Understanding schizophrenia and diabetes

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Alongside other risk factors for the development of type 2 diabetes, the presence of severe mental illness is often overlooked. A person with schizophrenia has a two to four times greater risk of developing diabetes than the general population and the prevalence of type 2 diabetes is between 15 and 18% in the schizophrenia population. A full understanding of this issue is vital.

People with schizophrenia are more likely to have risk factors for diabetes than the general population: for example, they more often have a family history of diabetes, are obese, have a sedentary lifestyle and smoke (Brown et al, 1999). A diet high in saturated fat and sugar and low in dietary fibre is commonly found among patients with schizophrenia (Brown et al, 1999). In addition, more than a quarter of those with schizophrenia have impaired glucose tolerance (IGT) (Cohn et al, 2002) – highly predictive of those who will develop type 2 diabetes.

OUTLINING THE PROBLEM

Despite improvements resulting from initiatives such as the *National Service Framework on Diabetes* (Department of Health, 2001, 2003), until recently there was little to help the non-specialist in managing patients with schizophrenia at high risk of, or already suffering from, diabetes. Previous debate around this issue has failed to provide a conclusive outcome with practical recommendations for practising physicians of whatever speciality. For that reason, an expert group, which included specialists in psychiatry, diabetes, pharmacy and psychopharmacology, reviewed all currently available data and sought a range of expert opinion, in preparation for the development of a series of pragmatic recommendations for the management of diabetes risk in people with schizophrenia. After a thorough review of the evidence a consensus statement was published, with individual supporting papers, earlier this year (Dinan et al, 2004).

The authors believe that diabetes is frequently poorly managed in patients with schizophrenia and other severe mental illness whereas early diagnosis and treatment might lead to a reduction in the all too common cardiovascular cause of death. For it is natural causes – not suicides, as is often believed – which are the leading cause of premature death in those with schizophrenia (Brown et al, 2000).

MANAGING PHYSICAL HEALTH IN SEVERE MENTAL ILLNESS

Care for patients with severe mental illness is usually carried out in specialist psychiatric units, by community psychiatric nurses (CPNs) and other specialist members of the community mental health team. Thus while there is a high standard of care for the mental illness, there is much less focus on physical conditions. Care of physical health is often assumed to be dealt with by the GP. It is important for staff treating mental illness to recognize that there are times when they feel challenged by non-psychiatric illness, and unsure about the best investigations and screening methods for physical illness like diabetes. Without being too prescriptive, the authors hope that the consensus statement will help guide the mental health specialist as well as alerting those involved in diabetes and cardiovascular medicine to this hidden group of high-risk patients.

The physical care of those with severe mental illness may not attract the attention it would if the symptoms of mental illness were not also there. Research by Dixon and colleagues (2000) has established that patients with severe mental illness are not treated as well as their peers without mental illness for a wide range of physical conditions including diabetes. It is hoped that the recommendations of the consensus statement, practical and rooted in real-life clinical

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practice, might contribute to some improvements for this vulnerable patient group.

Other hospital doctors also have a role in ensuring patients with schizophrenia who also have diabetes are identified and managed appropriately. General physicians, diabetes specialists, cardiologists and others who come into contact with those with severe mental illness should consider the possibility of diabetes, in the light of the increased risk. Recently published clinical practice recommendations advise that screening should be considered at 3-year intervals beginning at the age of 45 years, particularly in those with a body mass index (BMI) ≥25 kg/m^2 (American Diabetes Association, 2004). These recommendations also suggest that testing should be considered at an earlier age or be conducted more frequently in those who are overweight or if other additional diabetes risk factors are present (*Table 1*). If there is no record of a recent screen (within the past year) for glucose tolerance in the clinical records, hospital doctors should arrange for appropriate investigations (*Table 2*), particularly if there are symptoms suggestive of diabetes (*Table 3*).

TABLE 1.
Risk factors for type 2 diabetes

Family history of diabetes
Habitual physical inactivity
Race/ethnicity
Previously identified impaired glucose tolerance or impaired fasting glucose
History of gestational diabetes or delivery of a baby weighing >4 kg
Hypertension (140/90 mmHg in adults)
High density lipoprotein (HDL) cholesterol 35 mg/dl (0.90 mmol/litre) and/or a triglyceride level 250 mg/dl (2.82 mmol/litre)
Polycystic ovary syndrome
History of cardiovascular disease

From American Diabetes Association (2004)

TABLE 2.
Diagnosing impaired glucose tolerance and diabetes

Test	Result (mmol/litre)	Diagnosis
Two-hour oral glucose tolerance test	7.8–11.0	Impaired glucose tolerance
	>11.0	Diabetes
Fasting plasma glucose	6.1–7.0	Impaired fasting glucose
	≥7.0	Diabetes
Random plasma glucose	>11.0	Diabetes

TABLE 3.
Common symptoms of diabetes

Polyuria
Polydipsia
Nocturia
Unexplained weight loss
Loss of energy
Recurrent infections, e.g. candidal infections
Blurred vision

IMPERATIVE FOR SCREENING

The expert group suggested three parts of the NHS where screening might be offered: GPs and practice nurses in primary care, community pharmacists, and psychiatrists and CPNs, who will provide much of the health care of those with severe mental illness.

Currently as many as two thirds of cases of diabetes and IGT remain unidentified in people with schizophrenia (Subramaniam et al, 2003), largely because screening for disturbed glucose metabolism and diabetes is not usually a routine part of practice. Most health professionals that patients encounter have experience and expertise in mental health, but patients' symptoms may mask physical illness or be mistaken for signs of mental illness, leading to diagnostic confusion. The severity of symptoms may require inpatient care, but with limited access to the mainstream primary care or secondary care services for common conditions such as diabetes.

Patient groups have been critical of what they refer to as the 'neglect' of the physical health of those with severe mental illness. As medical professionals it is important to recognize where practice and procedures could be better. Those with schizophrenia have as much entitlement to high standards of care for physical illness as any other patient. There may be practical obstacles in terms of screening, diagnosis and management, but there are ways of organizing care that can reduce the likelihood of undiagnosed diabetes in people with schizophrenia.

MANAGING DIABETES RISKS IN PEOPLE WITH SCHIZOPHRENIA

The expert group's recommendations on management (*Table 4*) can reduce the risk of patients with schizophrenia falling between the gaps of specialist psychiatric care and diabetes management elsewhere in the NHS. It is important to avoid the risk that screening for and diagnosing diabetes in patients with schizophrenia becomes someone else's job. The expert group recommend a clear and unambiguous division of responsibility in which psychiatrists are respon-

sible for screening and diabetes risk management, while primary care clinicians and diabetes specialists are responsible for the subsequent management of diabetes.

Management of diabetes is not universally successful for every patient. If the patient is suffering from serious chronic mental illness his/her ability to adhere to treatment and change to a healthier lifestyle may become more of an obstacle to clinical success. Optimal management of diabetes involves a high degree of self-care, including adherence to regular oral medication, taking regular exercise, eating a healthier diet and keeping to a healthy weight. Patients with schizophrenia, even when well controlled on antipsychotic medication, are likely to need support in achieving control of their diabetes. One approach that has proved successful is the development of nurse-led clinics, which provide information and support.

Underlying these suggestions for different patient groups is the principle that the choice of antipsychotic medication should be based on achieving good control of the schizophrenia. Good control, in turn, should help improve physical health by increasing the success of strategies of increased physical activity levels and a healthier diet that can delay or prevent the development of type 2 diabetes. This is just one example of the complex interaction between diabetes and schizophrenia.

ANTIPSYCHOTICS AND GLUCOSE METABOLISM

While there appears to be an independent link between schizophrenia and diabetes, the role of antipsychotic medication in the development of diabetes is a matter of some debate. The condition itself has long been associated with disturbances to glucose metabolism and a high prevalence of diabetes (Maudsley, 1979). An increased risk of IGT and type 2 diabetes in those with schizophrenia was identified in the clinical literature in the decades before antipsychotic medication was introduced (Kooy, 1919; Lorenz, 1922; Henry and Mangan, 1925; Freeman et al, 1944; Braceland et al, 1945; Freeman, 1946).

More recent research has found impaired fasting glucose in young schizophrenia patients after their first episode of psychosis and before they begin antipsychotic medication (Ryan et al, 2003). Many patients with schizophrenia may already have IGT before they begin treatment. However, cases of diabetic ketoacidosis have been reported in patients taking antipsychotic medication (Jin et al, 2002). Therefore it appears that there is some level of increased risk, although there is no detectable difference between any of the individual members of the atypical antipsychotics and as such the association is probably a class effect.

Studies have suggested that schizophrenia patients taking atypical antipsychotics may be more likely to have impaired glucose metabolism than those taking the older typical treatments (Haddad, 2004). However, this link may be, at least partly, an artefact because patients taking atypical treatments are screened much more frequently than those taking typicals and so any effects on glucose metabolism are more likely to be identified in those taking the newer

TABLE 4.
Pragmatic pathways: management of diabetes in different groups of patients with schizophrenia

Patient group	Management
Patients never previously treated with antipsychotics, or switched to another antipsychotic	Screen with baseline random (or fasting) glucose and HbA_{1c}, repeat 4 months after initiating or changing an antipsychotic. If both baseline and 4-month levels are normal then perform annual random (or fasting) glucose
Patients without diabetes, established on an antipsychotic medication	Ask about symptoms of hyperglycaemia, and screen annually for glucose tolerance, with the results communicated between services
Patients with diabetes who are established on antipsychotic medication	Manage diabetes either in primary care or in diabetes specialist services, which have the experience and expertise to offer good standards of care. Hospital doctors in mental health should manage mental health and ensure that the appropriate services are actively managing physical health
Patients with severe mental illness with tests suggestive of IGT or type 2 diabetes	Manage the condition in a similar way to any patient: through a referral to a GP or specialist diabetes specialist services for a proper diagnostic work-up
Patients with a positive diagnosis of diabetes	Provide coordinated management of diabetes or IGT from the GP or specialist diabetes service, including an annual review. The future use of antipsychotic medication may need to be determined by a multidisciplinary clinical decision, but a change in antipsychotic medication will usually be unnecessary

HbA_{1c} = glycosylated haemoglobin; IGT = impaired glucose tolerance

treatments. There is no known mechanism to explain the effect of antipsychotic medication on glucose metabolism and therefore, while further data are awaited, it seems reasonable to conclude that antipsychotics as a class (both typical and atypical) represent one independent variable in the genesis of a disorder with a multivariate aetiology. The consensus group therefore supported the decision of the US Food and Drugs Administration, which asked manufacturers of all atypical antipsychotics in September 2003 to label their products with a warning on hyperglycaemia and diabetes, as these are mainly the first line of treatment.

CONCLUSIONS

It is clear there is an association between antipsychotics and impaired glucose metabolism, but whether this is a cause and effect relationship cannot be established with the evidence from studies that have largely been retrospective, with detection and selection bias, and an inability to control for confounding risk factors. Long-term randomized prospective trials will be the only way to identify causality (Haddad, 2004). There is much research to be done in this area to tease out exactly what is happening, but the main conclusion of the expert group is that the traditional risk factors are still the most important for any individual with or without severe mental illness, with schizophrenia increasing that risk independently. Use of antipsychotic medication increases the risk slightly – certainly by no more than 10% – and there is a possibility that atypical medication may pose a small increased risk on top of that.

Whatever the exact contributions of schizophrenia itself, the lifestyle that many people with schizophrenia have, and medication, people with schizophrenia are at high risk of diabetes and its complications. As with all co-morbidities an organized multidisciplinary approach is essential. Psychiatrists and other members of the mental health team are the best at treating schizophrenia. On the other hand, GPs and practice nurses in primary care, and diabetes specialists in secondary care have the knowledge, skills and patient throughput to be better at treating diabetes. HM

KEY POINTS

- There is accumulating evidence that schizophrenia is an independent risk factor for diabetes.
- The prevalence of diabetes in schizophrenia can be 2–4 times higher than in the general population and health-care professionals should be aware that this group is at higher risk of developing the disease.
- The effectiveness of antipsychotic medication should be the most important consideration when selecting treatment.
- Well-defined responsibilities and good communication between mental health teams, primary care teams and diabetes specialist services are critical to reducing the burden of diabetes in people with schizophrenia.
- Prospective, active comparator studies with a long-term follow up are needed to fully clarify the relationship between antipsychotics and diabetes.

Conflict of interest: Ted Dinan has lectured at meetings and served on advisory boards for companies promoting antipsychotic medications including AstraZeneca, Eli Lilly and Company, Janssen-Cilag and Pfizer. Robert Peveler has received hospitality and fees for speaking for AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Organon, Pfizer, Synthelabo and Wyeth. Richard Holt has received hospitality, educational grants and fees for lecturing and consultancy work from Eli Lilly and Company.

American Diabetes Association (2004) Diagnosis and classification of diabetes mellitus. *Diabetes Care* **27**(suppl 1): S5–S10

Braceland FJ, Meduna LJ, Vaichulis JA (1945) Delayed action of insulin in schizophrenia. *Am J Psychiatry* **102:** 108–10

Brown S, Birtwistle J, Roe L et al (1999) The unhealthy lifestyle of people with schizophrenia. *Psychol Med* **29:** 697–701

Brown S, Inskip H, Barraclough B (2000) Causes of the excess mortality of schizophrenia. *Br J Psychiatry* **177:** 212–17

Cohn T, Wolever T, Zipursky R et al (2002) Screening for diabetes and impaired glucose tolerance in patients on antipsychotic medication. *Int J Neuropsychopharmacol* **5** (Suppl 1): S168

Department of Health (2001) *National Service Framework for Diabetes. Guidance.* Department of Health, London

Department of Health (2003) *National Service Framework for Diabetes. Service Delivery.* Department of Health, London

Dinan TG, Holt RIG, Kohen D et al (2004) Schizophrenia and diabetes 2003: an expert consensus meeting. *Br J Psychiatry* **184**(suppl 47): 112

Dixon L, Weiden P, Delananty J et al (2000) Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophren Bull* **26:** 903–12

Freeman H (1946) Resistance to insulin in mentally disturbed soldiers. *AMA Arch Neurol Psychiatry* **56:** 74–8

Freeman H, Rodnick EH, Shakow D et al (1944) The carbohydrate tolerance of mentally disturbed soldiers. *Psychosom Med* **6:** 311–17

Haddad PM (2004) Antipsychotics and diabetes: review of non-prospective data. Schizophrenia and diabetes 2003: an expert consensus meeting. *Br J Psychiatry* **184**(suppl 47): 80

Henry GW, Mangan E (1925) Blood in personality disorders: biochemical studies. *AMA Arch Neurol Psychiatry* **13:** 743–9

Jin H, Meyer JM, Jeste DV (2002) Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: An analysis of 45 published cases. *Ann Clin Psychiatry* **14:** 59–64

Kooy FH (1919) Hyperglycemia in mental disorders. *Brain* **42:** 214–88

Lorenz WF (1922) Sugar tolerance in dementia praecox and other mental disorders. *AMA Arch Neurol Psychiatry* **8:** 184–96

Maudsley H (1979) *The Pathology of Mind.* 3rd edn. Macmillan, London

Ryan MCM, Collins P, Thakore JH (2003) Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psychiatry* **160:** 284–9

Subramaniam M, Chong S-A, Pek E (2003) Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. *Can J Psychiatry* **48:** 345–7