

# DIABETES, PSYCHOTIC DISORDERS AND ANTIPSYCHOTIC THERAPY:

## A CONSENSUS STATEMENT

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On behalf of the Consensus Panel



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A Consensus Statement

It is pre-publication and may not be changed in any form.

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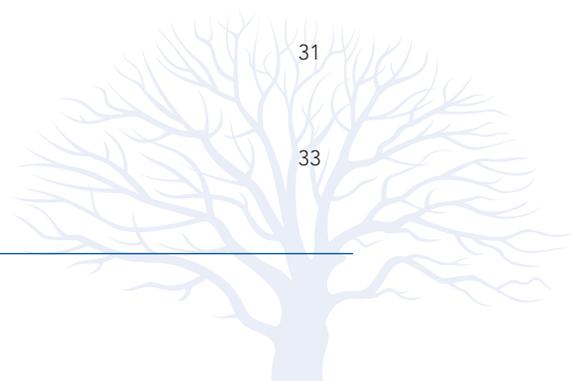
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## INTRODUCTION

A growing awareness of physical health needs in people with psychotic disorders has led to concern about the high prevalence of diabetes and 'subclinical' abnormalities of glucose metabolism such as impaired glucose tolerance. This consensus statement addresses key questions for clinicians about abnormal glucose metabolism in people with schizophrenia and other psychotic illnesses. We discuss the epidemiology of diabetes and links with mental illness and antipsychotic medication; the consequences of diabetes; approaches to detection; the assessment of the risks and benefits of antipsychotic therapy; the potential for prevention of diabetes; and areas for future research. Treatment of diabetes is not a primary focus of this document. The guidelines are based on the international medical literature and international experience, but designed to reflect Australian systems of health care and approaches to treatment.

The statement was developed by a consensus group\* with representatives from the disciplines of psychiatry, endocrinology, epidemiology, general practice, mental health nursing and pharmacy; and community/non-government organisation representation. After extensive pre-reading of the relevant literature, the group initially met for two days to define the issues of relevance to clinicians, review the existing evidence from a clinical perspective and make recommendations. A draft statement was developed, then submitted to a wider group\* for comment and further refinement. In contrast to guidelines that have been developed

in other countries, consumer and carer guidelines have been developed in parallel. In addition, the statement has considered the risks of diabetes within a wider context of improved physical health care for people with psychotic disorders, rather than as an isolated issue associated only with antipsychotic medication.

Two important general principles emerged. First, successful and optimal treatment of the psychotic disorder has priority. The advent of second generation antipsychotic medications has allowed more effective and better-tolerated treatment of psychotic illnesses, and represents a considerable advance. Second, all people taking antipsychotic medication should be screened for diabetic risk. Suggested protocols are outlined to help clinicians ensure that people with psychotic disorders receive appropriate and timely management of their physical disorders, which may sometimes require a more assertive approach than is currently the case.

Development of the consensus guidelines was made possible by an unrestricted educational grant from Eli Lilly Australia. The company had no input into the content of the guidelines.

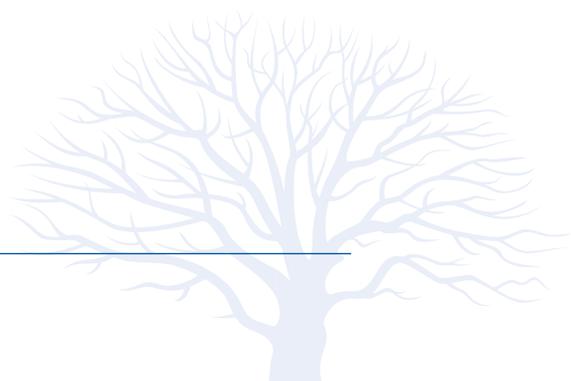
### **Associate Professor Tim Lambert**

Co-Chair of the Consensus Panel

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\* The members of the consensus panel and the reviewers are listed at the end of this statement in Appendix 1.



## EXECUTIVE SUMMARY

### EPIDEMIOLOGY

One in four Australians has abnormal glucose metabolism. Diabetes affects 7.5% of Australians and an additional 16% have impaired glucose tolerance or impaired fasting glucose levels. The prevalence of these conditions has increased rapidly, and is likely to increase further.

People with psychotic illnesses are at increased risk of diabetes because of the illness itself, poor diet and lack of exercise, and direct or indirect effects of antipsychotic and other psychotropic medication.

Most antipsychotic medications are associated with weight gain during maintenance therapy, although data on the 'real world' experience with some newer agents are lacking. There are differences between medications in their short-term effects on weight, but there is no reliable evidence from prospective, controlled studies on the long-term effects of specific antipsychotic medications on the incidence of diabetes.

### CONSEQUENCES OF DIABETES

Type 2 diabetes causes substantial morbidity and mortality. Accelerated cardiovascular disease is the most common cause of death in people with diabetes, and many have cardiovascular, renal or ocular complications by the time diabetes is diagnosed. The consequences of diabetes are likely to be at least as severe in people with psychotic disorders as in the general population.

### POPULATION HEALTH

Diabetes and mental health are two of seven national health priority areas identified by Federal, State and Territory Governments in Australia. In 2001 the National Health Priority Action Council identified high-prevalence mental illnesses as a common comorbidity to all seven areas. The Council has commissioned activity to ensure that the common mental health needs of people with physical conditions like diabetes are recognised, and that the physical health needs of people with

specific mental illnesses such as schizophrenia are identified and managed, and appropriate responses built into the health system.

### BARRIERS TO THE DETECTION AND TREATMENT OF DIABETES

The life circumstances of people with psychotic disorders need to be recognised by health care providers. Barriers to effective and comprehensive health care include stigma, alienation, poverty and features of the illness such as cognitive dysfunction. An integrated, multidisciplinary approach to physical and mental health care should be encouraged. All people with psychosis should have a general practitioner to manage the detection and treatment of physical comorbidities.

Continuing education of health professionals and others, including families and carers, is required to facilitate the care of metabolic disorders including diabetes in people with psychotic disorders. Long-term programs to improve diet and increase physical activity are required, as well as resources to facilitate access to such programs.

### PREVENTIVE ASPECTS

The primary goal of medical treatment is to provide effective control of psychiatric symptoms in people with psychotic illness, but the management of physical problems should proceed in parallel.

In people with prodromal psychotic symptoms or early psychotic illness, education about diet, exercise and health maintenance should commence as soon as possible. Frequent and recurrent education on daily activity and healthy diet should be an integral component of early intervention programs. In addition, the long-term service plans for individuals with psychosis should stress preventive and physical aspects of care.

Awareness among mental health professionals and people with psychotic illnesses of the general risk factors for diabetes, including family history and ethnicity, should be increased.

### MONITORING FOR DIABETES

The patient's general practitioner or physician, in collaboration with other relative health care providers, should assess the physical health of every patient with a psychotic disorder regularly. The psychiatrist, who may be the patient's only regular medical attendant, may have to identify the need for intervention where there is obvious obesity and an attendant risk of diabetes. Other relevant health care providers, including the pharmacist, case manager, nutritionist, and diabetes educator, can then become involved. The review should include specific attention to risk factors for diabetes.

Health professionals caring for people with psychotic disorders should identify them as being at high risk of diabetes and agree on protocols for individuals to ensure that monitoring is instituted and maintained. Ideally, fasting or random blood glucose levels should be assessed monthly for six months after initiating or changing antipsychotic therapy, then at least twice yearly. In cases where there are repeated changes in the antipsychotic medication or dose, clinical judgment on appropriate glucose monitoring will be required. In any case, blood glucose measurements should be obtained a minimum of twice yearly. Laboratory blood glucose measurements or finger prick measurements using a blood glucose meter are acceptable.

### TREATMENT OF DIABETES

Treatment of diabetes in people with psychotic illnesses should be based on the principles of treatment in the general population. Innovative strategies may be developed to ensure optimal treatment of diabetes in people with psychotic disorders. All health professionals involved in their care can contribute to the care of physical disorders including diabetes and obesity.

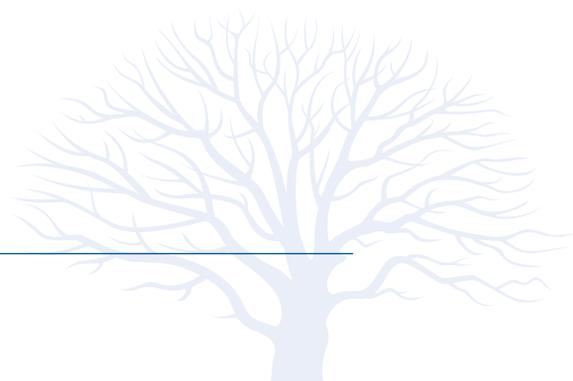
### RISKS AND BENEFITS

Clinical decisions about antipsychotic medication should be based on risk: benefit analyses that take account of the existing limited evidence. It is unlikely that the risk or presence of diabetes will be sufficient justification for ceasing antipsychotic therapy. Gaining optimal control of the psychosis should be the prime objective. People with psychotic illness and/or their guardians should be provided with full information regarding their treatments.

Diabetic ketoacidosis is an idiosyncratic adverse effect of the second generation antipsychotic medications. Prompt recognition and treatment of this complication should lead to rapid resolution.

### RESEARCH DIRECTIONS

Pressing clinical issues that require further research include the epidemiology of diabetes in people with psychosis, the optimal treatment of diabetes in people with psychotic disorders, and the optimal choice of antipsychotic therapy in people who also have diabetes or risk factors for diabetes.



## PHYSICAL COMORBIDITY IN PSYCHOTIC ILLNESS

Psychotic disorders and other disabling mental illnesses are associated with excess physical morbidity and mortality (E3) (see Appendix 2 for a definition of evidence codes), but there is a dearth of systematic research in the area. Life expectancy in people with psychotic disorders is 9-12 years lower than the general population, after accounting for suicide and accidents. Physical illness often remains unrecognised and untreated. Increased attention on

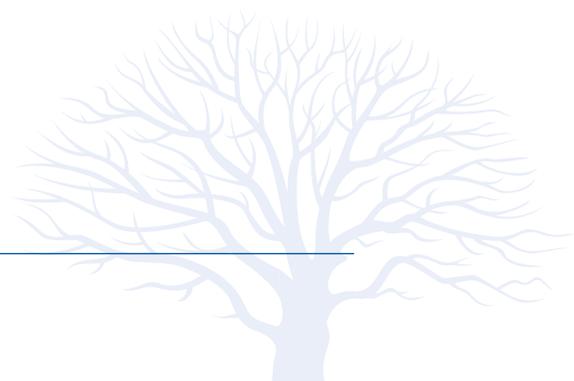
diabetes associated with psychotic illness and its treatment is warranted, within a context of the comprehensive care of physical and mental illness.

### **Key references**

Babidge et al, 2001; Coghlan et al, 2001; Lambert et al, 2003; Lawrence et al, 2001

### **Further information**

Appendix 3.



# THE EPIDEMIOLOGY OF DIABETES IN PEOPLE WITH PSYCHOTIC DISORDERS

## DIABETES IN THE GENERAL POPULATION

The AUSDIAB study provides current, detailed information on diabetes, prediabetic conditions and risk factors in the Australian population (E4). Appendix 4 provides a summary of the methodology and findings. About 7.4% of adult Australians have diabetes, but only half have been diagnosed. The number of people with diabetes has trebled since 1981.

The prevalence of impaired glucose metabolism (either impaired glucose tolerance or impaired fasting glucose - see Glossary for definitions) is 17.3% in men and 15.3% in women. Thus, almost one in four adult Australians has diabetes or a condition of impaired glucose metabolism. Furthermore, the prevalence of diabetes is projected to increase in the future. An increase in obesity, a clearly established risk factor for diabetes, is thought to be largely responsible for the rising prevalence of the disorder but other factors such as ageing of the population and a change in its ethnic mix may also have contributed.

### Key reference

Dunstan et al, 2002

### Further information

Appendix 4

## DIABETES IN PEOPLE WITH PSYCHOTIC DISORDERS

Abnormalities of glucose regulation have been recognised in psychotic disorders, particularly schizophrenia from the late 19th century, prior to the introduction of antipsychotic medication (E4). It is possible this association is part of the pathophysiology of schizophrenia. An underlying link between schizophrenia and diabetes may reflect a well-recognised link between dyskinesia and schizophrenia, which also preceded the use of antipsychotic medications.

### Key references

Lorenz, 1922; Braceland et al, 1945; Freeman, 1946; Langfeldt, 1952; Henderson and Ettinger, 2002

### Further information

Appendix 5.

***Abnormalities of glucose regulation have been recognised in psychotic disorders, particularly schizophrenia from the late 19th century, prior to the introduction of antipsychotic medication.***

## DIABETES ASSOCIATED WITH ANTIPSYCHOTIC THERAPY

A large number of individual case reports and case series and a few larger, systematic studies have described associations between antipsychotic treatment and the onset or exacerbation of diabetes. There are no long-term, randomised controlled trials to guide clinical practice in this area. However, the existing evidence suggests that the introduction of first generation antipsychotic medications (FGAs, see Glossary) was associated with a two- to three-fold increase in the prevalence of diabetes among treated patients (E3). The introduction of second generation antipsychotic medications (SGAs, see Glossary) was associated with a further increase, variously estimated at 10–50% (E3) (see Table page 7). The contribution of improved screening for disorders of glucose metabolism is not known. Evidence from systematic studies is summarised in Appendix 5.

A group of American organisations led by the American Diabetes Association recently published the outcomes of a consensus development conference on antipsychotic drugs, obesity and diabetes (American Diabetes Association et al, 2004). The conference recognised that SGAs are associated with adverse effects including obesity, diabetes and dyslipidaemia. It concluded that clozapine and olanzapine are associated with greater weight gain and a higher occurrence of diabetes and dyslipidaemia than risperidone and quetiapine, which appeared to have intermediate effects. Aripiprazole and ziprasidone did not appear to be associated with significant weight gain, diabetes or dyslipidaemia, although they had not been used as extensively as the other agents. The conference recommended baseline screening and ongoing monitoring for the development of significant weight gain, dyslipidaemia and diabetes. For people who respond well to antipsychotic medications, treatment can mean the difference between leading an engaged, fulfilling community life and being severely disabled.

In September 2003 the U.S. Food and Drug Administration (FDA) issued letters to pharmaceutical companies requesting that product labelling for all SGAs - Abilify® (aripiprazole, Bristol-Myers Squibb), Clozaril® (clozapine, Novartis), Geodon® (ziprasidone, Pfizer), Risperdal® (risperidone, Janssen-Cilag), Seroquel® (quetiapine, AstraZeneca) and Zyprexa® (olanzapine, Eli Lilly and Company) - include a warning and additional information about hyperglycaemia and diabetes, and a recommendation for regular monitoring of glucose control. The FDA acknowledged that the relationship between SGAs and glucose

abnormalities is complicated by an increased background risk of diabetes in people with schizophrenia and the growing incidence of diabetes in the general population. Precise risk estimates for hyperglycaemia-related adverse events in people treated with atypical antipsychotics are not available, and the existing data are insufficient to provide reliable estimates of differences between them.

The importance of weight gain to the development of type 2 diabetes is detailed in the recent American Diabetes Association position statement (American Diabetes Association et al, 2004).

#### ESTIMATES OF THE PREVALENCE OF DIABETES

Era	General population rate	Rate in people with psychosis
Pre-antipsychotic	Unknown	2.5-4.2% <sup>1,2</sup>
FGAs (since 1952)	3.4% (Busselton, 1981) <sup>3</sup>	17% <sup>1</sup>
SGAs (since 1990)	7.5% (Australia, 2000) <sup>4</sup>	19% <sup>5</sup>

1 Thonnard-Neumann, 1968; 2. McKee et al, 1986; 3. Glatthaar et al, 1985; 4. Dunstan et al, 2002; 5. Sernyak et al, 2002.

***The existing evidence suggests that the introduction of first generation antipsychotic medications was associated with a two- to three-fold increase in the prevalence of diabetes among treated patients. The introduction of second generation antipsychotic medications was associated with a further increase, variously estimated at 10-50%.***

#### Key references and further information

See Appendix 5.

#### MECHANISMS FOR LINKS BETWEEN PSYCHOTIC DISORDERS AND DIABETES

Obesity increases the risk of type 2 diabetes and weight gain is associated with a number of psychotropic medications, including antipsychotic medications. A hierarchy of potential short-term weight gain exists among antipsychotic medications

(E2) (Allison et al, 1999). The advent of new SGAs might lead to fewer adverse metabolic consequences, but long-term 'real world' data are lacking.

In the longer term, obesity seems to be less related to specific medications and more to behavioural factors including diet and exercise. These relationships have been described in the 'hare and tortoise' theory of antipsychotic-mediated weight gain (Lambert, 2002). However, non-controlled descriptions of cross-sectional weight gain are hypothesis-generating rather than hypothesis-testing, and a prospective study of a controlled cohort from inception of treatment is still required. People with psychosis are undoubtedly at risk of diabetes, but factors other than medication contribute to adverse metabolic outcomes. There is no evidence that people with psychosis are less vulnerable to the effects of obesity, and some evidence that they may be more vulnerable. Therefore, choice of medication should be made carefully, bearing in mind the risks and benefits of alternative options.

More research is required on the hypothesis that improvement of psychiatric symptoms during treatment with medications such as clozapine and olanzapine is associated with the extent of weight gain (Meltzer, 2001). A mechanism for the link between antipsychotic therapy and weight gain has been proposed, involving a direct interaction between orexin peptides and dopamine systems in the prefrontal cortex (Fadel et al, 2002). This suggests that, at least for some medications, body weight increase may be a marker of improvement in symptoms.

A recent study found that, compared to controls, people with schizophrenia had an increased incidence of central obesity (a risk factor for cardiovascular disease and diabetes) and higher levels of plasma cortisol (Thakore et al, 2002).

Previous exposure to antipsychotic medications did not appear to influence the findings, as both medication-naive and medication-free patients had equally high levels of visceral fat. The findings suggested that the schizophrenic illness itself influenced fat distribution and associated risks.

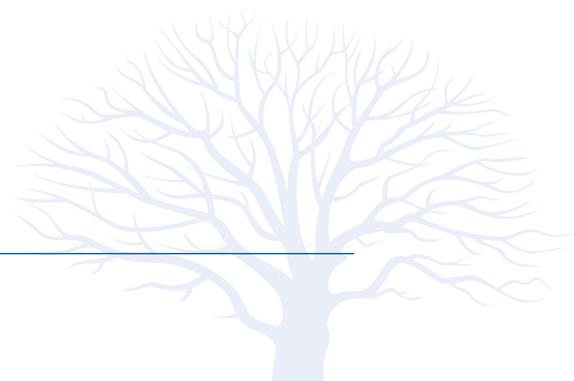
#### **Key references**

Allison et al, 1999; Lambert, 2002; Meltzer, 2001; Thakore et al, 2002

#### **Further information**

Appendix 6.

***In the longer term, obesity seems to be less related to specific medications and more to behavioural factors including diet and exercise.***



## THE PHYSICAL CONSEQUENCES OF DIABETES

Microvascular complications of diabetes include retinopathy, neuropathy and nephropathy. In Australia, diabetes is the most common cause of blindness in people younger than 60 and the second most common reason for commencing renal dialysis.

Macrovascular complications of diabetes include coronary artery disease, cerebrovascular disease and peripheral vascular disease. Diabetes significantly increases the risk of cardiovascular disease, which is the most common cause of death in people with the disorder. Cigarette smoking is common in people with psychotic illnesses, and adds markedly to cardiovascular risk. Smoking cessation should be strongly encouraged and

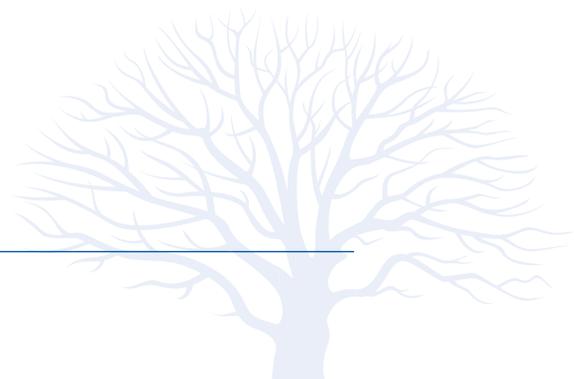
supported, taking advantage of specific programs that are available.

There is no evidence that the natural history of diabetes in people with psychotic disorders and other mental illnesses differs from that in people without such disorders. However, people living with a psychotic disorder have a higher rate of other cardiovascular risk factors including smoking and features of the metabolic syndrome. These abnormalities are associated with weight gain and include hypertension and dyslipidaemia, and may contribute to a high rate of cardiovascular mortality.

### **Key references**

NHMRC, 2000

Diabetes Research and Clinical Practice, 2003.



## THE PUBLIC HEALTH CONSEQUENCES OF DIABETES IN PEOPLE WITH PSYCHOTIC ILLNESS

Diabetes is associated with a significant burden in terms of national health costs, which are four times higher than in non-diabetics. In light of the links between diabetes and psychotic illness, the public health consequences of diabetes in people with schizophrenia and related disorders are likely to be substantial. There is a need for further research on the health economics of the two conditions.

In addition, the WHO Global Burden of Disease study estimated that, in 1990, psychiatric illnesses accounted for five of the leading 10 causes of Disability-Adjusted Life Years (DALYs) lost in people aged 15-44. Direct healthcare costs and indirect costs associated with schizophrenia are estimated at 0.3% to 2% of gross domestic product in developed countries (SANE Australia, 2002; Knapp, 1997).

Despite the increased physical health needs of those with psychotic illness, our health care systems struggle to provide necessary forms of integrated mental and physical health care or continuity of care across primary and specialised treatment services. Of particular importance, people with the more severe or enduring forms of psychotic illness struggle to have even their most basic physical health needs met and experience very poor access to regular physical review (by either a general practitioner or physician), let alone health promotion services (for example, smoking cessation programs and cancer screening). This lack of attention to appropriate health care needs contributes significantly to increased premature death.

The neglect of physical health needs in people with psychotic illness has now been recognised. Mental health is identified as a National Health Priority Area in its own right, and has now been recognised as a major theme across all other National Health Priority Areas (which include diabetes and vascular disease). Specifically, the National Health Priorities Area Action Council has commissioned activity to ensure not only that the common mental health needs of those with physical conditions like diabetes are recognised but also that the physical health needs of those with specific mental illnesses such as schizophrenia be identified. Key non-government groups such as the Mental Health

Council of Australia have also prioritised the need to improve the physical health care of those with mental illness. In this case, a consensus statement on Diabetes in Persons with Mental Illness could make a considerable contribution and its recommendations incorporated within specific national service improvement frameworks for management of persons with diabetes and the evolving national chronic disease strategy.

Implementation of specific recommendations of this consensus statement are dependent on recognition of the complex nature of the Australian health care system, its distributed responsibilities and the traditional divide between the mental health system and other parts of the medical system. Recent reforms in mental health service delivery under the Better Outcomes in Mental Health Care initiative (2001-2004) provide new opportunities for promoting integrated physical and mental health care, based largely on expanded services and improved quality of mental health care by Australian general practitioners. One in seven Australian general practitioners have undertaken additional mental health training and have access to increased funding and support to provide higher quality and better-integrated mental health care. The recognition and active management of diabetes in persons with psychotic illness could be specifically targeted for attention under this strategy.

### Key references

Murray and Lopez, 1996; Knapp 1997; Groom et al, 2003.

### Further information

WHO Burden of Disease study:

[www.who.int/health\\_topics/global\\_burden\\_of\\_disease/en/](http://www.who.int/health_topics/global_burden_of_disease/en/)

***People with the more severe or enduring forms of psychotic illness struggle to have even their most basic physical health needs met and experience very poor access to regular physical review, let alone health promotion services.***

## BARRIERS TO THE DETECTION AND TREATMENT OF DIABETES

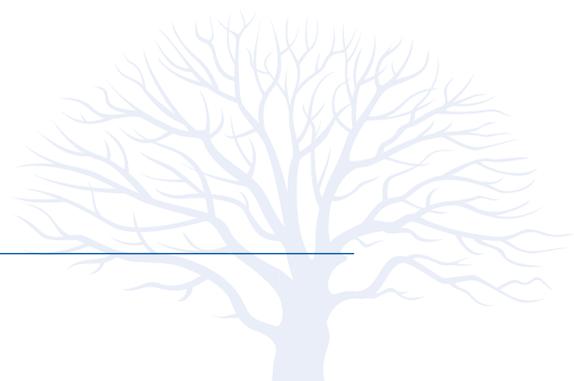
A range of barriers can prevent people with psychotic disorders from accessing optimal care of their physical health, including the prevention, detection and treatment of diabetes. Appendix 7 provides a summary.

### **Key references**

Coghlan et al, 2001; Lambert et al, 2003

### **Further information**

Appendix 7



## PREVENTION OF DIABETES AND ITS COMPLICATIONS

Obesity and diabetes are continuing to increase in the general population despite the efforts of the health system to alter dietary habits and exercise patterns. Barriers to health care in people with psychotic illness, discussed previously, are relevant to the prevention of diabetes, and the minimisation of complications once diabetes occurs.

Early identification of abnormal glucose metabolism can assist in targeting preventive measures. Improved diet and increased physical activity in middle-aged, overweight members of the general population can reduce the progression of prediabetic states to diabetes (Tuomilehto et al, 2001), and the UKPDS demonstrated that appropriate treatment of diabetes reduces complications (American Diabetes Association, 2000). There is little evidence on the effects of such interventions in people with psychotic disorders, but pilot studies indicate that exercise programs and dietary counselling can lead to healthier behaviours and improve a range of health outcomes (Aquila and Emanuel 1999).

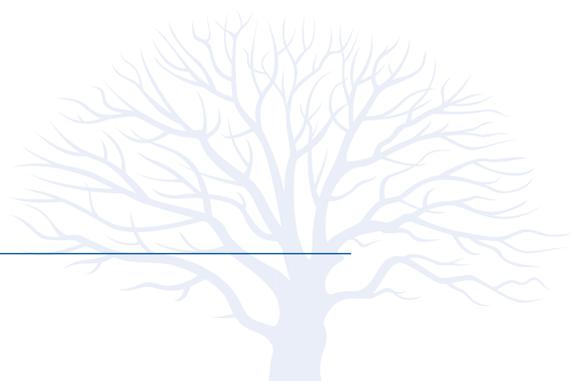
Exercise and dietary change can improve metabolic parameters even in the absence of weight loss.

Thus, prevention of diabetes can be adopted as an objective which is independent of efforts to prevent or treat obesity.

A range of approaches could be adopted for the prevention of diabetes in people with psychotic illness, from a 'top down' approach within mental health services through to individual work with patients. Medicare Benefits Schedule item numbers for general practitioners for enhanced primary care can facilitate an integrated approach to physical healthcare at the patient level. Modalities such as patient-held medical records could assist with monitoring of diabetes and coordination of preventive interventions.

Mortality and morbidity is higher in people with psychotic disorders than in the general population. Prevention of physical disease is a fundamental strategy that should be embraced by all health practitioners.

***Exercise and dietary change can improve metabolic parameters even in the absence of weight loss.***



## PEOPLE WITH PSYCHOTIC DISORDERS SHOULD BE MONITORED FOR THE METABOLIC SYNDROME AND DIABETES

The National Health and Medical Research Council has developed guidelines on population screening for diabetes. The guidelines recommend more intensive screening for some groups within the population known to be at higher risk, for example on the basis of family history, ethnicity, age, a history of gestational diabetes or other risk factors.

Issues in the detection of diabetes in people treated with antipsychotic therapy include the following:

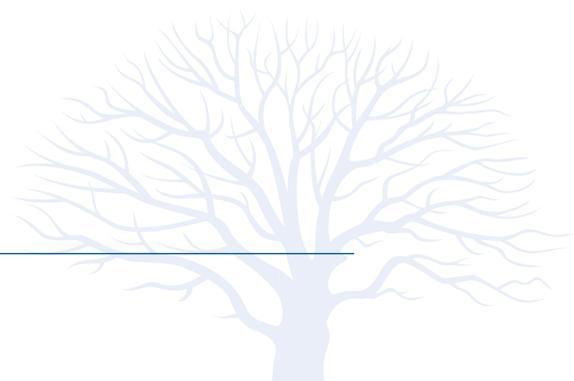
- Monitoring required when initiating antipsychotic treatment, or increasing the dose or changing antipsychotic medication.
- Monitoring required during continuing treatment.
- The monitoring required for rare adverse events such as acute metabolic disorders during antipsychotic treatment.

An algorithm for monitoring glucose metabolism in people treated with antipsychotic medication is shown in Figure 1 on page 14. Ideally, fasting or random blood glucose levels should be assessed monthly for six months after initiating or changing antipsychotic therapy, then at least twice yearly. In cases where there are repeated changes in the antipsychotic medication or dose, clinical judgment on appropriate glucose monitoring will be required. In any case, blood glucose measurements should be obtained a minimum of twice yearly. Laboratory blood glucose measurements or finger prick measurements using a blood glucose meter are acceptable.

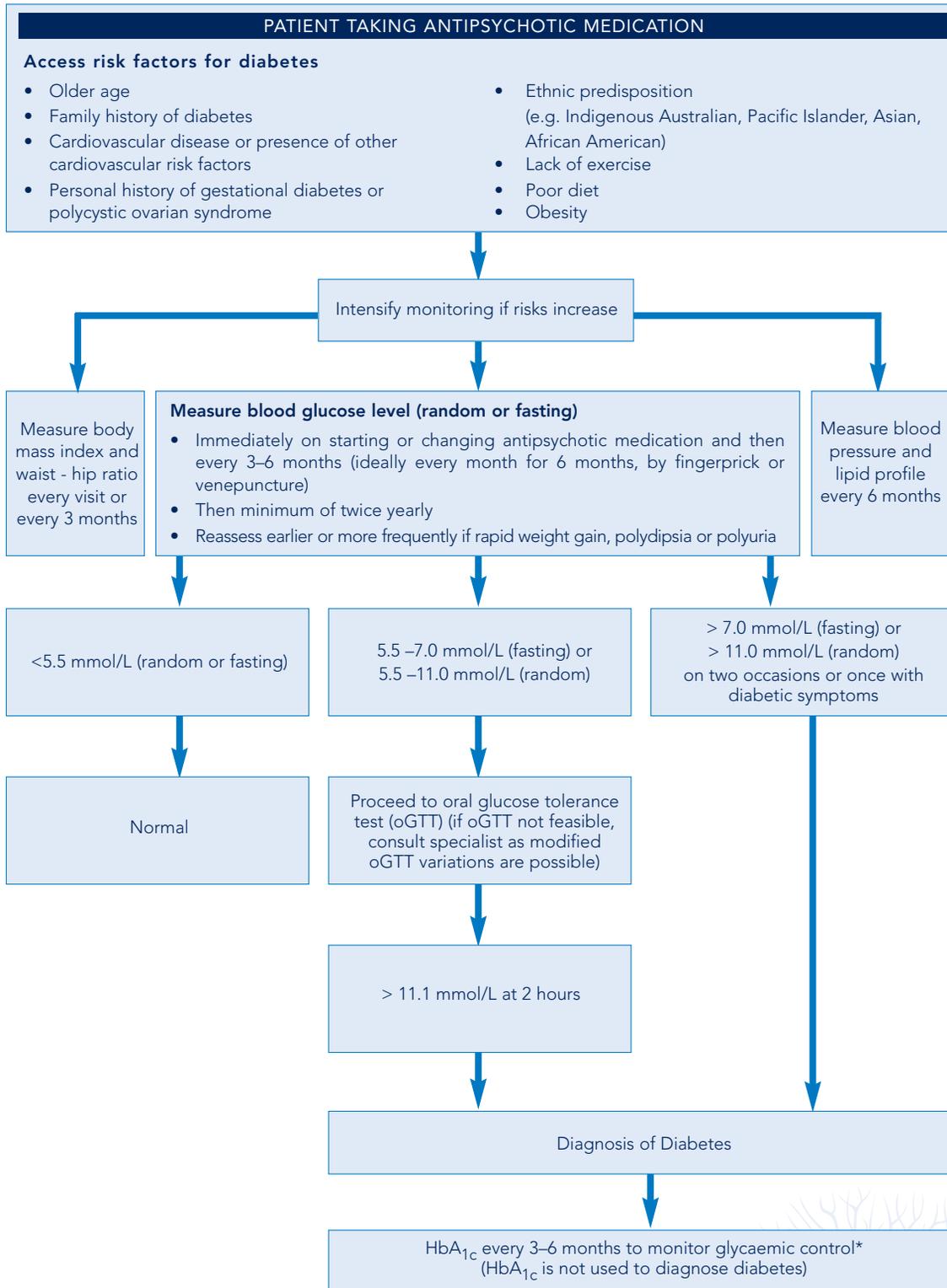
### **Further information**

Livingstone and Rampes, 2003.

***Ideally, fasting or random blood glucose levels should be assessed monthly for six months after initiating or changing antipsychotic therapy, then at least twice yearly.***



**FIGURE 1: ALGORITHM FOR MONITORING GLUCOSE METABOLISM IN PEOPLE TREATED WITH ANTIPSYCHOTIC MEDICATION**



\* Medicare covers up to 4 assessments per year

## TREATING DIABETES

Priorities of treatment need to be determined (see risks and benefits section page 17). In keeping with the principle that optimal treatment of the psychosis is the primary objective, attention to diabetes and cardiovascular risks may be highly problematic in people whose psychotic symptoms are poorly controlled. However, physical comorbidity should always be suspected.

All health professionals involved in the care of a patient with a psychotic disorder, including the psychiatrist in charge, can contribute to the care of physical disorders including diabetes and obesity. Consistent advice should be provided on issues such as diet, exercise and smoking. Depending on the local system of care, it is likely that general practitioners will be best placed to coordinate physical health care, with the support of appropriate specialists and other agencies, but 'shared care' can sometimes lead to a failure of care unless responsibilities are very clearly defined for each patient. Assertive community care models are ideal in coordinating physical and mental health care if they are adequately resourced and are able to access individuals who would not otherwise receive optimal treatment. Effective partnerships not just with the patient but also with family members and other key carers can contribute to monitoring and treatment.

Principles of treating diabetes in people with psychotic disorders are similar to those in the general population, although some additional issues could be considered:

- Exercise improves glucose metabolism even in the absence of weight loss, and can also improve affective symptoms of psychotic illness. Staged daily activity is recommended. A minimum target of walking for 30 minutes every day should be considered.
- Frequent and recurrent interventions to improve diet and increase exercise have been shown to improve glucose metabolism, but outcomes in

people with psychotic disorders have not been systematically evaluated. Group therapy and psychoeducation may be more effective than individual approaches.

- Cognitive impairment and other symptoms of psychotic disorders may act as barriers to dietary and exercise interventions and to adherence with medication for diabetes, but should not lead to undue pessimism about treatment. Achievable targets can enhance therapeutic alliances and provide meaningful rewards for individuals with the illness.
- The risk of overdose with diabetes treatments, especially insulin, needs to be considered.
- Metformin is the medication of first choice in obese individuals with type 2 diabetes. The risk of lactic acidosis is present but very low (Nisbet et al, 2004). Metformin does not cause weight gain and poses a low risk of hypoglycaemia. Twice-daily dosing is often required, which may add to difficulties with adherence.

A management protocol, including factors to consider in the choice of medication, is outlined in Appendix 8. Poor adherence to therapy is often cited as a reason for treatment failure in this patient population. The use of aids to adherence, such as blister packs, continued psychoeducation, and reminder cards should be considered for both antipsychotic and antidiabetic medication.

***All health professionals involved in the care of a patient with a psychotic disorder, including the psychiatrist in charge, can contribute to the care of physical disorders including diabetes and obesity. Consistent advice should be provided on issues such as diet, exercise and smoking.***

## THE BENEFITS OF TREATING DIABETES

Each percentage point reduction in glycosylated haemoglobin (HbA1c, see Glossary) in people with type 2 diabetes is associated with:

- a 35% reduction in microvascular complications
- a 25% reduction in diabetes-related deaths
- a 7% reduction in all-cause mortality
- a very strong trend ( $p=0.052$ ) for reduced cardiovascular complications, with a 16% reduction in the combined end-point of fatal and non-fatal myocardial infarction and sudden death.

Long-term intervention aimed at multiple risk factors including hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria has been shown

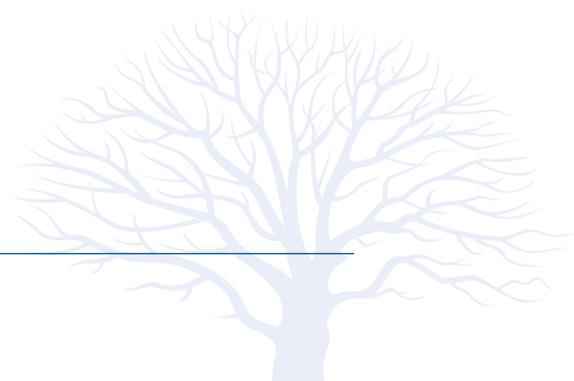
to reduce the risk of cardiovascular and microvascular events by about 50% (Gaede et al, 2003).

### Key references

American Diabetes Association, 2000, for a summary of the implications of the United Kingdom Prospective Diabetes Study (UKPDS)

Gaede et al, 2003

***Long-term intervention aimed at multiple risk factors including hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria has been shown to reduce the risk of cardiovascular and microvascular events by about 50%***



## RISKS AND BENEFITS OF ANTIPSYCHOTIC TREATMENT

Selection of an antipsychotic medication for a particular patient should be driven more by its capacity to reduce psychiatric symptoms than its diabetic potential alone, particularly in the absence of definitive information about causality and risk (Koller, 2003).

Pre-existing diabetes may be a relative contraindication to the prescription of medications that are known to have adverse short-term effects on weight and metabolism. However, it is not an absolute contraindication as effective treatment of the psychosis should be the primary aim.

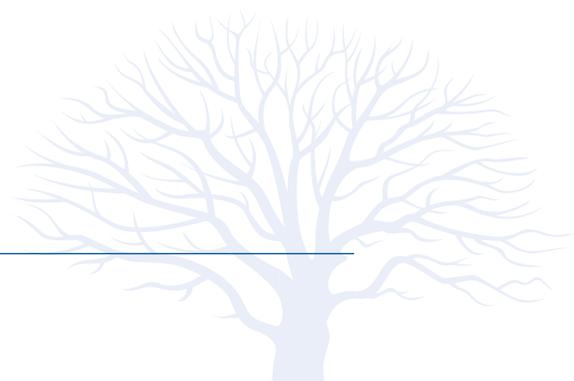
Informed consent should be obtained from patients or their guardians, with acknowledgment of the requirement to monitor for diabetes.

There have been several hundred case reports of apparent diabetic ketoacidosis occurring during treatment with SGAs. The literature on the topic and an assessment of the risks is included in Appendix 9.

### **Key references and further information**

Appendix 9

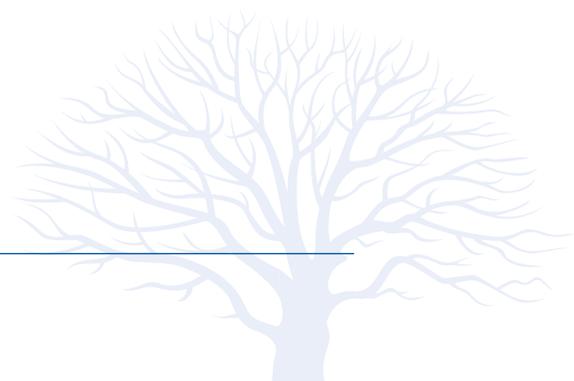
***Selection of an antipsychotic medication for a particular patient should be driven more by its capacity to reduce psychiatric symptoms than its diabetic potential alone, particularly in the absence of definitive information about causality and risk.***



## RESEARCH DIRECTIONS

There are substantial deficiencies in the evidence on links between psychotic illness, antipsychotic therapy and abnormal glucose metabolism. The strongest evidence relates to the epidemiology of diabetes in people with psychotic disorders, which clearly indicates the prevalence is significantly higher than in the general population. Whether psychosis itself increases the risk of diabetes, and whether specific antipsychotic medications have differential effects on glucose metabolism during

long-term treatment, routine use remains uncertain, and the mechanisms of any such links remain obscure. Evidence on the effects of diabetes, the benefits of treatment and the benefits of preventive activities are derived almost entirely from the general population. Where there is specific evidence based on people with psychotic disorders, subjects recruited into trials are not necessarily representative of those seen in clinical practice. Some specific issues for research are listed in Appendix 10.



## GLOSSARY

### **First generation antipsychotic medications (FGAs)**

'Typical' or 'conventional' antipsychotic medications. The prototypical agent, chlorpromazine, was first used in the mid-1950s. Other medications in this class include fluphenazine, thioridazine, haloperidol, droperidol, flupenthixol and zuclopenthixol.

### **Second generation antipsychotic medications (SGAs)**

'Atypical' antipsychotic medications. The prototypical agent, clozapine, was first used in Australia in the late 1980s. Other members of the class available in Australia are amisulpride, aripiprazole, olanzapine, quetiapine and risperidone.

### **Impaired glucose metabolism**

A general term encompassing diabetes and the 'prediabetic' disorders of impaired glucose tolerance (IGT, characterised by normal fasting glucose but elevated 2-hour blood glucose on the oral glucose tolerance test) and impaired fasting glucose (IFG, elevated fasting glucose but normal 2-hour result on the oral glucose tolerance test).

### **Glycosylated haemoglobin (HbA<sub>1c</sub>)**

A marker of long-term glycaemic control, expressed as a percentage. The average blood glucose level in the past 60 days can be estimated approximately from the formula:  $(\text{HbA}_{1c} \times 2) - 6.0$  mmol/L.

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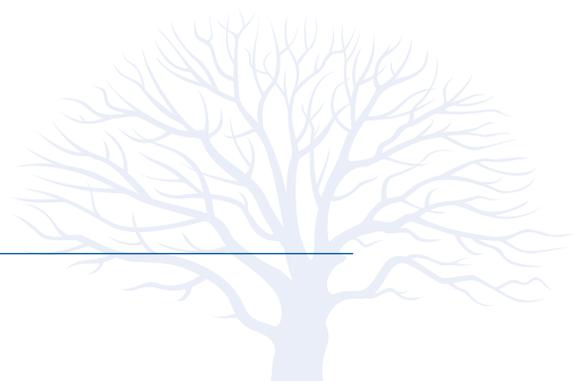
## APPENDIX 1

### MEMBERS OF THE CONSENSUS PANEL

1. Mr Simon Bell, pharmacist, Sydney
2. Dr Nicholas Carr, general practitioner, Melbourne
3. Dr Leon Chapman (co-chair), diabetologist, Melbourne
4. Dr Michael D'Emden, endocrinologist, Brisbane
5. Mr Steven Elsom, mental health nurse, Melbourne
6. Dr Grace Groom, Mental Health Council of Australia, Canberra
7. Professor Scott Henderson, psychiatrist, Canberra
8. Professor Ian Hickie, psychiatrist, Sydney
9. Associate Professor Linda Hoffman, endocrinologist, Hobart
10. Associate Professor Tim Lambert (co-chair), psychiatrist, Melbourne
11. Dr Alan Rosen, psychiatrist, Sydney
12. Professor Bruce Singh, psychiatrist, Melbourne
13. Professor Tim Welborn, endocrinologist, Perth
14. Dr Peter Wynn Owen, psychiatrist, Perth

### REVIEWERS

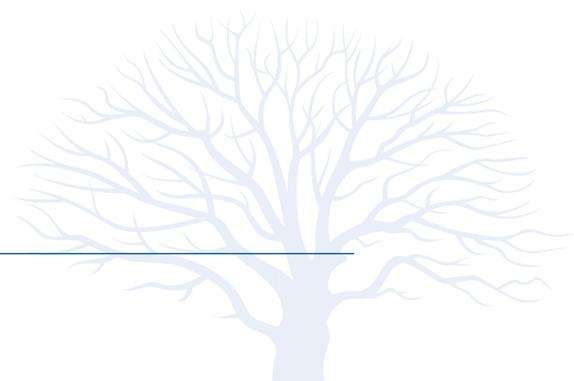
1. Mr John Bell, pharmacist, Sydney
2. Dr Elsa Bernardi, psychiatrist, Sydney
3. Dr Grant Blashki, general practitioner, Melbourne
4. Professor Vaughan Carr, psychiatrist, Newcastle
5. Professor David Castle, psychiatrist, Melbourne
6. Professor Stanley Catts, psychiatrist, Brisbane
7. Professor Donald Chisholm, endocrinologist, Sydney
8. Professor Michael Clinton, clinical nurse, Perth
9. Professor David Copolov, psychiatrist, Melbourne
10. Ms Linda Fellows, pharmacist, Perth
11. Mr Tony Fowke, National Consumer and Carer Forum, Perth
12. Associate Professor Tim Greenaway, endocrinologist, Hobart
13. Ms Brenda Happell, clinical nurse, Melbourne
14. Dr Dan Haupt, Washington State University, USA
15. Professor Mark Harris, general practitioner, Sydney
16. Ms Barbara Hocking, SANE Australia, Melbourne
17. Professor Assen Jablensky, psychiatrist, Perth
18. Professor Jayashri Kulkarni, psychiatrist, Melbourne
19. Dr Johanna Lammersma, psychiatrist, Adelaide
20. Ms Janet Meagher, National Consumer and Carer Forum, Sydney
21. Dr John Newcomer, Washington State University, USA
22. Professor Saxby Pridmore, psychiatrist, Hobart
23. Mr Rob Ramjan, Schizophrenia Fellowship of NSW, Sydney
24. Associate Professor Geoff Riley, psychiatrist, Fremantle
25. Ms Liz Stewart, National Consumer and Carer Forum, Sydney
26. Mr Keith Wilson, Mental Health Council of Australia, Fremantle



## APPENDIX 2

### CODES FOR LEVELS OF EVIDENCE BASED ON THOSE OF THE NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL (NHMRC, 1999)

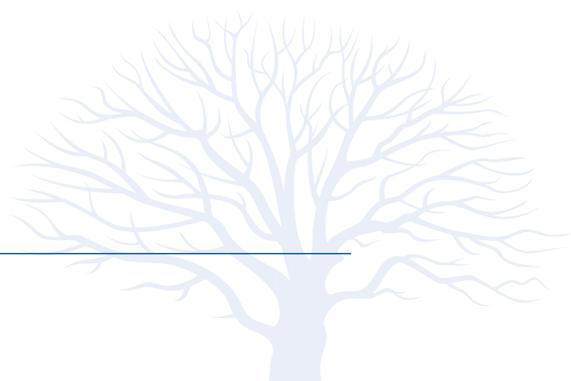
- E1 (Level I):** Evidence obtained from a systematic review of all relevant randomised controlled trials
- E2 (Level II):** Evidence obtained from at least one properly designed randomised controlled trial
- E3<sub>1</sub> (Level III-1):** Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
- E3<sub>2</sub> (Level III-2):** Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group
- E3<sub>3</sub> (Level III-3):** Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
- E4 (Level IV):** Evidence obtained from case series, either post-test or pre-test and post-test



## APPENDIX 3

### REPRESENTATIVE PUBLICATIONS ON PHYSICAL COMORBIDITY IN PEOPLE WITH SCHIZOPHRENIA

REFERENCE	KEY FINDINGS
Lawrence et al, 2001	Excess mortality associated with schizophrenia and other mental illnesses in Western Australia
Babidge et al, 2001	Excess mortality associated with schizophrenia and other mental illnesses in New South Wales
Brown et al, 2000	60% of excess mortality is attributable to physical illness, 28% to suicide and 12% to accidents
Ruschena et al, 1998	People in Victoria with schizophrenia are 2.9 times more likely to die of natural causes, especially cardiovascular disease
Koran et al, 1989	45% of patients in the Californian public mental health system had physical diseases, of which 47% were undetected by the treating doctor. Many were either causing or exacerbating the patient's mental illness
Koranyi, 1979	43% of psychiatric clinic patients had physical illnesses of which 46% had not been diagnosed by the referring doctor. Non-psychiatrist physicians failed to diagnose 33% of conditions, and psychiatrists failed to diagnose 50%
Hall et al, 1981	46% of patients admitted to a research ward had an unrecognised physical illness that either caused or exacerbated their psychiatric illness, 80% had physical illnesses requiring treatment, and 4% had precancerous conditions or illnesses



## APPENDIX 4

### DIABETES IN THE AUSTRALIAN POPULATION: THE AUSDIAB STUDY

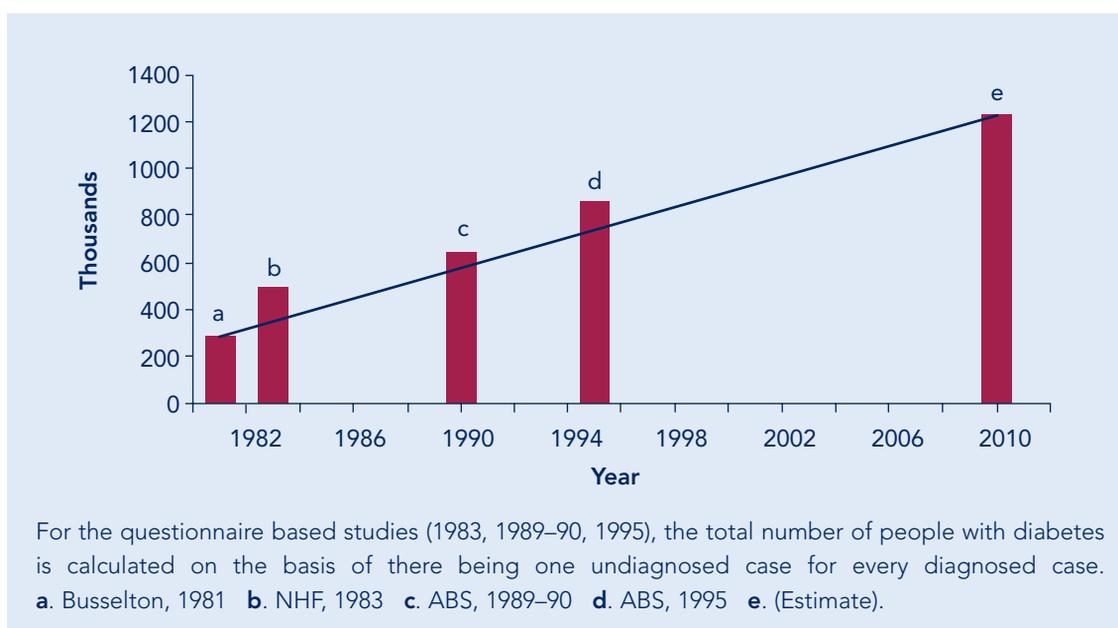
In 1999-2000 the study investigated a stratified random cluster sample of 11,247 community-dwelling adults aged 25 years or more living in all six states and the Northern Territory. The increase in the prevalence of diabetes and projected future increases are shown in the Figure 2.

AUSDIAB found that 39.1% of the population (48.2% of men, 30.2% of women) were overweight (BMI 25-29.9), and 20.5% (19.1% of men, 21.8% of

women) were obese (BMI>30). A total of 59.6% of participants were overweight or obese, and obesity was more than twice as common as in 1981.

Obesity is increasing despite stable or declining dietary intake of energy. It reflects a substantial reduction in levels of physical activity and is more common in people of lower socioeconomic status (Prentice and Jebb, 1995). It is estimated that Australians' level of physical activity 150 years ago was two to three times higher than today, equivalent to walking 8-16 km every day (Egger et al, 2001).

FIGURE 2: ESTIMATED DIABETES CASES IN AUSTRALIA



Taken from Welborn et al. Diabetes and Associated Disorders in Australia 2000. The Accelerating Epidemic. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) International Diabetes Institute, 2001.

## APPENDIX 5

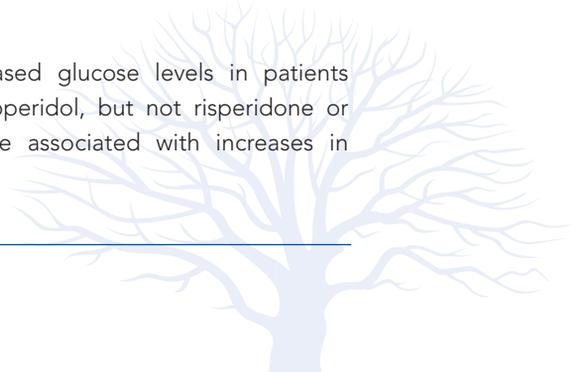
### EPIDEMIOLOGY OF DIABETES IN PEOPLE WITH PSYCHOSIS AND IN PEOPLE TREATED WITH ANTIPSYCHOTIC MEDICATIONS

#### Diabetes in people with psychotic disorders

- Ryan et al, 2003 Investigated glucose metabolism in 26 patients hospitalised with a first episode of schizophrenia but not yet treated with an antipsychotic medication. Average levels of blood glucose, insulin, cortisol and lipids were elevated compared to controls matched on the basis of age, sex, lifestyle and anthropometric measures. More than 15% of patients, but none of the healthy controls, had impaired fasting glucose. Supports the hypothesis that schizophrenia itself is associated with abnormal glucose metabolism and other metabolic disorders.
- Dynes 1969;  
Mukherjee et al, 1989 Family history of diabetes is more common in people with schizophrenia than the general population. Suggests diabetes and schizophrenia may share a common genetic link, and that psychosis is an independent risk factor for diabetes.

#### Antipsychotic therapy and diabetes

- Thonnard-Neumann, 1968 Introduction of FGAs in a psychiatric hospital was associated with an increase in the prevalence of diabetes increased from 4.2% in 1955 to 17.2% in 1966. About 25% of patients treated with 100 mg/day chlorpromazine or equivalent for a year or longer developed hyperglycaemia and glycosuria consistent with type 2 diabetes.
- McKee et al, 1986 Noted reports of an unexpectedly high proportion of psychiatric patients with diabetes throughout the 1960s. In two large psychiatric hospitals, 2.5% of patients had diabetes compared to an estimated population prevalence of 1%.
- Dixon et al, 2000 Schizophrenia Patient Outcomes Research Team (PORT) analysed data from more than 20,000 people treated during 1991, prior to the widespread use of SGAs, supplemented by interviews with 719 patients between 1994 and 1996. Rates of diagnosed diabetes significantly exceeded those in the general population.
- Meyer, 2002 A retrospective review of records of 37 patients treated with olanzapine and 39 treated with risperidone found olanzapine was associated with significantly greater increases in fasting glucose and lipid levels than risperidone.
- Newcomer et al, 2002 Oral glucose tolerance tests in 48 people with schizophrenia and 31 controls found clozapine and olanzapine were associated with increased levels compared to patients treated with typical antipsychotic medications and healthy controls, and risperidone was associated with increased glucose levels compared only to healthy controls.
- Wirshing et al, 2002 Retrospective chart review identified increased glucose levels in patients treated with clozapine, olanzapine and haloperidol, but not risperidone or quetiapine. Clozapine and olanzapine were associated with increases in triglyceride levels.



- Gianfrancesco et al, 2002  
Analysis of 7933 patients treated for a psychotic disorder found the incidence of type 2 diabetes compared to untreated patients was elevated in patients receiving clozapine (odds ratio 7.44), low-potency FGAs such as chlorpromazine and thioridazine (OR 3.46), olanzapine (OR 3.10) and high-potency FGAs such as haloperidol and fluphenazine (OR 2.13). Older age and greater use of non-antipsychotic psychotropic medication increased the risk.
- Koller et al, 2001, 2002, 2003,  
(Koller et al, 2003).  
Studies based on the FDA MedWatch Drug Surveillance System of spontaneously-reported adverse drug reactions identified new cases or exacerbations of abnormal glucose metabolism in 237 patients treated with olanzapine, 384 treated with clozapine, 46 treated with quetiapine and 131 treated with risperidone. Three of the studies lacked any denominator and were unable to assess incidence. Hyperglycaemia was significantly more common in patients treated with risperidone compared to patients treated with haloperidol
- Koro et al, 2002  
Database of 3.5 million United Kingdom general practice patients identified 19,637 individuals treated for schizophrenia. Olanzapine was associated with a higher risk of diabetes compared to patients who were treated with risperidone or FGAs, or who were untreated.
- Citrome, 2003  
Noted that five pharmacoepidemiological studies had all reported different conclusions on SGAs. The studies omitted important risk factors such as ethnicity, body mass index, family history of diabetes and level of physical activity.
- Lund et al (2001)  
Noted numerous case reports that linked clozapine to the development of diabetes and hyperglycaemia in patients with schizophrenia, but investigators had been unable to clearly demonstrate this association when compared to a control group receiving FGAs. Among 552 patients treated with clozapine and 2461 receiving FGAs, there was no overall difference in the prevalence of diabetes, hypertension or hyperlipidaemia between the groups.
- Sernyak et al, 2002  
Investigated more than 38,000 outpatients with schizophrenia treated during a four month period in 1999. Patients treated with SGAs were 9% more likely than those treated with FGAs to have diabetes. The prevalence of diabetes was significantly increased for patients receiving clozapine, olanzapine and quetiapine, but not risperidone. Among patients younger than 40, all SGAs were associated with an increased prevalence of diabetes. The four month period of data collection provided little information on the temporal relationships between treatment and the onset of diabetes and could not establish causality (Geller and MacFadden, 2003). There was no analysis of prior antipsychotic treatment or treatment duration (Gianfrancesco, 2003).
- Sernyak et al, 2003  
As in the general population, diabetes often remains undiagnosed in people with mental illness. In a sample of 121 people with schizophrenia not previously diagnosed as diabetic, 17% had impaired fasting glucose and 6% had diabetes.

## APPENDIX 6

### RISK FACTORS FOR DIABETES AND POSSIBLE MECHANISMS LINKING DIABETES AND PSYCHOTIC DISORDERS

#### **Some risk factors for diabetes in people with disabling mental illness.**

##### **Illness factors**

- Obesity compounded by poor diet and lack of physical activity.
- Apathy and amotivation that intensifies social isolation and self-neglect.
- Tobacco use, which can interfere with glucose metabolism.

##### **Therapy factors**

- A direct effect of antipsychotic, antidepressant and mood stabiliser therapy on body weight and metabolism.
- A sedative effect of some psychotropic therapy, contributing to physical inactivity.
- A lack of psychosocial support and encouragement of a healthy diet and exercise.

##### **Barriers to healthcare**

- Suboptimal access to healthcare.
- Suboptimal treatment once healthcare is accessed.
- Medication and illness may impair cognitive function.
- Difficulty communicating effectively with healthcare providers.

#### **Proposed mechanisms linking diabetes and psychotic illness**

Obesity is common in people with psychotic disorders. Studies in patients receiving first generation depot antipsychotic medications revealed a significantly higher prevalence of obesity than in the general population (Silverstone et al, 1988; Stedman and Welham, 1993). In a Victorian sample of patients who had been on stable antipsychotic therapy for at least six months, only 5-11% had a healthy weight and 55% were obese (Lambert, 2002). Analysis by lifetime use of antipsychotic medication found no significant difference in mean BMI in patients treated with clozapine, olanzapine, risperidone or first generation antipsychotic medications.

There is little evidence on whether weight gain is reversed after switching antipsychotic therapy. Weight gain has been associated with a favourable response to clozapine (Meltzer, 2001).

It has been proposed that antipsychotic medications might contribute directly to hyperglycaemia, as abnormal glucose metabolism has been reported to occur rapidly after the initiation of treatment and/or in the absence of significant weight gain. Proposed mechanisms include a direct effect on hypothalamic regulation of blood glucose, insulin release, insulin resistance or glucose utilisation (Gianfrancesco et al, 2002).

Several researchers have cautioned against prematurely attributing a high incidence of diabetes to a single cause such as antipsychotic medication (Dixon et al, 2000; Gianfrancesco et al, 2002). Both diabetes and schizophrenia probably result from complex interactions of polygenetic vulnerabilities and environmental factors, and links between them are yet to be elucidated.

## APPENDIX 7

### BARRIERS TO RECOGNITION AND MANAGEMENT OF MEDICAL ILLNESS IN PEOPLE WITH SCHIZOPHRENIA AND OTHER MENTAL ILLNESSES\*

#### Doctor/healthcare system factors

- Reticence of non-psychiatrists to treat people with serious mental illness.
- Lack of adequate follow-up of patients with mental illness, due to patients' itinerancy and lack of motivation.
- Changes of treating doctor, with the result that many patients do not have a longitudinal history available.
- Perception by specialist psychiatrists that physical health matters should be the province of referring doctors.
- Specialists' attention focused principally on patients' psychiatric problems, with physical examination conducted infrequently.
- Physical complaints regarded by psychiatrists as psychosomatic symptoms.
- Time and resources for physical/medical examinations not available in current mental-health service settings.

#### Patient/illness factors

- Poor general treatment compliance.
- Avoidance or neglect of contact with general practitioners or general healthcare services.
- Unawareness of physical problems because of cognitive deficits associated with mental illness.
- Patients' difficulty in communicating their physical needs and problems in general.
- Physical symptoms unreported/masked because of high pain tolerance in some patients, and reduction in pain sensitivity associated with use of antipsychotic drugs.
- In some patients, reluctance to discuss problems or volunteer symptoms and/or general uncooperativeness.
- Patients' difficulty in comprehending healthcare advice and carrying out required changes in lifestyle.

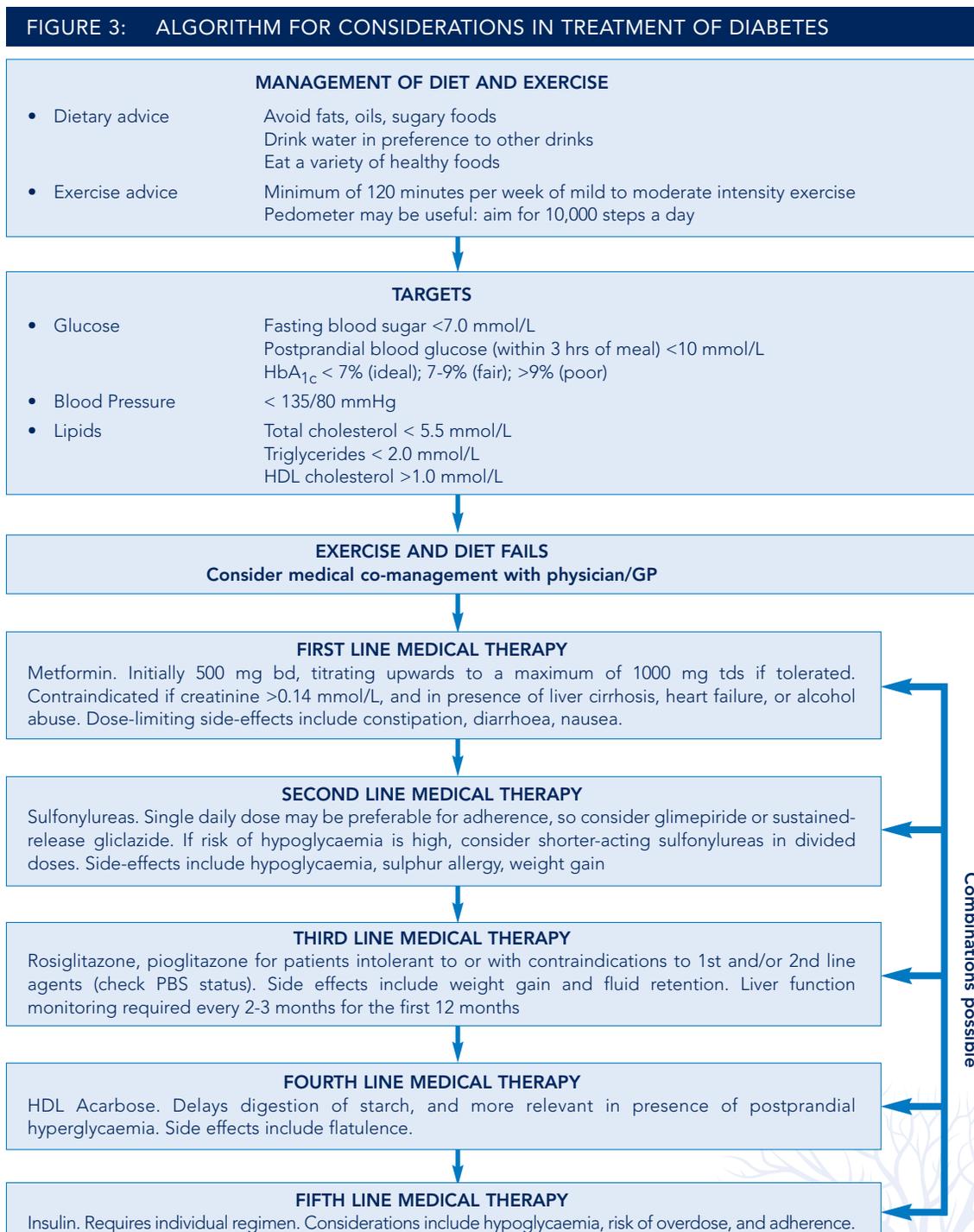
\* Taken from Lambert TJR, Velakoulis D, Pantelis C. Medical comorbidity in schizophrenia. *Medical Journal of Australia* 2003; 178: S67-S70.



## APPENDIX 8

### CONSIDERATIONS IN TREATMENT OF DIABETES

The following figure highlights some of the issues to be considered in treating diabetes in people with psychotic disorders. The algorithm is not comprehensive, and does not attempt to address all aspects of diabetes care.



## APPENDIX 9

### RISKS AND BENEFITS

Meltzer (2001) reviewed the issues to consider in assessing the benefits of antipsychotic therapy in relation to the risks of metabolic disorders such as diabetes. Even if it is established that SGAs are associated with a higher risk of diabetes, then clinicians, patients and, where appropriate, family members must balance the risk against the significant benefits of treatment which include improved cognition, reduced suicidality and less depression, and then select a course of treatment that includes a realistic monitoring program. A reduced incidence of disabling and stigmatising extrapyramidal symptoms from SGAs is an additional benefit. Improved cognition is an important determinant of function, relationships, employment and education, and presumably of the individual's capacity to manage physical health.

Meltzer cautioned against presenting the risks of therapy in a categorical, unqualified way. Instead, it is preferable to take preventive action where needed (including education about nutrition, diet and exercise), prescribe the lowest effective dose, and avoid ancillary medications which may exacerbate the problem. If concerns about metabolic abnormalities lead to greater attention to overall physical health, then links between antipsychotic therapy and diabetes may have a 'silver lining'.

A number of authors have stressed the need to provide effective antipsychotic therapy as the first priority in responding to distressing and disabling psychiatric symptoms.

Whether a patient will develop diabetes based only on exposure to specific antipsychotic drugs is not easily predictable, but the consequences of poor control of the symptoms of schizophrenia are obvious (Citrome, 2003). Similarly, apparent potential for weight gain should not be the sole reason for drug selection, as the clinical response and incidence of other adverse effects also need to be considered (Russell and Mackell, 2001).

Little evidence is available to guide decisions about switching antipsychotic therapy in response to the onset of diabetes or excessive weight gain, and whether the risks inherent in changing antipsychotic therapy will be justified by reduced metabolic side effects. No single antipsychotic medication should be regarded as contraindicated in people considered at risk of diabetes, but the risks should be recognised and patients monitored accordingly.

### DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is an acute metabolic complication of diabetes that results from a deficiency of insulin combined with excessive activity of glucagon, cortisol and catecholamines. It is more common in type 1 diabetes, but can occur as a rare complication of type 2 diabetes when the imbalance between anabolic and catabolic hormones becomes pronounced. Such situations can arise when insulin secretion is substantially reduced or insulin needs are substantially increased, for example during infection.

There have been several hundred case reports of diabetic ketoacidosis occurring during treatment with SGAs. None of the reports have originated from Australia. The true incidence is not known as most of these reports are on the basis of adverse event reporting such as the FDA MedWatch Surveillance Program, and the number of people treated worldwide with SGAs is unknown.

Reports involving clozapine and olanzapine are most numerous, but these antipsychotic medications have also very widely used in the treatment of schizophrenia. More recently, reports have also involved risperidone and quetiapine.

Existing case reports suggest that there is a true idiosyncratic association between SGAs and diabetic ketoacidosis, but the mechanism of action is unknown. Prior weight gain is not a consistent feature. It has been proposed that SGAs could have a direct effect on either insulin secretion or insulin resistance. Risk factors identified in case reports

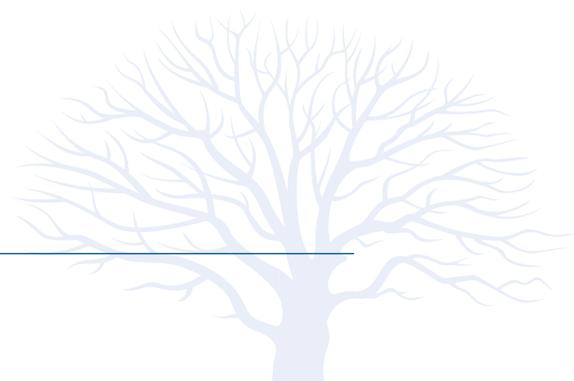
include non-Caucasian race and male gender. The risk does not appear to be related to dose of the antipsychotic medication, but in virtually all cases the episode occurred within six months of initiating antipsychotic therapy.

These case reports suggest the risk of diabetic ketoacidosis (and occasionally diabetes) is reversible on withdrawal of the antipsychotic

medication and, in general, re-challenge has led to a recurrence of elevated blood glucose levels. There is little information to guide clinicians in the choice of antipsychotic medication after an episode of diabetic ketoacidosis. However, one case report (Croarkin et al, 2000) describes a patient re-challenged with a different SGA who had no recurrence of ketoacidosis but still required insulin therapy.

#### Summary and interpretation:

- Cases of diabetic ketoacidosis generally occur within six months of initiating treatment.
- Fasting (if possible) blood glucose should be taken before and then at least monthly for the first 6 months after initiating antipsychotic treatment, or at any time if weight loss, polydipsia, polyuria or unexpected tiredness occur.
- There is little information to guide subsequent antipsychotic therapy if diabetic ketoacidosis occurs. Choice of treatment would depend on the clinical severity of the psychotic illness and the appropriateness of alternative medication.

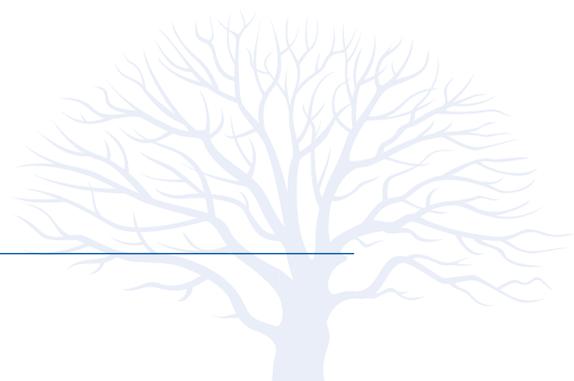


## APPENDIX 10

### RESEARCH DIRECTIONS

#### **Further research is required on the following issues:**

- The epidemiology of diabetes in people with psychosis (including the proportion who are undiagnosed) and its links with the illness, its treatment and psychosocial factors.
- Optimal treatment strategies for diabetes in people with psychotic disorders, and the outcomes of care (see the treatment flow-chart for current recommendations).
- Optimal choice of antipsychotic therapy in people who also have diabetes, and the effects of switching antipsychotic medications in response to diabetes or its risk factors.
- Techniques to prevent the development of diabetes or to reduce its complications, and the outcomes of such activity.
- The risks of diabetes in other disorders treated with antipsychotic medications, including bipolar disorder, and in other types of mental illness such as depression.
- The epidemiology of acute diabetic crises such as ketoacidosis and relationships with antipsychotic treatment.
- The mechanism of any link between antipsychotic medication and diabetic ketoacidosis.
- The benefits of increased awareness among all health care professionals of the relationships between mental illness and physical illness.
- The health economics and outcomes associated with improved identification and treatment of diabetes in this population.
- The potential benefits of establishing minimum data sets at federal, state and local level to provide better outcomes data, and the development of key performance indicators.





The logo which appears on the Consensus Statement, Companion Document for Consumers and Carers and consumer/carer leaflet links the three documents together under a unified symbol. The tree symbolises growth and vitality where the canopy represents the ever changing knowledge of the intricacies of the brain. The trunk reveals two faces, one speaking the other listening. This illustrates the authors' hope that the sharing of this new information will increase attention on this important global issue.