



Diabetes and antipsychotic drugs

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Summary

There is an increased risk of diabetes in patients with schizophrenia and this risk is elevated by some antipsychotic medications. The risk is greater with the atypical drugs clozapine and olanzapine and the low potency conventional antipsychotics than with risperidone or high potency conventional drugs. While weight gain may be a mechanism for the development of diabetes, a direct effect of these drugs on insulin action in muscle may also be an important contributor. Patients with major psychosis should be managed in the same way as other patients with diabetes, but difficulties in complying with diet, exercise and taking medication should be kept in mind. Treating cardiovascular risk factors is important.

Key words: schizophrenia, obesity, insulin resistance.

(Aust Prescr 2004;27:118-9)

Introduction

An impaired action of insulin (insulin resistance) in patients with schizophrenia was reported over 55 years ago and later confirmed in Australia.¹ The prevalence of diabetes in patients with schizophrenia was found to be higher than in the general population even before the widespread use of antipsychotic medication. The mechanisms underlying the relationship between schizophrenia and diabetes remain unknown.

Antipsychotic drugs and diabetes

It is now clear that some antipsychotic medications increase the risk of diabetes in patients with schizophrenia. Rarely, this may present as diabetic ketoacidosis. The atypical medications (Table 1) have become widely used because of their lower rate of extrapyramidal adverse effects compared to older classes of medication such as the phenothiazines and the butyrophenones. However, while some of the atypical drugs are better tolerated, they also increase the incidence of diabetes. In patients younger than 40 years of age, the odds ratio for developing diabetes is 1.63 if they are taking an atypical antipsychotic.²

Table 1

Classification of antipsychotic medications available in Australia

Atypical	Low potency* conventional	High potency conventional
amisulpride	chlorpromazine	droperidol
aripiprazole	pericyazine	flupenthixol
clozapine	thioridazine	fluphenazine
olanzapine		haloperidol
quetiapine		trifluoperazine
risperidone		

Not all antipsychotics increase the risk of diabetes to the same extent.³ In a survey of two large US health plans, the risk of developing diabetes over a year was found to be higher with olanzapine and 'low potency'* conventional antipsychotics, but not with risperidone or 'high potency' conventional drugs (Table 2).⁴ In one prospective study 36.6% of patients treated with clozapine developed diabetes over a five-year period.⁵

Mechanism of antipsychotic-induced diabetes

The mechanisms responsible for the elevated risk of diabetes associated with some antipsychotics are not fully understood. It is known that the atypical antipsychotics and some of the low potency conventional antipsychotics cause weight gain⁶ and that, at least for olanzapine and clozapine, the magnitude of this weight gain correlates with the magnitude of the therapeutic response.⁷ The weight gain in response to antipsychotic medication is also variable. Clozapine and olanzapine cause the greatest gain, risperidone and quetiapine moderate gain, and aripiprazole and amisulpride the least gain.⁸ However, at present insufficient information is available about some of the newer drugs to know what their weight gain and diabetogenic potential will prove to be with more widespread use.

Obesity can precipitate diabetes in susceptible people so weight gain is one mechanism for the increased incidence in diabetes. However, the fact that hyperglycaemia improves quickly after stopping the antipsychotic medication and that diabetes can appear in some patients who do not put on weight, suggests that other mechanisms must be involved. A prospective study of 82 patients treated with clozapine also found that the risk of developing diabetes was independent of weight gain.⁵

* Low potency is defined as 'equivalent or less potent than chlorpromazine'.¹⁰

Table 2

Risk of developing diabetes with antipsychotic medication⁴

Drug	Number of patients	12-month odds ratio (95% CI)
Untreated	2644	1.0
Low potency* conventional	302	4.972 (CI 1.967–12.612) [†]
High potency conventional	785	1.945 (CI 0.794–4.786)
Olanzapine	656	4.289 (CI 2.102–8.827) [†]
Risperidone	849	1.024 (CI 0.351–3.015)

CI confidence interval

[†] significant ($p < 0.05$) compared to untreated patients

Diabetes related to antipsychotic medication is associated with high insulin concentrations, so it seems that these drugs may aggravate the insulin resistance that already exists in patients with schizophrenia. While some of this is no doubt related to weight gain, it has also been shown that antipsychotics inhibit glucose transport into muscle. There is a strong correlation between the ability of these drugs to inhibit glucose transport *in vitro* and their capacity to induce hyperglycaemia *in vivo*.⁹

Management of diabetes in patients with schizophrenia

What needs to be taken into account when treating someone coping with the dual problems of schizophrenia and diabetes?

- Be alert to the increased risk of diabetes in patients with schizophrenia and the fact that some antipsychotic medications increase the risk. Check the patients' fasting blood glucose and monitor their weight.
- Monitor blood glucose more frequently in patients with known diabetes who commence antipsychotic medication.
- Advise about diet and exercise, but keep in mind that compliance may be particularly difficult for patients with schizophrenia.
- When prescribing hypoglycaemic drugs, try to use once-daily medication so that treatment can be more easily supervised. While metformin (the preferred first-line therapy) should be given twice daily there are now two sulfonylureas that are available as once daily medication (modified-release gliclazide and glimepiride).
- There is an increase in cardiovascular mortality in patients with schizophrenia so remember to regularly assess and vigorously treat cardiovascular risk factors such as dyslipidaemia and hypertension.
- In psychotic patients who have a family history of diabetes or in those who are from an ethnic group with a high

prevalence of diabetes (all non-Europeans), try to use an antipsychotic that has less potential for precipitating diabetes, such as risperidone or one of the high potency conventional drugs (Table 2).

The management of diabetes in patients with a major psychiatric illness is problematic. Weight loss or prevention of weight gain should always be attempted because of the known benefits to other comorbidities associated with obesity. However, even if successful, this approach alone may not reduce the risk of developing or worsening diabetes.

References

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

3. Patients with schizophrenia have an increased risk of cardiovascular disease.
4. Atypical antipsychotic drugs such as clozapine do not increase the risk of diabetes in patients with schizophrenia.