Guidelines for use of Metformin to manage Antipsychotic Induced Weight Gain in Adolescent patients (12-18 years old) – secondary care prescribing only

Aim
The purpose of this guideline is to provide prescribers with a comprehensive strategy for using metformin in the child and adolescent population where the use of an antipsychotic has resulted in notable weight gain.

The guideline provides:
- clear recommendations for weight monitoring before and after metformin is used
- clear guidance about other physical health monitoring that should be done before and after metformin is used
- detailed information about the adverse effects and risks associated with metformin
- clear guidance about how to use metformin in adolescents (dose escalation, maintenance dose, duration of therapy)

Background
The prevalence of obesity and diabetes in individuals diagnosed with schizophrenia and mood disorders is estimated to be approximately 1/5-2 times higher than in the general population\(^1\). There are many causes of weight-gain for those with mental illness. Lethargy and lack of motivation due to illness are possible contributory factors. Poor diet and limited exercise may also be influential.

It is known that various psychotropic medicines can cause weight gain and numerous mechanisms for this have been proposed. Increased appetite and thirst are regularly reported by patients taking anti-psychotics; patients often describe drinking large amounts of sugary drinks to quench the thirst. Endocrine changes leading to reduced metabolism of fats and glucose may occur and may be influenced by genetic makeup\(^2\). Of the older ‘typical’ antipsychotics, the weight-gain effects of phenothiazines are greater than butyrophenones. With the second generation antipsychotics, olanzapine and clozapine have the greatest potential to induce weight gain, whereas aripiprazole and amisulpiride are regarded as weight neutral, although individuals may gain weight with any of these drugs. Risperidone and quetiapine are ranked in between\(^3\).

The risk of psychotropic induced weight gain is higher in patients who are female, those with a family history of obesity, those who are younger (gain is reduced by 0.6kg for every extra 10 years of age) or have a relatively higher BMI to start\(^4\).

Although antipsychotic induced weight gain is now well recognised, other psychotropic medication may also induce significant weight gain, which should not be overlooked. These include tricyclic antidepressants, mirtazapine, MAOIs, valproate, carbamazepine, lamotrigine and lithium\(^5\).

How to manage antipsychotic induced weight gain
Non-pharmacological methods should always be considered first to manage antipsychotic induced weight gain\(^6\). Barriers to weight loss, such as poor diet and reduced physical exercise should be addressed in all cases, regardless of whether any further interventions are used. In the event that weight gain cannot be managed by lifestyle changes alone, a switch to an alternative antipsychotic with a lower propensity to cause weight gain should be considered as the next step\(^7\).

Pharmacological interventions to manage weight gain, such as metformin or orlistat, should only be considered when all of the above options have either been tried or deemed unsuitable\(^2\).

Metformin may be considered as a first line pharmacological option in adolescents once this position has been reached.

Summary of the literature:
Guideline produced and developed by Orla Macdonald (Lead Research Pharmacist), Dr Marta Costa (Core Trainee), and Dr Lopamudra Winters (ST6 in CAMHS)
Approved by Oxford Health NHS Foundation Trust Drugs & Therapeutics Committee 15\(^\text{th}\) October 2013

Recommendations for weight monitoring in adolescents
The Trust weight monitoring guidelines recommend that weight should be measured ‘regularly’ for the first 3 months of treatment with an antipsychotic; fortnightly for the first 6 weeks\(^8\). The Maudsley guidelines, recommend weekly monitoring for the first 3 months\(^9\).

In adolescents, we recommend that weight and BMI should be reviewed weekly during the first three months and the age adjusted z scores\(^*\) should be plotted on a centile chart. If the adjusted weight gain increases by >5% from baseline over the first 6-8 weeks treatment, then significant measures should be put in place to prevent any further increase.

After the first 3 months, weight and height should continue to be monitored at three monthly intervals for the remainder of the first year and then at least 6 months thereafter depending on physical need\(^10\).

Following Metformin initiation:
Weight, BMI and calculated z scores\(^*\) should be measured weekly, if still within initial 3 months after starting an antipsychotic, and then monthly thereafter, until weight has stabilised.

If metformin has not shown a benefit to weight management after 16 weeks of treatment, it should be discontinued.

\(^*\) Body mass index z-scores, also called BMI standard deviation (s.d.) scores, are measures of relative weight adjusted for child age and sex

---

1. Oxford Health NHS Foundation Trust
2. Lopamudra Winters (ST6 in CAMHS)
3. Approved by Oxford Health NHS Foundation Trust Drugs & Therapeutics Committee 15\(^\text{th}\) October 2013
We conducted a literature search of MEDLINE and EMBASE databases to find evidence for using metformin to manage antipsychotic induced weight gain in adolescents. Four studies\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\) and one case report\(^9\) were found. The studies are summarised below.

In 2002, Morrison et al administered 500mg TID metformin to 19 adolescents in a 12 week open label trial\(^5\). Participants were taking olanzapine, risperidone, quetiapine or valproate and had shown a weight gain over 10% of their baseline weight prior to enrolment. They were aged between 10 and 18 yrs (mean 14 yrs). Of the 19 patients, 15 lost weight, 1 remained unchanged and 3 gained weight. Mean changes in weight and BMI at the 12 week point were statistically significantly. Metformin was generally well tolerated; one patient withdrew in the first month because of diarrhoea.

In 2006, Klein et al administered 850mg BD metformin or placebo to 39 participants in a 16 week randomised, controlled trial\(^6\). Participants were taking olanzapine, risperidone or quetiapine and had shown a weight gain over 10% of their baseline prior to enrolment. They were aged between 10 and 17 years. Participants were given 500mg once daily for a week, then 500mg BD, then 850mg BD for 14 weeks. All participants were given 3 family sessions of dietary counselling during the study. Mean differences in BMI were found to be statistically significant at all time points (4, 8, 12 and 16 weeks). As the study was conducted in growing children, age corrected differences in the standard deviations for both weight and body mass index (z scores) were determined. These were found to be increased in the placebo group and decreased with metformin and these changes were significant from week 8 onwards. Metformin was well tolerated throughout.

In 2008, Arman et al administered 500mg BD metformin or placebo to 49 participants in a 12 week randomized controlled trial\(^7\). 17 patients were excluded due to incomplete use of drug or side effects and analysis was completed on just 32 patients. Participants took risperidone 6mg throughout the study. Metformin was started before any weight changes were observed as the study aimed to assess the effect of the drug at preventing weight gain. Participants were <20 years old. Results showed that participants in both groups gained weight (mean 1kg with metformin and 1.35kg with placebo) and metformin did not show significant benefit over placebo in the 12 week period. However six patients in the placebo group had >7% weight gain in contrast with one metformin patient.

In 2009, Shin et al administered up to 2000mg daily metformin to 11 participants in a 12 week open label study\(^8\). Participants were taking risperidone, aripiprazole or clozapine and had experienced weight gain of more than 10% above baseline prior to enrolment. Results showed that the mean reduction in weight, waist circumference and BMI was not statistically significant although 5 out of 11 patients lost weight and overall the sample did not continue to gain weight. Metformin was well tolerated throughout.

How to prescribe Metformin

- Initiate treatment at 500mg daily for two weeks, then increase to 500mg BD for two weeks, then increase to 850mg BD.

850mg BD is the recommended treatment dose\(^11\).

- If notable adverse effects occur (especially GI disturbance) it may be helpful to leave longer gap (3-4 weeks) between dose increases.

- Review use of metformin after 2-3 months on high (850mg BD) dose. If there has been no notable benefit (i.e. patient weight (height adjusted) has continued to increase rapidly) then discontinue.

- Slow release metformin (MR preparation) may be better tolerated but is considerably more expensive, so should only be used if immediate release is not tolerated.

Adverse effects of using Metformin

The most common adverse effects are gastrointestinal disorders, such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose can improve gastrointestinal tolerability\(^10\).

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. It has primarily been reported in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by assessing also other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia\(^10\).

Guideline produced and developed by Orla Macdonald (Lead Research Pharmacist), Dr Marta Costa (Core trainee), and Dr Lopamudra Winters (ST6 in CAMHS)
Approved by Oxford Health NHS Foundation Trust Drugs & Therapeutics Committee 15th October 2013
Licence status:
Metformin is licensed for the treatment of diabetes in children over 10, under specialist supervision only. It is not licensed for the management of obesity or antipsychotic induced weight gain, however the Trust Drugs and Therapeutics Committee has approved its use for this indication in the Trust. Therefore clinicians do not need to fill in an unlicensed medicines form in order to use it for antipsychotic induced weight gain in adolescents.

Algorithm:

**Antipsychotic treatment prescribed**
Give advice on risk of weight gain and encourage appropriate diet/exercise regime

**Measure weight / BMI**
Plot results on centile chart.

If significant weight gain occurs

**Prioritise non-pharmacological weight management techniques**
Review diet and exercise. Refer to dietician / physiotherapist.

If little benefit seen or lifestyle changes not possible

**Consider change of antipsychotic**

If weight gain continues or change not possible

**Start metformin.**

Monitor side effects and weight/BMI

**Review benefit after 16 weeks treatment**

No benefit

**Discontinue metformin**

Weight stabilised

**Continue metformin.**
Monitor for vitamin B deficiency.

References:


Guideline produced and developed by Orla Macdonald (Lead Research Pharmacist), Dr Marta Costa (Core trainee), and Dr Lopamudra Winters (ST6 in CAMHS)
Approved by Oxford Health NHS Foundation Trust Drugs & Therapeutics Committee 15th October 2013