Guidelines for the management of weight gain and metabolic disturbances linked with psychosis and antipsychotic drug treatment

Introduction

These guidelines are based on guidelines produced by the British Association for Psychopharmacology (BAP)\(^1\)

Excess deaths from cardiovascular disease are a major contributor to the significant reduction in life expectancy experienced by people with schizophrenia. Important risk factors in this are smoking, alcohol misuse, excessive weight gain and diabetes. Weight gain also reinforces service users’ negative views of themselves and is a factor in poor adherence with treatment. Being overweight and obesity, partly driven by antipsychotic drug treatment, are important factors contributing to the development of diabetes and cardiovascular disease in people with schizophrenia. There have been clinical trials of many interventions for people experiencing weight gain when taking antipsychotic medications but there is a lack of clear consensus regarding which may be appropriate in usual clinical practice. The BAP guidelines reviewed these trials and made consensus recommendations regarding appropriate interventions.

Guidance

See additional information below for more specific guidance and information about the monitoring and interventions listed below to manage weight gain.

1. Body mass index should be measured ideally prior to treatment with an antipsychotic and during treatments to monitor whether an individual is becoming overweight or obese.

2. Lifestyle interventions are recommended first-line and ‘booster interventions’ may be needed to maintain effect. These should usually be continued alongside other interventions if needed.

3. If lifestyle interventions alone are not successful consider switching to another antipsychotic if possible with a lower propensity to gain weight.

4. Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine.

5. Metformin can be an option if lifestyle interventions, switching and adjunctive aripiprazole (if appropriate) have failed and the patient’s GP is willing to initiate and monitor the metformin. An information sheet for GPs is available (see appendix 1).

6. **Very important:** The patient’s GP should be asked if they would be willing to initiate and monitor metformin use before any discussion takes place with the
patient about its use as any prescribing will need to be initiated and monitored in primary care.

7. If the GP then agrees to prescribe metformin if the patient agrees to a trial, it should be explained to the patient that the use of metformin for this indication would be an off-label use and that this is specific to their need and not a medication for use in people who just want to lose weight.

A simple leaflet for this indication is available on the Choice and Medication website:  
http://www.choiceandmedication.org/sussex/medications/171/

A copy of the SPC for metformin is available at:  
https://www.medicines.org.uk/emc/medicine/1043

8. Explain to the patient that the continued prescribing of metformin will only take place if weight loss of at least 3 kg has been achieved or other significant clinical benefits have been seen after approximately 12 weeks, e.g. if previously gaining weight rapidly, this rapid weight gain has stopped.

9. Explain to the patient that the need for continuing metformin treatment will be reviewed if the current antipsychotic is stopped or the weight is regained, with the possibility that the metformin will be stopped. In addition the continuing need for metformin will be reviewed at least annually.

10. If the patient agrees to a trial of metformin, obtain verbal consent, recording this in their care notes. Confirm with the GP that the patient is aware that is an unlicensed indication and informed consent has been obtained and recorded. Provide the GP with details of the patient’s latest weight and their pre-antipsychotic weight.

Additional information

Monitoring when starting and continuing treatment with antipsychotics

- Body mass index (BMI) should be used to monitor whether an individual is becoming overweight or obese. This requires frequent measurement of weight during the early stages of treatment: ideally weekly for the first 4–6 weeks and then every 2–4 weeks up to 12 weeks; but, as a minimum, once every 4 weeks for the first 12 weeks’ of treatment. Weight (and BMI) should then be assessed at 6 months and at least annually thereafter, unless the clinical situation demands more frequent assessment.

- In the long-term, blood glucose control should be monitored using glycated haemoglobin (HbA1c). However, as HbA1c provides a measure of longer-term control, in the early weeks of treatment, fasting or random plasma glucose may provide a more appropriate measure of glucose control. Glucose control should be further assessed at 12 weeks, 6 months and then annually.
If there is a change in antipsychotic medication, then when clinically relevant it is appropriate to re-visit all of the steps outlined above.

**Lifestyle interventions**

- Lifestyle interventions (mostly of the 'behavioural lifestyle intervention' type) are recommended as they have a positive effect in the majority of RCTs. In most circumstances they should be continued in addition to any additional intervention.

- On average, these interventions will reduce existing weight by approximately 3 kg more and BMI by approximately 1 kg/m² more, than the control treatment.

- They will attenuate weight gain in first-episode initiations of antipsychotics.

- There is no clear evidence regarding the optimal duration of engagement with such interventions. Evidence regarding maintenance of effects is limited in both those with long-standing and first episodes of illness. ‘Booster sessions’ may be required to maintain effects.

- A limited amount of evidence suggests that programmes work best if designed specifically for those with psychosis and if they combine elements of group and individual patient approaches.

**Antipsychotic switching**

- Switching to one of the antipsychotic medications with lower propensity for weight gain is a strategy that should be considered.

- Data suggest a hierarchy of antipsychotic medications with respect to weight gain, with the following medications appearing to carry the lowest risk for weight gain:
  - Aripiprazole, amisulpride, haloperidol, lurasidone

- Antipsychotics with a high risk of weight gain are:
  - Clozapine and olanzapine

- Antipsychotics with a medium risk of weight gain are:
  - Paliperidone, quetiapine and risperidone

- Clinicians must balance the possible benefit on weight of switching antipsychotic medication against the risks of inducing relapse of core psychotic symptoms.

**Adjunctive aripiprazole**

- Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine.
Three RCTs of the addition of aripiprazole to clozapine or olanzapine, only one of significant size, found a mean difference in weight loss for aripiprazole over placebo of just over 2 kg.

**Adjunctive metformin**

- In the context of recommendations regarding groups at high risk of diabetes in NICE PH38\(^2\), metformin should be considered as an adjunct to attenuate or reduce weight gain following antipsychotic medication.

- It should be emphasised that lifestyle interventions should have been fully explored and the other interventions considered, as above.

- Metformin has been compared to lifestyle intervention for weight reduction in a large 3-year RCT of people at high risk of diabetes in the general population.

- Metformin leads to a modest reduction in weight (approximately 2 kg) over the short and long term but is less effective than intensive lifestyle intervention.

- Its use in certain situations in people at high risk of diabetes is supported by NICE PH38\(^2\).

- In people taking antipsychotic medications, short-term trials have shown that metformin reduces weight, compared to placebo, by approximately 3 kg.

- It attenuates weight gain in first-episode initiations of antipsychotic medication by approximately 5 kg, compared to placebo.

- There are some risks attached to metformin that require appropriate monitoring, eg. renal function and vitamin B12 levels.

**References**


Information for GPs considering prescribing metformin for patients on an antipsychotic who have gained weight and have not responded to other interventions

The Sussex Partnership NHS Foundation Trust is not in position to initiate and monitor the use of metformin in patients who have gained weight on antipsychotic and who are not able to lose weight following lifestyle interventions and in whom switching to an alternative antipsychotic causing less weight gain is not an option. The Trust's Drugs & Therapeutics Group has supported metformin being recommended to GPs in line with Trust guidelines based on the BAP guidance for patients who may benefit and meet certain criteria.

Before considering prescribing metformin:

- There must be confirmation from the psychiatrist that:
  - Life style behavioural changes and if clinically appropriate, a switch to another antipsychotic with less potential to produce weight gain, have been tried first and also if appropriate adjunctive aripiprazole has been tried.
  - The patient has gained a minimum of 5kg since starting the antipsychotic treatment.
  - That the patient is aware that the prescribing just to lose weight or stop continuing rapid weight gain is unlicensed and that verbal consent to try metformin has been obtained from the patient and recorded.

- Remind the patient that the use of metformin for this indication would be an off-label use and that this is specific to their need and not a medication for use in people who just want to lose weight.

- Remind the patient that the continued prescribing of metformin will only take place if weight loss of at least 3 kg has been achieved or other significant clinical benefits have been seen after approximately 12 weeks, e.g. if previously gaining weight rapidly, this rapid weight gain has stopped.

- Remind the patient that the need for continuing metformin treatment will be reviewed if the current antipsychotic is stopped or the weight is regained, with the possibility that the metformin will be stopped. In addition the continuing need for metformin will be reviewed at least annually.

There is now a leaflet on the Choice and Medication website specifically written for patients on antipsychotics that need metformin to supplement diet and exercise as an approach to lose weight. This is available at the link: www.choiceandmedication.org/sussex/pdf/billmetformin.pdf

Prescribing should be in line with NICE diabetes guideline (CG87) and the British National Formulary. The key information is:

- The starting dose of metformin should be 500mg once daily, slowly increasing by intervals of at least 1 week (preferably longer, over two to three weeks) to a
usual maximum of 2g/daily, based on tolerability (The licensed maximum dose is 3g/daily, but doses above 2g/daily may not be tolerated) in divided doses.

- Metformin requires periodic monitoring of renal function, at baseline and then at least annually, with those at high risk of renal impairment or if deterioration suspected monitored at least 6 monthly. This is required due to an increased risk of lactic acidosis with administration of metformin when renal function drops below a Glomerular Filtration Rate (eGFR) of 45ml/min/1.73m². Metformin should be avoided if eGFR drops below 30ml/min/1.73m².

- Every face-to-face review of continuing metformin prescribing should be accompanied by reinforcing advice on healthy eating and physical activity to maximise the effect of the intervention.

- Advise alcohol avoidance with metformin due to the rare risk of lactic acidosis.

- The summary of product characteristics for metformin recommends withdrawing or interrupting treatment in patients at risk of tissue hypoxia or deterioration of renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or those who have recently had a myocardial infarction.

- Advise to take metformin with or after food to minimise gastric side effects.

**Basis for this advice**

The British Association for Psychopharmacology (BAP) published guidelines in April 2016¹ that covered guidance on managing patients who gained weight on antipsychotics. The main points of the guidance are:

1. Lifestyle interventions are recommended first-line and ‘booster interventions’ may be needed to maintain effect. These should usually be continued alongside other interventions if needed.

2. If lifestyle interventions alone are not successful consider switching to another antipsychotic if possible with a lower propensity to gain weight.

3. Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine.

4. Metformin can be an option if lifestyle interventions, switching and adjunctive aripiprazole (if appropriate) have failed and the patient is willing to take it outside of its licensed indication.

**Reference**