# ****Antipsychotics and schizophrenia and their relationship to diabetes****

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*John, a 28 year old cleaner was diagnosed with schizophrenia 5 years ago. His mental health had been stable for a number of years but following a stressful period at work he experienced a relapse. John was started on olanzapine in addition to aripiprazole which he had been taking since diagnosis. Three months later he presented to the emergency department with vomiting and abdominal pain. On initial assessment he was clinically dehydrated. His venous blood gas showed a significant acidosis. The admitting team initially referred John for a surgical review as they were concerned about the possibility of appendicitis. Before the surgeons arrived, a member of the team reviewed John’s results and noted that he had a blood glucose of 24mmol/l on the venous blood gas. Capillary ketones were elevated and a diagnosis of diabetic ketoacidosis (DKA) was made. John was treated with a fixed rate insulin infusion as per hospital protocol and reviewed by the diabetes team the following morning.*

## Introduction

Schizophrenia is a major psychiatric disorder with a lifetime prevalence of 1%. Symptoms of schizophrenia include hallucinations, delusions and disordered thoughts (collectively known as positive symptoms) as well as lack of motivation, social withdrawal and apparent lack of emotion (negative symptoms). An individual may experience symptoms from either or both of these categories. Men and women are equally susceptible to the condition, and initial manifestations of the illness typically present during an individual’s teenage or early adulthood years.

Schizophrenia is associated with significant increased morbidity and mortality [1]. The average life expectancy of an individual with schizophrenia is 62.8 years in UK men and 71.9 years in UK women [2]. This is 14.6 and 9.8 years earlier than expected for men and women without mental illness respectively. Approximately 75% of all deaths in people with schizophrenia are now caused by physical illness, with cardiovascular disease (CVD) being the commonest cause of death. All major CVD risks factors, including diabetes, are increased 2-3 fold in people with schizophrenia [3]. Traditional risk factors for Type 2 diabetes (T2DM), especially being overweight or obese, are observed more commonly in people with schizophrenia. 42% of people with schizophrenia had a body mass index (BMI) over 27 Kg/m2 compared to 27% of the general population in one study [4].

## Why is this important?

Predictors of morbidity and mortality in schizophrenia include T2DM. People with schizophrenia who develop diabetes are in addition more susceptible to the complications associated with the latter. Evidence highlights that they are 74% more likely to develop acute complications and more likely to develop microvascular or macrovascular complications [1]. Diabetes related deaths are six times more frequent with schizophrenia contributing to significant excess mortality [5].

## Relationship between diabetes and schizophrenia

The prevalence of T2DM is at least 2 fold greater in people with schizophrenia than in the general population. The prevalence of undiagnosed diabetes is also thought to be much higher and complications and mortality associated with diabetes is also increased in people with schizophrenia [6]. The prevalence of Type 1 diabetes is not increased in people with schizophrenia.

The relationship between schizophrenia and T2DM appears to be unidirectional; in that diabetes does not predispose to schizophrenia [7]. The increased risk of T2DM in people with schizophrenia, however, is not straightforward and the degree to which the risk is increased varies from 2-5 fold depending on the study quoted. The reasons for this variation is largely a result of the different methodological approaches used (longitudinal, cross sectional, case control, cohort), the different populations studied (age, sex, ethnicity differences, inpatient/outpatient) and the geographical areas covered by the studies.

Across the literature it appears that three themes emerge regarding the cause of the increased rates of obesity and consequently T2DM in people with schizophrenia. These include environmental factors, disease specific effects and antipsychotic treatment.

### Environment

Low socioeconomic status and income can affect an individual’s ability to make healthy lifestyle decisions [8]. The diet of people with schizophrenia is typically deficient in fruit and vegetables and high in fat [9]. Food choices may be linked directly to schizophrenia through deficient reward mechanisms and social isolation may also trigger excessive eating as a compensatory mechanism [10]. Excessively sedentary lifestyle with reduced rates of recommended ‘moderate’ activity may in part be due to the sedating effects of antipsychotic medications and/or poor sleep patterns [11, 12]. Smoking increases the risk of T2DM and people with schizophrenia are twice as likely to smoke than the general population [13].

### Disease specific effects

It is unclear if schizophrenia *per se* is causal in the development of diabetes. However, there is a shared genetic link between T2DM and schizophrenia [6]. It is of interest that in a major antipsychotic effectiveness trial 25.7% of participants had evidence of impaired glucose metabolism at the start of the trial (pre antipsychotic medication) as assessed by a fasting glucose concentration of >5.6 mmol/L [14]. Increased insulin resistance may be due to biological changes associated which schizophrenia which include increased cortisol and catecholamine secretion.

### Relationship between diabetes and antipsychotic medication

Antipsychotic medications may independently increase the risk of T2DM alongside other risk factors. A large meta-analysis found the prevalence of T2DM was 2.1% in people with early untreated schizophrenia compared to 12.8% in those taking antipsychotic medication [15].

Antipsychotic medications are crucial in alleviating what can be debilitating symptoms of schizophrenia, putting a patient’s mental health in a more stable position to then be better equipped to manage their physical health. It is important to remember that randomised controlled trials (RCT) have shown that antipsychotic medications improve psychotic symptoms, prevent relapse, hospitalisation, and decrease all-cause mortality, including suicide, in people with schizophrenia [14].With the exception of clozapine, which is used in refractory cases, all antipsychotics are deemed to be equally effective. It is well recognised, however, that individuals respond differently to the different antipsychotics available, both therapeutically and with regards to the side effects experienced. Symptom control, symptom remission, and functional recovery can only be realistic goals when treatments are both effective and well tolerated.

*John had been treated with 400mg monthly of intramuscular aripiprazole but due to the relapse in his mental health olanzapine 10mg daily, another second generation antipsychotic was added.*

There are no RCTs with glucose or glycated haemoglobin (HbA1c) as primary outcomes and so we cannot definitively say whether antipsychotic medication directly affects the risk of developing T2DM. The frequent changes in antipsychotic medication and the long natural history of T2DM make ascertaining the true relationship challenging. The lack of RCTs may be in part caused by researchers’ concerns around recruitment, retention rates and adherence to trial protocol.

Observational studies, from which one cannot infer causation, have been conducted using nationwide electronic databases. These have explored hospitalisation, mortality, and filled prescriptions. A review of seven large cohort studies indicated that the use of antipsychotics is associated with a lower risk of death or severe health problem when compared with no use, suggesting that antipsychotics do more good than harm [16].

While the side effect profile differs with individual antipsychotics, in general first-generation antipsychotics (FGA) are typically associated with stigmatising extrapyramidal symptoms whereas second-generation antipsychotics (SGA) are better tolerated but associated with more weight gain and T2DM. A recent population based study has challenged this view and actually found the risks to be similar (SGA ([HR] 1.32, 95% CI 1.01-1.75 vs FGAs ([HR] 1.82, 95% CI 1.30-2.55) [2].

Clozapine along with olanzapine are the SGAs most strongly associated with T2DM [17]. A meta-analysis of head-to-head comparisons of the SGAs found olanzapine and clozapine produced statistically significantly greater increases in glucose levels from baseline to endpoint than amisulpride, aripiprazole, quetiapine, risperidone and ziprasidone [18]. A further meta-analysis reported that the association of T2DM for olanzapine and clozapine also appears to be independent of whether they are used in antipsychotic naïve or chronic disease (RR 1.45, 95% CI 1.28-1.64 for clozapine and RR1.29, 95% CI 1.20-1.37 for olanzapine) [19].

Most people with schizophrenia will not develop T2DM and small differences in glucose measurements do not necessarily translate to increased rates of T2DM. Nonetheless, dysglycaemia below the diagnosis cut off for diabetes can be a risk marker for future CVD and mortality and it should be stressed that even small changes in glucose might still translate into clinical consequences in the long term.

While T2DM in antipsychotic-exposed adolescents and young adults is rare, these individuals are still more vulnerable to substantial health risks later in life. Systematic reviews and meta-analyses recognise that the relative risks of developing T2DM in these younger individuals is significantly higher than the general population and compared to those not on antipsychotics [20].

#### Mechanism

The mechanisms underpinning the increased risk of T2DM in people on antipsychotic medication are not fully understood and are likely to include effects on insulin resistance, either directly or mediated through weight gain, and effects on insulin secretion, possibly a result of direct toxicity to the pancreatic β-cell.

As discussed above antipsychotics are amongst the most obesogenic medications. It has been postulated that women may be at higher risk of antipsychotic induced weight gain [21]. A greater than 7% weight gain from baseline has been seen in up to 72% of those taking SGAs, and to a lesser extent with FGA [22]. SGA are antagonists of dopamine and serotonin receptors, both of which are involved in appetite regulation. Furthermore, antipsychotics are associated with a predisposition to depositing adipose tissue centrally [23], and it is well recognised that central obesity is strongly associated with insulin resistance and the development of T2DM. Clozapine and olanzapine have the highest risk of T2DM and also the highest risk of weight gain.

As in the general population, however, T2DM is not inevitable in everyone who gains weight. Furthermore there are a number of people who develop T2DM while taking antipsychotics who do so without weight gain as in the vignette. This has led to the notion that there may be a direct impairment of glucose homeostasis caused by antipsychotics. It is unclear whether antipsychotics directly cause T2DM through impaired β-cell function or through increased insulin resistance independent of changes in BMI but antipsychotics interact with β-cell receptors that can modify insulin secretion.

Antipsychotic medications have been associated with potentially fatal diabetic emergencies. A systematic review reported 72 cases of antipsychotic medication associated with DKA, the complication with which John presented [24]. The review found associated weight gain in only half of the reported cases and DKA was the first clinical presentation of diabetes in the majority. More than half were associated with antipsychotic medication polypharmacy. Autoantibodies were only measured in 13 cases but were negative in 85%. This supports the argument that these are generally not new cases of autoimmune type 1 diabetes and a direct toxic effect of the antipsychotic on the β-cell should be considered. Interestingly, some new onset cases of diabetes were reversed after discontinuation of the antipsychotic drug with recurrence of diabetes on re-challenging.

## Management

The burden of diabetes in people with schizophrenia is a concerning issue. Given the increased risk of T2DM and CVD in people with schizophrenia, special attention needs to be paid to preventing diabetes in this population where possible. This will involve the effective management of the metabolic effects of antipsychotic drugs as an integral component of managing a person with schizophrenia. If this can be achieved, the individual is likely to be in a better place to self-manage their physical health and adopt the advised treatment plans aimed at reducing their cardiovascular and diabetes risks.

### Screening and monitoring

Routine screening and monitoring for diabetes and reversible cardiovascular risk factors is paramount. There are differing views, however, between guidelines regarding how frequently healthcare professionals (HCPs) need to monitor the physical health of people with schizophrenia.

All people taking antipsychotics should also be encouraged to monitor their own weight if they have the capacity and resources to do so, and report any weight change to their treating clinician. The responsibility for tracking any changes in weight and other CVD risk factors ultimately lies with HCPs.

From a T2DM point of view, the recentBritish Association for Psychopharmacology (BAP) guidelines advise using fasting or random blood glucose measurements initially and at 12 weeks after commencing an anti-psychotic medication, followed by annual HbA1c measurements in the longer term [25]. A recent audit in the UK, however, found that only 56% of people with schizophrenia had a record of blood glucose or HbA1c [26]. In the event of weight gain or change in antipsychotic medications more frequent monitoring should be undertaken.

Given the increased morbidity and mortality associated with diabetes and CVD, all known cardiovascular risk factors such as smoking, hypertension and hyperlipidemia must also be addressed in these individuals. The 2016-2017 National diabetes audit (NDA) found that only 40.6% of people with T2DM and severe mental illness (SMI) received all their annual health care checks which is 10% less than people without SMI. It is encouraging, however, that a specific report for people with SMI and diabetes is now part of the NDA and this is a step forward in understanding the physical health needs for people with SMI.

### Access and education

Access to healthcare settings can be perplexing for people with schizophrenia. Equality of access and communication across boundaries is therefore required to best serve this population. Education of the mental health team should not be forgotten and diabetes services should consider how to provide a rolling education programme with their mental health colleagues. Many may be unfamiliar with the notion of metabolic risk and the importance of assessing and treating this. It is important to train mental healthcare professionals to take a thorough history for personal and family history of obesity and diabetes, both modifiable and non-modifiable risk factors as well as a lifestyle, diet and exercise history.

In order for people to seek advice and testing to confirm a diagnosis of diabetes, the importance of educating people with schizophrenia treated with antipsychotics and their families about the acute symptoms of diabetes cannot be underestimated. A number of large trials have recently shown that it is difficult to reverse risk factors once they are established. STEPWISE and CHANGE both showed no weight change despite a lifestyle educational programme and coaching programme respectively. The PRIMROSE trial also showed no improvement in cholesterol levels in the intervention group despite appointments with a trained primary care professional involving manualized interventions for CVD [27-29]. Whilst these trials have highlighted how prevention is key two other studies, the SCIMITAR (smoking cessation pilot) and Keeping the Body in Mind (a lifestyle and life skill intervention for positive cardio metabolic health in youth with first-episode psychosis), demonstrated more positive results. The SCIMITAR pilot study showed a reduction in smoking rates and in Keeping the Body in Mind participants maintained their baseline weight although this was a non-randomised service evaluation [13, 30].

### Pharmacological treatment for obesity and T2DM

*John started insulin as an inpatient given his osmotic symptoms and presentation with DKA. GAD antibodies were negative. Once discharged from hospital and over the following weeks, his insulin was slowly weaned and discontinued as metformin was up-titrated. He saw a dietitian and his BMI remained stable at 29kg/m2.*

The LESTER UK adaptation guidelines; ‘Don’t just screen; intervene’ (Image 1) were introduced in 2012 to help frontline primary care staff make assessments of cardiac and metabolic health with the aim to help cut mortality for people with severe mental illnesses [31]. Pharmacological management of metabolic factors including blood pressure and lipids are no different in people on antipsychotic medication.

Short term studies suggest metformin may attenuate antipsychotic-induced weight gain [32] while metformin has been shown to reduce the incidence of T2DM in the general population. Systematic reviews of short term RCTs of metformin found metformin reduced antipsychotic weight gain by a mean of -3.17 Kg (95%CI - -1.90 to -4.4) [32]. Greater weight loss, however, is likely to be needed to prevent T2DM. A double blind clinical trial of metformin versus placebo in combination with antipsychotics with a primary outcome of glucose measurements (HbA1c and OGTT) is currently recruiting [33]. While metformin is generally safe, it is not appropriate for individuals with alcohol dependence syndrome which is common in people with SMI (20.6% lifetime risk) because of the risk of lactic acidosis. A recent meta-analysis of 3 studies on GLP-1 receptor agonists (one with exenatide once weekly and two with liraglutide daily) showed promise that they are both effective and tolerable [34] treatments to facilitate weight loss with the aim of reducing the risk of T2DM.

If diagnosed with T2DM, the management in people with schizophrenia is similar to standard management. Diet and lifestyle changes should be encouraged where possible alongside diabetes medications as necessary. Metformin should be considered first line and GLP-1 receptor agonists to be used early on as second line. Pharmacological treatment should be escalated promptly as required, and SGL2T inhibitors may also be beneficial early on due to their weight loss properties.

*John’s GP was updated on his new diagnosis of T2DM and his mental health has remained stable since. Although unusual to have presented with DKA, it can occur, particularly when more than one antipsychotic is used. This acute presentation did, however, facilitate the prompt diagnosis of diabetes so that treatment could be commenced appropriately.*

## TAKE HOME MESSAGES

* **Schizophrenia is associated with significant increased morbidity and mortality.**
* **Antipsychotic medications are important to stabilise an individual’s mental health which puts them in a stronger position to address their physical health needs.**
* **Type 2 diabetes is common in people with schizophrenia and is likely a result of lifestyle, disease and treatment factors. Early and regular screening for diabetes in this population is advised.**
* **Diabetes can present acutely in people taking antipsychotic medications and the symptoms of diabetes must be explained to people taking these medications.**
* **Diabetes in people with schizophrenia is typically associated with an earlier age of onset than in the general population and more diabetes related complications.**
* **Treatment of T2DM in people with schizophrenia is generally the same as for those without schizophrenia. Lifestyle factors should be addressed and metformin used first line. A preference for GLP-1 receptor agonists second line may be appropriate.**

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