# Clozapine and refractory diabetes treatment

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### Article points

1. Clozapine, a potent antipsychotic drug, has been implicated in causing diabetes.
2. The authors outline a case report of a young Afro-Caribbean man with schizophrenia who was treated with clozapine and subsequently diagnosed with diabetes.
3. This case report highlights the need for both mental health and diabetes services to be aware of the potential association and to structure care plans accordingly.

### Key words

- Clozapine
- Schizophrenia

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**Young people with treatment-resistant paranoid schizophrenia may require clozapine, which is a highly potent antipsychotic drug that is recommended when other drugs have failed. Clozapine has significant side effects including potentially fatal agranulocytosis. It has also been implicated in causing diabetes. This case report details the complications caused by starting clozapine in a young Afro-Caribbean male with diabetes. It highlights the need for mental health and diabetes services to suspect clozapine in cases of refractory diabetes treatment and the need to consider reducing the dose, changing to alternative antipsychotic drugs or management with non-pharmacological therapies. The authors suggest clozapine should be avoided in young Afro-Caribbean people with diabetes.**

People with schizophrenia have a higher incidence of diabetes compared to the general population (Mukherjee et al, 1996). Clozapine is an effective antipsychotic drug that is recommended in cases of treatment-resistant paranoid schizophrenia (NICE, 2009) but it remains a second-line treatment due to its complex side effect profile, which includes fatal agranulocytosis.

To complicate matters, case reports from the late 1990s suggest that certain antipsychotic drugs including clozapine, olanzapine and quetiapine might cause diabetes (Popli et al, 1997; Goldstein et al, 1999; Sobel et al, 1999). The potential of clozapine to cause diabetes has also been highlighted by an epidemiological study reporting adverse drug events (Koller et al, 2001). The mechanism of causation has not been confirmed but suggestions include weight gain, which is a known side effect associated with antipsychotic drugs, especially clozapine (Allison et al, 1999; Henderson et al, 2005). Direct pharmacological effects on insulin and glucose metabolism by clozapine have also been suggested (Melkersson et al, 1999; Tovey et al 2005). Despite its potential association with causing diabetes, many psychiatrists are still faced with young people with treatment-resistant schizophrenia who require clozapine.

Clinical decision-making in this group of people is complicated by limited literature on the effect of initiating clozapine in young people with diabetes. This case report outlines the complications that can occur by introducing clozapine to a young Afro-Caribbean person with diabetes who has recently gained weight and highlights the need for mental health and diabetes services to be familiar with the implications of clozapine.

## Case report

The patient in this case report has consented to this publication but his details have been anonymised to help protect his identity. He is a young man in his 20s of Afro-Caribbean origin who has treatment-resistant paranoid schizophrenia. For many years he was treated with different antipsychotic drugs but still experienced distressing psychotic symptoms

including auditory hallucinations and paranoid delusions which resulted in numerous admissions to hospital. After several years of treatment with the antipsychotic flupentixol 200 mg intramuscular injection every 2 weeks, he had a further relapse in mental state and was admitted to a psychiatric hospital. Upon admission his routine physical examination was unremarkable. This included normal baseline blood testing, normal blood glucose level and normal ECG. His weight on admission was 86 kg with a BMI of 35 kg/m$^2$. There was no family history of diabetes.

The patient was advised to commence clozapine at an early stage, given his treatment-resistant paranoid schizophrenia and failure to respond to other antipsychotic drugs; however, he refused to comply with this medication. Therefore, flupentixol was gradually increased in dose.

## Diagnosis of diabetes

Twelve months into his admission, routine blood testing identified a raised blood glucose level of 12 mmol/L. Repeat fasting blood glucose samples confirmed the presence of diabetes. Blood tests including urea and electrolytes, liver function tests and lipids were taken and found to be normal apart from a slightly raised cholesterol level of 5.1 mmol/L, which responded well to treatment with simvastatin. His baseline $HbA_{1c}$ was raised at 62 mmol/mol (7.8%). At the time of identifying his diabetes, his weight had not increased and remained at 86 kg.

He was referred to the GP and the specialist diabetes clinic where he was diagnosed with type 2 diabetes. Three months of diet control and exercise were initially recommended but the individual remained mentally unwell and due to his impulsivity could not maintain a healthy diet. Due to poor glycaemic control, he was then commenced on metformin, which was increased over 3 weeks to 500 mg three times a day. Gliclazide was then added, which was increased to 120 mg twice per day. His diabetes became relatively well controlled. After rising to 140 mmol/mol (15%), his $HbA_{1c}$ returned to 64 mmol/mol (8%) but his mental state remained poor.

Six months after developing diabetes, the patient agreed to commence treatment with clozapine. At this stage, his weight had increased to 110 kg. His flupentixol depot was stopped and the dose of clozapine was gradually increased to 150 mg twice per day. His long standing psychotic symptoms improved but within 1 month of starting clozapine his diabetes control rapidly worsened. The patient's blood glucose increased to levels persistently higher than 20 mmol/L. He also started to experience repeated acute medical crises over the next few weeks. During one of these emergencies, he had burning chest pain, raised blood glucose of 24.1 mmol/L, raised blood pressure of 144/87 mmHg, tachycardia over 100 beats per minute but was apyrexial and negative for urine ketones. These episodes required repeated transfer to A&E for acute medical treatment. During such episodes his blood glucose was often greater than 30 mmol/L but he was always negative for urine ketones and no impairment of consciousness occurred. Good fluid intake prevented the occurrence of non-ketotic hyperosmolar syndrome.

Ongoing advice was obtained from the diabetes specialist and the diabetes outreach nurse. The gliclazide was increased to 160 mg twice per day and he was also commenced on sitagliptin, 100 mg per day. These measures did not control his diabetes and he was therefore started on insulin injections, which were rapidly increased in dose. He also received treatment from the visiting podiatrist and dental nurse due to ongoing infections.

## A change in antipsychotic therapy

Following 3 months of aggressive treatment of his diabetes his blood glucose levels could not be controlled and continued to remain above 20 mmol/L. A trial reduction in the dose of clozapine only led to a negligible reduction in blood glucose levels. The clinical team therefore made a decision to stop treatment with clozapine, which was changed to aripiprazole, a newer type of oral antipsychotic drug. This led to an immediate and substantial improvement in blood glucose levels, which returned to approximately 5 mmol/L with an $HbA_{1c}$ of 43 mmol/mol (6.1%). His medication was optimised with very rapidly-acting insulin, 20 units per day in divided post-prandial doses, as well as insulin levemir (16 units in the morning and 26 units at night) combined with ongoing treatment with metformin 1000 mg per day and simvastatin 20 mg per day. During the next 6 months his weight

### Page points

1. A young Afro-Caribbean male was commenced on clozapine to treat his treatment-resistant paranoid schizophrenia.
2. Whilst his psychotic symptoms improved with clozapine, his diabetes control worsened rapidly, with blood glucose levels higher than 20 mmol/L.
3. He also experienced repeated acute medical crises which required urgent care. His blood glucose often increased to over 30 mmol/L during these episodes.
4. Aggressive treatment to control his diabetes did not work so the decision was made to stop treatment with clozapine. This led to an immediate improvement in blood glucose levels.

*"Our case report, in the context of previous literature, highlights the intolerability of starting clozapine in a young Afro-Caribbean patient with diabetes who has recently gained weight."*

reduced to 94 kg. His psychotic symptoms improved and he started to respond better to psychological therapy and was able to work towards discharge.

## Discussion

This case report cannot confirm that the patient's treatment with depot antipsychotic medication caused his diabetes. It remains possible that his diabetes occurred independently of his prescribed medication. The patient did not gain weight in the year prior to developing diabetes, which suggests that adiposity was not implicated in his development of diabetes. After developing diabetes he gained 24 kg in weight over 6 months. The cause of his weight gain is uncertain but is likely to have been due to metabolic changes associated with developing diabetes, compounded by treatment with depot antipsychotic medication. The rapid deterioration of his diabetes in the month after commencing clozapine implicates clozapine as the causative agent but cannot confirm that this was the cause. The patient was receiving treatment with other medications, which means that drug interactions cannot be excluded.

**Box 1. The side effect profile of clozapine.**

- Constipation.
- Tachycardia.
- Nausea.
- Sedation.
- Hyper salivation.
- Postural hypotension.
- Agranulocytosis.
- Convulsions.
- Blurred vision.
- Dry mouth.
- Restless legs syndrome.
- Muscle stiffness.
- Urinary retention and incontinence.
- Weight gain.
- Neuroleptic malignant syndrome.
- Temperature derangement.
- Confusion.
- Diabetes.
- Swallowing problems.
- Diabetes.
- Pancreatitis.
- Pneumonia.
- Cardiac problems, including pericarditis and myocarditis.
- Death.

### Consistency with current research

Whilst it is possible that clozapine is more likely to cause diabetes than other antipsychotics, conflicting evidence exists. Lund et al (2001), in their retrospective cohort analysis, failed to identify increased rates of diabetes, hyperlipidaemia or hypertension in people receiving clozapine compared to those receiving conventional antipsychotic drugs. Although in a subgroup analysis of younger people aged 20–34 years, they found that clozapine significantly increased the risk of diabetes and hyperlipidaemia but not hypertension. This is consistent with the results of our case report. Furthermore, our patient was of Afro-Caribbean origin, which is not an isolated finding and is consistent with previous case reports (Ai et al, 1998; Patel and Allin, 2011), suggesting that Afro-Caribbean origin is potentially an additional factor to be considered when evaluating impaired glucose tolerance in clozapine therapy.

The rapid onset of severe derangement of glucose metabolism after being switched to clozapine is consistent with the findings of Howes et al (2004), who found that glucose impairment occurs within 4 months of starting clozapine. Our patient's development of medical crises also accords with Nihalani et al (2007), who found that the majority of life-threatening complications occur within the first 3 months of clozapine treatment.

The potential serious risks of starting clozapine in people with diabetes are also indicated in a recent case report by Patel et al (2011), who described serious derangement of glucose metabolism leading to fatal pneumonia within a month of starting clozapine in a 43-year-old Afro-Caribbean patient with diabetes.

### Clinical implications

Clozapine is a very potent antipsychotic drug that has a complex side effect profile, summarised in *Box 1*. Clearly, there is a need for evidence-based

prescribing of clozapine based on a balance of risks and potential benefits. Our case report, in the context of previous literature, highlights the intolerability of starting clozapine in a young Afro-Caribbean person with diabetes who has recently gained weight. This suggests that in such cases clozapine should ideally not be initiated.

This case report also highlights the importance of appropriate physical monitoring. In particular, the emergence of diabetes was only identified on routine screening, which enabled early detection before physical symptoms occurred. Several authorities have suggested guidelines for diabetes surveillance when initiating antipsychotic medication. In the UK, the *Maudsley Prescribing Guidelines* suggests that a pre-treatment fasting blood glucose level should be repeated after 1 month, 6 months and then annually, with more frequent assessments if clinically indicated (Taylor et al, 2009). We suggest that in addition to blood glucose levels, monitoring of weight, blood pressure, routine blood tests including renal, liver function and lipids should be undertaken, in addition to ECG monitoring. We also suggest that more frequent monitoring may be required in younger Afro-Caribbean people.

## Recommendations

Where possible, clozapine should be avoided in young Afro-Caribbean people with diabetes who have gained weight. Instead, alternative antipsychotics and non-pharmacological treatments such as psychological therapy should be considered. When GPs, diabetes specialists or diabetes outreach services are contacted by psychiatric wards for advice on diabetes management in people being treated with clozapine, we suggest that the psychiatric team should be advised that clozapine may be a causative agent and to consider lowering the dose of clozapine or ideally changing to an alternative antipsychotic drug.

In cases where clozapine is the only effective drug, attempts to control the deranged blood glucose levels with oral antidiabetes drugs and insulin could be attempted but only if reasonable stability of blood glucose levels can be achieved. If this proves unsuccessful, there is likely to be no feasible option other than discontinuing clozapine and managing the psychiatric complications using all alternative measures.

Advice should always be given to monitor for signs of acute problems, such as impaired conscious level, increased thirst, urinary frequency or urinary ketones, given the potential for medical emergencies such as diabetic ketoacidosis or non-ketotic hyperosmolar syndrome. In cases where acute problems occur, emergency transfer from the psychiatric ward to A&E should be recommended.

In conclusion, we suggest that clozapine should be avoided in young Afro-Caribbean people with diabetes who have recently gained weight. ■


Ai D, Roper T, Riley J (1998) Diabetic ketoacidosis and clozapine. *Postgrad Med J* **74**: 493–4

Allison DB, Mentore JL, Heo M et al (1999) Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* **156**: 1686–96

Goldstein L, Sporn J, Brown S et al (1999) New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics* **40**: 438–43

Henderson DD, Cagliero E, Gray C et al (2000) Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *Am J Psychiatry* **157**: 975–81

Henderson DD, Nguyen DC, Copeland PM et al (2005) Clozapine, diabetes mellitus, hyperlipidaemia and cardiovascular risks and mortality: Results of a 10 year naturalistic study. *J Clin Psychiatry* **66**: 1116–21

Howes O, Bhatnagar A, Gaughran F et al (2004) A prospective study of impairment in glucose control caused by clozapine without changes in insulin resistance. *Am J Psychiatry* **161**: 361–3

Koller E, Schneider B, Bennett K et al (2001) Clozapine-associated diabetes. *Am J Med* **111**: 716–23

Lund B, Perry P, Brooks J, Arndt S (2001) Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension. A claims-based approach. *Arch Gen Psychiatry* **58**: 1172–6

Melkersson K, Hulting A, Brismar K (1999) Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychosis. *J Clin Psychiatry* **60**: 783–91

Mukherjee S, Decina P, Bocola V et al (1996) Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* **37**: 68–73

NICE (2009) *Schizophrenia: Core interventions in the treatment and management of schizophrenia in primary and secondary care (update)*. CG82. NICE, London. Available at www.nice.org.uk/CG82 (accessed 06.03.13)

Nihalani N, Tu X, Lamberti et al (2007) Diabetic ketoacidosis among patients receiving clozapine: A case series and review of socio-demographic risk factors. *An Clin Psychiatry* **19**: 105–12

Patel S, Allin M (2011) Physical complications in early clozapine treatment: a case report and implications for safe monitoring. *Ther Adv Psychopharmacol* **1**: 25–9

Popli, A, Konicki E, Jurjus G et al (1997) Clozapine and associated diabetes mellitus. *J Clin Psychiatry* **58**: 108–11

Sobel M, Jaggers E, Franz M (1999) New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *J Clin Psychiatry* **60**: 556–7

Taylor D, Paton C, Kapur S (2009) *The Maudsley Prescribing Guidlines*. 10th edition. Informa Healthcare, London

Tovey E, Rampes H, Livingstone C (2005) Clozapine-induced type-2 diabetes mellitus: possible mechanisms and implications for clinical practice. *J Psychopharmacol* **19**: 207–10


### Page points

1. The authors recommend that, where possible, clozapine should be avoided in young Afro-Caribbean people with diabetes who have gained weight and that alternative treatment should be sought.
2. When clozapine is the only effective drug, attempts to control the deranged blood glucose levels with oral antidiabetes drugs and insulin could be attempted but only if reasonable stability of blood glucose levels can be achieved.
3. The authors also suggest that people treated with antipsychotic medication should be monitored for blood glucose, weight, blood pressure and routine blood tests. They also suggest that more frequent monitoring may be required in younger Afro-Caribbean people.