

Australian Diabetes Society Position Statement:

The prevention and management of type 2 diabetes in the context of psychotic disorders

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Working Party recommendations

- All patients who have a serious mental illness should be routinely screened and monitored for evidence of diabetes and cardiometabolic disease by their general practitioner. In cases where a general practitioner is not available, the responsibility would be with the psychiatric team.
- At a minimum, the following should be measured at baseline and at regular intervals thereafter:
 - Height (at baseline), weight and waist circumference (3-6 monthly or if new antipsychotic initiated)
 - Blood pressure (3-6 monthly or if new antipsychotic initiated)
 - Blood glucose levels, preferably fasting (6 monthly or if new antipsychotic initiated)
 - HbA1c screening (annually for diagnosis of diabetes;), every 3 months as part of management of diabetes)
 - Serum lipids (12 monthly or more frequently if indicated, eg if antipsychotic initiated)
- Modifiable risk factors for diabetes and cardiovascular disease (e.g. smoking, hypertension, dyslipidaemia, lack of physical activity, poor diet and sleep disturbances) should be addressed. Relevant health care programmes should be utilised (e.g. fitness programmes that enable those with mental illness to access facilities at a modified cost and smoking cessation programmes). Ideally, there should be input from a dietitian and exercise physiologist.
- Appropriate medications for diabetes (hyperglycaemia) and co-morbidities such as hypertension and dyslipidaemia should be initiated where appropriate.
- Appropriate referrals should be organised as needed .eg. to a diabetes educator , dietitian, endocrinologist, cardiologist or for a sleep study where needed.
- Changing antipsychotic medications should only ever be undertaken in collaboration with the patient's psychiatrist. If the change is inappropriate, the switch may potentially increase the risk of an exacerbation of psychotic symptoms, particularly if the patient has previously been trialled on the medication.
- Integrated, collaborative, multidisciplinary care is recommended. Where this cannot be provided within a single clinic or centre, alternative referral pathways will need to be established (i.e. referrals to cardiologists, endocrinologists, diabetes clinics, diabetes educator, dietitians, exercise physiologists, etc.)
- Members of a patient's care team need to develop collaborative working relationships with appropriate communication and collaboration with the patient and his/her family.
- Educational resources allocated toward case manager and general practitioner empowerment are central to the appropriate management of patients.

Summary

Over a decade ago, an Australian Consensus Statement (1) concerning the prevention and management of diabetes in people with a psychotic illness emphasized the following points:

- Psychotic illness by itself and its treatment are associated with an increased risk of diabetes and worsening glycaemic control in those with pre-existing diabetes.
- The early detection and treatment of hyperglycaemia and other metabolic disorders among people who have a psychotic illness, as well as the institution of appropriate preventative measures, are key public health issues.
- All antipsychotic medications can contribute to the development of diabetes, although the newer, second-generation antipsychotic (SGA) medications ('atypical' antipsychotics) appear more likely to be associated with metabolic sequelae, particularly diabetes and weight gain, than first-generation antipsychotic (FGA) medications ('typical' antipsychotics).
- The effective management of a patient's psychosis should take priority over any concerns about the potential metabolic sequelae of pharmacotherapy. However, the risk of such sequelae means that the cardiometabolic health of any patient on antipsychotic medication should always be both routinely monitored and appropriately managed.
- Patients treated with antipsychotic agents need to undergo both baseline and ongoing regular metabolic assessments, including evaluations of body weight, blood glucose concentration, lipid levels and blood pressure.
- Hyperglycaemia and its potential complications need to be actively managed in individuals who are on antipsychotic therapy and have diabetes.
- Optimally managing patients who have psychotic illness requires a multidisciplinary approach with primary healthcare practitioners playing a central role if/when this is possible.

In this Position Paper, the following observations have been added.

- Despite the dissemination of national and international guidelines, recent Australian data continue to demonstrate a sobering disparity between the mean age of death for those with psychosis (mean age in men 45 years and for women 47 years) compared with the general population's male and female life expectancy of 79 and 84 years respectively, largely due to premature cardiovascular death (2). There has not been systematic uptake of screening for

diabetes and co-morbidities, management or referral to diabetes or metabolic services by those working in mental health (3). This is poignant in light of data highlighting the three times higher rate of diabetes in those suffering from a psychotic illness when compared with that in the general Australian population (4).

- The management of a patient's diabetes and physical health must go beyond basic screening. Management should include appropriate interpretation of results, the formulation of a management plan tailored to meet the needs of that particular individual and the establishment of a cycle of testing and review to ensure management and outcomes are optimised.
- Lifestyle factors and other potentially modifiable risk factors (smoking, dyslipidaemia, sleep disorders and hypertension) play a significant role and need to be addressed.
- Antipsychotic medications have traditionally been 'blamed' for the high prevalence of diabetes and metabolic disease among people who have a serious mental illness. The addition of antipsychotic agents will likely result in a deterioration in glycaemic and metabolic control where there is pre-existing diabetes. Patients will require intensification of monitoring, lifestyle advice and likely glucose lowering therapy. Where there is not pre-existing diabetes, weight gain and other factors will likely increase the risk of the development of diabetes.
- There are multiple potential barriers (patient, health professional and/or health system-based) to optimally managing the cardiometabolic health of individuals who have a psychotic illness.
- Ideally, people who have comorbid serious mental illness and diabetes should be managed by members of an integrated multidisciplinary care team, one that is able to effectively address both mental and physical healthcare issues.
- If integrated multidisciplinary care is not available, referral pathways should be established so that patients can be referred to appropriate health professionals in a timely manner.

1. Introduction and objectives

Interventions in type 2 diabetes aimed at achieving improved glycaemic control can decrease the rate of microvascular complications (5,6). Multifactorial interventions targetting blood pressure and lipid management can also significantly reduce such individuals' risk of cardiovascular disease and related events (7). The prevalence of diabetes among people who have a serious mental illness, particularly those with psychotic disorders, is significantly higher than that observed in the general population (1, 8–19) . These individuals' risk of developing diabetes or cardiometabolic related sequelae (e.g. heart disease and stroke) is often not adequately addressed (9,15).

More than two-thirds of patients with schizophrenia die of coronary heart disease, compared with approximately one third of individuals in the general population. The median all-cause standardised mortality ratio for people with schizophrenia compared to that in the general population rose from 1.84 in the 1970s to 3.20 in the 1990s (20, 21). The decline in the rates of cardiovascular mortality among the general population (i.e. over the past 20 or 30 years) has not been observed among people with serious mental illnesses (15, 20-30), suggesting that there has been a disparity in the level and/or quality of care aimed at maintaining or improving patients' cardiometabolic health and reducing their cardiovascular risk.

Australian data highlight this disparity. In a recent Australian study of mortality in schizophrenia, the mean age of death for men was 45 years and for women, 47 years, compared to the general population's male and female life expectancy of 79 and 84 years, respectively (2). In addition, in the second Australian National Survey of Psychosis, the adjusted mortality rate for those with psychosis for the period of the study (10 months) was 12.5 per 1000 persons, with a standardized mortality of 5.5 (4). Beyond the increased rates of suicide, consistent with international data, there was a major contribution to mortality by the dramatic increase in the rates of diabetes mellitus, obesity and early cardiovascular disease.

The higher prevalence of diabetes and the failure to adequately manage such individuals' cardiometabolic risk factors such as obesity, dyslipidaemia, hypertension and smoking may at least partly explain the 'mortality gap' between such individuals and those in the general population (15, 20-30). For example, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, 13% of study participants had diabetes (compared with 3% of age-matched controls), 68% of study participants smoked (compared with 35% of controls) and 27% had hypertension (compared with 17% of controls) (47).

Australian Consensus Guidelines regarding the prevention and management of diabetes in people

with psychotic disorders were published in 2004 (1). However, there has been little evidence of any improvement in the care of these patients. In 2012, 8 years after the publication of these guidelines, the National Mental Health Commission Report noted that patients with psychosis continued to have 3 times the rate of diabetes as compared to the general population, labelling the increase in physical morbidity and mortality as a “national disgrace” (4). A recent national survey of psychiatrists’ attitudes to physical health care, particularly related to screening for diabetes, obesity and the metabolic syndrome in patients with mental illness has revealed some awareness of the importance of physical health but no increase of or system of screening, interpretation of results or appropriate referral for management (3).

A working party, which was provided funding support from the National Diabetes Supply Scheme was therefore convened by the Australian Diabetes Society to suggest ways in which the overall cardiometabolic health, particularly diabetes and diabetes risk, of individuals who have a psychotic illness might be better monitored and further improved. The group which consisted of clinicians from several states who had an interest in the care of patients with psychosis, reviewed and considered the following broad issues. Literature referenced is not exhaustive as this paper is not a systematic literature review but rather a review of pertinent publications.

1. The reported rates of diabetes, cardiovascular disease and mortality among people with a serious mental illness, compared with those observed among the general population.
2. Previously published Australian Consensus Guidelines (1), regarding the prevention and management of diabetes in people with psychotic disorders, as well as other relevant clinical practice guidelines and consensus statements (including documents from Europe, North America and the United Kingdom).
3. The contributions of medications for serious mental illness, particularly antipsychotic medications, which might contribute to the increased prevalence of diabetes among people who have a serious mental illness.
4. Strategies for managing the physical health of patients who have a serious mental illness and current initiatives aimed at facilitating and further improving achieved outcomes in this regard.
5. Barriers to the optimal physical care of patients who have a serious mental illness, particularly with respect to their cardiometabolic health, and what might be done to help address or overcome such barriers.

This Position Statement summarises the working party's broad observations and conclusions. The purposes are essentially three-fold.

- a) To remind healthcare providers that patients with serious mental illness have an enhanced risk for diabetes and cardiovascular disease. This enhanced risk is not confined to the effects of antipsychotic medications, but also relates to the enhanced CV risk due to modifiable risk factors such as poor diet, reduced physical activity and smoking.
- b) To remind healthcare providers about the importance of not only effectively monitoring but also appropriately managing the physical health of individuals who have a serious mental illness, particularly with respect to their cardiometabolic health.
- c) To encourage the development and implementation of models of care that will further assist healthcare practitioners to optimally manage the physical health of patients who have a serious mental illness. Managing diabetes is complex and will involve a range of health practitioners who can provide appropriate education, promote changes in self-care behaviour and who can prescribe appropriate pharmacotherapy when required. Longer-term approaches to care need to be considered in this regard.
- d) Recommendations regarding appropriate screening for diabetes and cardiovascular disease in those with serious mental illness

2. The burden of diabetes among people with a serious mental illness

A comprehensive body of literature, including a growing number of published consensus statements and clinical practice guidelines, has indicated that individuals with serious mental illnesses, particularly psychotic disorders, are at substantially increased risk of developing diabetes (1, 8-16). Amongst such individuals, diabetes often remains either undiagnosed or sub-optimally managed. Other cardiometabolic risk factors are often poorly monitored or inadequately addressed (9,15,16).

The increased prevalence of diabetes in those with psychosis appears to be independent of any antipsychotic agents being used. Epidemiological studies have revealed that the prevalence of diabetes tends to be two- to three-fold higher amongst individuals with schizophrenia than it is amongst those in the general population (16). These also include but are not limited to the following studies. A study from Belgium (17) found that a significant proportion of patients with schizophrenia had diabetes at the time of their first episode of psychotic illness, with the prevalence of diabetes increasing to 16.5% among those with a long duration of illness (more than 20 years) and the prevalence of diabetes among 15 to 25-year olds with schizophrenia being five times higher than that observed in the general population. In a study from Singapore, the prevalence of previously diagnosed diabetes among drug-naïve patients with schizophrenia was 4.9%, but a further 16% and 30.9% of these individuals were diagnosed with diabetes and impaired glucose tolerance, respectively, following glucose tolerance tests (18). A recent Australian study demonstrated that

nearly one in every four patients with a mental illness had diabetes (mean age = 41 years) and that one-quarter of these patients had been diagnosed with diabetes only upon hospital admission for their mental illness (5).

3. Monitoring and detecting patients' risk of diabetes or diabetes-related complications

Position statements and guidelines have recognised the need for patients who have a serious mental illness to be regularly monitored for potential physical health issues e.g. diabetes and related sequelae and for any identified such problems to be managed appropriately (1, 10-13). Recommendations vary slightly, but emphasize the importance of monitoring anthropometric indices, such as body weight, height (BMI) and waist circumference, which are established risk factors for the development of Type 2 diabetes, as well as blood pressure, blood glucose and lipid levels (1). It should be emphasized that monitoring by itself, though, is insufficient. Findings need to be reviewed and interpreted with appropriate management and longer term follow up instigated.

Working Party recommendations

- All patients who have a serious mental illness should be routinely screened and monitored for evidence of diabetes and cardiometabolic disease.
- General practitioners may be best placed to coordinate this physical health care. However, a significant proportion of patients may not have a General Practitioner. In these cases, the responsibility would be with the psychiatric team.
- At a minimum, the following should be measured at baseline and at regular intervals thereafter
 - Height (at baseline), weight and waist circumference (at every visit for the latter two)
 - Blood pressure (at every visit)
 - Blood glucose levels- fasting preferably (6 monthly or more frequently if indicated)
 - HbA1c screening annually for diagnosis of diabetes, 3 monthly for management of diabetes
 - Serum lipids (6 to 12 monthly).
- Modifiable risk factors for diabetes and cardiovascular disease (e.g. smoking, hypertension, dyslipidaemia, lack of physical activity, poor diet, obstructive sleep apnoea) should be actively addressed. Relevant health care programmes should be utilised (e.g. fitness programmes that enable those with mental illness to access facilities at a modified cost and smoking cessation programmes). Ideally, there should be input from a dietitian and exercise physiologist. The health care programmes will vary by geographical area.
- Appropriate medications for diabetes (hyperglycaemia) and co-morbidities such as hypertension and dyslipidaemia should be initiated where appropriate.

- If possible, drugs for diabetes which will minimise weight gain are preferred. The options will be subject to PBS guidelines (see ADS 2016 guidelines and check PBS subsidy criteria).
- The institution of or a change to an antipsychotic agent will likely result in the need to intensify pharmacological therapy for diabetes.
- Appropriate referrals should be organised when necessary eg to a diabetes educator, dietitian, endocrinologist and cardiologist, and where obstructive sleep apnoea is suspected, a sleep physician.
- If available, a multidisciplinary team consisting of physicians, allied health and psychiatrists would be best equipped to conjointly manage the physical and mental health needs of the patient.

4. The Role of Antipsychotics

There is an increasing number of antipsychotic agents used in Australia. Second generation or atypical antipsychotics include clozapine, olanzapine, risperidone, paliperidone, quetiapine, amisulpride, aripiprazole, ziprasidone, asenapine and lurasidone in addition to depot preparations. These medications have a variety of metabolic effects and may cause hyperprolactinaemia. These effects will vary depending on the particular medication used and dosage. The potential role of antipsychotic medications as contributors to weight gain and the development of diabetes among people with psychotic disorders has been covered in the previous Australian Consensus Guidelines (1). Antipsychotic medications can have a significant adverse effect on patients' lipid profiles, blood glucose concentrations and fat metabolism. There are several potential mechanisms mediating these observed metabolic effects of antipsychotic medications (31–39). The mechanisms underlying the increases in appetite, weight gain and body fat that have been associated with the use of second-generation antipsychotic (SGA) medications ('atypical' antipsychotics) are yet to be fully elucidated, but may involve several different peptide, neurotransmitter and/or receptor systems in the appetite and reward systems in the brain.

Weight gain tends to occur most rapidly during the first few weeks to months of antipsychotic therapy (40-41). In one study, treatment-naïve patients demonstrated a weight gain of 8.5 kg within the first 10 weeks of olanzapine therapy (41). There is some heterogeneity between the available antipsychotic medications, with respect to their propensity to cause weight gain (42, 43). Ideally medications which are potentially more metabolically neutral would be preferred. Aripiprazole and ziprasidone seem to exert more 'metabolically neutral' effects, compared with drugs such as olanzapine and clozapine. It should be noted that clozapine is regarded as being the most effective antipsychotic medication and is used for treatment resistant schizophrenia. However, clozapine use is associated with both metabolic and cardiovascular derangements (eg hyperglycaemia, including rarely, precipitation of diabetic ketoacidosis

in addition to hyperlipidaemia and arrhythmias). The association between weight gain and drug treatment is not novel. Reports of an association between the use of antipsychotic medications and diabetes risk date back to the 1950s (44, 45).

Antipsychotics, mood stabilisers and antidepressants are often prescribed in combination, which may compound any metabolic derangements. Some of these agents, eg: valproate may be as orexigenic as olanzapine.

Multiple different factors (including genetic predisposition) are likely to contribute to the increased risk of diabetes and other cardiometabolic abnormalities that are not solely attributable to the use of antipsychotic therapy. (16, 47–56). For example, Holt and colleagues (49) have reported that, although typical and atypical antipsychotic medications are likely to play a significant role in the genesis of diabetes and obesity among people with psychotic illnesses, traditional modifiable cardiovascular risk factors – such as poor dietary habits and lack of physical activity – are also substantial contributors to the increased prevalence of diabetes in this population.

Working Party recommendations

- If/when feasible a switch to antipsychotic medication that is more metabolically neutral would be potentially beneficial.
- Changing antipsychotic medications should only ever be undertaken in collaboration with the patient's psychiatrist. If the change is inappropriate, the switch may potentially increase the risk of an exacerbation of psychotic symptoms.

5. Overcoming barriers to optimal management of patients' cardiometabolic health

There are multiple potential barriers to the adequate physical healthcare of individuals who have a serious mental illness, none of which should be insurmountable (57-75), and they are summarised below.

1. Barriers may be related to the person and their illness. These include poor adherence to treatment recommendations (58); poor awareness of existing physical health problems due to cognitive deficits related to mental illness and/or the use of antipsychotic medication (59,60). Other unique factors include homelessness or itinerancy, difficulty in communicating symptoms due to social deficits and/or stigma (63,64) and a general mistrust of having tests (58) or discussing problems (61,62). People with psychotic illnesses may avoid or neglect contacting general practitioners or general health care services (58). Physical symptoms may also be masked by the use of antipsychotic medications (60, 62).

2. Barriers related to the health professional include a lack of monitoring of patients and screening for diabetes by psychiatric services as frequently as recommended. There may be the belief that the diagnosis, prevention and/or management of diabetes and physical health problems are not the responsibility of psychiatric teams and should be undertaken by other healthcare professionals (62-66,67,68); Moving patients into community mental health care can place a burden on non-medical case managers to provide a range of services that they are not necessarily trained to deliver (69). Physical healthcare professionals may be reluctant to monitor and manage the cardiometabolic health of patients who have a serious mental illness, such as schizophrenia (70). Discrimination against those with mental illness, for example, due to stigma or a belief that those with mental illness may be difficult or dangerous to treat has consistently been reported (71–74)

Healthcare system-related impediments to the delivery of optimal physical healthcare (e.g. geographical, organisational and/or educational) (57,75) should also be considered. A lack of continuity of care between the initial treating doctor and community care teams can make it difficult for healthcare professionals to gain a clear or complete picture of a patient's medical history (59,62). Furthermore, financial barriers such as the cost of accessing services and medication expenses, particularly where there is polypharmacy may also cause more impediments (69,70).

Working Party's Recommendations

- Patient and illness-related factors should be considered when managing patients.
 - Poor / inadequate adherence to prescribed pharmacotherapy and recommended dietary / lifestyle recommendations
 - Unawareness of physical health problems due to cognitive deficits related to mental illness
 - A general mistrust of having tests or discussing problems
 - Difficulty in communicating symptoms (e.g. due to social deficits and/or stigma)
 - Avoidance or lack of contact with general practitioners or general health care services
- Barriers at the level of the healthcare professional should be addressed
 - Failure to adequately monitor cardiometabolic / cardiovascular risk factors
 - Confusion about who should be monitoring patient's physical health
 - Lack of requisite expertise / resources such as relevant patient management guidelines
 - Reluctance of some healthcare professionals (e.g. GPs, dietitians, etc.) to treat patients who have a serious mental illness
 - Stigmatisation / discrimination against those with serious mental illness (e.g. a belief that it will be 'too difficult' to effectively monitor or manage such patients' physical health)
- Barriers related to the healthcare system should also be considered in the management

- A lack of sufficiently well integrated/coordinated care between the initial treating doctor, community care teams and/or other healthcare professionals involved in a patient's care
- Geographical and/or organisational separations (e.g. between different health services)
- Financial barriers to care (e.g. cost of access to services and cost of medications)

6. Lifestyle intervention and the role of metformin

Patients with a psychotic illness frequently receive no formal advice regarding their diet or level of physical activity. Clear verbal and written information about how these factors might affect their risk of developing diabetes should be provided, Specific practical advice about how to go about making recommended changes should be provided. Structured, supervised, group-based educational sessions may be highly beneficial in this regard; for example, coordinated by an exercise physiologist, dietitian and/or other allied health professional.

Non-pharmacological interventions do have the potential to reduce the amount of weight gain associated with SGA treatment and other orexigenic psychotropic agents (76). Weight loss can be achieved with resource-intensive interventions, comprised of strict diets and intensive physical training among hospitalised patients (77) or during short treatment periods (≤ 12 weeks) (78). Although some studies have not shown any clear benefit of 'standard' lifestyle intervention (79) where only 7% of participants lost $> 5\%$ of their initial body weight with no effect of the intervention, others have shown clear benefits (80). In a study of patients admitted for psychiatric rehabilitation, 37.8% of those allocated to tailored weight management and group exercise had lost $> 5\%$ of their initial body weight at 18 months as compared to 22.7%. More recently, the results of the STRIDE study demonstrated benefits in terms of lipids, glucose, weight and Framingham Risk Scores with lifestyle intervention (81). Intervention participants lost 4.4 kg more than the control group over 6 months and 2.6 kg over 12 months. These studies may have their limitations including methods of randomisation, types of advice and intervention. However, the results indicate that despite barriers in adherence of the patients and the potential orexigenic effects of antipsychotic medications, these non pharmacological interventions can be as effective in this population as they are in the general population.

The efficacy of pharmacotherapy to attenuate antipsychotic induced weight gain has been investigated (78, 82-86), with metformin being the most studied to date. The results of various meta-analyses suggest that if a pharmacological agent is to be considered, that metformin is likely to be the most suitable agent for the prevention and treatment of weight gain associated with SGA medication (83-85). These results though also need to be interpreted with some caution (90). The

role of appropriate lifestyle interventions may account for at least some of the reported beneficial effect of metformin in this setting (88).

Studies indicating that metformin has no beneficial effect on patients' body weight have involved relatively older cohorts, with longer disease and treatment durations, while the more 'significant studies', that have suggested a beneficial effect from metformin, have involved younger individuals, with shorter histories of psychotic illness (86). A recent meta-analysis indicated that the beneficial effects of metformin appeared to be greatest in those with first episode psychosis (87). In an analysis of 40 studies, where pharmacotherapy was considered to attenuate weight gain, the most substantive evidence of benefit was with metformin usage (3.17kg weight difference as compared to placebo). Drugs such as topiramate and reboxetine have also been studied as weight loss agents in this setting but these carry the possibility of significant side effects and the potential for drug interactions.

Female patients who are prescribed metformin should be advised about the possibility of resumption of menstruation if periods have been irregular, and a potential increase in fertility (91,92). In Australia, metformin is neither TGA-registered nor listed on the Pharmaceutical Benefits Scheme for indications other than the treatment of diabetes. If metformin is to be considered for use, it should only be considered after consultation with a physician and after a detailed discussion with the patient regarding the indications, contraindications, precautions and cost (private script so not subsidised).

Overall, the potential value of lifestyle measures should not be underestimated, particularly in light of diabetes prevention studies (98-100) which have highlighted the benefits of physical activity and appropriate dietary modifications among those with impaired glucose tolerance.

7. Optimising patient care and follow up: Screening and going beyond screening

1. Screening

Monitoring and management of cardiometabolic health remains suboptimal (3, 6, 12, 66, 93, 94). A recent Australian study (9) revealed little evidence to suggest that community-treated individuals with persistent psychosis are uniformly receiving adequate physical health care, with respect to cardiometabolic risk factor management, despite the existence of relevant guidelines (1). A US survey revealed a broad disparity between clinicians' awareness of the need to monitor the metabolic health of patients who are on second-generation antipsychotic (SGA) therapy and the actual performance of such monitoring (66). 97% of participating psychiatrists indicated that they believed monitoring for cardiometabolic risk factors in this clinical setting was 'very serious' or 'serious'. However, 95% of SGA-treated patients did not have their

waist circumference measured, 60–65% did not have their blood glucose regularly checked. 70–75% did not undergo regular lipid monitoring. A retrospective, population-based study of Medicaid claims data in the USA has also revealed low rates of screening and monitoring, with respect to blood glucose and lipid concentrations, among patients initiated on SGA therapy (93). The publication of an American Diabetes Association consensus statement on antipsychotic drugs and diabetes similarly has not led to substantially increased rates of blood glucose and lipid testing among SGA-treated individuals in the USA (94). In Belgium a universal structured screening and monitoring protocol was introduced in 2003 (95).

In the United Kingdom, a quality improvement programme conducted among multidisciplinary community-based clinical mental health teams found that only 11% of patients were initially being screened for components of the metabolic syndrome. Encouragingly, this percentage had risen to 23% (0–48%) by the time participating outreach teams were re-audited (68). Programme interventions had included the distribution of local baseline data and an educational slide kit (i.e. to help 'local champions' disseminate the audit findings), a poster offering a guide to patient screening, and physical health check reminder cards for service users. Elsewhere in the United Kingdom, a coordinated health screening clinic was successfully established as part of a pilot programme designed to help monitor the physical health of people who have schizophrenia and better ensure adequate patient follow up (the clinic was set up using existing staff and resources, and without any specific additional funding); however, it is unclear whether screening continued beyond the pilot study or what interventions were sustained.(96).

2. Beyond Screening

It is also important to be able to properly interpret the results of screening and monitoring and appropriately manage any detected concerns or abnormalities. In Canada in a controlled in-patient environment, the introduction and use of a physical health monitoring sheet failed to improve patients' BMI, degree of central obesity, blood pressure or smoking status due to the absence of adequate resources to ensure that these abnormalities were managed with appropriate resources and by appropriately qualified health professionals. (97). These findings further highlight the need for appropriate resources and staffing to not only screen but also to ensure that abnormalities are detected, interpreted and managed.

3. Establishing appropriate referral pathways and models of care

Intervention studies (6,7,98–100) have demonstrated the potential benefits of initiating and maintaining appropriate preventative interventions such as pharmacotherapy, diet and lifestyle interventions. The results of several studies indicate that offering more assertive and integrated care may be a potentially more successful way to help meet the complex needs of patients who have a serious mental illness. In this model of care, patients with mental illness are both screened and managed by a physical healthcare practitioner (medical or nursing), usually within the same clinic that

the patients attend for their mental health appointments allowing a patient's physical health status to be both assessed and addressed when he/she presents for his/her mental health appointment. A multidisciplinary team approach at one site (ideally including physician, general practitioner, diabetes educator, dietitian and exercise physiologist) contributing to the initial and ongoing management of patients would be optimal but resources will vary. There are several examples of this approach in Australia (100-102).

Patients should be directed to the most appropriate healthcare professional – or group of health professionals when required. The optimal referral pathway(s) in each case will clearly vary from person to person and depend on many different factors, such as the patient's geographic location, the availability of local resources and, importantly, whether the person has a general practitioner who can help coordinate his/her care. Practical resources for those working in mental health have been developed which guide screening and management (103)

Summary of Working Party's recommendations regarding optimizing patient care and improving health outcomes

Managing the Individual/person with severe mental illness

Integrated, collaborative, multidisciplinary care is recommended:

- Where this cannot be achieved within a single clinic or centre, alternative referral pathways will need to be established (i.e. referrals to cardiologists, endocrinologists, diabetes clinics, diabetes educator, dietitians, exercise physiologists, etc.)
- Members of a person's care team need to develop collaborative working relationships with appropriate communication and collaboration with the person and his/her family
- The person's case manager and or general practitioner will be instrumental in coordinating the management of the patient. Therefore, educational resources allocated towards empowering case managers and general practitioners are central to management.

8. Summary

- The prevention, early detection and treatment of cardiometabolic diseases, such as diabetes, remain important public health issues in people with psychosis
- All individuals with psychotic disorders should be routinely screened for evidence of cardiometabolic disease (e.g. diabetes). Every effort should be made to implement appropriate preventative strategies and/or interventions.
- Diabetes and cardiometabolic abnormalities need to be appropriately managed and monitored and may require discussion with or referral to an appropriate healthcare professional (e.g. endocrinologist, diabetes educator, dietitian, exercise physiologist, etc.) or a group of healthcare professionals (e.g. a diabetes clinic)

9. Conclusions

The cardiometabolic health of our population living with a psychotic illness needs to be closely monitored and appropriately managed. The prevention and management of diabetes and diabetes-related sequelae can be both complex and time-consuming when dealing with people who are living with a serious mental illness, and there are many potential barriers to the optimal care of such individuals.

Management of people with severe mental illness in a multidisciplinary fashion, with mental and physical healthcare professionals collaborating in a genuinely integrated way, is likely to help address or overcome at least some of these barriers. Management would include appropriate referral and the establishment of referral pathways.

Bi-directional educational initiatives – aimed at both mental and physical healthcare professionals – are also likely to be beneficial in raising awareness of the poor physical health of people with severe mental illness.

The provision of appropriate funding and/or other incentives designed to help promote the development and implementation of integrated, multidisciplinary models of care for people who have a serious mental illness would potentially improve health outcomes.

References

1. Lambert TJR, Chapman L. Diabetes, psychotic disorders and antipsychotic therapy: A consensus statement. *Med J Aust* 2004; 181: 544–48.
2. O'Connor N, Hunt GE, O'Hara-Aarons M et al. The Sydney Mental Health Client Mortality Audit: what does it tell us and what are we to do? *Australasian Psychiatry* 2014;22(2):154-159.
3. Screening for the metabolic syndrome in Australia: a national survey of psychiatrists' attitudes and reported practice in patients prescribed antipsychotic drugs. *Australasian Psychiatry* 2016; 24(1):62-66.
4. National Mental Health Commission, 2012: A Contributing Life, the 2012 National Report Card on Mental Health and Suicide Prevention. Sydney: NMHC.
5. The Diabetes Control and Complications Trial Research Group (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–86.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.
7. Gæde P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. *N Engl J Med* 2003; 348: 383–93.
8. Dent E, Chen RCY, et al. High incidence of diabetes among Australians with severe mental illness. Abstract presented at the Australian Diabetes Society Annual Scientific Meeting, 2011.
9. Feiler G, Chen RCY, Pantelis C, Lambert TJR. Health behaviours of community-treated patients with psychosis. *Australasian Psychiatry* 2012; 20: 208–13.
10. De Hert M, Dekker JM, Wood D, et al. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009; 24: 412–24.
11. Woo V, Harris SB, Houlden RL. Canadian Diabetes Association Position Paper: Antipsychotic

medications and associated risks of weight gain and diabetes. *Canadian Journal of Diabetes* 2005; 29: 111–12.

12. American Diabetes Association. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 2004; 27: 596–601.

13. Expert Group. 'Schizophrenia and Diabetes 2003' Expert Consensus Meeting, Dublin, 3–4 October 2003: Consensus summary. *Br J Psychiatry* 2004; 184: s112–s114.

14. De Nayer A, De Hert M, et al. Conference report: Belgian consensus on metabolic problems associated with second-generation antipsychotics. *Int J Psychiatry Clin Pract* 2005; 9: 130–37.

15. Holt R. Cardiovascular disease and diabetes in people with severe mental illness: Causes, consequences and pragmatic management. *PCCJ Practice Review* (e-publication ahead of print; doi:10.3132/pccj.2011.085).

16. Holt RIG, Bushe C, Citrome L. Diabetes and schizophrenia 2005: Are we any closer to understanding the link? *J Psychopharmacol* 2005; 19: 56–65.

17. De Hert M, Van Winkel R, Van Eyck, et al. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: A cross-sectional study. *Clin Pract Epidemiol Ment Health* 2006; 2:14 (doi:10.1186/1745-0179-2-14).

18. Subramaniam M, Chong SA, Pek E. Diabetes mellitus and impaired glucose tolerance in patients with schizophrenia. *Can J Psychiatry* 2003; 48: 345–47.

19. McIntyre RS, Konarski JZ, Misener VL, et al. Bipolar disorder and diabetes mellitus: Epidemiology, etiology and treatment implications. *Ann Clin Psychiatry* 2005; 17: 83–93.

20. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005; 150: 1115–21.

21. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; 64: 1123–31.

22. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: Follow-up over 34–38 years. *J Affect Disord* 2002; 68: 167–81.

23. Brown AD, Barton DA, Lambert GW. Cardiovascular abnormalities in patients with major depressive disorder: Autonomic mechanisms and implications for treatment. *CNS Drugs* 2009; 23: 583–602.
24. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 1997; 171: 502–08.
25. Capasso RM, Lineberry TW, Bostwick JM, et al. Mortality in schizophrenia and schizoaffective disorder: An Olmsted County, Minnesota cohort: 1950–2005. *Schizophr Res* 2008; 98: 287–94.
26. Casey DE, Haupt DW, Newcomer JW, et al. Antipsychotic-induced weight gain and metabolic abnormalities: Implications for increased mortality in patients with schizophrenia. *J Clin Psychiatry* 2004; 65(Suppl 7): 4–18.
27. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 2006; 3: A42.
28. Laursen TM, Munk-Olsen T, Agerbo E, et al. Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* 2009; 66: 713–20.
29. Lawrence DM, Holman CD, Jablensky AV, Hobbs MS. Death rates from ischaemic heart disease in Western Australian psychiatric patients 1980-1998. *Br J Psychiatry* 2003; 182: 31–36.
30. Ösby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* 2000; 45: 21–28.
31. Roerig J, Steffen K, Mitchell J. Atypical antipsychotic-induced weight gain: Insights into mechanisms of action. *CNS Drugs* 2011; 25: 1035–59.
32. Kroeze W, Hufeisen S, et al. H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 2003; 28: 519–26.
33. Kim SF, et al. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA* 2007; 104: 3456–59.

34. Gautam SJ, Han FF, et al. A critical role for beta cell M3 muscarinic acetylcholine receptors in regulating insulin release and blood glucose homeostasis in vivo. *Cell Metab* 2006; 3: 449–61.
35. Starrenburg FC, Bogers JP. How can antipsychotics cause Diabetes Mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. *Eur Psychiatry* 2009; 24: 164–70.
36. Dwyer DS, Donohoe D. Induction of hyperglycemia in mice with atypical antipsychotic drugs that inhibit glucose uptake. *Pharmacol Biochem Behav* 2003; 75: 255–60.
37. Beck B. Neuropeptides and obesity. *Nutrition* 2000; 16: 916–23.
38. Fadel J, Bubser M, Deutch AY. Differential activation of orexin neurons by antipsychotic drugs associated with weight gain. *J Neurosci* 2002; 22: 6742–46.
39. Wang Q, Huang XF. Effects of chronic treatment of olanzapine and haloperidol on peptide YY binding densities in the rat brain. *Exp Neurol* 2008; 209: 261–67.
40. Tarricone I, Ferrari Gozzi B, Serretti A, et al. Weight gain in antipsychotic-naïve patients: A review and meta-analysis. *Psychological Med* 2010; 40: 187–200.
41. Fraquas D, Correll C, et al. Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: Comprehensive review of prospective head-to-head and placebo-controlled comparisons. *European Neuropsychopharmacology* 2011; 21: 621–45.
42. Correll CU, Manu P, Olshanskiy V, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009; 302: 1765–73.
43. Volavka J, Czobor P, et al. EUFEST Study Group. Efficacy of antipsychotic drugs against hostility in the European First-Episode Schizophrenia Trial (EUFEST). *J Clin Psychiatry* 2011; 72: 955–61.
44. Hiles BW. Hyperglycemia and glycosuria following chlorpromazine therapy. *JAMA* 1956; 162: 1651.

45. Norman D, Hiestrand WA. Glycemic effects of chlorpromazine in the mouse, hamster, and rat. *Proc Sac Exp Biol Med* 1955; 90: 89–91.
46. Smith M, Hopkins D, Peveler, et al. First-versus second generation antipsychotics and risk for diabetes in schizophrenia: Systematic review and meta-analysis. *Br J Psychiatry* 2008; 192: 406–11.
47. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial; Prospective data from phase 1. *Schizophr Res* 2008; 101; 273–86.
48. Osborn DP, Levy G, Nazareth I, et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psych* 2007; 64: 242–49.
49. Holt RIG, Peveler RC. Association between antipsychotic drugs and diabetes. *Diabetes Obes Metab* 2006; 8: 125–35.
50. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naïve patients with schizophrenia. *Am J Psych* 2003; 160: 284–89.
51. Thakore JH, Mann JN, Vlahos I, et al. Increased visceral fat distribution in drug-naïve and drug-free patients with schizophrenia. *Int J Obes* 2002; 26: 137–41.
52. Ryan MCM, Flanagan S, Kinsella U, et al. Atypical antipsychotics and visceral fat distribution in first episode, drug-naïve patients with schizophrenia. *Life Sciences* 2004; 74: 1999–2008.
53. Lamberti J, Crilly J, Maharaj K. Prevalence of adult-onset diabetes among outpatients receiving anti-psychotic drugs. *Schizophr Res* 2003; 60(Suppl): S360.
54. Jones P. The early origins of schizophrenia. *Br Med Bull* 1997; 53: 135–55.
55. Dinan TG. Stress and the genesis of diabetes mellitus in schizophrenia. *Br J Psychiatry Suppl* 2004; 47: S72–S75.
56. Robillard R, Rogers NL, Whitwell B, Lambert T. Are cardiometabolic and endocrine

abnormalities linked to sleep difficulties in schizophrenia? A hypothesis driven review. *Clinical Psychopharmacology and Neuroscience* 2012; 10: 1–12.

57. Lambert TJR, Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care. *Med J Aust* 2009; 190: S39–S42.

58. Brown S, Inskip H, Barracough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000; 177: 212–17.

59. Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry* 1999; 60: 10–15.

60. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Medical comorbidity in schizophrenia. *Schizophr Bull* 1996; 22: 413–30.

61. Druss BG. Improving medical care for persons with serious mental illness: challenges and solutions. *J Clin Psychiatry* 2007; 34: 363–75.

62. Anath J. Physical illness and psychiatry disorders. *Compr Psychiatry* 1984; 25: 586–93.

63. Phelan M, Stradins L, Morrison S. Physical health of people with severe mental illness. *BMJ* 2001; 322: 443–44.

64. Kim MM, Swanson JW, Schwartz MS, et al. Healthcare barriers among severely mentally ill homeless adults: Evidence from the five-site health and risk study. *Adm Policy Ment Health* 2007; 34: 363–75.

65. Lai DW, Chau SB. Effects of service barriers on health status of older Chinese immigrants in Canada. *Soc Work* 2007; 52: 261–69.

66. Buckley PF, Miller DD, Singer B, et al. Clinicians' recognition of the metabolic adverse effects of antipsychotic medications. *Schizophr Res* 2005; 79: 281–88.

67. Barnes TR, Paton C, Cavanagh MR, et al. A UK audit of screening for the metabolic side effects of antipsychotics in community patients. *Schizophr Bull* 2007; 33: 1397–1403.

68. Barnes TR, Paton C, Hancock E, et al. UK Prescribing Observatory for Mental Health. Screening for the metabolic syndrome in community psychiatric patients prescribed antipsychotics:

A quality improvement programme. *Acta Psychiatr Scand* 2008; 118: 26–33.

69. Sernyak MJ. Implementation of monitoring and management guidelines for second-generation antipsychotics. *J Clin Psychiatry* 2007; 68 (Suppl 4): 14–18.

70. Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry* 1999; 60: 10–15.

71. Abbey S, Charbonneau M, et al. Stigma and discrimination: Position paper. *Can J Psych* 2011; 56(10 insert): 1–10.

72. Thornicroft G, Rose D, Kassam A. Discrimination in health care against people with mental illness. *Int Rev of Psych* 2007; 19: 113–22.

73. Gateshill G, Kucharska-Pietura. Attitudes towards mental disorders and emotional empathy in mental health and other healthcare professionals. *The Psychiatrist* 2011; 35: 101–105.

74. Minas H, Zamzam R, et al. Attitudes of Malaysian general hospital workers towards mental illness and diabetes. *BMC Public Health* 2011; 11: 317.

75. Hovitz-Lennon M, Kilbourne AM, Pincus HA. From silos to bridges: Meeting the general health care needs of adults with severe mental illness. *Health Aff (Millwood)* 2006; 25: 659–69.

76. Gabriele, JM, Dubbert PM, Reeves RR. Efficacy of behavioural interventions in managing atypical antipsychotic weight gain. *Obes Rev* 2009; 10: 442–55.

77. Centorrino F, Wurtman JJ, Duca KA, et al. Weight loss in overweight patients maintained on atypical antipsychotic agents. *Int J Obes (Lond)* 2006; 30: 1011–16.

78. Wu RR, Zhao JP, Jin H, et al. Lifestyle intervention and metformin for treatment for antipsychotic-induced weight gain: A randomized controlled trial. *JAMA* 2008; 299: 185–93.

79. Goldberg RW, Dickinson F, Lucksted A et al Living Well: An Intervention to Improve Self-Management of Medical Illness for Individuals With Serious Mental Illness. *Psychiatric Services* 2013;64:51-57

80. Daumit GL, Dickerson FB, Wang N et al. A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness. *N Engl J Med* 2013; 368:1594-1602

81. Green, CA, Yarborough BJ, Leo MC et al. The STRIDE weight loss and lifestyle intervention for

individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry* 2015; 172 (1) 71-81

82. Lykkegaard K, Larsen PJ, Vrang N, et al. The once-daily human GLP-1 analog, liraglutide, reduces olanzapine-induced weight gain and glucose intolerance. *Schizophr Res* 2008; 103: 94–103.

83. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate anti-psychotic related weight gain and metabolic abnormalities: A systematic review and meta-analysis. *Neuropsychopharmacology* 2010; 35: 1520–30.

84. Ehret M, Goethe J, Lanosa M, Coleman CI. The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: A meta-analysis. *J Clin Psychiatry* 2010; 71: 1286–92.

85. Bjorkhem-Bergman L, Lacruz A, Rangel N, et al. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: A systematic review and meta-analysis. *Psychopharmacol* 2010; 25: 299–305.

86. Newall, H, Myles N, Ward P, et al. Efficacy of metformin for prevention of weight gain in psychiatric populations: a review. *International Clinical Psychopharmacology* 2012; 27: 69–75.

87. Mizuno, Y, Suzuki T, Nacagawa A et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophrenia Bulletin* 2014;40:1385-1403

88. Alvarez-Jimenez M, Hetrick S, Gonzalez-Blanch C, et al. Non-pharmacological management of antipsychotic-induced weight gain: Systematic review and meta-analysis of randomized controlled trials. *Br J Psych* 2008; 193: 101–07.

89. Strack T. Metformin: A review. *Drugs Today (Barc)* 2008; 44: 303–14.

90. Scheen AJ. Drug interactions of clinical importance with antihyperglycaemic agents: An update. *Drug Safety* 2005; 28: 601–31.

91. Howlett HC, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Safety* 1999; 20: 489–503.

92. Wu RR, Jin H, Gao K, et al. Metformin for treatment of antipsychotic-induced amenorrhea and weight gain in women with first-episode schizophrenia: A double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 2012; 169: 813–21.
93. Morrato EH, Newcomer JW, Allen RR, Valuck RJ. Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs: A retrospective, population-based study of Medicaid claims data. *J Clin Psychiatry* 2008; 69: 316–22.
94. Morrato EH, Newcomer JW, Kamat S, et al. Metabolic screening after the American Diabetes Association's Consensus Statement on antipsychotic drugs and diabetes. *Diabetes Care* 2009; 32: 1036–42.
95. De Hert M, van Winkel R, et al. Physical health management in psychiatric settings. *Eur Psychiatry* 2010; 25 (Suppl 2): S22–28.
96. Millar HL. Development of a health screening clinic. *Eur Psychiatry* 2010; 25 (Suppl 2): S29–33.
97. Vasudev K, Thakkar PB, Mitcheson N. Physical health of patients with severe mental illness: an intervention on medium secure forensic unit. *Int J Health Care Qual Assur* 2012; 25: 363–70.
98. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes by changes in lifestyle in subjects with impaired glucose tolerance. *N Eng J Med* 2001; 344: 1343–50.
99. Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *N Engl J Med* 2002; 346: 393–403.
100. Pan X, Li G, Hu Y, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; 20: 537–44.
101. Kritharides L, Chow V and Lambert T. Cardiovascular disease in patients with schizophrenia. *Med J Aust* 2017; 206 (2): 91-95.
102. Samaras K; Correll CU; Curtis J, 2016, 'Premature mortality and schizophrenia - The need to heal right from the start', *JAMA Psychiatry*, vol. 73, pp. 535 – 536.

103. Curtis J; Newall H; Samaras K, 2011. <http://www.heti.nsw.gov.au/Global/HETI-Resources/psychiatry/Psychiatry%20Positive%20Cardio%20Metabolic%20Algorithm%202011.pdf>