale for weight gain appears to be increased calorie intake and decreased energy expenditure<sup>4,10</sup>. This may be due to increased appetite, increased intake of high calorie fluids if experiencing dry mouth and sedation leading to less activity<sup>10,17,18</sup>.

Other proposed mechanisms include reduced metabolism, increases in prolactin levels, increases in leptin levels and changes to cytokine levels that may be involved in body weight regulation<sup>4,17,18</sup>.

## Management Options

Prevention of weight gain should be the primary objective. Treatment of drug-induced weight gain is not well documented in the literature and guidelines for weight management of the general population are generally appropriate for patients with mental illness<sup>19</sup>. Dietary changes are important and exercise is critical in weight loss and maintenance of a healthy weight<sup>19</sup>.

## DYSLIPIDEMIA

Although data is limited, evidence suggests that antipsychotic medications can affect

serum lipids and increases in lipids appear to be correlated with weight increases<sup>10</sup>.

Clozapine and olanzapine are associated with the greatest increases in serum lipids, with quetiapine and risperidone having intermediate effects<sup>10,11</sup>. Aripiprazole and amisulpride do not appear to affect lipid levels<sup>10,20</sup>.

## RECOMMENDED MONITORING

Recommended monitoring for metabolic function in patients taking antipsychotic medications should include:

- ❖ **Monthly blood sugar levels (BSLs) for 6 months when starting, changing or altering dose of antipsychotic, then 6 months once stabilised.** (*Finger prick measurements using a blood glucose meter is acceptable for monitoring purposes.*)
- ❖ **If diabetes diagnosed, Hb1Ac every 3-6 months - Hb1Ac  $\leq$ 7%.**
- ❖ **Body mass index (BMI) and waist:hip ratio every 3 months - BMI  $<$ 25kg/m<sup>2</sup>, waist:hip ratio  $<$ 0.8 women,  $<$ 0.9 men.**
- ❖ **Lipid profile and blood pressure every 6 months - Cholesterol  $<$ 5.5 although ideally  $<$ 4.0, BP  $<$ 135/80.**

Recommendations from The Diabetes, Psychotic Disorders and Antipsychotic Therapy: Consensus Statement 2004<sup>15</sup>.

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## Paraldehyde – Friend or Foe?

Paraldehyde is a liquid sedative medication, first introduced before 1900 and best known for its strong aroma and disagreeable taste. Clinical uses of paraldehyde have included anaesthesia, treatment of muscle spasms in tetanus, treatment of convulsions (including status epilepticus), treatment of alcohol withdrawal symptoms and sedation<sup>1</sup>.

Despite the lack of published information on paraldehyde's effectiveness for sedation or rapid tranquillisation, it has been used with apparent success for these purposes. There is no information readily available to compare the effectiveness of paraldehyde to other currently available sedative agents.

At present, there are no applicable guidelines for paraldehyde's use for sedation or rapid tranquillisation. Paraldehyde should be used as a last resort and the decision to use it should be based on a review of its advantages and disadvantages in each patient.

### Advantages

- It is a rapidly acting hypnotic - the onset of hypnosis occurs within 10-15 minutes after oral and 2-3 minutes of intramuscular (IM) administration. Sleep usually lasts 4-8 hours.
- It can be given orally, but it must be well diluted - it may be diluted with milk or fruit juice<sup>2</sup>. Oral doses range from 4 to 10mL<sup>1,2</sup>.
- Oral and IM forms are readily absorbed.
- It can be given rectally, although absorption is slower - if given rectally, it must be diluted with oil or isotonic sodium chloride at the time of administration.
- Little effect is seen on respiration and blood pressure at therapeutic doses – however respiratory depression and hypotension may occur at high doses.

### Disadvantages

- It has a very unpleasant taste.
- Oral and rectal administration may cause irritation - it should never be given to patients with gastric disorders or colitis.
- IM paraldehyde is very painful and sterile abscesses and nerve damage have been reported - no more than 5mL should be administered per

site and care should be taken to avoid the vicinity of nerve trunks.

- IV paraldehyde is not recommended as it may cause pulmonary oedema, haemorrhage, hypotension, cardiac dilatation, circulatory collapse and thrombophlebitis - pulmonary oedema is a frequent factor for deaths due to paraldehyde and cough is an early symptom.
- There is considerable variation in response to paraldehyde – deaths have been reported with ingestion of as little as 25mL
- The product must be opened immediately before use - exposure to air and light may induce the decomposition of paraldehyde.
- Use of the decomposed product of paraldehyde has led to severe corrosion of the stomach and rectum, metabolic acidosis and death - vials of paraldehyde should not be used if the liquid has turned a brown colour, or smells like vinegar.
- As it is incompatible with many plastics and rubber, it is recommended that all-glass syringes should be used for its administration. However in clinical practice, plastic syringes have been utilised. This is acceptable, though only for the immediate administration or measurement of paraldehyde doses.
- Prolonged use may lead to dependence.
- It has no analgesic properties – it may produce excitement or delirium in the presence of pain.
- It can cause skin rash, toxic hepatitis, nephrosis and metabolic disorders.
- A large part of the unchanged drug (11-28%) is excreted through the lungs, imparting an unpleasant smell to the breath.
- It should not be used in patients with liver impairment or bronchopulmonary disease due to its metabolism by the liver and excretion through the lungs.
- It should not be given to a patient intoxicated by alcohol - possible potentiation of CNS depression may occur. There are 8 reports of patients who have died suddenly with concurrent paraldehyde use.
- The wholesale cost is approximately **\$120** per 5mL ampoule - **safer, more cost effective alternatives are available.**

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#### Acknowledgment

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