Efficacy of metformin for prevention of weight gain in psychiatric populations: a review

Hannah Newall[a], Nicholas Myles[a], Philip B. Ward[b], Katherine Samaras[c,d], David Shiers[f] and Jackie Curtis[b,e]

There is uncertainty with regard to the appropriate use of metformin for the prevention and management of second-generation antipsychotic-induced weight gain and metabolic abnormalities. We aim to systematically review the primary literature and to provide recommendations with regard to the use of metformin in psychiatric populations prescribed second-generation antipsychotics. The authors undertook a literature search of Medline, EMBASE, and PsycINFO using the search terms; antipsychotic OR atypical antipsychotic AND weight AND metformin. Narrative review was undertaken without additional statistical analysis. The search provided 198 results from which 10 original research papers were identified: six randomized controlled trials and one open-label study for adults and two randomized controlled trials and one open-label study for children and adolescents. Four meta-analyses were also identified. We concluded that if weight gain occurs after second-generation antipsychotic initiation, despite lifestyle intervention, metformin should be considered. Further studies with adequate statistical power are required to determine the efficacy of metformin in those with chronic psychotic illness. *Int Clin Psychopharmacol* 27:69–75 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

International Clinical Psychopharmacology 2012, **27**:69–75

Keywords: antipsychotic, first-episode psychosis, metformin, weight gain

[a]Faculty of Medicine, [b]School of Psychiatry, University of New South Wales, [c]Department of Endocrinology, St Vincent's Hospital, [d]Diabetes and Obesity Program Garvan Institute of Medical Research, [e]Early Psychosis Programme, Eastern Suburbs Mental Health Programme, Sydney, Australia and [f]GP (retired) North Staffordshire and former joint lead on National Early Intervention in Psychosis Programme, UK

Correspondence Dr Jackie Curtis, MBBS, 26 Llandaff St, Bondi Junction, NSW 2022, Australia
Tel: +44 612 9366 8611; fax: +44 612 9387 1070;
e-mail: j.curtis@unsw.edu.au

Received 6 June 2011 **Accepted** 12 September 2011

Introduction

Increasing use of second-generation antipsychotics (SGA) in major psychiatric illness has shifted clinical concern from extrapyramidal side effects to other health consequences, namely weight-gain and adverse cardiometabolic risk. SGA medications, particularly clozapine and olanzapine and to a lesser extent quetiapine and risperidone, are associated with weight gain, disrupted glucose metabolism, and abnormal lipid profile (Stahl *et al.*, 2009); changes that occur early in the course of the treatment (Tarricone *et al.*, 2010). The 20% discrepancy in life expectancy in people who suffer psychotic illness compared with the general population is overwhelmingly due to higher rates of cardiovascular diseases (Hennekens *et al.*, 2005). Furthermore, risk may be compounded by genetic predisposition, illness-associated sedentary lifestyle (Pramyothin and Khaodhiar, 2010), and high rates of tobacco smoking (De Leon and Diaz, 2005).

The underlying mechanism of metabolic dysregulation is poorly understood. Although causation is presumably complex and multifactorial, weight gain after the initiation of SGA medication appears to be the factor promoting the majority of cardiovascular risk (Foley and Morley, 2011). There is evidence that the antipsychotic binding affinity for specific receptor subtypes, primarily H_1 and 5-HT_{2C} (Kroeze *et al.*, 2003; De Luca *et al.*, 2007), correlates with degree of weight gain. 5-HT_{2C} receptor antagonism may downregulate leptin-mediated appetite suppression and satiety signalling from the gut, whereas H_1 antagonism is known to cause mild sedation that may promote physical inactivity (Reynolds and Kirk, 2010).

The multifactorial nature of SGA-induced weight gain makes development of pharmaceuticals to counterpoise adverse cardiometabolic parameters problematic. Potential agents are limited to nonspecific pharmaceuticals known to have weight loss effects in nonpsychiatric populations. Although there is a paucity of comparative literature, a recent meta-analysis has shown metformin to have the greatest impact on SGA-induced weight gain (Maayan *et al.*, 2010).

Metformin is an oral antihyperglycaemic agent used primarily for the treatment of type 2 diabetes mellitus. Metformin is recognized as a weight neutral agent in patients suffering from type 2 diabetes and may also have weight-attenuating properties in obese adolescents (Rezvanian *et al.*, 2010) and patients suffering from polycystic ovarian syndrome (Katsiki *et al.*, 2009). Its mechanism of action involves suppression of hepatic gluconeogenesis, stimulation of glucose uptake by skeletal muscle (Wiernsperger and Bailey, 1999), and augmentation of insulin activity by strengthening adenosine monophosphate kinase signalling (Kim *et al.*, 2011).

0268-1315 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/YIC.0b013e32834d0a5b

This study aims to undertake a systematic review to identify all available clinical studies, in both pediatric and adult populations, in which metformin has been investigated as a therapy for the prevention or attenuation of weight gain or improvement of metabolic parameters in psychiatric populations treated with SGA medications.

Methods

Online literature search of Medline 1966 to April 2011, EMBASE 1988 to April 2011, and PsycINFO 1967 to April 2011 was undertaken using the search terms; antipsychotic OR atypical antipsychotic AND weight AND metformin, which yielded 198 results. The search was limited to English language publications. The title and abstract of 79 original research and meta-analytical articles were reviewed resulting in the identification of 10 suitable original research papers: six randomized controlled trials (RCTs) and one open-label study conducted in adults, and two RCTs and one open-label study conducted in children and adolescents. One open-label study (Baptista *et al.*, 2001) was excluded because of a small sample size (five patients). One RCT was excluded due to lack of information on weight-associated outcomes (Baptista *et al.*, 2007b) and another (Fernandez *et al.*, 2010) because the study shared a cohort previously reported in another RCT (Carrizo *et al.*, 2009). Four meta-analyses (Bjorkhem-Bergman *et al.*, 2010; Ehret *et al.*, 2010; Maayan *et al.*, 2010; Praharaj *et al.*, 2011) were identified.

Ten studies and four meta-analyses included in this review are summarized in Tables 1 and 2. Statistical data from the source material are reported, no additional statistical analysis was performed.

Results

In all but one study, metformin was the only active pharmaceutical intervention. One study (Baptista *et al.*, 2008) investigated the efficacy of metformin combined with sibutramine (a medication since withdrawn), compared with controls receiving metformin with placebo. Wu *et al.* (2008b) was the only study group to compare metformin, lifestyle intervention, and a combination of both to placebo. Two studies (Arman *et al.*, 2008; Wu *et al.*, 2008a) investigated treatment-naïve first-episode psychosis (FEP), whereas the remainder of studies investigated patients receiving SGAs for between 3 months and 30 years. Dosing of metformin varied between 500 and 3400 mg daily in divided doses. All but one RCT (Wu *et al.*, 2008b) did not control for lifestyle or dietary interventions; two of the RCTs (Arman *et al.*, 2008; Baptista *et al.*, 2008) did not specify any lifestyle or dietary interventions. The remaining RCTs provided varied dietary and exercise advice to both metformin and placebo groups.

The primary outcomes in various studies included:

(1) Body weight (BW), body mass index (BMI), fasting blood sugar levels (BSL), insulin resistance, and lipid profile (Baptista *et al.*, 2006, 2007a, 2008; Chen *et al.*, 2008; Carrizo *et al.*, 2009).
(2) BW, BMI, and BSL (Klein *et al.*, 2006; Arman *et al.*, 2008; Wu *et al.*, 2008a, 2008b).
(3) BW and BMI (Morrison *et al.*, 2002).

Schizophrenia was the primary diagnosis in the majority of studies with a minority diagnosed with bipolar, schizoaffective, and pediatric behavioural disorders.

Studies conducted in adult populations with established illness (Table 1)

Carrizo *et al.* (2009) assessed metformin in 61 clozapine-treated patients, with a mean duration of treatment of 86.5 months and a mean age of 38.9 years. Metformin showed a statistically significant effect on BW and BMI compared with placebo. Metformin had no significant effect on fasting BSL compared with placebo; however, there was a slight reduction in fasting insulin and HbA1c in the metformin group compared with placebo. High-density lipoprotein increased in the metformin group compared with placebo, with no significant changes in other lipid parameters.

Baptista *et al.* (2007a) assessed the utility of metformin in 80 patients with schizophrenia with a mean duration of treatment 6.7 months and mean age of 44.5 years. This study found no differences in weight, glucose, or lipid outcomes between the metformin and placebo groups.

A subsequent study conducted by Baptista *et al.* (2008) compared metformin with coadministered sibutramine to metformin with placebo. This study found significant decrease in waist circumference, fasting BSL, fasting insulin, low-density lipoprotein, and total cholesterol in the metformin and placebo groups at study conclusion compared with the baseline. However, this study lacked a double-placebo group and therefore cannot be considered a true RCT of metformin alone.

A third study conducted by Baptista *et al.* (2006) in 40 patients with schizophrenia with a mean age of 47.7 years, investigated the efficacy of metformin in patients newly commenced on olanzapine. This is the only study investigating metformin for prevention of weight gain in chronic populations, newly commenced on SGA medication. Although this RCT showed no significant differences between placebo and metformin groups, there was a reduction in BSL, serum insulin, triglycerides, and insulin independent of weight loss in the metformin group alone.

Wu *et al.* (2008b) performed the only RCT, which provided a group that controlled for lifestyle intervention. Patients ($n = 128$) with a diagnosis of first-episode psychosis with a mean age of 26.3 years who had gained greater than 10% of BW within 12 months after commencing treatment with clozapine, olanzapine, risperidone, or sulpiride were randomized to receive either

Table 1 Comparison of adult studies assessing impact of metformin on weight, glucose and lipid-related parameters

Study and ethnicity	Treatment length	Intervention/ demographic	Nonpharmacological intervention	Outcomes	Significant outcomes in metformin group compared with placebo at study end
Carrizo *et al.* (2009) Hispanic	14 weeks RCT	31 patients CLZ+MET 30 patients CLZ+PBO CLZ treatment >3 months Schizophrenia	Informal dietary and exercise advice given to both groups	BW, BMI, WC BSL, insulin, HbA1c, HOMA-IR HDL, non-HDL, triglycerides	Weight-related 2.03 kg reduction in BW 0.73 reduction in BMI Glucose-related 2.9 μIU/ml reduction in insulin O.1 reduction in HbA1c Lipid-related 5.6 mg/dl increase in HDL
Wu *et al.* (2008a) Chinese	12 weeks RCT	20 patients OLZ+MET 20 patients OLZ+PBO Treatment naïve FEP inpatients	Calorie controlled diet (7980–9250 kJ/day) Moderate exercise (30 min/day)	BW, BMI, WC, WHR BSL, insulin, IRI	Weight-related 4.97 kg reduction in BW 1.72 reduction in BMI Glucose related 5.97 μIU/ml reduction in insulin 1.27 reduction in IRI
Wu *et al.* (2008b) Chinese	12 weeks RCT	32 patients SGA+MET 32 patients SGA+MET+LSI 32 patients SGA+LSI+PBO 32 patients SGA+PBO FEP patients gaining >10% BW within a year of commencing treatment with either CLZ, OLZ, RISP, SLP	Psychoeducational program. AHA step 2 diet. 30 min of moderate exercise per day. Controlled across groups	BW, BMI, WC BSL, insulin, IRI	Weight-related 7.8 kg reduction in BW (LSI+MET) 6.3 kg reduction in BW (MET) 4.5 kg reduction in BW (LSI) 3.0 reduction in BMI (LSI+MET) 2.4 reduction in BMI (MET) 1.7 reduction in BMI (LSI) 4.2 cm reduction in WC (LSI+MET) 3.5 cm reduction in WC (MET) 2.1 cm reduction in WC (LSI) Glucose-related 9.0 mg/dl reduction in BSL (LSI+MET) 12.6 mg/dl reduction in BSL (MET) 9.0 mg/dl reduction in BSL (LSI) 16.0 μIU/ml reduction in insulin (LSI+MET) 14.8 μIU/ml reduction in insulin (MET) 4.8 μIU/ml reduction in insulin (LSI) 4.0 reduction in IRI (LSI+MET) 3.9 reduction in IRI (MET) 1.4 reduction in IRI (LSI)
Baptista *et al.* (2008) Hispanic	12 weeks RCT	13 patients OLZ+MET+SIB 15 patients OLZ+MET+PBO Schizophrenia patients with >10 year exposure to SGA Commenced on OLZ for >4 months	Non-specific physical activity and healthy diet according to inpatient standards	BW, BMI, WC BSL, insulin, HbA1c, HOMA-IR Total cholesterol, LDL, HDL, triglycerides	Nil between group differences
Baptista *et al.* (2007a) Hispanic	12 weeks RCT	40 OLZ+MET 40 OLZ+PBO Bipolar and schizophrenia patients with >4 month exposure to OLZ	Diet and physical activity recommendations	BW, BMI, WC BSL, insulin, HbA1c, HOMA-IR Total cholesterol, triglycerides, HDL, LDL	Nil between group differences
Baptista *et al.* (2006) Hispanic	14 weeks RCT	20 OLZ+MET 20 OLZ +PBO Schizophrenia and schizoaffective patients with >10 year exposure to long acting injectable FGA, OLZ added as oral	Diet between 2500–3000 calories provided	BW, BMI, WC BSL, insulin, HOMA-IR Total cholesterol, triglycerides, LDL, HDL	Nil between group differences
Chen *et al.* (2008) Taiwanese	8 weeks Open label	24 OLZ+MET Schizophrenia patients with >3 month exposure to OLZ	Controlled diet 25–35 calories per kg	BW, BMI BSL, insulin, HOMA-IR Triglycerides, total cholesterol, LDL, HDL	Weight related 2.2 kg reduction in BW 0.9 reduction in BMI Glucose related 3.9 μIU/ml reduction in insulin 1.6 reduction in HOMA-IR Lipid related 38.1 mg/dl reduction in triglycerides

BSL, fasting blood sugar level; BW, body weight; CLZ, clozapine; FEP, first-episode psychosis; HbA1c, glycosylated hemoglobin; HDL, fasting high-density lipoprotein; HOMA-IR, homeostatic method of assessment – insulin resistance; IRI, insulin resistance index; LDL, fasting low-density lipoprotein; LSI, lifestyle intervention; MET, metformin; OGTT, oral glucose tolerance test; OLZ, olanzapine; PBO, placebo; RCT, randomized controlled trials; RISP, risperidone; SGA, second-generation antipsychotic; SLP, sulpiride; WC, waist circumference; WHR, waist-to-hip ratio.

Table 2 Comparison of child and adolescent studies assessing the impact of metformin on weight and glucose-related parameters

Study and ethnicity	Treatment length	Intervention/demographic	Nonpharmacological intervention	Outcomes assessed	Significant outcomes at study conclusion
Arman *et al.* (2008) Saudia Arabian	12 weeks RCT	49 FEP treatment-naive patients randomized to either RIS+MET RIS+PBO	None reported	BW, BMI BSL	Nil difference between groups
Klein *et al.* (2006) USA	16 weeks RCT	18 patients SGA+MET 20 patients SGA+PBO Patients with various diagnoses who had gained >10% baseline weight in <12 months of treatment with unspecified SGA	Nutritional counselling, individualized goals provided for patients	BW, BMI, WC BSL, insulin, HOMA-IR	Weight related (age corrected) 4.08 kg reduction in BW 1.12 reduction in BMI 4.65 cm reduction in WC
Morrison *et al.* (2002) USA	12 weeks Open label	19 patients SGA+MET Patients with various diagnoses who had gained >10% baseline weight in <12 months of treatment with unspecified SGA	None specified	BW, BMI	Weight related 2.93 kg reduction in BW 2.22 reduction in BMI

BSL, fasting blood sugar level; BW, body weight; HOMA-IR, homeostasis method of assessment – insulin resistance; MET, metformin; PBO, placebo; RCT, randomized controlled trials; RIS, risperidone; SGA, second-generation antipsychotic.

metformin with lifestyle intervention, metformin alone, lifestyle intervention alone, or placebo. There was significant improvement in BW, BMI, waist circumference, BSL, serum insulin, and insulin resistance index in all intervention groups compared with placebo. Metformin with lifestyle intervention had significantly better outcomes than metformin or lifestyle intervention alone.

Chen *et al.* (2008) conducted an open-label study in 24 patients with schizophrenia treated with olanzapine for a mean of 5.7 months and mean age of 40.3 years. Metformin was shown to have a significant impact on BW, BMI, BSL, serum insulin, homeostatic method of assessment – insulin resistance, and triglycerides compared with baseline.

Studies conducted in pediatric and adolescent populations (Table 2)

Klein *et al.* (2006) investigated the utility of metformin in 39 pediatric patients with a mean age of 13.1 years who had gained more than 10% of their pretreatment weight within 12 months of commencing either olanzapine, risperidone, or quetiapine. As the study was conducted in growing children, age-corrected changes in the standard deviation of weight and BMI were used. Metformin was shown to have a significant impact on reducing BW, BMI, and waist circumference compared with placebo.

Morrison *et al.* (2002) performed an open-label study in 19 patients with a mean age of 14 years who had gained more than 10% of their pretreatment weight after commencing treatment with olanzapine, risperidone, quetiapine, or valproate. Metformin was shown to have a significant impact on reducing BW and BMI compared with placebo.

Studies conducted in first-episode psychosis or drug-naïve populations

Arman *et al.* (2008) conducted a RCT to determine the impact of metformin on 49 pediatric patients with FEP recently commenced on risperidone. Patients had a mean age of 11.3 years. There were no significant differences in weight or glucose related parameters between metformin and placebo groups.

Wu *et al.* (2008a) conducted a RCT of 40 FEP to determine the impact of metformin in patients newly commenced on olanzapine. Patients had a mean age of 25 years and normal BMI (range: 18.5–23.9) at study beginning. Although BW and BMI increased in both groups, there was significant attenuation of these parameters in the metformin group compared with placebo. Those patients receiving metformin had a significant reduction in serum insulin and insulin resistance index compared with placebo.

Meta-analysis (Table 3)

Two meta-analyses (Ehret *et al.*, 2010; Maayan *et al.*, 2010) that included studies examining various SGA medications showed a significant reduction in BW, BMI, and waist circumference in the metformin group compared with placebo. There was a significant reduction in serum insulin and triglycerides in one meta-analysis (Maayan *et al.*, 2010) and a reduction in homeostatic method of assessment – insulin resistance in the other (Ehret *et al.*, 2010). Heterogeneity in outcome was very high across all analyses.

One meta-analysis (Praharaj *et al.*, 2011) included studies in which olanzapine was the only treatment. This study showed a greater absolute BW reduction than reported in other meta-analyses. Heterogeneity was insignificant.

One meta-analysis (Bjorkhem-Bergman *et al.*, 2010) reported weight reduction as a percentage of pretreatment weight. Proportional reduction was significant in the metformin group compared with placebo, heterogeneity was very high. On sub group analysis weight loss was greater in those patients who had gained greater than 10% of their pretreatment weight after commencing SGA therapy.

Table 3 Comparison of meta-analyses evaluating metformin for weight loss in patients treated with second-generation antipsychotics

Study	Samples included	Inclusion criteria	Significant pooled outcomes (metformin to placebo)
Maayan *et al.* (2010)	Eight RCTs (Baptista *et al.*, 2006, 2007a, 2008; Klein *et al.*, 2006; Arman *et al.*, 2008; Wu *et al.*, 2008a, 2008b; Carrizo *et al.*, 2009)	Meta-analysis of all potential pharmacotherpaies for weight loss in patients receiving SGA Pediatric and adult studies pooled Any SGA	2.94 kg reduction in BW (I^2=91%) 2.26 cm reduction in WC 7.22 μIU/ml reduction in insulin 28.07 mg/dl reduction in triglycerides Changes in HDL, LDL, HOMA-IR, and fasting BSL not significant
Ehret *et al.* (2010)	Six RCTs (Baptista *et al.*, 2006, 2007a; Klein *et al.*, 2006; Arman *et al.*, 2008; Wu *et al.*, 2008a, 2008b)	Meta-analysis of metformin's impact on BW, BMI, WC, and HOMA-IR compared with placebo Pediatric and adult studies pooled Any SGA	3.16 kg reduction in BW (I^2=84%) 1.21 reduction in BMI 1.99 cm reduction in WC 1.71 reduction in HOMA-IR
Praharaj *et al.* (2011)	Four RCTs (Baptista *et al.*, 2006, 2007a, 2007b; Wu *et al.*, 2008a, 2008b)	Meta-analysis of metformin for reduction of weight gain in olanzapine-treated patients BW, BMI, and WC primary outcome	5.02 kg reduction in BW (I^2=0%) 1.42 reduction in BMI (I^2=85%) 1.82 cm reduction in WC (I^2=0%)
Bjorkhem-Bergman *et al.* (2010)	Five adult RCTs (Baptista *et al.*, 2006, 2007a; Wu *et al.*, 2008a, 2008b; Carrizo *et al.*, 2009) Two pediatric RCTs (Klein *et al.*, 2006; Arman *et al.*, 2008)	Meta-analysis to determine percentage of BW reduction in patients receiving any SGA Subgroup analysis on adult patients, pediatric patients and patients with >10% increase in pretreatment BW	4.8% decrease in BW in adults (I^2=92%) 4.1% decrease in BW in children and adolescents 7.5% decrease in BW for patients experiencing >10% increase in BW after commencing SGA treatment

BW, body weight; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment – insulin resistance; LDL, low-density lipoprotein; RCT, randomized controlled trial; SGA, second-generation antipsychotic; WC, waist circumference.

Discussion

The current literature suggests that metformin is the most suitable agent for the prevention and treatment of weight gain associated with SGA medication (Maayan *et al.*, 2010). Four RCTs (Klein *et al.*, 2006; Wu *et al.*, 2008a, 2008b; Carrizo *et al.*, 2009) indicate that metformin has a statistically significant impact on BW and BMI, whereas meta-analysis suggests that metformin may induce weight loss of up to 3 kg (Ehret *et al.*, 2010) and reduce BW by approximately 5% in adult and pediatric patients treated with a variety of SGA medications (Bjorkhem-Bergman *et al.*, 2010). Furthermore, weight loss may be enhanced in patients at an increased risk of weight gain, namely those exposed to olanzapine and those who gain greater than 10 kg after first SGA exposure (Bjorkhem-Bergman *et al.*, 2010).

Although encouraging, various limitations inherent in the current literature merit discussion. First, there is a paucity of adequately powered studies available, with only four of nine RCTs able to draw statistically significant conclusions. The majority of nonsignificant studies were conducted in relatively older cohorts with longer disease and treatment duration, which may confound comparisons with the younger cohorts of the significant studies. This observation is mirrored by the substantial heterogeneity of meta-analyzed effect size (see Table 3).

Second, lifestyle intervention is only controlled for in one RCT (Wu *et al.*, 2008b), whose results indicate that lifestyle intervention combined with metformin is superior to either intervention alone. A recent meta-analysis found structured lifestyle intervention to attenuate SGA-induced weight gain resulted in pooled weight loss of 2.56 kg (Alvarez-Jimenez *et al.*, 2008). Considering most RCTs provided uncontrolled lifestyle advice to both metformin and placebo groups, it is possible that this is accounting for a large proportion of the effect size. Repetition of the methodology used by Wu *et al.* (2008b) in drug-naïve populations is desirable.

Third, most primary research has been conducted in Asian and Hispanic populations, with two (Wu *et al.*, 2008a, 2008b) of the significant studies conducted in the former group. Normative BMI varies between ethnic groups, and recommended BMI and waist circumference reference ranges for Asians are less than for other populations (World Health Organisation, 2004). Furthermore, waist circumference is superior to BMI in predicting the risk of diabetes (Klein *et al.*, 2007), whereas excess waist circumference constitutes a cardiovascular risk factor in those who are neither overweight nor obese on BMI measurement (Meisinger *et al.*, 2006). Wu *et al.* (2008b) was the only study to show between-group statistically significant reductions in waist circumference with metformin.

Although none of the studies reviewed here directly report on the side effects of metformin or its potential interaction with atypical antipsychotic medication, metformin has a safety profile established through long-term use. Gastrointestinal symptoms (nausea, bloating, and diarrhoea) are the most commonly reported adverse drug reactions, reported in up to 30% of patients; however, these symptoms can largely be avoided by gradual dose titration and appropriate food intake (Scheen, 2005). Lactic acidosis is known to occur at a rate of approximately 3 in 100 000 patients usually as a result of inappropriate prescribing in patients with impaired renal function (Strack, 2008). Importantly metformin is not metabolised by hepatic P_{450} enzymes and is not reported to have any significant drug–drug interactions, or specific interactions with antipsychotic medications (Howlett and Bailey, 1999).

Current recommendations regarding metformin are conflicting. One author has proposed a guideline for the use of metformin in patients with cumulative risk factors (Hasnain *et al.*, 2010), whereas others cite poor statistical power of the primary evidence and inadequate weight loss as grounds to advise against routine use of metformin (Desilets *et al.*, 2008; Bushe *et al.*, 2009). Although we agree that the utility of metformin has not been elucidated in older populations with longer treatment duration, the significant efficacy of metformin in younger populations with shorter illness and treatment duration makes use of metformin in this group advantageous. The augmented efficacy of metformin in those patients who have gained greater than 10% of their BW within 1 year of commencing SGA treatment indicates this group may also benefit from the use of metformin.

Weight gain associated with SGA medications is most rapid during the first 12 weeks of treatment and universal in FEP regardless of antipsychotic used (Tarricone *et al.*, 2010). Younger patients may also be at increased risk of diabetes and there is evidence that risk diminishes with increasing age (Hammerman *et al.*, 2008). Utilisation of metformin in the early stages of SGA treatment is proven to substantially mitigate weight gain at a time of major cardiometabolic vulnerability. Psychosis typically manifests in late adolescence or early adulthood (Kirkbride *et al.*, 2006) and weight gain at this stage of treatment contributes to increased cardiovascular risk regardless of future weight loss (Must *et al.*, 1992). For this reason, mitigation of weight gain in early stages of treatment is potentially more clinically advantageous than net weight loss in chronic patients who have undergone indeterminate weight gain.

The desirability of preventing avoidable weight gain is not simply about mitigating risk of premature cardiovascular morbidity and mortality. The impact of rapid weight gain for any young person undergoing the social and psychological transition from adolescence to adulthood is considerable and is also the time at which psychosis typically manifests. The dual stigma and discrimination (Hatzenbuehler *et al.*, 2009) encountered by individuals suffering both psychotic illness and obesity contributes to psychological distress (Simon *et al.*, 2006), poor self-esteem (De Hert *et al.*, 2006), and may impact medication compliance, risking relapse. Avoidance of this is both advantageous to the individual and reduces health costs associated with relapse (Knapp *et al.*, 2004). Weight gain compromises quality of life, general health, and decreases physical and social functioning (Kolotkin *et al.*, 2006), imposing role limitations that have been shown to be a more important issue to people living with psychosis than the psychiatric condition itself (Dixon *et al.*, 2001).

We have developed a clinical decision tool incorporating the current evidence to detect and assertively intervene in antipsychotic induced weight gain, with the aim of actively preserving cardiometabolic health (Curtis *et al.*, 2011); *http://www.ceti.nsw.gov.au/www/472/1001127/displayarticle/1007767.html*). It is our recommendation that all patients commencing atypical antipsychotic medication be monitored for metabolic side effects, including monitoring of weight, waist circumference, BMI, blood pressure and fasting blood glucose or HbA1c, and lipid profile. Structured lifestyle and nutritional advice should be provided for all patients presenting with FEP and chronic mental illness. In those who gain greater than ten percent of their BW despite lifestyle intervention, there is evidence that metformin is an effective pharmacological adjunct to lifestyle. Metformin efficacy in the at-risk is supported by evidence showing weight reduction in obese, euglycemic adolescents (Casteels *et al.*, 2010; Rezvanian *et al.*, 2010). Not including metformin as part of the clinical armamentarium risks missing an important opportunity to positively influence the health trajectory of patients suffering psychotic illness.

Conclusion

Metformin is efficacious in preventing weight gain in younger population groups and those who gain substantial weight within 1 year of commencing SGA treatment. The primary literature has a variety of limitations, nevertheless the literature uniformly demonstrates that metformin with lifestyle intervention is effective in these patient groups.

Acknowledgements

Statement of interests: David Shiers is currently a member of the Guideline Development Group (GDG) for new NICE guidance for children and young people affected by psychosis and schizophrenia and the views expressed are not those of the GDG, NCCMH or NICE.

Conflicts of interest

There are no conflicts of interest.

References

Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD (2008). Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry* **193**:101–107.

Arman S, Sadramely MR, Nadi M, Koleini N (2008). A randomized, double-blind, placebo-controlled trial of metformin treatment for weight gain associated with initiation of risperidone in children and adolescents. *Saudi Med J* **29**:1130–1134.

Baptista T, Hernandez L, Prieto LA, Boyero EC, de Mendoza S (2001). Metformin in obesity associated with antipsychotic drug administration: A pilot study. *J Clin Psychiatry* **62**:635–655.

Baptista T, Martinez J, Lacruz A, Rangel N, Beaulieu S, Serrano A, *et al.* (2006). Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. *Can J Psychiatr Rev Canad Psychiatr* **51**:192–196.

Baptista T, Rangel N, Fernandez V, Carrizo E, El Fakih Y, Uzcategui E, *et al.* (2007a). Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: a multicentric, double-blind, placebo-controlled trial. *Schizophr Res* **93**:99–108.

Baptista T, Sandia I, Lacruz A, Rangel N, De Mendoza S, Beaulieu S, *et al.* (2007b). Insulin counter-regulatory factors, fibrinogen and C-reactive protein

during olanzapine administration: effects of the antidiabetic metformin. *Int Clin Psychopharmacol* **22**:69–76.

Baptista T, Uzcategui E, Rangel N, El Fakih Y, Galeazzi T, Beaulieu S, De Baptista EA (2008). Metformin plus sibutramine for olanzapine-associated weight gain and metabolic dysfunction in schizophrenia: a 12-week double-blind, placebo-controlled pilot study. *Psychiatr Res* **159**:250–253.

Bjorkhem-Bergman L, Asplund AB, Lindh JD (2010). Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. *Psychopharmacol* **25**:299–305.

Bushe CJ, Bradley AJ, Doshi S, Karagianis J (2009). Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *Int J Clin Prac* **63**:1743–1761.

Carrizo E, Fernandez V, Connell L, Sandia I, Prieto D, Mogollon J, *et al.* (2009). Extended release metformin for metabolic control assistance during prolonged clozapine administration: a 14 week, double-blind, parallel group, placebo-controlled study. [Erratum appears in Schizophr Res 2009 Nov; 115(1):96]. *Schizophr Res* **113**:19–26.

Casteels K, Fieuws S, Van Helvoirt M, Verpoorten C, Goemans N, Coudyzer W, *et al.* (2010). Metformin therapy to reduce weight gain and visceral adiposity in children and adolescents with neurogenic or myogenic motor deficit. *Pediatr Diabet* **11**:61–69.

Chen C-H, Chiu C-C, Huang M-C, Wu T-H, Liu H-C, Lu M-L (2008). Metformin for metabolic dysregulation in schizophrenic patients treated with olanzapine. Progr Neuro Psychopharmacol. *Biol Psychiatr* **32**:925–931.

Curtis JE, Newall H, Samaras K (2011). The heart of the matter: cardiometabolic care in youth with psychosis. *Early Intervent Psychiatr* (In press).

De Hert M, Peuskens B, Van Winkel R, Kalnicka D, Hanssens L, Van Eyck D, *et al.* (2006). Body weight and self-esteem in patients with schizophrenia evaluated with B-WISE. *Schizophr Res* **88**:222–226.

De Leon J, Diaz FJ (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* **76**:135–157.

De Luca V, Mueller DJ, De Bartolomeis A, Kennedy JL (2007). Association of the *HTR2C* gene and antipsychotic induced weight gain: a meta-analysis. *Int J Neuropsychopharmacol* **10**:697–704.

Desilets AR, Dhakal-Karki S, Dunican KC (2008). Role of metformin for weight management in patients without type 2 diabetes. *Ann Pharmacother* **42**: 817–826.

Dixon L, Goldberg R, Lehman A, McNary S (2001). The impact of health status on work, symptoms, and functional outcomes in severe mental illness. *J Nervous Mental Disease* **189**:17–23.

Ehret M, Goethe J, Lanosa M, Coleman CI (2010). The effect of metformin on anthropometrics and insulin resistance in patients receiving atypical antipsychotic agents: a meta-analysis. *J Clin Psychiatr* **71**:1286–1292.

Fernandez E, Carrizo E, Fernandez V, Connell L, Sandia I, Prieto D, *et al.* (2010). Polymorphisms of the LEP- and LEPR genes, metabolic profile after prolonged clozapine administration and response to the antidiabetic metformin. *Schizophr Res* **121**:213–217.

Foley DL, Morley KI (2011). Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Arch Gen Psychiatr* **68**: 609–616.

Hammerman A, Dreiher J, Klang SH, Munitz H, Cohen AD, Goldfracht M (2008). Antipsychotics and diabetes: an age-related association. *Ann Pharmacother* **42**:1316–1322.

Hasnain M, Vieweg WVR, Fredrickson SK (2010). Metformin for atypical antipsychotic-induced weight gain and glucose metabolism dysregulation: review of the literature and clinical suggestions. *CNS Drugs* **24**:193–206.

Hatzenbuehler ML, Keyes KM, Hasin DS (2009). Associations between perceived weight discrimination and the prevalence of psychiatric disorders in the general population. *Obesity* **17**:2033–2039.

Hennekens CH, Hennekens AR, Hollar D, Casey DE (2005). Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* **150**:1115–1121.

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

Katsiki N, Georgiadou E, Hatzitolios AI (2009). The role of insulin-sensitizing agents in the treatment of polycystic ovary syndrome. *Drugs* **69**:1417–1431.

Kim HG, Hien TT, Han EH, Hwang YP, Choi JH, Kang KW, *et al.* (2011). Metformin inhibits P-glycoprotein expression via the NF-B pathway and CRE transcriptional activity through AMPK activation. *Br J Pharmacol* **162**:1096–1108.

Kirkbride JB, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, *et al.* (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Arch Gen Psychiatr* **63**:250–258.

Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA (2006). A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatr* **163**:2072–2079.

Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R. Association for Weight, M., Obesity, P., Naaso, Obesity, S., American Society for, N. & American Diabetes, A. (2007). Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Diabetes Care* **30**:1647–1652.

Knapp M, King D, Pugner K, Lapuerta P (2004). Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *Br J Psychiatr* **184**:509–516.

Kolotkin RL, Crosby RD, Corey-Lisle PK, Li H, Swanson JM (2006). Performance of a weight-related measure of quality of life in a psychiatric sample. *Qual Life Res* **15**:587–596.

Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, *et al.* (2003). H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* **28**:519–526.

Maayan L, Vakhrusheva J, Correll CU (2010). Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* **35**: 1520–1530.

Meisinger C, Doring A, Thorand B, Heier M, Lowel H (2006). Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. *Am J Clin Nutri* **84**:483–489.

Morrison JA, Cottingham EM, Barton BA (2002). Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatr* **159**:655–657.

Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH (1992). Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. *N Eng J Med* **327**:1350–1355.

Praharaj SK, Jana AK, Goyal N, Sinha VK (2011). Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *Br J Clin Pharmacol* **71**:377–382.

Pramyothin P, Khaodhiar L (2010). Metabolic syndrome with the atypical antipsychotics. *Curr Opin Endocrinol Diab Obes* **17**:460–466.

Reynolds GP, Kirk SL (2010). Metabolic side effects of antipsychotic drug treatment–pharmacological mechanisms. *Pharmacol Therap* **125**: 169–179.

Rezvanian H, Hashemipour M, Kelishadi R, Tavakoli N, Poursafa P (2010). A randomized, triple masked, placebo-controlled clinical trial for controlling childhood obesity. *W J Pediatr* **6**:317–322.

Scheen AJ (2005). Drug interactions of clinical importance with antihyperglycaemic agents: an update. *Drug Safety* **28**:601–631.

Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, Van Belle G, Kessler RC (2006). Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatr* **63**:824–830.

Stahl SM, Mignon L, Meyer JM (2009). Which comes first: atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatrica Scandinavica* **119**: 171–179.

Strack T (2008). Metformin: a review. *Drugs of Today* **44**:303–314.

Tarricone I, Ferrari Gozzi B, Serretti A, Grieco D, Berardi D (2010). Weight gain in antipsychotic-naive patients: a review and meta-analysis. *Psychol Med* **40**:187–200.

Wiernsperger NF, Bailey CJ (1999). The antihyperglycaemic effect of metformin: therapeutic and cellular mechanisms. *Drugs* **58 (Suppl 1):**31–39. discussion 75–82.

World Health Organisation (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* **363**:157–163.

Wu R-R, Zhao J-P, Guo X-F, He Y-Q, Fang M-S, Guo W-B, *et al.* (2008a). Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiatr* **165**:352–358.

Wu R-R, Zhao J-P, Jin H, Shao P, Fang M-S, Guo X-F, *et al.* (2008b). Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA* **299**:185–193.