Reminder of important clinical lesson

Dramatic weight loss associated with commencing clozapine

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The authors report the case of a 44-year-old man with a long history of chronic enduring schizophrenia who experienced dramatic weight loss after commencing treatment with clozapine, an antipsychotic medication characteristically associated with the greatest degree of weight gain among medical treatments for schizophrenia. He was obese with a body mass index (BMI) of 41.5 kg/m², but after commencing clozapine therapy he experienced an improvement in psychotic symptoms and 40% loss of his body weight attained through an altered diet and exercise regime, which resulted in him attaining a normal BMI of 24.8 kg/m².

BACKGROUND

Clozapine is the most effective treatment for treatment resistant schizophrenia. However, its use is limited due to its tolerability profile including weight gain and metabolic dysregulation. This case demonstrates a significant symptomatic and functional improvement achieved with clozapine therapy which was associated with a striking weight loss and improvement in the individual's metabolic parameters and cardiovascular risk factors.

The case acts as an important clinical reminder, as it highlights that with a sustained improvement in the individual's mental state, beneficial interventions could be implemented to establish significant and sustained weight loss and a reversal of cardiovascular risk factors.

CASE PRESENTATION

The patient is a 44-year-old male who is resident in a community based high support hostel. He has a 20-year history of paranoid schizophrenia. He was admitted to the psychiatric unit in University Hospital Galway, Ireland following a relapse of his psychotic illness. His illness at this stage had shown a longitudinal course consistent with incomplete remission (ICD-10 F20.04) and he met the criteria for treatment resistant schizophrenia.

Over the previous years he had received a number of first and second generation antipsychotic medications (haloperidol, chlorpromazine, thioridazine, flupenthixol decanoate depot, zuclopenthixol decanoate depot, olanzapine, amisulpride and aripiprazole) at adequate doses, for durations greater than 6 weeks and frequently in combination, with some symptomatic improvement but without full remission in his illness. He was largely adherent with his oral and depot medication. He had persistent psychotic symptoms and a fluctuating illness course with frequent exacerbation of his psychosis necessitating multiple hospitalisations. At times of relapse of his psychotic illness he characteristically suffered from intrusive psychotic symptoms, with thought broadcasting, thought insertion and thought withdrawal most prominent. He had persisting persecutory delusions which were heightened at times of psychotic relapse. He displayed moderate

to severe negative symptoms and had impaired social and occupational functioning in the 5 years prior to his admission. At the time of this admission to hospital he was being treated with a combination of olanzapine 20 mg daily and aripiprazole 30 mg daily. He had been taking olanzapine for 5 years prior to this admission. He had gained some 25 kg since commencing olanzapine 5 years previously and an overall weight gain of 40 kg since his illness began.

He had previously been offered clozapine treatment in his illness course but had been unwilling to commit to the programme of phlebotomy required. However, during this admission he consented to the treatment programme and was commenced on clozapine which was titrated over the course of 5 weeks to a dose of 500 mg/day (serum level 480 µg/l).

Prior to the initiation of clozapine therapy, his weight was 127 kg (body mass index (BMI) 41.5 kg/m²). His physical examination was normal excluding the finding of truncal obesity with a waist circumference of 112 cm (44 inches). He was not hypertensive.

INVESTIGATIONS

Prior to treatment with clozapine he had hypercholesterolaemia with a fasting total cholesterol of 6.3 mmol/l (3.0–5.0 mmol/l- reference range) and dyslipidaemia with a raised triglyceride level of 2.6 mmol/l (0.4–2.0 mmol/l) and a low-density lipoprotein (LDL) cholesterol level of 3.6 mmol/l (0.0–3.0 mmol/l). His high-density lipoprotein (HDL) cholesterol was normal at 1.2 mmol/l (1.0–2.0 mmol/l). His fasting plasma glucose was normal at 5.1 mmol/l (4.4–5.5 mmol/l-fasting reference range). Other haematology and biochemical parameters were within the normal range. His ECG showed a normal sinus rhythm with no evidence of abnormalities of ventricular repolarisation such as T wave abnormalities or QT_c prolongation.

His fasting cholesterol (4.1 mmol/l), triglyceride (1.0 mmol/l) and LDL (2.4 mmol/l) levels normalised after 9 months of treatment with clozapine. He continues to have a normal HDL (1.3 mmol/l) and there has been no evidence of glucose dysregulation.

His thyroid function remained normal and his full blood chemistry profile was normal. There was no evidence of an emergent psychiatric disorder which may have contributed to his weight loss, such as obsessiveness with weight reduction and he scored in the subclinical range on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

TREATMENT

Clozapine 150 mg in the morning and 350 mg at night.

OUTCOME AND FOLLOW-UP

He experienced gradual weight loss following the commencement of clozapine and associated with a concerted effort to engage in a low calorie diet and exercise regime, with a reduction in weight from 127 kg to 76 kg (BMI 41.5 kg/m²– 24.8 kg/m²) over a period of 3 years. He lost 24 kg of weight during the first year of treatment with clozapine. This was followed by a loss of 27 kg over the next 18 months, representing a 40% loss of weight in total and a normal BMI of 24.8 kg/m².¹ His weight has been subsequently stable at 76 kg over 6 months of follow-up. He has not developed hypertension since the commencement of clozapine. He has tolerated clozapine well with no adverse side effects save for constipation.

He remained physically well. There was no symptomatology consistent with gastrointestinal pathology which may have caused his weight loss.

He has not been rehospitalised in the 3 years since commencing clozapine whereas prior to clozapine therapy he was hospitalised on 11 occasions over a 20-year period. He has experienced a marked symptomatic improvement and a significant improvement in his psychosocial functioning and insight. He lives independently and is a keen participant in group activities such as art and cooking classes. He has re-established a meaningful relationship with his immediate family members, from whom he was estranged, who he now visits on a regular basis. He has sustained a weight control programme and currently walks approximately 3–4 km at least 5 days per week and attends a local gym twice weekly, where he engages in 60 min of aerobic exercise on a treadmill. He also swims on two occasions per week. He has a much reduced calorie intake and has maintained a high fibre and low fat/cholesterol diet.

DISCUSSION

This case study is striking because clozapine use is consistently associated with the greatest degree of weight gain compared to other antipsychotic medications.² Clozapine is the most effective antipsychotic medication for patients with treatment resistant schizophrenia³ but its use is limited by its tolerability profile including weight gain, metabolic dysregulation and the risk of agranulocytosis. The cumulative incidence of patients becoming overweight on clozapine exceeds 50%⁴ with a mean weight gain of 4.45 kg at 10 weeks of treatment,⁵ compared to a mean weight gain of 4.15 kg for olanzapine and 2.1 kg for risperidone⁵ and with an average weight gain of 11.7 kg over a period of 8 years of treatment.⁶

The mechanism of weight gain with clozapine is uncertain but a number of different mechanisms of action are thought to contribute. The affinity of clozapine for the H1 receptor and the 5HT_{2c} receptor is most closely linked

to this increased weight gain, although affinity for D₂, 5-HT_{1A}, and α₂-receptors may also be involved.⁷ There is evidence that clozapine interrupts hypothalamic control of body weight which may be due to antipsychotic induced leptin resistance in the hypothalamus.⁸

The use of direct participation in exercise group activities⁹ and direct management of diet in supervised accommodation¹⁰ have shown some success in promoting weight loss for patients with severe mental illness. These were two approaches which were utilised in our patient's case. There was an improvement in the degree of severity of the negative symptoms of schizophrenia which he displayed. This was associated with increased levels of motivation, improved initiative and an ability to engage more fully in goal directed physical activity.

Another recent case series reported weight loss following treatment with clozapine in three patients, with percentage loss of body weight of 49%, 21% and 19%,¹¹ which the authors speculate could be due to genetic variation in neuroreceptors. A further case series reported weight loss in five patients who failed to respond to clozapine treatment. They described a range of weight loss from 4 kg to 13 kg and hypothesised that early weight loss may be an indicator of a poor clinical response to clozapine in treatment resistant schizophrenia.¹² It has been reported that up to 10% of patients on clozapine will develop obsessive-compulsive symptoms.¹³ The development of obsessiveness with food or compulsive exercise or dieting was not present in this case to explain the dramatic weight loss. Rather it appears that the clinical improvement in symptoms and functioning provided by the switch to clozapine facilitated a recovery which, among other quality of life improvements, resulted in the full reversal of weight increase built up over many previous years of psychotic illness and its treatment.

Learning points

- ▶ Clozapine is the most effective antipsychotic medication for treatment resistant schizophrenia but its use is limited by its tolerability profile such as weight gain and metabolic dysregulation.
- ▶ Risk factors for cardiovascular disease (CVD) such as obesity, smoking, diabetes, hypertension and dyslipidaemia are more common in patients with schizophrenia than in the general population and the use of clozapine can induce weight gain and worsen CVD risk factors.
- ▶ This case demonstrates that despite the risks of substantial weight gain and dyslipidaemia which are characteristically experienced by many patients on this treatment, the significant symptomatic and functional improvement achieved with clozapine therapy can in fact completely reverse these risks.
- ▶ The patient had a sustained response to clozapine therapy with a significant reduction in psychotic symptoms which was associated with improved physical health and quality of life.

Competing interests None.

Patient consent Obtained.

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