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# 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

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**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**

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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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4 **and Metformin. Do the data inform as to potential guideline development? A**  
5 **systematic review of clinical studies.**  
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9 **Chris J Bushe,<sup>1</sup> Andrew J Bradley,<sup>1</sup> Sara Doshi,<sup>2</sup> Jamie Karagianis<sup>3</sup>**

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36 This work was sponsored by Eli Lilly and Company. At the time of this review, CB, AB,  
37 JK and SD were employees of Eli Lilly and Company.  
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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

## SUMMARY

**Background:** Changes in weight and metabolic parameters have been commonly reported in patients with schizophrenia. Metformin has been evaluated in clinical studies to prevent or reduce weight gain and changes in metabolic parameters in non-diabetic subjects. We undertook a systematic review of the efficacy and safety of metformin in reducing weight gain and metabolic abnormalities in non-diabetic subjects with schizophrenia or bipolar disorder taking antipsychotic medication to establish if these data could potentially drive guideline development. **Methods:** Medical databases were searched using terms including ‘antipsychotic’, ‘atypical antipsychotic agent’, ‘antipsychotic agents’, ‘antipsychotic-drug’ and ‘metformin’ and ‘weight’. Studies reporting weight and/or metabolic outcomes in non-diabetic subjects with schizophrenia and bipolar disorder were included regardless of methodological type and subject age. **Results:** Nine randomised double-blind studies and two open cohort studies evaluating metformin and changes in weight in trials up to 16 weeks were identified. 495 participants received antipsychotics (mostly olanzapine), and three studies were in subjects aged <18 years. The adult studies predominantly utilised non-Caucasian subjects with chronic schizophrenia. Weight and lifestyle intervention programmes were provided to all cohorts in eight studies, which confounded interpretation of the data. In ten studies, the addition of metformin to antipsychotic treatment was associated with either significantly attenuated weight gain or weight loss compared with control groups. Nine studies measured various glucose parameters. In four studies, subjects prescribed metformin had significantly improved glucose parameters relative to controls. The two studies of metformin in patients with first-episode schizophrenia demonstrated the largest improvement in weight and glucose parameters. **Conclusions:** Metformin may have some value in reducing or preventing weight gain and changes in metabolic parameters during treatment with antipsychotic medication particularly in first-episode psychosis; however, it has been predominantly studied short-term and in non-Caucasian populations. A number of new trials are due to report data 2009-2013 to aid definitive interpretation of the role of metformin.

Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 **Further longer-term studies are warranted before definitive guidelines can be**  
4 **established.**  
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8 **Review Criteria**

9 All databases were reviewed to identify any study in the English language that evaluated  
10 metformin for non-diabetic subjects with schizophrenia, bipolar disorder or other  
11 psychosis who were receiving antipsychotic treatments. There was no age restriction.  
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15 **Message for the Clinic**

16 There is no definitive answer as to the efficacy of metformin as a weight prevention or  
17 reduction agent in patients with psychosis although data are promising but not yet  
18 sufficient to inform guideline development. No Caucasian subjects have been studied and  
19 antipsychotic usage has been predominantly restricted to olanzapine. Our findings are  
20 broadly similar to those data in the general population where metformin shows promise  
21 but long term relevant clinical trials in a variety of ethnic populations remain to be  
22 undertaken. Metformin appeared to be well tolerated. The most common adverse event  
23 during concomitant treatment was minor transient gastrointestinal discomfort and  
24 metformin would appear to have no unexpected safety issues in a psychosis population.  
25 Trial retention rates are encouraging. Data from a number of currently ongoing and  
26 planned clinical trials will further aid understanding of the role of metformin in these  
27 subjects.  
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30 **Keywords:** schizophrenia; bipolar disorder; metformin; glucose; weight management;  
31 antipsychotics; olanzapine  
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39 The paper has been written by the named authors without editorial assistance other than  
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## INTRODUCTION

Metformin has been used in the treatment of type 2 diabetes for over 2 decades and, despite the development of newer agents, is the initial option for monotherapy recommended in guidelines in the US, Asia and Europe, including those of the American Diabetes Association and the International Diabetes Federation [1]. Metformin is regarded as a weight neutral agent in contrast to other oral hypoglycaemic agents and is the most commonly used biguanide, with a mode of action of reducing glucose production, enhancing the sensitivity of hepatic tissue to insulin and improving glucose muscle uptake [2].

Changes in some glucose and lipid parameters have been very commonly reported in patients with all forms of severe mental illness (schizophrenia and bipolar disorder). It has been suggested that such changes may relate to a combination of genetic predisposition, lifestyle factors and psychotropic treatments. [3-7]. Changes in weight and metabolic parameters during treatment with atypical antipsychotics are among the risks that physicians consider in making treatment decisions for individual patients [5, 8, and 9].

An independent National Institute of Mental Health study in the US, CATIE, found clinically significant weight gain over 18 months to be very common, ranging from 30% in subjects taking olanzapine to 16% in those taking quetiapine, 14% in those taking risperidone, 12% in those on perphenazine and 7% in those on ziprasidone [4]. In another 6-month study among chronic schizophrenia subjects with predominantly negative symptoms, clinically significant weight gain was measured in 19% and 13% of the olanzapine- and quetiapine-treated cohorts, respectively [6]. In a 26 week clinically significant weight gain >7% was measured in 40% of Olanzapine and 21% aripiprazole patients (p<0.05 between treatments). [10].

The aforementioned studies were conducted predominantly in subjects with chronic schizophrenia. Data from first-episode treatment naïve and early psychosis, however, showed greater changes in weight and metabolic parameters [8, 9, and 12]. The EUFEST study, an independent European study of first-episode psychosis (FEP), found that 17% of subjects were already overweight according to their body mass index (BMI >25) and had significant metabolic dysfunction at baseline (hyperglycaemia 7%,

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3 hyperlipidaemia 23%) [12]. During the 1-year study among subjects receiving  
4 antipsychotic treatment, 37-86% gained >7% body weight (p=.053 between treatments);  
5 44% were overweight (p=0.585 between treatments); 28-56% had hypercholesterolemia  
6 (p=0.276 between treatments); and 22-30% had hyperglycaemia (p=0.794 between  
7 treatments). A prospective, randomised, Spanish FEP study utilising olanzapine,  
8 risperidone and haloperidol reported mean weight gain ranging from 8.9-10.9 kg at 1 year  
9 (treatment differences non significant), which equates to 75-87.% of each cohort gaining  
10 >7% body weight [8]. Molindone, a first generation antipsychotic, has recently become  
11 utilised to treat children and adolescents with early onset schizophrenia spectrum  
12 disorders [11, 22] in whom weight and body image may be of significant concern. The 8-  
13 week TEOSS study reported significantly less weight gain in the molindone cohort than  
14 the olanzapine and risperidone cohorts [11]. A cochrane review in 2007 reported  
15 significantly more weight loss with molindone than other typicals (RR 2.78; CI 1.10-  
16 6.99; NNH 5 , CI 2-77).[22] and the weight reduction potential of Molindone has been  
17 recognised since 1977 [63]

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There has been some degree of attention paid to prevention and/or reduction of weight gain over the last decade in subjects with severe mental illness, and there is general agreement that lifestyle interventions (LI) should precede any pharmacological treatments [3, 13-16]. Even moderate weight loss of 5-15% of bodyweight may have significant health benefits [17]. Various types of LIs, ranging from a one-to-one nursing programme and behavioural groups to a telephone/postal service, have been undertaken [15, 18-20]. Many of these programmes have given encouraging results, but the results cannot be considered definitive as the controlled studies have tended to be short (12-14 weeks) and the uncontrolled studies and service evaluations, although showing positive results, often have tended to fail to retain subjects over the longer term [14,15,21].In addition, there is only a single preliminary report of the usage of dietary/lifestyle management in an acute inpatient cohort despite literature suggesting rates of weight gain are typically greatest in early phases of treatment [20].

A Cochrane review of behavioural programmes in schizophrenia found a body weight change in prevention studies of -4.87 kg at up to 24 weeks (confidence interval [CI] -7.1, -2.6), but the weight change in reversal studies was only -1.69 kg (CI -2.8,-0.6)

**Deleted:** Furthermore, 33% of subjects receiving ziprasidone developed a BMI >25, in contrast with 45% and 54% in the quetiapine and olanzapine groups, respectively (p = not significant).¶

**Deleted:** Metabolic adverse effects may be measured in the absence of weight change [5]

**Deleted:** and in first-episode subjects

[14]. Various types of pharmacotherapy have also been tried, but the Cochrane review concluded these showed only a modest short-term benefit. Drugs studied in this Cochrane review include amantadine, dexfenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, phenylpropranolamine, reboxetine, sibutramine and topiramate, with a reduction of 1.16 kg vs. controls in prevention studies increasing to a 3.85 kg reduction in reversal studies ( $p < 0.05$ ) [14].

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Metformin has been used in non-diabetic non-psychiatric populations with the aim of weight reduction and prevention of type 2 diabetes in high-risk cohorts and has shown some success. With regard to weight reduction, however, much of the data has been derived from uncontrolled studies and is not definitive [23, 24]. In the Diabetes Prevention Programme study, 3234 non-diabetic subjects with impaired glucose tolerance were randomised to metformin, LI or placebo arms over 4 years [25]. The incidence of diabetes mellitus (DM) was reduced by 58% in the LI arm and 31% in the metformin arm, with average weight loss of 5.6 kg and 2.1 kg, respectively, at the end of the 4-year period. Metformin has also shown success in weight reduction in females with polycystic ovary syndrome (PCOS), [26]. Data from other clinical areas is however equivocal. A systematic review of studies of metformin usage in obese or overweight adults reported that among 57 published studies only nine met randomisation and blinding criteria. The review concluded that in 2005 there was insufficient evidence to recommend metformin for these populations unless they had DM or PCOS [23].

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We undertook a systematic review to identify all available clinical studies of subjects with schizophrenia, psychosis or bipolar disorder, in whom metformin has been investigated with the aim of either reducing weight gain or improving metabolic parameters.

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## METHODS

### Data sources and study selection

We conducted an online literature search of the Biosis Previews (1989 to date), Current Contents (July 1993 to date), Embase (1988 to date), Medline (1966 to date), Medline In-Process (very recent articles not yet included in Medline) and PsycInfo (1806 to date) databases to identify any study that evaluated metformin for non-diabetic subjects with schizophrenia, bipolar disorder or other psychosis who were receiving antipsychotic

Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 treatments. There was no age restriction. The search terms used were ‘antipsychotic’,  
4 ‘atypical antipsychotic agent’, ‘antipsychotic agents’, ‘antipsychotic-drug’ and  
5 ‘metformin’ and ‘weight’. The search was restricted to publications in the English  
6 language.  
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9 A total of 35 potential manuscripts were identified. After an initial review of these  
10 data, it was determined to include all study types regardless of methodology, thus not  
11 limiting the review to only randomised and blinded studies.  
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13 After viewing, 11 published studies were included.  
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### 15 **Data extraction**

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17 Tables were created to record data from identified publications along with study  
18 methodology, sample and comparison populations and study period.  
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**Deleted:** A number of studies were identified by their abstract as being potential sources of data.

### 20 **Statistical analysis**

21 Statistical calculations from the source data are reported and no additional statistical  
22 analysis was performed.  
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## 24 **RESULTS**

### 25 **Studies included**

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27 Eleven studies were identified and included a total of 495 subjects receiving  
28 antipsychotic medications (2 paediatric subjects received valproate only). Details of the  
29 11 studies are presented in Tables 1 -4.  
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**Deleted:** In five of the studies, all subjects received olanzapine, and seven of the studies contained a placebo cohort arm [27-36]. In one of the paediatric studies, risperidone was administered to all subjects [31].

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32 Three of the studies involved paediatric and adolescent subjects with varying  
33 forms of psychosis [27, 29, 31]. Interpretation of one of the paediatric studies, the Arman  
34 et al. study, is complicated by the fact that a schizophrenia diagnosis was made in  
35 children (cohort mean ages 9-11 years). The remaining eight studies were all undertaken  
36 in adult schizophrenia subjects.  
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39 Five of the studies were conducted in Venezuela by the same investigator and it is  
40 not possible to evaluate any possible cohort overlap. The paediatric studies were  
41 undertaken in the US and Iran, and the remaining three studies in China and Taiwan.  
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43 Baseline weights and BMI reflected the predominant ethnicity of subjects (Asian and  
44 Hispanic). No adult study was undertaken in a Caucasian population.  
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### 46 **Data synthesis**

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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

The studies can be considered in two groups relating to cohort size. The five largest studies randomised 40 to 128 subjects in a double-blind manner. In the other six studies, between 5 and 38 subjects were included, and two of these studies were open label [27,32]. Positive results were found in four of the five largest studies [30, 33, 34, 40], with unequivocal positive results reported in the two most recent studies from China in first-episode subjects [30, 34]. Ten of the studies can be regarded as giving positive findings for metformin in terms of weight, BMI and other metabolic parameters.

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Lifestyle and dietary interventions were included for all study participants in eight studies, and in the largest study LI formed a specific arm of the trial [30]. Although effective and superior to placebo, LI was inferior to both metformin and the combination of metformin with LI. Metformin with LI was however more effective than metformin alone [30].

The studies can also be divided into FEP and chronic psychosis (predominantly schizophrenia). Two studies were undertaken in FEP, one focused on prevention [34] and one on reversal of early weight gain [30] and are both positive studies for metformin. Only two other studies can be considered as preventative studies [30,35], and one of these constitutes the only negative study of metformin on weight [35].

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Seven of the studies included a placebo cohort, olanzapine was the only antipsychotic given in five out of 11 studies; one study used only risperidone [31], one used only clozapine[40] and the other studies included small numbers of subjects on various antipsychotics with. Data synthesis did not allow any meta-analytic calculation due to a lack of homogeneity amongst study design and the confounding nature of the lifestyle interventions.

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## DISCUSSION

### Overview

Our systematic review of the 11 studies of metformin in subjects with schizophrenia and psychosis found that there is no unequivocal answer as to the value of using routine adjunctive metformin. Many of the studies do, however, provide promising data to suggest that definitive work in this cohort of subjects prone to adverse metabolic outcomes might be valuable. In ten out of the 11 studies, the results of weight change in

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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 the metformin cohort could be regarded as giving positive outcomes, with caveats that  
4 include lack of powering and the common usage of lifestyle and weight management  
5 programmes in all cohorts. The one study that failed to show any benefit was the longest  
6 adult study, conducted over 14 weeks in a chronic schizophrenia inpatient cohort (mean  
7 antipsychotic exposure 30.7 years) for whom olanzapine was being added to an existing  
8 depot formulation [35]. With a sample size of 40, this study may have been  
9 underpowered to detect a difference and cumulative antipsychotic doses may have  
10 exceeded current maximal limits [39]. The most recent study, placebo controlled over 14  
11 weeks in clozapine subjects found a significant effect size for metformin (0.70) but based  
12 only on a completer analysis [40].  
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### *Can these data be regarded as definitive for guideline development?*

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24 There are significant limitations to any interpretation of this eclectic mix of  
25 studies that include an absence of Caucasian cohorts. Many of the studies do not give  
26 clear data on whether any powering was undertaken to establish cohort size. Almost all  
27 the subjects had a diagnosis of schizophrenia and most subjects were receiving  
28 olanzapine; hence, extrapolation to any other treatment populations or medications may  
29 be presumptive. In addition, all the studies were short term (8-16 weeks), and this may be  
30 regarded as too short a time period over which to make any conclusions. Longer term  
31 studies are required to inform on any potential CVD risk reduction by metformin. The  
32 temporal course of weight gain and metabolic change has not been fully established in  
33 schizophrenia, although current data suggest that rates of weight gain are typically  
34 greatest in early phases of treatment and very common in FEP regardless of  
35 antipsychotic [8,9,22]. The CATIE Phase I cohort that was given olanzapine had initial  
36 cholesterol elevation that reverted to baseline measurements by 9 months into the study  
37 [37]. Additionally, the numbers of olanzapine subjects with abnormal glucose (>100  
38 mg/dl) fell from 35% to 27% at 3 months [38]. Such data make it complex to suggest a  
39 specific time period for any future clinical research of metformin in metabolic regulation.  
40 We found no data on metformin usage in other forms of severe mental illness such as  
41 bipolar disorder  
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***Should metformin be utilised in conjunction with weight management and lifestyle programmes?***

It is complex to try and separate any metformin effects from those of adjunctive weight, lifestyle and exercise programmes, as these were utilised in eight studies for all participants. In the largest and best designed study (due to its randomised double blind design, larger patient numbers and testing of multiple interventions), metformin alone was found to be superior to LI on weight and glucose measures, but the combination of metformin and LI was superior to metformin with regard to body weight and BMI reductions [30]. This contrasts with findings from a large study in non-diabetic non-mentally ill subjects at risk of diabetes in whom metformin did reduce both weight and DM incidence over 4 years but was inferior to LI. Data generated from the general population may not necessarily be extrapolated to the schizophrenia population [25]. Such programs were relatively short in duration, but they were often effective, and may have masked positive effects of metformin. In addition, many subjects were chosen for the studies who were highly motivated to achieve weight loss or who had family situations that would encourage correct administration of the LI [30]. In the original case series, subjects whom were well motivated to lose weight lost 3.3 kg (+ -1.7) over the initial 4 weeks without metformin and subsequently lost 1.3 kg (+ -1.1) during 8 weeks of metformin treatment [28]. In a later cohort (n = 28) randomised to metformin/sibutramine or placebo, all subjects received a comprehensive programme regarding “healthy lifestyle” [36]. The study was not powered to show any differences but, despite the success of the lifestyle programme, weight loss was numerically greater in the metformin/sibutramine cohort than placebo (-2.8 kg vs. -1.4 kg; p = 0.19). Lipid and glucose parameters showed numerically greater improvement in the active cohort, which only reached significance with a greater triglyceride reduction (p = 0.012). Thus, the improvement being observed in weight, glucose and most lipid parameters in the placebo cohort can only be attributed to the lifestyle programme. In the largest study in chronic subjects (n = 80), predominantly with schizophrenia, where again some weight management programme was provided, significant weight loss was achieved in the metformin cohort over 12 weeks, 1.4 kg (standard deviation [SD] 3.2; p = 0.01), but there

**Deleted:** and cannot be regarded currently as routine practice

**Deleted:** Reasonable evidence exists though to suggest that the addition of metformin provides additional benefits in that positive results for metformin were found in almost all studies

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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

was no difference compared to the placebo group, as weight was maintained in that cohort, presumably due to the weight management programme [33].

In one of the three studies in which weight management was not provided, a chronic and severe schizophrenia inpatient cohort was provided with a calorie-“restricted” diet of 2500-3000 kcals [35]. This study found significant steady weight gain in both the metformin and placebo cohorts, with increases of 5.5 and 6.3 kg, respectively, over 14 weeks. Antipsychotic dosage was high as subjects continued with their depot schedule (fluphenazine decanoate 25 mg or haloperidol 100 mg monthly) in addition to commencing olanzapine 10 mg daily.

The three most positive studies all derive from Asian cohorts in which lifestyle programmes were prominent. A small, open-label, 8-week study (n = 24) in subjects receiving olanzapine for 6 months found that weight, glucose and lipid parameters were significantly decreased [32]. It should be noted, however, that the subjects were admitted to an inpatient unit for a prescriptive diet of 25-35 kcal/kg. Weight was reduced by 2.2 kg and BMI by 0.9.

The most promising data comes from the two Asian studies that evaluated patients with FEP [30,34]. The first placebo-controlled study evaluated the ability of metformin to prevent weight gain and utilised inpatients given prescriptive diet and exercise over 12 weeks. The metformin cohort showed significant weight and BMI differences from 8 weeks onwards vs. placebo. The mean weight gain in the placebo cohort of 6.87 kg (SD 4.23) at 12 weeks was significantly greater than the metformin cohort (1.9 kg [SD 2.72];  $p < 0.02$ ).

The second Asian study evaluated placebo, metformin, metformin and lifestyle changes (LC), or LC alone over 12 weeks [30]. This is the largest of the studies and included 128 subjects with first-episode schizophrenia whom had gained >10% of their pre-drug weight. The LC plus metformin cohort had the largest decrease in BMI of 1.8 (95% CI 1.3-2.3) with significant improvement in insulin resistance, followed by metformin and then LC alone, with all three groups reporting decreases in BMI and insulin resistance. In contrast, in the placebo cohort there was an increase in BMI and worsening of insulin resistance. Importantly, this study concluded that the combination of metformin and LC was the most effective regimen, and individually metformin was

**Deleted:** The study population included clinically stable but severe schizophrenia inpatients whom might be considered less likely candidates for good response to a weight management programme.

**Deleted:** The baseline demographic of a mean age 25 years and a BMI of 21-22 is similar to EUFEST [12].

**Deleted:** In the EUFEST study, the olanzapine cohort had a mean weight gain of 13.9 kg (standard error (SE) 1.7) after a year with no weight management intervention [12].

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superior to LC. The lifestyle programme included psycho-educational, dietary and exercise programmes, and would seem to be similar to the Wellbeing Support Programme from the UK in addressing all these valid cardiovascular disease (CVD) risk factors [3,19]. A further strength of this study was that subjects were receiving a variety of antipsychotics (clozapine, olanzapine, risperidone and sulpiride), and hence conclusions are not restricted to olanzapine subjects only.

### ***Do adverse events during treatment with metformin preclude usage in SMI?***

The most common adverse event associated with metformin was mild gastrointestinal discomfort and with no unexpected adverse events and high completion rates the studies, indicated that subjects found metformin tolerable. No major adverse effects were reported; in particular, no evidence of lactic acidosis or falls in vitamin B levels was found [34]. Some studies reported minor transient gastrointestinal discomfort requiring transient dose adjustment [32,36]. These minor gastrointestinal adverse effects are similar to those found in placebo-controlled trials in overweight, insulin-resistant subjects in whom diarrhoea, nausea and vomiting were the only adverse drug events reported more commonly than placebo [46]. There is no evidence that metformin has any adverse effects on the psychosis [28,30,32,34,35] in studies up to months measuring various rating scales.

In Despite some speculation that metformin may reduce IGF-1, and hence worsen symptomatology, there seems to be no evidence in this systematic review to support any deterioration of the mental state [47, 48].

### ***What is known about metabolic and coagulant parameters in these studies?***

#### **Lipids**

Changes in lipids were only measured in five studies. There were no consistent changes in lipids, although confounding by the potential benefit of a lifestyle programme and the short term nature of the studies makes interpretation complex. The metformin/sibutramine and the clozapine studies report beneficial changes in most lipid parameters [36, 40]. In a larger study over 12 weeks there were no differences between metformin and placebo with a trend for superiority in the placebo cohort [33]. In a chronic inpatient cohort on metformin without weight management, lipid changes tended

**Deleted:** Subjects had been on treatment for 8 months and, importantly, can also be regarded as in an early phase of their illness. In due course CVD outcomes will be needed to assess any longer term benefits of metformin [41-45, 49, 50]

**Deleted:** In one inpatient study over 12 weeks, there was an increase in the Brief Psychiatric Rating Scale (BPRS) in both active (+20.7 +/-12.2) and placebo (+14.7 +/-9.4) cohorts that was ascribed to the stress of the lifestyle programme [36]. In an earlier case series, the same author, working with motivated outpatients, reported a reduction in BPRS (p = 0.039) during the initial placebo phase that did not change during the subsequent metformin phase [28] where no lifestyle programme was given. In chronic inpatients who began on olanzapine in addition to a depot typical, BPRS significantly improved in both the metformin and placebo cohorts, mainly over an initial 7-week period [35]. Clinical Global Impressions and Global Assessment of Functioning scores remained stable over 8 weeks with metformin [32]. Additionally, in first-episode subjects in a placebo-controlled 12-week study, there were no clinical effects on either the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms [34]. Among

**Deleted:** first-episode subjects treated for 8 months in the largest metformin study, there were also no increases in any adverse events in the metformin cohorts compared with placebo [30]. Positive and Negative Syndrome Scale scores did not alter from baseline in any of the metformin or other cohorts

**Deleted:** Elevation in triglycerides were significantly reduced in the metformin/sibutramine treatment group (p = 0.012) but not in the placebo group

Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 to be significantly better in the metformin cohort despite significant weight gain in both  
4 cohorts over 14 weeks [35]. Finally, in a Taiwan-based cohort of 24 subjects studied over  
5 8 weeks, triglyceride was the only lipid to decrease significantly [32].  
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### 8 **Glucose**

9 Changes in glucose were reported in nine studies. Interpretation of glucose changes is  
10 complex due to the confounders of weight management and altered diets; however, in  
11 general terms metformin was associated with beneficial changes. The original small case  
12 series found that whilst glucose and insulin parameters improved during the placebo  
13 phase, there was significant worsening during the metformin phase in both glucose and  
14 insulin area under the curve [28]. However, most data are consistent with the known  
15 profile of metformin. In the 12-week placebo study of subjects with chronic  
16 schizophrenia and the clozapine study, glucose remained unaltered in both cohorts, but  
17 beneficial changes in HOMA-IR and insulin were found in metformin cohorts [33, 40]. In  
18 a further study in chronic schizophrenia inpatients, patients treated with metformin  
19 experienced a reduction in glucose, while patients treated with placebo did not. Both  
20 cohorts, however, had decreases in insulin and in HOMA-IR [35]. Additionally, glucose,  
21 insulin and HOMA-IR all decreased over 8 weeks in the open-label metformin cohort  
22 reported by Chen et al. in 2008 [32]. In the metformin/sibutramine study, reductions in  
23 glucose were seen in both groups, though only significantly so in the placebo cohort, and  
24 insulin levels decreased in both cohorts [36].  
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33 Where metformin has been evaluated in first-episode subjects, results have been  
34 promising. The Chinese study in 40 FEP subjects found significantly reduced increases in  
35 insulin and insulin resistance by 8 weeks [34]. The largest current study of metformin in  
36 128 FEP subjects, reported that metformin and LI combined was the most efficacious  
37 treatment in reducing weight, BMI, fasting glucose, insulin and insulin resistance [30].  
38 These treatments, given together or individually, were also all superior to placebo in  
39 cases where increases in these parameters were measured. These reductions were  
40 measured at 4 weeks for the metformin cohorts.  
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### 47 **Leptin, fibrinogen and C-reactive protein**

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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 Three of these studies have evaluated changes in markers of endothelial dysfunction  
4 (CRP), procoagulant states (fibrinogen) and leptin associated with metformin and have  
5 reported preliminary data [33,36,40]. The data potentially suggest that metformin may  
6 decrease leptin however no statistically significant changes have been reported. In a 12-  
7 week placebo controlled study metformin was associated with a tendency to decrease  
8 leptin ( $p=0.078$ ), with leptin and body weight correlating positively, but with no changes  
9 in other parameters (CRP, fibrinogen, cortisol and growth hormone) [33]. Further post-  
10 hoc analysis suggested that CRP levels reduced in women ( $p=0.016$ ) but not men in the  
11 metformin cohort however a similar trend was found in the placebo cohort. In the second  
12 12-week study metformin in combination with sibutramine was not associated with any  
13 difference from placebo in leptin or fibrinogen [36] although there was a reduction in  
14 fibrinogen from baseline in the metformin/sibutramine cohort. No conclusions can be  
15 drawn from these data however larger and longer studies may be indicated, as these  
16 factors may be critical in the development of cardiovascular disease. In a more specific  
17 study over 14-weeks leptin decreased non-significantly in the metformin cohort  
18 contrasting with a small increase in the placebo cohort [62]. Fibrinogen decreased in both  
19 cohorts whereas CRP was unchanged.  
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32 ***Metformin for weight reduction in the general population. Are there differences***  
33 ***compared with SMI subjects?***  
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36 Metformin is regarded as weight neutral when used as an antihyperglycaemic agent in  
37 type 2 diabetic subjects. This is in contrast to sulphonylureas, glitazones and insulin [2].  
38 The value of metformin in overweight subjects with type 2 diabetes as a cardioprotective  
39 and mortality reducing agent has been established by an all-cause mortality reduction of  
40 36% ( $p = 0.011$ ) over a median of 10.7 years [51,52]. In addition, the Diabetes Prevention  
41 Programme Research Group study reported that over an average follow-up of 2.8 years  
42 significant weight loss was measured in hyperglycaemic non-diabetic overweight  
43 subjects (BMI 34 at baseline) both with metformin (2.1 kg) and LI (5.6 kg) compared  
44 with placebo ( $p < 0.001$ ) [25]. Consequently, metformin has been trialled in non-diabetic  
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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 populations as a potential weight reduction agent. Individual trials in general have been  
4 encouraging, but definitive proof is still lacking. In a small cohort (n = 31) of non-  
5 diabetic subjects with BMI >30, significant reductions in weight and waist measurements  
6 were found over 28 weeks, in addition to improvement in other metabolic parameters  
7 [53]. However, this is one of only five studies evaluating the effect of metformin on  
8 weight as a primary outcome when PCOS is excluded [24].  
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12 Our findings in a schizophrenia population are not dissimilar to systematic  
13 reviews where metformin has been trialled in other populations, in that definitive data is  
14 not yet present to support a potentially encouraging hypothesis of weight loss. A  
15 systematic review of nine trials of metformin in overweight and obese general population  
16 adults, published between 1970 and 2002 and ranging from 15 days to 1 year, concluded  
17 that unless subjects had diabetes mellitus or PCOS there was insufficient evidence to  
18 support the use of metformin [23]. Among the nine studies, weight loss was the primary  
19 outcome measure in only a single 8-week study of 34 women [54]. Interpretation of the  
20 significant weight loss observed in most of the placebo cohorts is complex.  
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26 A meta-analysis and systematic review from the Cochrane group that analyzed  
27 metformin usage in PCOS concluded that although there were reports of weight loss  
28 during treatment, this was not found to be significant on meta-analysis [55]. Of note,  
29 many of the studies in the meta-analysis had small cohorts and were of short duration.  
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32 Open and randomised studies have continued to postulate that metformin when used for  
33 PCOS may be a successful weight reduction agent, although the degree of weight loss  
34 may not be great [56,57]. In a cohort of women with PCOS whom were obese (BMI >30)  
35 and morbidly obese (BMI >37), doses of metformin 1500-2550 mg/day over 8 months  
36 along with “advice on diet and exercise” resulted in a weight loss of only 1.5-3.6 kg in  
37 the obese cohort (p = 0.04) and 3.8-3.9 kg in the morbidly obese cohorts [56].  
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**Deleted:** This study speculated that higher metformin doses may be required.

41 Metformin has also been combined with fluoxetine in an open-label pilot study in  
42 females performed in an obesity clinic with the active cohort achieving BMI reduction of  
43 3.43 over 6 months [58]. The usage of metformin in child and adolescent obesity has also  
44 been debated, with a cautious conclusion that in short-term small trials metformin may  
45 have some benefit in weight reduction [59]. The most recent review of metformin and its  
46 effects on weight in a general population excluded studies evaluating PCOS and the  
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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 conclusions are similar to those mentioned above [24]. The five trials where weight was a  
4 primary outcome are small (26-66 metformin subjects), of short duration (3-7 months)  
5 and none are randomised or placebo controlled. As with our review, many of these  
6 studies also include weight and LI programmes as well as motivated subjects. The precise  
7 benefits of metformin are, therefore, difficult to determine precisely. In the seven studies  
8 where weight was a secondary outcome, the duration of the studies tended to be longer,  
9 but weight reduction was less in the shorter-term studies. Also, in the randomised  
10 placebo-controlled studies, weight loss on metformin was only slightly better than on  
11 placebo (1.2-2.5 kg) in trials lasting more than 12 months. In the six adolescent trials, the  
12 results again showed modest weight loss and had similar flaws to the adult trials. The  
13 authors of the Cochrane review conclude that their findings in 2008 are concurrent with  
14 those of the 2005 systematic review, with both agreeing that larger, longer trials are  
15 needed [23,24]. In due course CVD outcomes will be needed to assess any longer term  
16 benefits of metformin [41-45, 49, 50]  
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### 28 **Planned and ongoing clinical trials with metformin in SMI**

29 There are 10 clinical trials on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) relating to metformin as a  
30 prophylactic agent in adults (n=5) and subjects under 18 years (n=5) that are reported as  
31 completed ( unpublished), ongoing or planned ( Table 5) (60). Study length ranges 12  
32 weeks to 5 years and clinical endpoints include efficacy parameters ( hospitalisation and  
33 discontinuation rates) and metabolic parameters ( incidence of DM, glucose and lipid  
34 parameters). The majority are randomised controlled trials. These studies when complete  
35 may address better the role of metformin as a prophylactic agent and it can be noted that  
36 no further studies in first episode psychosis subjects have been planned.  
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40 The studies primarily will be undertaken in USA and hence are likely to include a  
41 broader profile of ethnic cohorts than currently reported studies. The cohort sizes (up to  
42 240 subjects ) allow appropriate powering to address the primary endpoints and in 6  
43 studies lifestyle intervention programmes are provided to all study participants allowing  
44 the question to be addressed of what additional benefits metformin provides to targeted  
45 physical health programmes. It is likely that enough data will be reported from these  
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Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3 trials to allow guideline development to be assisted. Two trials are of specific interest.  
4 Study NCT 00816907 is a pilot study (n=80) in adult schizophrenia or schizoaffective  
5 subjects with BMI >27 kg/m<sup>2</sup> over 16 weeks measuring various metabolic parameters  
6 due to complete august 2009 and which allows a larger definitive trial to be designed.  
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8 Study NCT 00617240 is a placebo controlled 24-week randomised study in subjects 10-  
9 17 years receiving antipsychotics also measuring metabolic parameters due to complete  
10 January 2010. In both these studies all subjects will receive a form of lifestyle  
11 intervention.  
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## 15 16 17 **CONCLUSION**

18 Despite some promising data, there seems to be insufficient current evidence to conclude  
19 definitively that metformin should be used as an adjunct to weight and lifestyle  
20 programmes in patients with schizophrenia. All the current data is essentially short term,  
21 mostly 12-week studies, and any conclusions can only be applied to olanzapine and the  
22 ethnic cohorts investigated. No Caucasian subjects have been studied. The most  
23 promising data are in subjects with FEP where metformin is used as either a prophylactic  
24 agent or to reduce early weight and metabolic changes. These limited studies suggest that  
25 metformin seems to have few specific adverse events when utilised in this way.  
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29 Therefore, with the above caveats, metformin has generally been associated with  
30 improvement in metabolic parameters in schizophrenia, but well-powered and longer-  
31 term clinical trials are needed. Metformin will not reduce the necessity for lifestyle  
32 programmes that aim to reduce other major CVD risk factors such as smoking, dietary  
33 choices and improve exercise rates [19]. It is encouraging to see a number of future  
34 United States based studies due to complete in 2009-2010 [60]. Exercise may be a critical  
35 factor to address within these future trials [61]. At the current time, there would seem to  
36 be better longer-term evidence supportive of the usage of lifestyle and weight  
37 management programmes instead of metformin, with recent data suggesting that such  
38 programmes would be of value especially in FEP and in the initial 6-month period after  
39 treatment change [12, 13, 15, and 50]. However the combination of metformin with such  
40 programmes may be the optimal combination. Our findings differ little from those where  
41 metformin has been utilised for weight reduction in more general populations and the  
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1                    Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

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3                    need for future research in both populations of this cheap and seemingly tolerable drug  
4                    seems compelling. The data currently however do not inform broadly enough to enable  
5                    specific guideline development of metformin usage in SMI.  
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9                    **Acknowledgements**

10                    We thank Tracy Craig for her editorial check and advice on our final manuscript.

11  
12                    **Author contributions**

13                    Systematic review conception by all authors. The manuscript was written by all the  
14                    named authors without editorial support other than an editorial check. The main drafting  
15                    authors were CB and AB. Search terminology and referencing SD. Data extraction CB  
16                    and AB. Overview and authorship JK. Data analysis all authors.  
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**Table 1. Randomised Double Blind Studies Examining the Effects of Metformin on Antipsychotic Associated Weight Gain and Other Metabolic Parameters in Children & Adolescents with Psychiatric Disorders.**

Study, Locale, Type, Pharmacological Interventions and Doses.	Study Population	Non Pharmacological Interventions	Prevention or Treatment and Outcomes Assessed	Study Completion Rate	Statistically Significant Outcomes
Arman S et al (2008) Iran. RDB, 12 weeks. RIS +MET vs. RIS + PBO RIS 2-6mg/day. MET 500mg/day week 1, 1000mg/day thereafter.	49 schizophrenia or schizoaffective patients aged <20 yrs taking RIS (2-6mg/day). Mean age MET group 11.25 yrs, PBO group 8.93 yrs. Mean baseline BMI MET group 17.42kg/m <sup>2</sup> , PBO group 17.01 kg/m <sup>2</sup>	None reported	Prevention of RIS associated weight gain. Changes in BW, BMI, FG.	32/49 (65%)	<b>Weight Related (Within Group)</b> BW (p<.013) & BMI (p<.005) significantly increased in the RIS +PBO group over the 12 weeks BW (p<.001) & BMI (p<.015) significantly increased in the RIS +MET group over the 12 weeks. Both BW and BMI decreased in the RIS + MET group over the first 4 weeks, but then increased over the next 8 weeks. <b>(Between Group)</b> BW (p<.026) & BMI (p<.013) were significantly higher in the RIS + PBO group than the RIS + MET group at week 4. No significant differences were found at week 12. The percentage of weight gain was significantly higher in the RIS +PBO group than the RIS + MET group (p<.006). The % of patients with ≥7% BW gain was significantly higher in the RIS +PBO group than the RIS + MET group (p<.033) <b>Glucose Related</b> Fasting glucose not reported in paper.
Klein et al. (2006) USA. RDB, 16 week study. AAP + MET(n=18) vs AAP + PBO (n=20) Doses of AAP not stated. Subjects could also be taking other	38 children ( 39 entered but 1 dropped out) aged 10–17 years who had gained more than 10% of their pre-drug weight during less than 12 months of treatment with a AAP – OLZ	Nutritional counselling was provided at baseline and weeks 4, 8 & 12. After initial assessment of diet and exercise individualised	Prevention of further weight gain in patients taking AAP. BW, BMI, WC, FI, FG, HOMA-IR. OGTT was	30/38 = (78.9%)	<b>Weight Related (Within Group)</b> AAP + MET group BW remained stable. BMI & WC decreased. AAP + PBO group BW, BMI & WC all increased. (p values not stated) Because the study was conducted in growing children, the age-corrected changes in the standard deviations for both

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<p>psychotropic drugs but those know to effect body weight must have been at on a stable regime for at least 30 days prior to study and remain on that regime during the course of the study. MET 850mg/day</p>	<p>(n=11), RIS (n=14)or QUET (n=14). Diagnoses were Bipolar, attentional disorder, schizophrenia, oppositional defiant disorder, autism and Asperger's, Tourette's Disorder, schizoaffective disorder, depression. Baseline BMI not stated but 9 PBO treated and 8 MET treated had baseline BMI above the 95th percentile for their age (categorized as obese).</p>	<p>areas for improvement and goals were set for small changes. Each subject was given the healthy food choices meal planning tool (American Dietetic Association).</p>	<p>recommended at the end of the study for children with BMI&gt;95<sup>th</sup> percentile for their age or gain of &gt;10% of baseline weight during the study associated with high FI (&gt;20uU/ml) or FG (&gt;95mg/dL).</p>	<p>weight and body mass index (z scores) were determined Z scores for BW and BMI decreased in the MET group and increased in the PBO group (p values not stated) <b>(Between Group)</b> Differences were significant at all time points for BW &amp; BMI (week 16 p&lt;.0001) and at weeks 8, 12, &amp; 16 for WC (week 16 p=.003) Z scores were significantly lower in the MET group than PBO group for BW ((p=.0008) and BMI (p=.0006) at week 16.  <b><u>Glucose Related</u></b> <b>(Within Group)</b> HOMA-IR increased in the AAP+PBO group and decreased in the AAP +MET group. (p values not stated) <b>(Between Group)</b> The differences in HOMA-IR were marginally significant at weeks 4 (p=.08) and significant at week 8 (p=.03) but not at week 12 (p=.17) Significantly fewer children in the AAP +MET group than the AAP + PBO group were recommended for OGTT. (2 vs 10 respectively p&lt;.01)</p>
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**Table 2, Open Label Studies Examining the Effects of Metformin on Antipsychotic Associated Weight Gain and Other Metabolic Parameters in Children & Adolescents with Psychiatric Disorders.**

Study, Locale, Type, Pharmacological Interventions and Doses.	Study Population	Non Pharmacological Interventions	Prevention or Treatment and Outcomes Assessed	Study Completion Rate	Statistically Significant Outcomes
Morrison et al. (2002) USA Open label AAP or valproate + MET (n=19). 8 week study for 2 patients and 12 week study for 17 patients. AAP and VLP doses not stated. MET 1500mg/day	19 children (mean age 14.1 yrs.) taking OLZ, RIS, QUET or VLP with weight gain over 10% of baseline. OLZ n=8 OLZ+VLP n=4 RIS n=3 RIS + VLP n=1 VLP n=2 QUET n=1. Baseline BMI not stated.	Patients instructed not to change diet or physical activity during the study.	Prevention of further weight gain in patients taking AAPs or VLP. BW and BMI.	12/19 (70.5%)	<b>Weight Related</b> 15/19 patients lost weight, 1 remained unchanged and 3 gained weight. BW loss was significant (at alpha level of .01) at week 12 (p=.008). BMI reduction was significant at weeks 4 (p=.001) and week 12 (p=.003)

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**Table 3. Randomised Double Blind Studies Examining the Effects of Metformin on Antipsychotic Associated Weight Gain and Other Metabolic Parameters in Adults with Psychiatric Disorders.**

Study, Locale, Type, Pharmacological Interventions and Doses.	Study Population	Non Pharmacological Interventions	Prevention or Treatment and Outcomes Assessed	Study Completion Rate	Statistically Significant Outcomes
Carrizo et al. (2009). Venezuela. RDB, 14 weeks. CLZ +MET XR (n=31) vs. CLZ+PBO (n=30). CLZ 196.8mg/day MET 1000mg/day	61 CLZ treated patients, mean age ~39, mean baseline BMI ~28kg/m <sup>2</sup> . 93% mixed hispanics, 7% white. Of completers 94% DSM-IV schizophrenia.	At the site of the study all patients routinely received recommendations for a healthy lifestyle which encouraged programmed physical activity and nutritional advice. Compliance with this programme was not monitored.	Treatment of CLZ associated weight and metabolic changes. BW, BMI, WC, SG, SI, lipids, HbA1c, HOMA-IR, leptin, cortisol.	54/61 (88.5%)	<p><b><u>Weight Related (within group)</u></b>  A significant decrease in BW was seen in the CLZ+MET group at weeks 7 (p=0.01) and week 14 (p=0.01).  A significant decrease in BMI was seen in the CLZ +MET group at weeks 7 (p=0.01) and week 14 (p=0.01).  A significant decrease in WC was seen in the CLZ +MET group at week 7 (p=0.04)</p> <p><b><u>Between Group</u></b>  CLZ + MET was significantly superior to CLZ + PBO on BW (p=0.01) and BMI (p=0.01) at week 14.</p> <p><b><u>Glucose related (Within group)</u></b>  There was a significant decrease in SG at week 7 in the CLZ+MET group (p=0.01) and CLZ+PBO group (p=0.05)  There was a significant decrease in SI in the CLZ+MET group at week 14 (p=0.004)  There was a significant increase in HbA1c at week 14 in the CLZ+MET group (p=0.006) and the CLZ+PBO group (p=0.001).  HOMA-IR decreased significantly in the CLZ+MET group at week 14 (p=0.02).</p> <p><b><u>(Between group)</u></b>  There was a significantly greater reduction in SI at week 14 in the CLZ+MET group than the CLZ+PBO group (p=0.04)  The increase in HbA1c at weeks 7 (p=0.03) and week 14 (p=0.04) was significantly greater in the CLZ+PBO group than the CLZ+MET group.</p>

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					<p><b>Lipid Related (Within group)</b> HDL-C increased significantly in the CLZ+MET group at week 7 (p=0.001) and week 14 (p=0.01) TG:HDL-C ratio decreased significantly in the CLZ+MET group at week 14 (p=0.04)</p> <p><b>(Between group)</b> HDL-C increased significantly more in the CLZ+MET group than the CLZ +PBO group at week 7 (p=0.002) and week 14 (p=0.001). TG:HDL-C ratio decreased significantly in the CLZ+MET vs. the CLZ+PBO group at week 14 (p=0.02)</p>
<p>Wu et al (2008)a China RDB, 12 weeks. OLZ + MET (n=20) vs. OLZ + PBO n=20) OLZ 15mg/day MET 750mg/day</p>	<p>40 treatment naïve, 1<sup>st</sup> episode inpatients with schizophrenia. Mean age 25 Baseline BMI = 21.4kg/m<sup>2</sup></p>	<p>Patients hospitalised, served 3 meals a day (7980-9250 Kilojoule/day) Moderate exercise for at least 30 mins per day otherwise no special diet or exercise programme.</p>	<p>Prevention of OLZ associated weight gain. Changes in BW, BMI, WC, WHR, FG, FI, ≥7% BWG, HOMA-IR</p>	<p>37/40 (92.5%)</p>	<p><b>Weight Related</b> Significantly lower mean increases in BW (p&lt;.02), BMI (p&lt;.02), BWG ≥7% significantly lower with OLZ +MET (16.7%) vs. OLZ + PBO (63.16%) (p&lt;.001)</p> <p><b>Glucose Related</b> Significantly lower FI (p&lt;.001), HOMA-IR (p&lt;.001) in OLZ +MET group vs. OLZ+PBO group.</p> <p>All significant differences were present at week 8 and 12.</p>
<p>Wu et al (2008)b China RDB, 12 weeks. (AP + MET (n=32) vs. AP + MET+ LSI (n=32) vs. AP +LSI+PBO (n=32) vs. AP + PBO (n=32). CLZ 115.0mg/day OLZ 5.9mg/day RIS 2.7mg/day SLP 562.9mg/day MET 750mg/day</p>	<p>128 1<sup>st</sup> episode patients with DSM-IV schizophrenia aged 18-45 yrs. Patients must have gained &gt;10% BW within 1<sup>st</sup> year of treatment with CLZ, OLZ, RISP, SLP. Baseline BMI = 24.5kg/m<sup>2</sup></p>	<p>For those in the lifestyle intervention groups the following were delivered.</p> <ol style="list-style-type: none"> <li>1. Psychoeducational programme focussed on the roles of eating and activity in weight management weeks 4, 8 and 12.</li> <li>2. Dietary intervention following the American Heart Association step 2 diet.</li> </ol>	<p>Treatment of AP associated weight gain. Changes in BW, BMI, WC, FG, FI, HOMA-IR</p>	<p>118/128 (92.2%)</p>	<p><b>Weight Related (Within Group)</b> AP+MET+LSI group had significant decreases in BW, BMI, WC, (p&lt;.05 for all) at weeks 4, 8 &amp; 12. AP+MET group had significant decreases in BW, BMI, WC, (p&lt;.05 for all) at weeks 4, 8 &amp; 12. AP+LSI+PBO had significant decreases in BW, BMI, (p&lt;.05) at weeks 4,8, &amp; 12. WC was only significantly reduced at week 4 (p&lt;.05) AP+PBO group had significant increases in BW, BMI, WC, at weeks 4, 8 &amp; 12. (p&lt;.05)</p> <p><b>(Between Group)</b> MET+LSI was significantly superior to MET alone on BW (p=.02), BMI (p=.01) &amp; WC (p=.03) LSI alone on BW (p=.01), BMI (p&lt;.001) &amp; WC (p&lt;.001) &amp; PBO on BW, BMI &amp; WC (p&lt;.001 for all).</p>

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		<p>3. For the first week of the study walking or jogging on a treadmill 7 X a week for 30mins. For the rest of the study exercise was home based on a programme developed by the therapist and patient. Patients and carers kept a record of exercise taken.</p>			<p>MET alone was significantly superior to LSI alone on BW (p=.004), BMI (p=.006) &amp; WC (p&lt;.001) &amp; PBO on BW, BMI &amp; WC (p&lt;.001 for all). LSI alone was significantly superior to PBO on BW, BMI &amp; WC (p&lt;.001 for all). <b>Glucose Related (Within Group)</b> AP+MET+LSI group had significant decreases in FG, FI &amp; IRI at weeks 4, 8 &amp; 12. (p&lt;.05) AP+MET group had significant decreases in FG, FI &amp; IRI at weeks 4, 8 &amp; 12. (p&lt;.05) AP+LSI+PBO had significant decreases in FG (weeks 8 &amp; 12) FI &amp; IRI (weeks 4, 8 &amp; 12) (p&lt;.05). AP+PBO group had significant increases in FI &amp; IRI at weeks 4, 8 &amp; 12 (p&lt;.05). <b>(Between Group)</b> No significant differences between MET+LSI &amp; MET alone. MET+LSI significantly superior to LSI alone on FI &amp; IRI (p&lt;.001) MET +LSI significantly superior to PBO on FG (p=.006), FI and IRI (p&lt;.001). MET alone significantly superior to LSI on FG (p=.04), GI &amp; IRI (p&lt;.001). MET alone significantly superior to PBO on FG, FI &amp; IRI (p&lt;.001 for all). LSI alone significantly superior to PBO on FG (p=.04), FI &amp; IRI (p&lt;.001).</p>
<p>Baptista et al. (2008) Venezuela RDB. OLZ+MET+SIB (n=13) vs. OLZ +MET+ PBO (n=15). 12 weeks. OLZ 11.3mg/day (in 4 months prior to study period, OLZ dose during study not</p>	<p>30 DSM-IV schizophrenia patients aged &gt;18 yrs, ≥4 months OLZ treatment and willing to lose weight or prevent excessive</p>	<p>All subjects were inpatients and participated in a programme for improved physical activity and healthy diet (details not stated).</p>	<p>Assessment of effects of MET + SIB or MET +PBO on BW and metabolic dysregulation in OLZ treated patients with schizophrenia. BW, BMI, WC,</p>	<p>28/30 (93%)</p>	<p><b>Weight Related (Within Group)</b> MET + SIB significantly reduced BW (p=.008), BMI (p=.006) &amp; WC (p=.013) from baseline. MET+PBO significantly reduced WC (p=.016). <b>(Between Group)</b> No significant between group differences were found.  <b>Glucose Related (Within Group)</b></p>

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<p>stated).</p> <p>Up to week 4 MET 850mg/day SIB 10mg/day. From week 5 MET 3400mg/day SIB 40mg/day</p>	<p>weight gain. Baseline BMI = 25.7kg/m<sup>2</sup> (MET + SIB) 26.8kg/m<sup>2</sup> (PBO)</p>		<p>FG, FI, HbA1c, HOMA-IR, lipids, leptin, cortisol, fibrinogen,</p>		<p>MET+SIB significantly reduced FG (p=.055) FI (p&lt;.001) &amp; HOMA-IR (p&lt;.001). MET + PBO significantly reduced FG, FI &amp; HOMA-IR (p&lt;.001 for all). <b>(Between Group)</b> No significant between group differences were found.</p> <p><b>Lipid Related (Within Group)</b> Met + SIB significantly reduced TC &amp; LDL (p&lt;.001). MET+PBO significantly reduced TC (p=.029), &amp;LDL (p=.026) TG increased significantly in the MET+PBO group (p&lt;.001). <b>(Between Group)</b> The increase in TG was significantly higher in the MET+PBO group than the MET+SIB group (p=.012)</p>
<p>Baptista et al (2007). Venezuela. RDB, 12 weeks. OLZ + Met (n=40) vs. OLZ +PBO (n=40) OLZ 10.3mg/day MET 850-2550mg/day</p>	<p>80 patients (76 DSM-IV schizophrenia and 4 DSM-IV bipolar disorder) .aged &gt;18 yrs, &gt; 4months OLZ treatment. Patients willing to lose weight or prevent excessive BW gain. Baseline BMI 25.0kg/m<sup>2</sup> (MET) 26.18kg/m<sup>2</sup> (PBO)</p>	<p>Recommendations for healthy food &amp; physical exercise to control WG were given at the beginning of the study.</p>	<p>Assessment of effects of MET on BW in OLZ treated patients with schizophrenia or bipolar disorder. BW, BMI, WC, FG, HbA1c, FI, HOMA-IR, lipids, leptin, cortisol, growth hormone. Fibrinogen, C-reactive protein.</p>	<p>72/80 (90%)</p>	<p><b>Weight Related (Within Group)</b> A strong motivation to control BW was observed in most patients, who spontaneously increased their physical activity and engaged in healthy food programs. MET group had significant BW (p=.01) &amp; BMI (p=.01) reductions. No significant changes in BM or BMI for PBO group. <b>(Between Group)</b> Marginal significance seen for between group differences in BW (p=.09) <b>Glucose Related (Within Group)</b> In the MET group FG, FI &amp; HOMA-IR remained stable but HbA1c significantly increased (p=.011) FI (p=.001) &amp; HOMA-IR (p=.006) increased in PBO group. <b>(Between Group)</b> No significant between group differences were found. <b>Lipid Related (Within Group)</b> In the MET group HDL significantly decreased (p=.007)</p>

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					No significant changes were found in the PBO group. <b>(Between Group)</b> A marginally significant difference was seen between LDL with PBO decreasing vs. the MET group (p=.055)
Baptista et al. (2006) Venezuela. RDB, 14 weeks. OLZ+MET (n=20) vs. OLZ+PBO (n=20) OLZ 10mg/day MET 850-1750mg/day	40 clinically stable patients with schizophrenia or schizoaffective disorder maintained on conventional antipsychotics and switched to OLZ + Met n=20 OLZ+PBO n=20 Baseline BMI = 23.1kg/m <sup>2</sup> (MET) 23.01kg/m <sup>2</sup> (PBO)	A balanced diet of 2500-3000 Kcal daily was provided but there was no control over smoking, snacking or exercise.	Prevention of weight gain and insulin resistance in OLZ treated schizophrenia patients. BW, BMI, WC, FG, FI, Lipids, HOMA-IR	37/40 (92.5%)	<b><u>Weight Related</u></b> <b>(Within Group)</b> OLZ + MET significantly increased BW, BMI & WC (p<.01 for all). OLZ + PBO significantly increased BW, BMI & WC (p<.01 for all). <b>(Between Group)</b> No significant between group differences were found. <b><u>Glucose Related</u></b> <b>(Within Group)</b> OLZ+MET group significantly decreased basal glucose levels (p<.02) FI (p<.01) & HOMAR-IR (p<.001) OLZ + PBO group significantly decreased post-load glucose (75g orally), FI & HOMA IR (p<.01 for all). <b>(Between Group)</b> No significant between group differences found.  <b><u>Lipid Related</u></b> <b>(Within Group)</b> OLZ +MET group significantly increased TG (p<.001). TC significantly decreased (p<.001) and HDL significantly increased (p<.02). OLZ +PBO group LDL (p<.05) & HDL (p=.001) significantly increased <b>(Between Group)</b> No significant between group differences were found.
Baptista et al. (2001) Venezuela. Double blind PBO controlled pilot study. Patients were prescribed (under blind conditions) PBO for 4	5 female patients with DSM IV schizophrenia chronically treated with antipsychotic	Patients wanted to lose but were not put on a diet or exercise plan.	Treatment of weight gain associated with long term AP use. Measures were BW, OGTT performed, FG,	5/5 (100%)	<b><u>Weight Related</u></b> During PBO treatment patients lost weight at marginal significance (p=.08) whereas weight lost during MET treatment was non significant. <b><u>Glucose Related</u></b> During PBO treatment the glucose & insulin AUC did not change significantly but during MET treatment they increased

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weeks then MET for 8 weeks. Various APs MET 500-2550mg/day	drugs and wanting to lose weight. (Actual age not stated). Baseline BMI ranged from 28.8 to 43.8kg/m <sup>2</sup>		FI, prolactin.		significantly (p=.043 & p=.037, respectively).
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AAP – Atypical Antipsychotic, AP = Antipsychotic, AUC = area under curve, BMI = Body Mass Index, BW = body weight, CLZ = Clozapine, FH = family history, FG = Fasting Glucose, FI = Fasting Insulin, HDL = high density lipoprotein cholesterol, HOMA-B = HOMA beta cell function, HOMA-IR = Homeostasis Assessment for Insulin Resistance, IRI – Insulin resistance index, IVGTT = intravenous glucose tolerance test, LDL = low density lipoprotein cholesterol LSI = Life Style Intervention, MET = Metformin, MET XR = Metformin extended release, OGTT = oral glucose tolerance test, OLZ = olanzapine, PBO = Placebo, Pt = patient, RDB = Randomised Double Blind, RISP = Risperidone, SG= serum glucose, SI=serum insulin, SIB = Sibutramine, SLP = Sulpiride, TC = total cholesterol, TG = triglyceride, VLP = Valproate, WC = Waist Circumference, WHR = Waist to Hip Ratio, wk = week,  $\geq 7\%BWG$  = proportion of patients who gain  $\geq 7\%$  of their baseline body weight,

**Table 4. Open Label Studies Examining the Effects of Metformin on Antipsychotic Associated Weight Gain and Other Metabolic Parameters in Adults with Psychiatric Disorders.**

Study, Locale, Type, Pharmacological Interventions and Doses.	Study Population	Non Pharmacological Interventions	Prevention or Treatment and Outcomes Assessed	Study Completion Rate	Statistically Significant Outcomes
Chen et al. (2008) Taiwan	24 DSM-IV schizophrenia patients	Subjects admitted to an inpatient facility for diet	Treatment of OLZ associated metabolic	24/24 (100%)	<u>Weight Related</u> Significant decrease in mean BW

Systematic review of metformin in non-diabetic SMI subjects (Bushe, Bradley, Doshi and Karagianis 2008)

<p>Open label prospective study, 8 weeks. OLZ + MET (n=24) OLZ 11.5mg/day MET 1500mg/day</p>	<p>aged 18-60. FG <math>\leq</math>126mg/dL no personal or FH of diabetes. Patients must have been receiving OLZ for &gt; 3months. Baseline BMI 25.8kg/m<sup>2</sup></p>	<p>stabilisation with an isocaloric diet (25-35 Kcal/kg) before and during the active treatment period. Subjects' activities provided by the hospitals did not change during the study process.</p>	<p>disturbance. BW, BMI. IVGTT performed and following measures taken, FG, FI, TG, lipids, HOMA-IR, HOMA-B, insulin secretion, glucose disappearance rate.</p>	<p>&amp; BMI at week 8 (P&lt;.01) <b>Glucose Related</b> Significant decrease in mean FG, FI, insulin secretion, HOMA-IR, HOMA-B by week 8. (p&lt;.01 for all). <b>Lipid Related</b> Significant decrease in TG at weeks 2 &amp; 4 (p&lt;.05) and week 8 (p&lt;.01)</p>
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AAP – Atypical Antipsychotic, RDB = Randomised Double Blind, LSI = Life Style Intervention, AP = Antipsychotic, BW = body weight, BMI = Body Mass Index, WC = Waist Circumference, WHR = Waist to Hip Ratio, FG = Fasting Glucose, FI = Fasting Insulin, TG = triglyceride, TC = total cholesterol, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol,  $\geq$ 7%BWG = proportion of patients who gain  $\geq$ 7% of their baseline body weight, HOMA-IR = Homeostasis Assessment for Insulin Resistance, HOMA-B = HOMA beta cell function, IRI – Insulin resistance index, CLZ = Clozapine, OLZ = olanzapine, RISP = Risperidone, SLP = Sulpiride, VLP = Valproate, MET = Metformin, SIB = Sibutramine, PBO = Placebo, FH = family history, IVGTT = intravenous glucose tolerance test, OGTT = oral glucose tolerance test, AUC = area under curve

**Table 5. Planned, Ongoing and Unpublished Studies of Metformin and Antipsychotics registered on ClinicalTrials.gov**

Study Name, Identifier and estimated completion date.	Study Subjects and Study Location	Study Objectives, Design and Outcomes Measures
<p>The Assessment of the Safety, Efficacy, and Practicality of an Algorithm Including Amantadine, Metformin and Zonisamide for the Prevention of Olanzapine-Associated Weight Gain in Outpatients With Schizophrenia NCT00401973 Study Completed.</p>	<p>Schizophrenia or schizoaffective subjects aged 18-65 yrs. United States, Brazil, Israel, Korea, Mexico, Puerto Rico, Russia. N - 207</p>	<p>Whether treatment with amantadine, MET or zonisamide can prevent or reverse the weight gain and changes in metabolic parameters that are associated with OLZ treatment.</p> <p>Prevention, Randomized, Open Label, Active Control, Parallel Assignment, Safety/Efficacy Study. 22 weeks. Patients prescribed OLZ with LSI compared with OLZ patients given LSI then sequential use of amantadine, MET and zonisamide if weight gain&gt;3kg, or OLZ patients given LSI then sequential use of MET, amantadine and zonisamide if weight gain&gt;3kg.</p> <p>Outcomes - WG, TG, TC, LDL-C, FG, HbA1c, Eating Inventory, Food Craving Inventory.</p>
<p>A Five Year, Prospective, Randomized, Blinded, Controlled Trial Comparing the Efficacy of a Modified Diabetes Prevention Protocol and the Standard Comprehensive Outpatient Care in Lowering the Incidence of New Onset Diabetes Among People Treated for Schizophrenia and Are at Risk to Develop Type II Diabetes Mellitus. NCT00182494 Completion date planned Jan 2009 but web page indicates study still recruiting.</p>	<p>Schizophrenia subjects aged 18-65 treated with antipsychotics for at least 2 years, gained &gt;10% body weight and with IFG or IGT. Canada. N – estimated 200</p>	<p>To test the effectiveness of a tailored lifestyle modification programme (for people with schizophrenia) with or without MET in individuals with schizophrenia in the prevention of diabetes.</p> <p>Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Efficacy Study Schizophrenia patients treated with AP are randomised under double blind conditions to a tailored lifestyle modification programme + MET or PBO and compared to patients randomised to a conventional diabetes prevention programme + MET or PBO. Follow up is for 5 years.</p> <p>Outcomes – prevention of diabetes, changes in lifestyle, eating and activity patterns.</p>

Study Name, Identifier and estimated completion date.	Study Subjects and Study Location	Study Objectives, Design and Outcome Measures
MET to Prevent the Metabolic Complications of OLZ. NCT00682448 Completion August 2009	Subjects aged >18 yrs diagnosed with Schizophrenia, Schizoaffective Disorder, Bipolar I or II or major depression with psychotic features who will be started on or who have just started taking olanzapine. United States. N – estimated 60.	To examine the efficacy and safety of MET to attenuate the metabolic side effects associated with OLZ.  Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Crossover Assignment, Efficacy Study. Patients will receive OLZ + PBO for 6 months and then given open label MET for a further 6 months or OLZ+MET for 6 months then continue on open label MET for a further 6 months.  Outcomes – BW, insulin resistance, dyslipidaemia, OGTT, HbA1c.
Comparison of Optimal Antipsychotic Treatments for Schizophrenia Pilot Study NCT00802100 Completion September 2009	Schizophrenia or Schizoaffective subjects aged 18-40 years treated with antipsychotics for <5 years. United States. N – estimated 60.	To compare the safety and effectiveness of OLZ, PER and ARI, with additional medications, MET, simvastatin and benztropine to limit treatment side effects, in adults with schizophrenia.  Treatment, Randomized, Single Blind (Outcomes Assessor), Active Control, Parallel Assignment, Safety/Efficacy Study Patients randomised under single blind (outcomes assessor) conditions to OLZ, ARI or PER. Side effects to all three antipsychotics monitored, and, depending on the side effect medications added to the treatment regimen. Increased cholesterol simvastatin added; weight gain, MET added; EPS benztropine added. Participants assigned to olanzapine or perphenazine automatically add MET or benztropine, respectively, to their regimens. Participants will also undergo a behavioural treatment aimed at reducing cardiovascular risk factors.  Outcome of antipsychotic efficacy is defined as completion of the trial without psychiatric hospitalization, clinician decision to discontinue treatment, or patient decision to discontinue treatment. Other outcomes – vital signs, WC, BW.

Study Name, Identifier and estimated completion date.	Study Subjects and Study Location	Study Objectives, Design and Outcome Measures
<p>MET in the Treatment of Antipsychotic-Induced Weight Gain in Schizophrenia (METS) - Pilot Study NCT00816907 Completion August 2009</p>	<p>Subjects 18-65 years with schizophrenia or schizoaffective disorder with BMI &gt;27kg/m<sup>2</sup> United States. N- estimated 80</p>	<p>To evaluate MET in treating people with schizophrenia or schizoaffective disorder who are overweight and also taking AP medications.</p> <p>Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Efficacy Study. 16 weeks. Participants taking AP randomly assigned to receive either MET or PBO, All participants will also receive LSI.</p> <p>Outcomes - body weight, WHR, and vital signs; clinical interviews about medication adherence, side effects, and alcohol use; and monthly blood tests to assess levels of lipids, SG, SI, and HbA1c</p>
<p>Improving Metabolic Parameters of Antipsychotic Child Treatment With Ziprasidone, Aripiprazole, and Clozapine. NCT00617058 Completion Sept 2010.</p>	<p>Children aged 10-17 with diagnosis of a schizophrenia spectrum disorder, bipolar disorder, various mood or disruptive/aggressive disorders. United States. N – estimated 60</p>	<p>To evaluate the relative risks and benefits of two approaches to the control of weight gain and other negative side effects in children and adolescents using ARI, ZIP or CLZ.</p> <p>Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study. 26 weeks Patients randomised to one of 2 treatments for 26 weeks.</p> <ol style="list-style-type: none"> <li>1. Healthy lifestyle instruction (nutritional and physical activity surveillance and advice) + continuation of current antipsychotic;</li> <li>2. Add MET + continuation of current antipsychotic</li> <li>3. No Intervention + continuation of current antipsychotic</li> </ol> <p>Outcomes - BMI, BW, fat mass, changes in SI, cholesterol, TG, incidence of metabolic syndrome.</p>
<p>Improving Metabolic Parameters of Antipsychotic Child Treatment. NCT00806234 Completion June 2013</p>	<p>Subjects aged 8-17 years diagnosed with a schizophrenia or bipolar spectrum disorder currently taking OLZ, QUET or RISP. United States. N – estimated 240</p>	<p>To assess the efficacy of switching from OLZ, QUET or RISP to ARI compared to the addition of MET to current antipsychotic therapy or continuation of current antipsychotic alone.</p> <p>Treatment, Randomized, Single Blind (Outcomes Assessor), Factorial Assignment, Safety/Efficacy Study. 24 weeks. Participants randomly assigned to one of three conditions:</p> <ol style="list-style-type: none"> <li>1. gradual switch of current AAP medication to ARI,</li> <li>2. addition of metformin to current AAP medication,</li> </ol>

		<p>3. no change to treatment with current AAP medication.</p> <p>Outcomes - BMI z score change, body fat mass, whole body ISI, TG, LDL, incidence of metabolic syndrome.</p>
<b>Study Name, Identifier and estimated completion date.</b>	<b>Study Subjects and Study Location</b>	<b>Study Objectives, Design and Outcome Measures</b>
<p>A Prospective Open-Label Trial of MET for Weight Control of Paediatric Patients on Atypical Antipsychotic Medications. NCT00391261 Completed October 2007</p>	<p>Subjects currently taking OLZ, QUET or RISP aged 10 to 18 years with diagnosis of schizophrenia spectrum disorder, bipolar disorder or pervasive developmental disorder. United States. N - estimated 11</p>	<p>To evaluate the effectiveness, safety, and tolerability of MET treatment in children and adolescents suffering from weight gain secondary to use of OLZ, QUET or RISP.</p> <p>Treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study. 12 weeks. Patients will continue on their current antipsychotic and have MET added. At consent patients were given healthy lifestyle advise but patients were asked NOT to change lifestyle or diet during the study.</p> <p>Outcomes - Changes in BW, BMI, skin fold test, abdominal girth.</p>
<p>MET for Weight Control in Adolescents Taking Atypical Antipsychotics- Double Blind Placebo Controlled Study. NCT00845936 Completion - May 2010</p>	<p>Subjects 12-20 years treated with AAP experiencing weight gain. Israel. N – estimated 30.</p>	<p>To assess the effect of MET on body weight of children and adolescents treated by AAP.</p> <p>Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment. Patients taking atypical antipsychotics randomised to MET or PBO for 12 weeks. No LSI given.</p> <p>Outcomes- BW, BMI, WC, BP, Blood cholesterol, FG, FI and Leptin levels. For safety- B12, Folate, lactate</p>
<p>MET Mitigation of AAP-Induced Metabolic Dysregulation in Adolescent Youth. NCT00617240 Completion - January 2010</p>	<p>Subjects aged 10-17 years with a SPMI paediatric diagnosis that meets DSM IV criteria and is frequently treated with AAP. N – estimated 40.</p>	<p>To determine whether starting MET in conjunction with an AAP and LSI will prevent or reduce the amount of weight gain and the metabolic changes in adolescent youth typically seen with AAP medication.</p> <p>Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Efficacy Study. 26 weeks. Patients randomised to receive AAP + MET or PBO. All subjects given LSI.</p> <p>Outcomes - BMI, BW, fat mass, SI, cholesterol, TG, incidence of metabolic</p>

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*AAP = Atypical Antipsychotic, AP = Antipsychotic, ARI=aripiprazole, AUC = area under curve, BMI = Body Mass Index, BP= blood pressure, BW = body weight, CLZ = Clozapine, FG = Fasting Glucose, FI = Fasting Insulin, ISI= insulin sensitivity index, LDL = low density lipoprotein cholesterol LSI = Life Style Intervention, MET = Metformin, OGTT = oral glucose tolerance test, OLZ = olanzapine, PBO = Placebo, PER = perphenazine, QUET= quetiapine, RISP = Risperidone, SG= serum glucose, SI=serum insulin, SIB = Sibutramine, SLP = Sulpiride, TC = total cholesterol, TG = triglyceride, WC = Waist Circumference, ZIP = ziprasidone.*