Article

BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment

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Abstract

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. Monitoring of relevant physical health risk factors is frequently inadequate, as is provision of interventions to modify these. These guidelines review issues surrounding monitoring of physical health risk factors and make recommendations about an appropriate approach. 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. These guidelines review these trials and make recommendations regarding appropriate interventions. Interventions for smoking and alcohol misuse are reviewed, but more briefly as these are similar to those recommended for the general population. The management of impaired fasting glycaemia and impaired glucose tolerance ('pre-diabetes'), diabetes and other cardiovascular risks, such as dyslipidaemia, are also reviewed with respect to other currently available guidelines.

These guidelines were compiled following a consensus meeting of experts involved in various aspects of these problems. They reviewed key areas of evidence and their clinical implications. Wider issues relating to primary care/secondary care interfaces are discussed but cannot be resolved within guidelines such as these.

Keywords

Alcohol misuse, antipsychotic, aripiprazole, cardiovascular disease, diabetes, dyslipidaemia, guidelines, interventions for weight gain, lifestyle, metformin, obesity, overweight, psychosis, risk assessment, schizophrenia, smoking cessation, switching

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Introduction

During the last 20 years there has been an increased focus on the problem of premature mortality among people with schizophrenia. In part this has been driven by concerns about weight gain, concerns that have increased following the introduction of newer antipsychotic medications. Local and national audit programmes have highlighted the poor quality of monitoring and management of potential physical health problems in people with all types of mental health disorder but particularly for those with psychotic illnesses. This has culminated in an increased drive not only to achieve greater equality in health care resource distribution for those with mental health problems, compared to those with physical health problems, but also to ensure that those with mental health problems receive proper care for their physical health problems (Royal College of Psychiatrists, 2010, 2013).

These aspirations have been partially recognised by the UK National Health Service (NHS) in its document '*No Health Without Mental Health: A Cross-Government Mental Health Outcomes Strategy for People of All Ages*' (Department of Health, 2011: paragraphs 3.26–3.30) and through the institution of a specific set of standards for the annual assessment of the quality of physical health care provided by mental health trusts to people with psychosis, delivered through the national commissioning for quality and innovation (CQUIN) programme (NHS England, 2015: indicators 4a and 4b). However, considerable progress and commitment will be required to make a significant impact on patient outcomes. It is thus important that clinical staff have access to appropriate evidence based recommendations regarding how best to monitor and manage physical health problems, and particularly risk factors for cardiovascular and metabolic disorders, in people with mental illnesses.

A previous review in the *Journal of Psychopharmacology* (Barnett et al., 2007) reported the conclusions of a pharmaceutical industry funded consensus meeting examining metabolic and cardiovascular risk in schizophrenia. That review examined relevant risk factors in some detail and the effects of antipsychotic medications. Recommendations were made regarding assessment and monitoring of these risks. However, review of potential strategies for intervention was limited, in large part because of the lack of available clinical trial and meta-analysis data at that time.

The guidelines presented here focus on recent considerations in relation to risk factors for cardiovascular and metabolic disorders in people with psychosis, including: assessment of risk factors; the evidence of ongoing failure to monitor relevant risk factors adequately and then particularly on the evidence relating to suggested strategies for the management of weight gain. While interventions for other risk factors (e.g. smoking and alcohol misuse) are also important, the evidence regarding these has been reviewed elsewhere but is summarised here. Relevant aspects of the current national guidelines regarding management of pre-diabetes states, diabetes and other cardiovascular risks, such as dyslipidaemia, are discussed. The management of other relevant disorders, such as hypertension, should be as within the general population, taking into account any possible interactions between antihypertensive, or other, medications and psychotropic medications.

(Note: The term 'dyslipidaemia' is frequently used in this document. Our usage is explained in Appendix 1.)

Scope of these guidelines

The aim of these guidelines is to provide recommendations regarding the monitoring and management of risk factors for diabetes and cardiovascular disease (CVD), in adults over the age of 18 years with psychosis, taking into account the effects of antipsychotic medications and with particular emphasis on overweight and diabetes. Most of the evidence reviewed in support of these recommendations comes from studies of people with schizophrenia. However, a proportion also comes from studies that include people with other forms of psychosis, who are receiving treatment with the same antipsychotic medications as those with schizophrenia. Thus, it seems reasonable that most of the findings relating to cardiometabolic risk and its management can be generalised across the spectrum of common psychotic disorders, although they can most reliably be applied to people with schizophrenia.

We also review relevant key points from current National Institute for Health and Care Excellence (NICE) guidelines on the management of diabetes and cardiovascular risk.

These guidelines are intended to inform psychiatrists, general practitioners, pharmacists, nurses, other mental health practitioners and commissioners of services about current evidence and to facilitate discussions at local level regarding how best to provide the relevant care for people with psychoses. This is an important clinical problem given the significant excess mortality from CVD suffered by this group.

At the outset it was decided that we would not attempt to carry out a comprehensive review of data relating to children and young people with psychosis. We recognise the problem of weight gain in young people, and appropriate interventions for this, as an important topic but decided that the paucity of good data relating to this group would make it impossible to write similarly evidence based recommendations. Appendix 2 provides a brief discussion of links between these guidelines and parallel issues for young people with psychosis.

It was also decided that it would not be feasible to carry out a similarly evidence based review in relation to the monitoring and management of cardiometabolic risk factors in people with intellectual disability, and the possible effects of antipsychotic medications on these. Many of the factors involved in people with intellectual disability becoming overweight or obese are very different to those in the populations in which the randomised controlled trials (RCTs) reviewed here have been carried out. The majority of prescribing of antipsychotics in this group is not for psychotic disorders. Many studies of interventions for weight gain in this population are open studies without a control arm. Again, while this is an important topic, it would seem best for it to be addressed by a group with specialist expertise in managing people with intellectual disability who would have these guidelines available as a starting point.

As health inequalities for people with a learning disability have been highlighted in a number of national reports, attention is drawn to the recommendation by the Royal College of General Practitioners (RCGP) that people with an intellectual disability should have an annual health check. The RCGP provides a comprehensive and practical guide for this (Hoghton, 2010).

Summary of methodology

A group of nationally recognised experts was invited to an initial meeting on 15 January 2015. Each was asked to give a brief

Table 1. Categories of evidence and strength of recommendations.

Categories of evidence for causal relationships and treatment
Ia: evidence from meta-analysis of randomised controlled trials
Ib: evidence from at least one randomised controlled trial
IIa: evidence from at least one controlled study without randomisation
IIb: evidence from at least one other type of quasi-experimental study
III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Proposed categories of evidence for observational relationships
I: evidence from large representative population samples
II: evidence from small, well-designed, but not necessarily representative samples
III: evidence from non-representative surveys, case reports
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendation
A Directly based on category I evidence from meta-analysis of randomised controlled trials, at least one large, good quality, randomised controlled trial or replicated, smaller, randomised controlled trials
B Directly based on category II evidence from meta-analysis of randomised controlled trials, at least one large, good quality, randomised controlled trial or replicated, smaller, randomised controlled trials, or extrapolated[a] recommendation from category I evidence
C Directly based on category III evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case–control studies, or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence from expert committee reports or opinions and/or clinical experience of respected authorities, or extrapolated[a] recommendation from category I, II or III evidence
S Standard of good practice

[a]Extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.

presentation on a key area relating to the problem with, where appropriate, emphasis on RCTs and meta-analyses. Each presentation was followed by a discussion of the important issues in order to identify consensus, on the one hand, and areas of uncertainty on the other. A literature review was then compiled of evidence for the consensus points. This review and recommendations was circulated to the consensus group participants. Their feedback was, as far as possible, incorporated into the final version of the guidelines.

The guideline recommendations are linked to relevant evidence through the literature review. However, our methodology and available funding did not allow for a systematic review of all possible data from primary sources. Existing systematic reviews and RCTs were identified from MEDLINE and EMBASE and from the Cochrane Database. Published NICE guidelines on schizophrenia, pre-diabetes, diabetes, lipid modification and substance abuse (CG1, CG82, CG115, CG155, CG178, CG181, CG185, CG189, NG28, PH38 and QS80) were also considered.

Strength of evidence and recommendations for these guidelines

The categories of evidence applied to the literature reviewed, and the strength of the recommendations made, are described in Table 1, which is derived from Shekelle and colleagues work on the development of clinical guidelines (Shekelle et al., 1999). 'Strength of recommendation' is rated A to D according to category of evidence. A lower rating implies a less extensive or robust body of evidence but not necessarily lesser clinical importance. The category S represents a standard of care, which describes a consensus based on good practice standards rather than evidence.

Randomised controlled trials must have an appropriate control treatment arm. For primary efficacy this should include a placebo condition, although for 'lifestyle-type' interventions and psychological treatments this may not be feasible.

Summary of literature review and recommendations

It is important to remember that any decisions regarding monitoring of a person's physical health risks, and the decision regarding possible intervention for such risks, should always be carried out in collaboration with that individual and, where appropriate, a carer or family member. This is perhaps particularly relevant for some of the interventions discussed which require significant cooperation from the person involved.

Background

- Life expectancy is reduced by 20 years in people with schizophrenia. Physical illness, and particularly CVD, is the main contributor to this (I).
- A significant proportion of people with schizophrenia develop diabetes and/or have other risk factors for CVD (especially smoking, overweight/obesity and alcohol misuse) (I). These factors are associated with increased CVD and consequent increased mortality (I).
- Overweight is an important risk factor for diabetes and CVD in people with schizophrenia. Factors driving weight gain and the risk of diabetes include: poor lifestyle (II); effects of antipsychotic treatment (which varies between drugs and which can result in profound weight increase in the first few weeks of treatment) (I);

pharmacogenetic differences between individuals (II) and direct effects of some antipsychotic medications to interfere with insulin secretion (II).
- Assessment of risk factors for metabolic disease and CVD is vital and should be carried out regularly. Evidence from national audit programmes in secondary care is that monitoring of such risk factors is inadequately carried out (I).
- Use of cardiovascular risk prediction models, such as QRISK2, is valuable (I). However, QRISK2 has limitations for this population (e.g. only validated for those aged over 25 years). In the future, general population prediction models may be supplanted by a risk score specifically developed for people with psychosis on antipsychotic medications. Current risk scores for the general population may underestimate cardiovascular risk for people with psychosis.

Monitoring for physical health risk factors (these are all category S)

- The measurements below should be assessed before starting an antipsychotic, or as soon as possible afterwards, and then at the intervals indicated.
- 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 (HbA_{1c}). However, as HbA_{1c} 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.
- The lipid profile should be assessed at 12 weeks, 6 months and then annually. In order to assess cardiovascular risk, for example using the QRISK2 cardiovascular risk model, the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio will be required. A random, rather than fasting, sample can be used if a fasting sample cannot be obtained.
- Blood pressure should be monitored at 12 weeks, 6 months and annually thereafter.
- If there is a change in antipsychotic medication then, when clinically relevant, it is appropriate to re-visit all of the steps outlined above.
- Tobacco smoking and alcohol use should be enquired about at all opportunities.
- It is important to take ethnicity into account when evaluating BMI results.

Recommended interventions for overweight and obesity

Most published RCTs examine the effects of an intervention versus placebo, or other appropriate control, to reduce existing weight gain. The majority of the trials of pharmacological interventions also include some form of lifestyle approach (usually not intensive) for both treatment groups. Some studies in people in their first episode of psychotic illness examine attenuation of weight gain versus standard regimens.

Most clinical trials have been for short or intermediate durations of between 6 and 12 weeks. A few have been for 24 weeks or longer.

While it is not feasible to provide meaningful comparative figures for the mean reduction in weight induced by specific strategies, in general most strategies result in weight reduction in the range of 2 kg to 3.5 kg and a drop in BMI of around 1 kg/m^2. (Note: an increase of 1 kg/m^2 results in an 8.4% increase in risk for the development of diabetes.)

- Lifestyle interventions (mostly of the 'behavioural lifestyle intervention' type)
  - Lifestyle interventions are recommended as they have a positive effect in the majority of RCTs (A). These should almost always be part of the first line of approach and in most circumstances should be continued in addition to any additional intervention (S).
  - On average, these interventions will reduce existing weight by approximately 3 kg more, and BMI by approximately 1 kg/m^2 more, than the control treatment.
  - They will attenuate weight gain in first-episode initiations of antipsychotics (B).
  - 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 (C).
  - 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 (C).
- Antipsychotic switching
  - Extrapolation from the evidence, below, suggests that switching to one of the antipsychotic medications with lower propensity for weight gain is a strategy that should be considered (B).
  - Much of the evidence to support antipsychotic switching strategies inevitably comes from meta-analyses of the differential effects of different medications on weight. These data suggest a hierarchy of antipsychotic medications with respect to weight gain, with the following medications appearing to carry the lowest propensity for weight gain: haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride and asenapine (asenapine is only licensed for bipolar mania in the UK) (A).
  - Only four RCTs have directly examined antipsychotic switching for the specific purpose of weight reduction. These supported switching from olanzapine to either aripiprazole or quetiapine with an approximately 3 kg greater weight reduction with switching compared to no change (B).
  - Clinicians must balance the possible benefit on weight of switching antipsychotic medication against the risks of inducing relapse of core psychotic symptoms (S).

- Adjunctive aripiprazole
  - Adjunctive aripiprazole is recommended as a possible intervention for weight gain associated with clozapine and olanzapine (B).
  - 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 (B).
  - Extrapolation of this effect to weight gain induced by other antipsychotic medications is not supported by current evidence.
- Adjunctive metformin
  - In the context of recommendations regarding groups at high risk of diabetes in NICE PH38, metformin should be considered as an adjunct to attenuate or reduce weight gain following antipsychotic medication (A). It should be emphasised that lifestyle interventions should have been fully explored and the other interventions, above, considered.
  - 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 (A).
  - Its use in certain situations in people at high risk of diabetes is supported by NICE PH38 (S).
  - In people taking antipsychotic medications, short-term trials have shown that metformin reduces weight, compared to placebo, by approximately 3 kg (A). It attenuates weight gain in first-episode initiations of antipsychotic medication by approximately 5 kg, compared to placebo (A).
  - There are some risks attached to metformin that require appropriate monitoring (renal function and vitamin B_{12}) (S).

Other interventions for overweight and obesity

A wide variety of other treatments have been subject to clinical studies (Table 3). On the basis of currently available evidence, those summarised below are not recommended for use in routine clinical practice. For some, the evidence either suggests no beneficial effect or is currently inadequate to justify their consideration in other than exceptional clinical circumstances. For some, the consensus view is that the adverse event profile outweighs potential benefits in the majority of clinical circumstances.

With respect to the treatments described below, the majority of RCTs have been of relatively short duration and involved relatively small numbers of participants – around 30–60.
(A number of other drugs studied in this context have either been withdrawn from use, because of safety issues, or are not currently available in the UK. These are not included in this summary but are discussed in the main literature review.)

- Orlistat has been subject to RCTs in the general population where it reduces weight by approximately 3 kg over 1 year (A). However, long-term use is extremely limited by high rates of discontinuation. In two trials in psychosis an effect was seen only in men (B). Clinical experience suggests high rates of discontinuation in this patient group, making it of little value in routine clinical practice (C).
- Three out of four RCTs of topiramate as an adjunct to antipsychotics reported statistically significant weight loss, ranging from 1.5 kg to 5 kg. One RCT supports an effect to attenuate weight gain in people with a first episode of psychosis (B). However, the risk–benefit profile of topiramate is severely limited by its adverse effects (B).
- Reboxetine has consistent data from three trials suggesting benefit, but all are from a single research group with no independent replication yet available (B).
- Glucagon-like peptide-1 (GLP-1) receptor agonists have been found to be effective for weight reduction in obesity in the general population, and liraglutide has been given marketing authorisation for this use (A). However, there are no RCT data yet available for this use in people with psychosis taking antipsychotic medications.
- Non-RCT data give tentative support to the use of bariatric surgery in extreme obesity in a few selected people with schizophrenia. There are no adequate long-term follow-up data available for this population (C).
- Amantadine, melatonin and zonisamide have all been subject to RCTs that suggest a beneficial effect. However, available data are too limited to make any recommendation regarding their use.
- Clinical trials of atomoxetine, dextroamphetamine, famotidine, fluoxetine, fluvoxamine and nizatidine have failed to show benefit (B).

Interventions for smoking and alcohol misuse

- Tobacco smoking
  - Tobacco smoking is an important additive risk factor for diabetes and CVD, and those who smoke should be referred to smoking cessation services (S).
  - Evidence suggests that all of the treatments below are most effective if delivered as part of an overall smoking cessation programme (A).
  - Use of nicotine replacement therapy (NRT) in smokers with psychosis is supported by open label studies (B).
  - Individual RCTs of buproprion have small numbers of participants, and most do not demonstrate statistically significant effects, but meta-analysis of these support its use in psychosis (A).
  - Only one of three RCTs of varenicline demonstrates a statistically significant effect, but meta-analysis of these RCTs suggests a significant effect (A).
- Alcohol misuse
  - The negative impact of harmful alcohol use, abuse or dependence in people with schizophrenia requires that their alcohol use, as well as use of other substances, is assessed and that treatment is appropriately focused on any harmful substance use, abuse or dependence (S).
  - Optimisation of antipsychotic treatment, following existing guidance, may have a role to play in reducing substance misuse (D).
  - Clozapine should be considered in patients with persisting harmful substance use, abuse or dependence,

because it has been reported to reduce substance use and improve psychosis, but the supporting data are still preliminary (D).
    - Specific medication for relapse prevention in patients with alcohol dependence should be considered, such as naltrexone or acamprosate (D).

Management of the increased risks for diabetes and CVD

The management of the medical consequences of weight gain and obesity should be in primary care. Initial investigations may be by either the mental health team or the primary care team.

- Potential pre-diabetic states should be investigated and managed as per NICE guidelines for the general population, except that annual screening for this is recommended for those with psychosis receiving antipsychotic medications (S).
- The prescription of metformin for those not responding to intensive lifestyle interventions needs to be considered in the context of the individual (S).
- Diabetes should be managed by the general practitioner or a specialist physician, where necessary, as per existing NICE guidelines (S).
- Dyslipidaemia, especially in the context of a person with diabetes, should be actively managed according to existing NICE guidelines for the general population (S). There is no contraindication to the prescription of a statin in people prescribed antipsychotics.
- Hypertension should be managed according to standard NICE guidelines. Practitioners should be aware of possible increased hypotensive effects when some antihypertensive medications are combined with antipsychotics (S).

Service delivery issues

- Clinical commissioning groups and trusts, working with clinicians in both primary and secondary care, need to ensure that appropriate agreements are in place with regard to who takes the lead responsibility for the monitoring and management of physical health for people with psychosis at the different stages of their care.
- This should include sharing of core clinical information between primary and secondary care.
- Primary and secondary care services need to consider how best to provide 'lifestyle' type interventions within the context of available local provision.

The literature reviewed to support these recommendations is described below.

Background

The problems

The life expectancy of people with schizophrenia is reduced by over 20 years (Tiihonen et al., 2009). A meta-analysis of 18 international studies indicated that 60% of this excess mortality was caused by physical illness (Brown, 1997). Recent large cohort studies in Australia and the USA have confirmed this increased risk of premature mortality, and suggest the gap between people with schizophrenia and the general population may be widening (Lawrence et al., 2013; Olfson et al., 2015). Excess deaths from CVD are the major contributor to this and people with schizophrenia are twice as likely to die from CVD compared to those in the general population (Osborn et al., 2007a, 2015). An increased prevalence of important cardiovascular risk factors is well documented in people with schizophrenia (Casey et al., 2004; De Hert et al., 2011). Meta-analysis suggests that, compared to placebo, most antipsychotic medications are associated with weight gain, which in turn increases the likelihood of developing a range of physical illnesses, including diabetes, CVD and cancer. Meta-analysis of 78 publications, which included 24,892 participants found that 35.3% of people taking antipsychotic medications manifest so-called 'metabolic syndrome' (Mitchell et al., 2013). The literature reviewed in this document sometimes uses the categorical construct of 'metabolic syndrome', most recently described as the combination of central obesity with two out of four of hypertension, raised fasting glucose, low HDL cholesterol and raised triglyceride levels (Alberti et al., 2005). Use of this terminology has sometimes been useful as a way of summarising an important group of risk factors into a single risk factor for the development of diabetes and CVD.

It is important, however, to recognise the individual risk factors for the development of diabetes and CVD, as well as making an estimation of overall risk for CVD, and then consider the provision of appropriate interventions for these individual risk factors. Cigarette smoking and misuse of alcohol are important risk factors for CVD in many people with psychosis. Overweight is a further important risk factor for CVD and diabetes. It is recognised as a common problem among people with schizophrenia (e.g. De Hert et al., 2009b). Significant weight gain can be identified within 6–8 weeks of commencing antipsychotic treatment (Foley and Morley, 2011), and early weight gain appears to be a predictor of longer term weight gain (Kinon et al., 2005). A prospective study found that a more than 5% weight gain after 1 month was the best predictor of long-term weight gain (Vandenberghe et al., 2015). In the EUFEST study, of individuals experiencing their first episode of schizophrenia, weight gain of 7% or greater of initial body weight was found in 65% of the follow-up population at 1 year (Kahn et al., 2008). In a study of individuals in the early stages of treatment for a first episode of psychosis, Correll et al. (2014) found a pattern of increases in several metabolic risk indices after an average of 47 days of antipsychotic treatment.

Weight gain also reinforces service users' negative views of themselves and may lead to poor adherence with treatment (Faulkner et al., 2007; Lester et al., 2011; Weiden et al., 2004). It is also the most distressing side-effect reported by callers to the SANE helpline (Fakhoury et al., 2001).

Monitoring of patients for the presence of important cardiovascular and metabolic disease risk factors, such as smoking, misuse of alcohol, weight gain, elevated plasma glucose, dyslipidaemia and hypertension is thus essential. However, it is clear from the results of the National Audit of Schizophrenia for England and Wales (Crawford et al., 2014; Patel et al., 2014; Royal College of Psychiatrists, 2012, 2014) and from the Royal College of Psychiatrists prescribing observatory for mental

health (POMH) audits (Barnes et al., 2007, 2008) that such monitoring is not routinely carried out and that at best only around one third of patients will have adequately comprehensive monitoring of physical health risk factors once in any 12-month period. The National Audit of Schizophrenia also demonstrated that the frequency of intervention for identified risk factors is poor, for example, only 52% for elevated BMI and 56% for elevated plasma glucose.

In 2011, the UK national charity Rethink Mental Illness established the independent schizophrenia commission to collect evidence from a wide variety of sources regarding the care of people with schizophrenia. In their report '*The abandoned illness*' (Schizophrenia Commission, 2012) they also noted the evidence of premature mortality and the need to improve delivery of effective physical health care.

People with psychotic illness and their families are often frustrated because the monitoring of relevant risk factors and provision of appropriate interventions are sometimes poor, often due to lack of clarity within services regarding whose responsibility these should be. Furthermore, they want to know about the possible physical health risks at the commencement of treatment in order to guide their choices regarding medication and help them understand potential preventative strategies. A common complaint is that these issues are often not adequately discussed. In the second round of the National Audit of Schizophrenia (Royal College of Psychiatrists, 2014), only 39% of people with schizophrenia felt they had been given adequately understandable information about their current medication.

Factors driving metabolic and cardiovascular risk in psychosis

Clinical factors. De Hert et al. (2009a) report 'metabolic syndrome' to be elevated two to three times in people with schizophrenia above the prevalence in the general population. Obesity and diabetes are also substantially increased in schizophrenia, with estimates of relative risk of 1.5–2 and 2, respectively (De Hert et al., 2009b; Holt and Mitchell, 2015). This is also seen in the UK population. A Northern Ireland study of people with schizophrenia showed a high prevalence of obesity (40%) and metabolic syndrome (38%) (Yevtushenko et al., 2008).

These metabolic disturbances are multifactorial in origin (Holt and Mitchell, 2015; Manu et al., 2015). Several disease-related factors appear to contribute. Poor self-care appears to be associated with a poor diet. People with psychosis consume more saturated fat (Ryan et al., 2003), more refined sugar (Stokes and Peet, 2004), less fibre (Osborn et al., 2007b) and less fruit and vegetables (McCreadie, 2003) than the general population. Many people with psychotic illness have a rather sedentary lifestyle (Daumit et al., 2005) and take less exercise than the general population (Osborne et al, 2007b). The higher prevalence of smoking in people with schizophrenia, even in the early stages of the illness (Barnes et al., 2006), appears to have no protective effect on body weight and has been reported to be associated with increased liability to metabolic syndrome (Yevtushenko et al., 2008).

People with schizophrenia are also disproportionately represented within inner-city areas where health inequalities are found to be greatest (World Health Organization, 2010). Deprivation has also been recognised as an important factor in the risk of diabetes (Connolly et al., 2000) and CVD in the general population, and is included in the QRISK2 algorithm (Hippisley-Cox et al., 2007). People with mental illness are also likely to experience inferior medical care compared to the general population (Mitchell et al., 2009).

Thus, lifestyle and disease factors may contribute to metabolic pathology in people with psychosis. One question that then arises is whether there is an inherent metabolic pathology in schizophrenia apparent at, or prior to, the onset of psychosis. The answer to this appears to be negative. Studies with drug-naive people with a first episode of schizophrenia found no significant differences in a range of metabolic measures, including blood glucose, lipids, insulin and measures of fat deposits (Arranz et al., 2004; Zhang et al, 2004). This lack of any significant metabolic difference from the healthy population has also been reported for drug-naive participants in the EUFEST study (Fleischhacker et al., 2013).

Pharmacological and pharmacogenetic factors. It is clear from the initial meta-analysis of RCT data by Allison et al. (1999) to the recent indirect, multiple treatments, meta-analysis from Leucht et al. (2013), that treatment with most antipsychotic drugs can lead to significant weight gain, and that antipsychotics vary in their liability to induce weight gain. The latter analysis employed data from 212 trials in people with schizophrenia, with a mean duration of illness of 12.4 years, and used data from the sixth week (or closest time-point to this) of each trial. It distinguishes three essentially discrete groups of drugs with respect to weight gain (Table 2). In a meta-analysis of 48 direct comparison RCTs, Rummel-Kluge et al. (2010) described three similar clusters, and observed that the magnitude of changes in glucose and cholesterol fell broadly into the same clusters.

Table 2. Rank order of liability for weight gain among oral antipsychotic drugs.

	Risk of weight gain	Notes
Olanzapine	High	1
Clozapine	High	2
Chlorpromazine	High/medium	3
Quetiapine	Medium	4, 5
Risperidone	Medium	4, 5
Paliperidone	Medium	4, 6
Asenapine	Low	7
Amisulpride	Low	7
Aripiprazole	Low	7
Lurasidone	Low	7, 8
Ziprasidone	Low	7, 8
Haloperidol	Low	8

Adapted from the multi-comparison meta-analysis by Leucht et al., 2013.
Notes: 1. Significantly greater than quetiapine; 2. Not significantly greater than the 'medium' group due to the high reported variance of relative weight gain; 3. Not significantly differentiated from either 'medium' or 'high' groups; 4. Significantly lower than olanzapine; 5. Significantly greater than asenapine; 6. Significantly greater than amisulpride; 7. Not significantly greater than haloperidol; 8. Not significantly greater than placebo.

Such meta-analyses are likely to underestimate the effects of the various antipsychotic medications as many participants in these RCTs will have been prescribed antipsychotics for some time before recruitment to a clinical trial. Treatment of drug-naive people with first-episode psychosis has been shown to have rapid and profound effects on body weight, with average increases of 7–8% for risperidone and 13% for olanzapine over 3 months (Templeman et al., 2005; Zhang et al., 2004). Along with this increase in weight, reflecting fat deposition, are seen changes in other cardiovascular risk factors, including elevations in total cholesterol and triglycerides (Zhang et al., 2004). The latter study also showed a substantial elevation in circulating leptin, an anorexigenic hormone secreted by adipose tissue. Such an elevation is expected in people with increasing fat mass, but in this case the effect of this hormone in diminishing food intake is lost. This suggests that one mechanism for antipsychotic-induced weight gain might be interference with the hormonal control of food intake and body weight (Reynolds and Kirk, 2010).

Strong candidates for the pharmacological mechanisms that might be responsible for this weight gain are provided by the known receptor activities of the antipsychotic drugs (reviewed by Reynolds and Kirk, 2010). Perhaps the best candidate for the particularly large effects of olanzapine and clozapine on body weight is an antagonism, or inverse agonism, at the serotonin 2C ($5\text{-}HT_{2C}$) receptor, although antagonism at other candidate receptors, such as the histamine H_1 receptor, provide alternative or additional mechanisms. Both of these receptors are involved in hypothalamic mechanisms controlling food intake and their antagonism could disrupt normal hormonal regulation of this system. Other strongly implicated receptors include alpha adrenoceptors, other serotonin receptors and inevitably the dopamine D2 receptor (DRD2), at which all antipsychotic drugs act and which has an involvement in both hypothalamic mechanisms and in appetite and reward.

A few antipsychotic drugs appear to have relatively little effect on body weight (Table 2). For some, notably aripiprazole and ziprasidone, this may reflect more than just the lack of a hyperphagic effect. Animal experiments suggest these drugs have a protective effect against olanzapine-induced food intake and weight gain (Snigdha et al., 2008), which reflects the increasing clinical use of adjunctive aripiprazole, discussed below. The pharmacological mechanism has not been studied, but may relate to partial agonism at certain serotonin receptors and/or to aripiprazole's partial agonist action at DRD2 receptors.

While drugs vary substantially in their effects on body weight and other metabolic factors, individual responses also vary profoundly. Some people demonstrate rapid and substantial gains in weight on antipsychotic regimens that in others appear to have little or no effect. While lifestyle and diet may contribute, it is apparent that genetic factors are important in this individual variability of antipsychotic drug-induced weight gain.

Common functional polymorphisms in many candidate genes implicated in the control of body weight and various aspects of energy and lipid metabolism have been investigated for association with weight gain in people receiving antipsychotic drug treatment, and with metabolic pathology in chronic schizophrenia (reviewed by Lett et al., 2012; Reynolds, 2012). Perhaps the strongest and most replicated findings are the associations with promoter polymorphisms in the $5\text{-}HT_{2C}$ receptor and leptin genes. There are also several other possible genetic polymorphisms involving pharmacological targets of antipsychotic drugs (e.g. alpha-2_A adrenoceptor), in genes involved in the hypothalamic control of food intake and body weight (e.g. melanocortin 4 receptor; leptin receptor) and other genes emerging from studies of genetic risk factors for obesity and other metabolic disturbances (e.g. fat-mass and obesity associated gene (FTO); methylenetetrahydrofolate reductase (MTHFR)).

Not only are genetic factors important in contributing to antipsychotic-induced weight gain, it is also apparent that they influence the rate or extent of weight loss following a pharmacotherapeutic intervention. Thus, some of the polymorphisms consistently reported as associated with weight gain also affect the extent of weight loss in people who, having developed metabolic risk factors following antipsychotic drug treatment, were switched to treatment with an antipsychotic with low weight risk (Roffeei et al., 2014).

These genetic factors associated with drug-induced weight gain and its metabolic consequences provide clues as to the underlying mechanisms, and in the future may provide opportunities for personalised medicine in the predictive assessment of metabolic risk with antipsychotic drug treatment.

Antipsychotic medications and diabetes. One aspect of the metabolic pathology of schizophrenia is a two-fold increase in diabetes. The aetiology of this is complex, with genetic, lifestyle and disease-specific treatment factors to consider (Holt and Mitchell, 2015). Observational studies have indicated that compared with the general population, the risk of diabetes is higher among people receiving antipsychotic medication (Vancampfort et al., 2013) and is higher in people with schizophrenia who have experienced multiple episodes, compared to first-episode and untreated individuals (Mitchell et al., 2013).

Antipsychotics are likely to increase the risk of diabetes through weight gain as this increases insulin resistance. However, this does not explain all the excess diabetes risk because some individuals receiving antipsychotics develop diabetes without weight gain. Changes in glucose regulation have been shown in people without diabetes with schizophrenia, taking antipsychotic medications, independent of adiposity (Newcomer et al., 2002). Insulin resistance has been demonstrated in non-obese people taking antipsychotic medications (Henderson et al., 2005). The strongest evidence for abnormalities of glucose regulation appears to be in people receiving clozapine and olanzapine (Newcomer, 2005), with olanzapine also demonstrating greater elevations in glucose levels than other antipsychotics, except clozapine (Rummel-Kluge et al., 2010). Furthermore, weight gain does not explain why some individuals develop diabetic ketoacidosis while receiving antipsychotics as this implies a marked reduction in insulin secretion.

Although the underlying pharmacological mechanism has not been studied extensively, the interaction of antipsychotics with pancreatic β-cell receptors may interfere with normal insulin secretion. For example, a correlational analysis of clinical data suggested that antagonism of the muscarinic M3 receptor may be the mechanism of this effect (Silvestre and Prous, 2005), while experimental studies of islet cells have drawn the same conclusion (Johnson et al, 2005). This effect is via M3 receptor

mediation of glucose-dependent parasympathetic acetylcholine regulation of insulin secretion by pancreatic β-cells. In addition to these pancreatic effects, further in vitro work suggests that various antipsychotics may impair insulin-mediated glucose uptake and glycogen synthesis.

Tobacco smoking. People with schizophrenia have much higher rates of tobacco smoking than the general population, something that has been recognised for over 50 years (Hughes et al., 1986; Kelly and McCreadie, 2000). Individuals in their first episode of illness are significantly more likely to be smokers than a population matched for age and sex (odds ratio 6.04; 95% confidence interval (CI) 3.03 to 12.02; Myles et al., 2012). There is also evidence in people with schizophrenia that nicotine has greater effects on some aspects of cognitive performance (Barr et al., 2008), and that there is abnormal regulation of high affinity nicotinic receptors compared to healthy people (Breese et al., 2000).

Smoking is clearly established as an important risk factor for the development of coronary heart disease in the general population. Recent data from a primary care population in the UK confirm that smokers with severe mental illness acquire a similar level of risk from smoking (Osborn et al., 2015). Smoking is also an established risk factor for the development of diabetes (InterAct Consortium, 2014; Wannamethee et al., 2001; Willi et al., 2007).

Misuse of alcohol. A significant proportion of people with schizophrenia misuse alcohol. A meta-analysis reported median current alcohol use disorder rates at 9.4% and median lifetime rates of 20.6% (Koskinen et al., 2009). This is an additional risk factor for CVD and diabetes.

It is clear that heavy use of alcohol increases risk for CVD (coronary artery disease, stroke and peripheral arterial disease), hypertension, cardiomyopathy (and subsequent heart failure) and various cardiac rhythm disturbances (e.g. alcohol can prolong the QT interval). Controversy continues regarding whether or not light and moderate drinking may be protective for CVD for some individuals. While many studies suggest this may be the case, there is evidence of publication bias and cigarette smoking is a possible confounder. A recent study using data from the Health Survey for England found a beneficial effect of light or moderate consumption on all-cause mortality to be limited largely to women 65 years of age or older (Knott et al., 2015), suggesting that any 'cardiovascular' benefits may be outweighed by other alcohol-related harms. This conclusion is also supported by the recent review of guidelines for the consumption of alcohol by the UK Department of Health (2016), in which increased risks for various cancers are highlighted. Low and moderate alcohol consumption may increase serum HDL cholesterol but moderate consumption may also increase the risk of hypertriglyceridaemia. The potential of an increased calorie intake from alcohol increases the risk of overweight and obesity. Heavy drinking and binge drinking also increase the risk of diabetes, although low consumption may reduce the risk (see Fernandez-Sola, 2015, for a review of these issues).

Assessment of physical health risk factors

The first NICE clinical guideline on the care of people with schizophrenia (CG1) (NICE, 2002) made rather general reference to issues relating to physical health and did not make very specific recommendations regarding the management of cardiometabolic risk factors. Growing concerns about weight gain and the development of diabetes and CVD were reflected in more detailed guidance in clinical guideline 82 (NICE, 2009), which was an update of NICE CG1. However, the most recent guideline (CG178) (NICE, 2014a) provides detailed guidance, particularly in sections 1.1.3, 1.3.6.4, 1.3.6.5 and 1.5.3. This guidance is also reflected in quality statements 6 and 7 of the recent NICE quality standard for psychosis and schizophrenia in adults (QS80) (NICE, 2015b) with regard to both monitoring of physical health and provision of advice about diet and physical activity. The most recent NICE guideline for bipolar disorder (CG185) (NICE, 2014c) makes very similar recommendations regarding the monitoring and management of physical health risks for people with that diagnosis.

In relation to 'physical health', NICE CG178 (NICE, 2014a) recommends an assessment of smoking, physical activity, weight, waist circumference, blood pressure, fasting blood glucose, HbA_{1c} and fasting lipids. These measurements are among those commonly proposed as important risk factors for the development of CVD, and in part have been driven from the findings of the long running Framingham Heart Study (https://www.framinghamheartstudy.org). They also include important risk factors for the development of type 2 diabetes. (Note: While assessment of waist circumference has some theoretical advantage over BMI, the former is often measured incorrectly and loses validity above a BMI of 35 kg/m^2. Furthermore, the most recent NICE clinical guideline on obesity (CG189) (NICE, 2014d) advises the use of BMI, with waist circumference as a supplementary measure in certain circumstances (paragraphs 1.2.2 and 1.2.3).) Thus, we would suggest that the recommendation to measure waist circumference in NICE CG178 should not be mandatory and instead would recommend that BMI should be calculated from the weight and recorded. It is important to take ethnicity into account when interpreting BMI data – a BMI >22.9 kg/m^2 is considered elevated for those of South Asian or Chinese ethnicity. Experience from the National Audit of Schizophrenia is that BMI is documented in only 52% of service users' case records and that waist circumference is even less frequently documented.

In relation to alcohol use, CG178 (NICE, 2014a) recommends assessment of alcohol consumption and discussion of this with the individual (sections 1.3.3.1 and 1.3.6.7) but relates this to the management of mental state symptomatology rather than physical health issues. We would recommend that alcohol consumption should be included in any proper assessment of physical health risk factors.

While it is clearly important to intervene when the results of these assessments are outside appropriate limits, a global assessment of the risk of serious physical illness is also important. This may be useful, for example, in persuading the person with psychotic illness to adopt a change in lifestyle or in the decision whether or not to prescribe a statin. The evidence is clear that, for example, prediction of the risk for CVD is much better if multiple variables are used for the assessment of the risk. In primary care in the UK it is common practice to employ the QRISK2 CVD risk calculator (http://www.qrisk.org) to estimate the 10-year risk of a CVD event, such as stroke, transient

ischaemic episode, myocardial infarction or angina. In the USA a cardiovascular risk prediction model has been developed from the Framingham Heart Study data for use in primary care (D'Agostino et al., 2008). QRISK2 has been externally validated and has been demonstrated to have better discriminative properties than the Framingham model for the UK population (Collins and Altman, 2012).

However, both of the above 'risk scores' have been developed using data derived from samples of the general population. Osborn and colleagues (2015) have made the argument that such 'risk scores' may not properly reflect the risks faced by those with psychotic illness for whom there may be possible links to the illness itself, for whom physical inactivity can be a significant feature and for whom the effects of antipsychotic medications may play a part. A specific problem with QRISK2 is that it is validated for people over the age of 30 years and thus may not adequately assess risk for younger people early in their illness.

Using data from the health improvement network, collected as part of their PRIMROSE research programme (prediction and management of cardiovascular risk in people with severe mental illnesses; www.ucl.ac.uk\primrose), Osborn et al. (2015) have developed two CVD risk prediction models that perform better than existing models in populations with severe mental illnesses. These both predict observed risk better than the general population models, whether such models are derived from US or UK general populations.

The simpler of their models employs BMI, rather than blood lipid values, but produces an almost identical result without the need for the collection of lipid data. The variables employed are: gender, age, systolic blood pressure, weight, height, presence of diabetes, smoking history, prescription of antidepressants, presence of an alcohol problem, deprivation score, specific serious mental illness diagnosis and prescription of first and/or second generation antipsychotic medications. Thus, the variables involved are similar to those used for the prediction of risk in the general population and are similar to those recommended by NICE for people with psychosis. However, the additional information, which should be readily available in an individual's case records, appears to add an improved level of discrimination between those who will have a CVD event and those who will not.

Conventionally, in the UK, a high risk for CVD, with implications for treatment, was regarded as having a 20% or greater risk of such over the course of 10 years. It is not yet clear if this is the most appropriate threshold for those with severe mental illness. More recent guidelines (CG181) have proposed that a 10% risk should trigger consideration of treatment with statins (NICE, 2014b). Further work is essential to determine the optimal risk thresholds for people with psychotic illness and to explore the cost effectiveness of such thresholds. In the meantime, the use of current risk prediction models remains appropriate, and it is essential that people with psychosis receive timely screening for their risk of CVD and should be offered statins when their risk exceeds 10%.

NICE guidance and observations of current practice in the UK

Two national audit programmes have provided data on the extent to which NICE guidelines for the management of people with schizophrenia have been followed by trusts. The POMH is a national quality improvement programme within the Royal College of Psychiatrists' Centre for Quality Improvement, which examines discrete aspects of prescribing practice and in which all mental health trusts in the UK are invited to take part. A POMH audit involving 48 assertive outreach clinical teams (n=1966 service users from 21 trusts) found no evidence that measures of obesity, blood pressure, blood glucose control and plasma lipids had been documented during the previous 12 months in 67%, 60%, 60% and 68% of patients, respectively. For those cases in which there was evidence of screening, actual results were only available for between 50% and 70% of individuals, varying across specific measures. In a questionnaire to clinical teams it emerged that around one third of staff were uncertain whether responsibility for physical health screening lay with the mental health team or the primary care team, less than half were confident about interpretation of the results and there was a widespread lack of access to simple equipment for the task. Repeat audits, using samples from similar clinical teams, over the following 6 years have demonstrated substantial improvements in practice (Barnes et al., 2008, 2015).

The National Audit of Schizophrenia has reported the results of an audit programme in which all mental health trusts in England and Wales are asked to participate (Crawford et al., 2014; Patel et al., 2014; Royal College of Psychiatrists, 2012, 2014). In the second round of this audit (Royal College of Psychiatrists, 2014), all eligible mental health trusts participated (n=64) and were asked to make a random selection of 100 people with schizophrenia or schizoaffective disorder from among those managed in the community, and who had been in contact with services for at least 12 months. Data relating to user perceptions of services, prescribing, monitoring of physical health care and psychological therapies were collected for 5608 patients. The results showed that, in the previous 12 months, only 33% of participants had comprehensive monitoring of the five major cardiometabolic health risk factors (smoking, BMI, blood glucose control, blood lipids and blood pressure). Similar to the findings in the POMH audits, only 53% had a record of BMI in the previous year and 56% a record of blood glucose control. Of equal concern was the fact that, where the results of monitoring indicated a need for intervention, there was only evidence that this had occurred in 71% of those with elevated BMI, 36% of those with hyperglycaemia and 25% of those with elevated blood pressure.

Data from the service user questionnaire suggested that there was a significant number of cases where some of these risk factors may have been monitored in primary care but that staff in the trusts were unaware of the results. It is clear, however, that despite people with persistent psychotic illness having increased risks of cardiometabolic disorders, particularly if they are being treated with antipsychotic medications, inadequate attention is paid to screening for, and monitoring of, these risks, sharing information between primary and secondary care teams and to appropriate intervention.

Interventions

The following sections discuss possible interventions for excessive weight gain, smoking and alcohol misuse. In the context of evaluating the effectiveness of interventions for weight gain, widely accepted thresholds are that weight gain of 7% or more is regarded as clinically significant and weight loss of 5% or more

of body weight is associated with a decrease in cardiovascular risk and mortality. Furthermore, for every 1 kg/m^2 increase in BMI in the general population, the risk of developing new-onset type 2 diabetes increases by 8.4%. It should also be remembered that this is an area of treatment where motivation and engagement is important and that this may also determine an individual's decision to enter a clinical trial.

The data reviewed come almost exclusively from studies in adult populations, usually over the age of 18 years. Thus, particularly in relation to pharmacological interventions, appropriate cautions and restrictions must be applied if these are being considered for children and young people.

Lifestyle interventions

The NICE guideline on schizophrenia (CG178) (NICE, 2014a: paragraph 1.1.3) and the NICE guideline on obesity (CG189) (NICE, 2014d: paragraph 1.4) both recommend lifestyle interventions as the initial approach for people who have become overweight or obese. The NICE public health guidance on preventing type 2 diabetes (PH38) (NICE, 2012) also recommends this approach as the first line for those in the general population at moderate or high risk of developing diabetes. Such lifestyle interventions involve strategies to: increase physical activity; improve eating behaviour; improve the quality of a person's diet; and reduce energy intake. An ideal programme should involve all of these.

Randomised controlled trials confirm the success of lifestyle interventions as primary treatments of obesity in the general population, as noted in a foresight programme report to the government on obesity (*Foresight: Tackling obesities – future choices project*; Government Office for Science, 2007; https://www.gov.uk/government/publications/reducing-obesity-future-choices). A systematic review of RCTs of behavioural interventions for obesity, in adults, versus (for most studies) usual care or remaining on a waiting list, found 44 studies with data suitable for meta-analysis (Dombrowski et al., 2010). Studies that combined dietary and physical activity approaches, rather than providing either alone, were more successful with a mean difference in weight reduction from the control group of 2.9 kg (95% CI −4.3 to −1.5 kg) at 12 months.

At a population level the North Karelia project in Finland (Puska et al., 1998), in which emphasis was put particularly on influencing the dietary and smoking habits of the population, but also physical activity, resulted in a 59% reduction in mortality from coronary heart disease in men over a 20-year period.

An increasing number of studies have demonstrated the effectiveness of lifestyle intervention for people receiving antipsychotic medication (Bruins et al., 2014; Caemmerer et al., 2012). These interventions are often termed 'behavioural lifestyle programmes' as they commonly include elements of counselling or cognitive approaches to understanding eating behaviours. Most involve group sessions to discuss diet and exercise programmes, but also offer individual sessions. However, there are large variations in study design and a paucity of studies with long-term (1 year or more) follow-up. No clinical trial has directly compared the effectiveness of different lifestyle intervention programmes.

Bruins and colleagues (2014) identified 25 RCTs suitable for meta-analysis, which, combined, included 1518 people with psychotic disorder (schizophrenia, schizoaffective disorder and bipolar disorder) treated with antipsychotics. The sample size varied from 14 to 291, although only two RCTs had more than 100 participants, and the proportion of trial dropouts varied from 0% to 39%. The various lifestyle interventions were aimed at either helping people to lose weight or prevention of weight gain. The outcomes included body weight and/or metabolic measurements. In 14 studies the duration of intervention was less than 3 months, in seven studies 3–6 months, and in only four studies did the interventions last for more than 12 months. The frequency and duration of exercise sessions varied from 2 hours per week to 30 minutes daily. Most studies combined physical activity and dietary restrictions. Some studies also included one or more of motivational interviewing, cognitive behaviour therapy or counselling.

Data were reported in terms of standard mean differences and the overall effect size of lifestyle interventions on weight was −0.63 (95% CI −0.84 to −0.42; $P<0.00001$), with effect sizes of −0.52 for weight loss interventions and −0.84 for weight gain prevention interventions. Comparison of individual trials did not show evidence for the superiority of any specific intervention. Individual and group approaches to an exercise intervention were less effective alone than a combination of both approaches. The lifestyle interventions also demonstrated significant positive effects on waist circumference, triglycerides, fasting glucose and insulin. There were no significant overall effects on blood pressure or cholesterol.

The meta-analysis of Caemmerer et al. (2012) included 17 RCTs, 15 of which were included in the analysis of Bruins et al. (2014), and which combined included 810 people with psychotic disorder. This meta-analysis reported data in terms of mean differences and found that intervention versus control treatment resulted in an overall mean reduction in weight of −3.12 kg (95% CI −4.03 to −2.21; $P<0.0001$) and a reduction in BMI of −0.94 kg/m^2 (95% CI −1.45 to −0.43; $P<0.0003$).

The largest of the studies in the Bruins and colleagues meta-analysis was the ACHIEVE study (Daumit et al., 2013) in which 291 participants were randomly assigned to either a behavioural weight management programme (with a mixture of group and individual sessions) or standard advice with the option to attend quarterly health classes. The programme ran for 18 months and 279 participants were available for assessment at this point. At 18 months the mean between-group difference in weight was −3.2 kg (95% CI −5.1 kg to −1.2 kg; $P=0.002$) in favour of the intervention group; 37.8% of the participants in the intervention group lost 5% or more of their initial weight versus 22.7% of the control group.

Two more recently published RCTs of reasonable size are InSHAPE and STRIDE. An initial clinical trial of the InSHAPE 'health coaching' programme demonstrated effectiveness for weight loss (Bartels et al., 2013). The more recent trial was designed to replicate the application of this programme in normal clinical settings with a full range of service users (Bartels et al., 2014). That trial examined effects on weight and cardiorespiratory fitness in 210 participants who were randomly allocated to the InSHAPE programme or to fitness club membership alone for a 12-month period. At the end of 12 months ($n=169$ completers) the intervention participants achieved significant reduction in overall cardiovascular risk (⩾5% weight loss or improved walking distance on 6-minute walk test) in 51% of cases versus 38% in the control group. Although the mean change in weight

for the intervention versus control group was statistically significantly different it was modest (–2.4 kg vs. +0.3 kg; P=0.029). There were no between-group differences in calorie consumption or overall dietary balance between fat, sweets, fruit and vegetables and no group differences in lipid values. However, both groups reduced daily calorie consumption by around 15%. At the end of a 6-month period following the end of the intervention there was evidence of maintenance of the improvements in cardiovascular risk: by 46% of InSHAPE participants versus 37% of control participants.

The STRIDE study (Green et al., 2015b) recruited 200 participants whose BMI was 27 kg/m^2 or greater and who had been receiving antipsychotics for 30 days or more. The intervention involved dietary changes, moderate calorie restriction and moderate physical exercise supported by two facilitators. Intervention sessions were for 2 hours per week for the first 6 months, followed by maintenance sessions over a 6-month period. The intervention group lost more weight than the control group at 6 months (n=181 completers; mean difference −4.4 kg; 95% CI −6.96 to −1.78) and also at 12 months (n=170 completers; mean difference −2.6 kg; 95% CI 5.14 to −0.07). (An omnibus Wald test including time and group gave P=0.004 for the significance of difference in weight loss.) BMI was also significantly different at 12 months (–0.97 kg/m^2; 95% CI −1.88 to −0.06; P<0.004). Weight loss of 5% or more of body weight at 12 months was achieved by 47% of the intervention group. In the intervention group fasting glucose decreased from baseline to 12 months by 0.33 mmol/l versus 0.17 mmol/l increase in the control group (P<0.02) but there were no significant changes in cholesterol (total, HDL and low-density lipoprotein (LDL)), triglycerides or blood pressure. Weight loss was achieved regardless of which antipsychotic medication the participant was taking. While weight loss in the intervention group continued at a slower pace in the 6-month maintenance phase of the study, the control group began to lose weight, rather than gain weight, during this phase such that at 12 months there was no statistically significant difference in the proportions with weight loss of 5% or greater. Rates of attrition did not vary between the initial and follow-up phases of the trial.

Programmes providing some similar interventions have been organised in the UK. For example, a programme in the northwest of England, run from 2000 to 2008, initially provided weekly group intervention sessions and reported data from an observed cohort of 113 people with psychosis (Holt et al., 2010). Sixty-four participants completed follow-up at 1 year and 35 at 2 years. Weight loss continued over the period of the programme and the mean weight loss at 2 years was 7.2 kg (±0.6 kg).

Two RCTs have examined the effects of behavioural lifestyle programmes in people during their first episode of psychosis, that is, at the commencement of antipsychotic treatment. Alvarez-Jimenez and colleagues in Santander recruited 61 participants (within 6 weeks of starting antipsychotics) to either their early behavioural intervention (EBI) programme, offered for 3 months, or routine care (Alvarez-Jimenez et al., 2006) and subsequently followed up this group at 2 years (Alvarez-Jimenez et al., 2010). At 3 months those in the EBI group had gained significantly less weight than the routine care group (+4.1 kg vs. +6.9 kg; P<0.01) and BMI was less affected by treatment (+1.40 kg/m^2 vs. +2.39 kg/m^2; P=0.01). Significantly fewer of those in the EBI group increased their body weight by 7% or more. At 6 months the difference between the EBI and routine care groups only just reached statistical significance, but at 24 months the differences were no longer statistically significant for weight (EBI +9.98 kg vs. routine care +11.46 kg) or BMI (+3.46 kg/m^2 vs. +3.94 kg/m^2). No metabolic or blood pressure data were reported.

The keeping body in mind (KBIM) programme in Sydney recruited 28 participants (within 4 weeks of starting antipsychotics) to either their KBIM programme or standard care for a 12-week period (Curtis et al., 2015). The KBIM group gained 1.8 kg versus 7.8 kg for the standard care group (P<0.001). Only 13% of the KBIM group had weight gain of 7% or more versus 75% of the standard care group. There were no significant changes in fasting lipids, triglycerides or glucose in either group. Daily calorie consumption was only assessed in the KBIM group but decreased by 25% from baseline (P<0.001).

The data from these two studies of intervention early in treatment are promising but the numbers of participants included are relatively small and in the Santander study the effects were not sustained. A recent UK RCT recruited 105 participants, attending early intervention services, to a healthy living intervention (Lovell et al., 2014), but found no significant benefit on weight or BMI over 12 months, with 78% of 'intervention group' participants completing at least six to eight sessions. However, these patients could have a history of illness of up to 3 years at study entry and their mean age was 5 years older than the participants in the Sydney study, suggesting they are commencing the intervention after a much longer period of antipsychotic treatment.

A further UK programme for young people with psychosis, supporting health and promoting exercise (SHAPE), has been running in the Worcester Health and Care NHS Trust. This provides a 12-week programme of dietary advice, lifestyle interventions (including smoking cessation and exercise) and gym membership for 1 year, to people attending their early intervention in psychosis team. Preliminary data from the first cohort of 17 participants indicate attenuation of weight gain of a similar magnitude to that seen in the studies above (Smith et al., 2014). One feature of this programme, commented upon by its service users, is that it is designed specifically for them and that this makes it more appealing to attend than a generic programme at a leisure centre aimed at the general population. This is also a feature of most of the programmes reviewed above.

Summary. Overall, the available data suggest that programmes (mainly so-called 'behavioural lifestyle programmes') aimed at improving diet and increasing physical activity can have a positive effect, compared to routine care, to help individuals reduce existing antipsychotic-induced weight gain or attenuate weight gain in those commencing treatment for their first episode of psychosis. Across studies, mean reduction in weight, compared to control treatment, is around 3 kg and reduction in BMI, compared to control, is around 1 kg/m^2. Attenuation of weight gain, compared to control treatment, in people experiencing a first episode of psychosis varies widely (2.8–6 kg) but there are only three RCTs.

There is no clear evidence regarding the optimum length of engagement with such interventions. It is also clear that while there may be some maintenance of the benefits from such interventions, the trend is for benefits over routine care to diminish over time. This is similar to the findings for similar programmes in the general population (Aronne et al., 2009) and argues strongly for the need to make booster sessions available over the long term.

Antipsychotic switching

While lifestyle interventions are always going to be important, consideration of the potential role of the person's existing antipsychotic medication is also important. Ideally, regular measurement of weight at initiation of treatment, and thereafter, will provide a baseline and a trajectory of weight gain against which the effect of any subsequent change in medication can be assessed. In the vast majority of situations, low dosage or discontinuation of antipsychotic treatment is unlikely to be feasible without significant risk of clinical relapse. However, for certain dose-related adverse effects (e.g. sedation) a reduction in antipsychotic dose may be beneficial, when symptom control allows. For other side-effects, such as weight gain, there appears to be no clear relationship with antipsychotic dose (Newcomer, 2005; Simon et al., 2009). Switching to a different antipsychotic medication, which evidence suggests may have a lower liability for weight gain, commends itself as an appropriate and worthwhile treatment option for consideration.

Few studies have directly examined the effect of switching antipsychotic medication on weight and other metabolic measurements, such as plasma glucose and cholesterol. Thus, consideration of the likely benefits of switching antipsychotic medication must be approached mainly through consideration of the relative effects of different antipsychotics on these measures. The problem with such an approach is that the relative liability of individual antipsychotics for weight gain and metabolic side-effects (Allison, 1999; Leucht et al., 2013; Taylor et al., 2012) is based on RCT data, which are limited. First, these problems are not always reported in antipsychotic trials. Secondly, reports of side-effects in antipsychotic RCTs may reflect a range of different assessment measures and criteria (Pope et al., 2010). Furthermore, the inter-patient variation for these side-effects may be greater than the differences in liability between individual drugs. The summary below refers primarily to differences in propensity for weight gain as fewer studies have provided comparable data for other metabolic variables.

In an indirect, multiple treatments, meta-analysis of 212 short-term clinical trials, Leucht and colleagues (2013; summarised in Table 2) suggested that all antipsychotics examined induced statistically significantly more weight gain than placebo, except for haloperidol, lurasidone and ziprasidone (not currently available in the UK). (The other antipsychotics examined were: aripiprazole, amisulpride, asenapine, paliperidone, risperidone, quetiapine, sertindole, chlorpromazine, iloperidone, clozapine, zotepine and olanzapine. Note that this meta-analysis did not include depot or long-acting injectable compounds.) As indicated in Table 2, antipsychotics could be divided into three essentially separate groups on the basis of their influence on body weight, in which haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride and asenapine had the smallest effect. Most of the differences found were in the ranges of standard mean differences suggested as 'small' and 'medium' (Cohen, 1988).

Direct meta-analysis can only compare those treatments for which direct comparative clinical trials exist. Inevitably, not all of the many possible direct comparisons have been subject to specific clinical trials, hence the value of the indirect meta-analysis approach above. Rummel-Kluge and colleagues (2010) identified 48 RCTs, mainly comparing olanzapine or risperidone with another antipsychotic, in which there were usable data on weight, glucose or cholesterol, for their meta-analysis of direct treatment comparisons. These trials included amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole and ziprasidone. The analysis suggested that the medications included would fall into the same three clusters identified by the much larger indirect meta-analysis summarised in Table 2. The findings for changes in glucose and cholesterol fell broadly into these same clusters.

There is a small number of published clinical trials examining the effect on weight of switching from one antipsychotic to another. A Cochrane Systematic Review (Mukundan et al., 2010) identified four studies (n=636 participants) with adequate data, in which antipsychotic medication was switched specifically to ameliorate weight gain. The conclusion was that switching from olanzapine to aripiprazole or quetiapine resulted in weight loss and a decrease in fasting blood glucose. Only a switch to aripiprazole resulted in an improved lipid profile. There were no significant differences in clinical outcomes between switchers and those participants not switched.

The World Federation of Societies of Biological Psychiatry (WFSBP) has published a guideline on the long-term treatment of schizophrenia and management of antipsychotic-induced adverse effects (Hasan et al., 2013), which includes the management of weight gain and metabolic changes. Their conclusions were similar to those of the Cochrane Review for weight and metabolic measurements with regard to switching from olanzapine to aripiprazole or quetiapine. They also concluded that switching from olanzapine or risperidone to ziprasidone, but not from first generation antipsychotics to risperidone, was beneficial for both weight and metabolic measurements (data from an open label study by Weiden et al., 2008).

The WFSBP guideline was able to include the more recent study of Stroup and colleagues (2011). In that study, people clinically stable on olanzapine, quetiapine or risperidone, but who were at increased risk for CVD, were randomly assigned to remain on their current treatment or switch to aripiprazole. Study assessors, but not study participants or their clinicians, were blind to treatment allocation. The results showed a significant reduction in non-HDL cholesterol (the primary outcome measure) and significant reduction in weight for the aripiprazole group (–3.6 kg vs. −0.7 kg; P<0.0001). There were no differences in measures of glucose metabolism and no differences between switchers and those not switched in symptom outcomes.

More recently, a pharmaceutical industry sponsored trial of lurasidone demonstrated mean weight loss (observed cases analysis) of 1.9 kg over 6 months, with 29.0% showing more than 7% weight loss, when participants were switched to open-label lurasidone after 6 weeks of treatment with olanzapine (Stahl et al., 2013).

Summary. The results of the indirect and direct meta-analyses suggest three clusters of antipsychotic medications, with respect to liability for weight gain (Table 2). There is thus some rationale to switch from an antipsychotic with greater propensity for weight gain to one with a lower propensity, which in terms of medications available in the UK means to haloperidol, lurasidone, aripiprazole, amisulpride or (in bipolar mania) asenapine. The studies included in the Cochrane and WFSBP guidelines suggest that switching from olanzapine to aripiprazole may be worthwhile with more limited data supporting switches from

quetiapine and risperidone to aripiprazole, olanzapine to quetiapine and olanzapine to lurasidone. Switches to ziprasidone may be worth considering but this is not currently an option in the UK.

Any decision to switch antipsychotic must take into account any risks of reduced clinical efficacy in terms of psychotic symptom control and relapse prevention. It also requires discussion with the service user regarding the benefits and risks, including other potential adverse effects that may be more common with the alternative medication, and the possibility that the alternative antipsychotic medication may also cause weight gain in some individuals. Hence, although haloperidol is an available option, consideration must be given to the high risk of extrapyramidal side-effects with this, as well as the disincentive of these to good medication adherence, making it an unlikely choice.

Use of adjunctive aripiprazole

Aripiprazole is a dopamine D2 receptor partial agonist with a different profile of adverse effects to other antipsychotic medications. Meta-analysis indicates a relatively small effect to increase weight compared to the majority of other antipsychotic medications (Leucht et al., 2013). In a 26-week RCT of aripiprazole versus olanzapine, in people with schizophrenia who had experienced acute relapse on their previous antipsychotic medication (n=317), the aripiprazole group had a mean weight loss of 1.37 kg against weight gain of 4.23 kg in the olanzapine group (P<0.001) (McQuade et al., 2004). This potential to reduce weight in some people when switched from other antipsychotics led to the consideration of aripiprazole as an adjunct to other treatments that had induced weight gain, particularly clozapine, when switching may not be an option due to lack of response to other medications.

There have been three clinical trials that have reported data on weight, examining the use of adjunctive aripiprazole with clozapine and one examining adjunctive aripiprazole with olanzapine. The first of these was an open-label study of aripiprazole 15–30 mg daily added to clozapine (mean dose 455 mg/day) for 6 weeks in 13 people with chronic schizophrenia (Henderson et al., 2006). Eight people completed the trial and two withdrew at week 4. There was a significant mean decrease in weight of 2.7 kg (P<0.003) with only one of these 10 participants showing a small increase in weight (<5%). There were statistically significant decreases in fasting total cholesterol and total triglycerides but fasting glucose showed a small, but non-significant increase.

The same group then reported the results of a 10-week placebo controlled, double-blind crossover study comparing the effects of 15 mg/day of aripiprazole versus placebo on weight, lipids and glucose metabolism in overweight and obese people with schizophrenia treated with a stable dose of olanzapine (Henderson et al., 2009). Participants received either aripiprazole for 4 weeks, followed by a 2-week treatment adjuvant washout and then placebo for 4 weeks or the reverse of this. The order of these two possible regimens was randomly assigned. No information was provided regarding any ongoing lifestyle advice. Fourteen out of 15 participants completed the full trial. Following 4 weeks of treatment with aripiprazole there was a significant decrease in weight compared to placebo treatment (–1.3 kg (SD 2.1) vs. +1.0 kg (SD 1.5); P<0.003) and a parallel decrease in BMI (–0.4 kg/m^2 vs. +0.3 kg/m^2; P<0.004). Total serum cholesterol, HDL cholesterol and LDL cholesterol and fasting glucose did not change significantly but there were significant decreases in triglycerides (P=0.001) and total very LDL cholesterol (P=0.01).

Fleischhacker and colleagues (2010) carried out a multicentre, double-blind RCT of aripiprazole versus placebo added to clozapine in 207 outpatients (n=190 completers) with schizophrenia who did not have optimal control of symptoms on clozapine and had experienced weight gain of at least 2.5 kg on clozapine. The main, 16-week phase of the study was double-blind and was followed by a 12-week extension phase on an open-label basis for eligible participants. No information was provided regarding any ongoing lifestyle advice. The mean clozapine dose before randomisation was 384 mg/day in the aripiprazole group and 363 mg/day in the placebo group. Aripiprazole doses (and 'dummy'/placebo aripiprazole doses) began at 5 mg/day but could be increased after 2 weeks. At 16 weeks, doses were between 5–15 mg/day: mean 12.0 mg/day in the actual aripiprazole group and 11.1 mg/day in the 'placebo' aripiprazole group. At the end of week 16 the aripiprazole group had a greater mean decrease in body weight than the placebo group (–2.53 kg vs. −0.38 kg; mean difference −2.15 kg, 95% CI −3.17 to −1.12; P<0.001) and a statistically significant difference was maintained in those who completed the open-label phase at week 28. The weight change was paralleled by reductions in BMI and waist circumference. Weight loss of 7% or greater was achieved by 21% of the aripiprazole group and 13% of the placebo group. Aripiprazole was also associated with a significant decrease in total cholesterol (P=0.002) and LDL cholesterol (P=0.003) but no change in triglycerides or fasting glucose. There were no statistically significant changes in symptom scores on the PANSS.

A further double-blind placebo controlled RCT of aripiprazole added to clozapine was carried out in 38 participants (n=30 completers) with the primary aim of investigating effects on glucose metabolism (Fan et al., 2013). The primary outcome measure was the frequently sampled intravenous glucose tolerance test, which assesses insulin sensitivity and the effectiveness of glucose metabolism. This measure improved significantly in the aripiprazole group versus the placebo group along with a reduction in plasma LDL. Lean body mass, but not fat mass, was significantly decreased. There was a non-significant decrease in weight of −1.5 kg in the aripiprazole group and an increase of +0.3 kg in the placebo group. There were no significant differences in PANSS symptom scores.

A meta-analysis of the data from the three double-blind studies (Mizuno et al., 2014) found a mean difference between aripiprazole and placebo of −2.13 kg (95% CI −2.87 to −1.39; P<0.00001). The most commonly reported adverse effects of the combination treatment are nausea, headache, insomnia, anxiety and restlessness.

The studies above have not demonstrated a significant change in schizophrenia symptom scores with the addition of aripiprazole. Muscatello and colleagues reviewed the case studies, case series and open label clinical trials of adjunctive aripiprazole and concluded that the data provided some, but not conclusive, support that this might be a useful strategy for further symptom improvement in people whose illnesses remained relatively treatment unresponsive despite clozapine (Muscatello et al., 2011). In the same publication they describe a 24-week double-blind RCT of aripiprazole versus placebo in 40 participants receiving

clozapine (n=31 completers). The results showed a significant improvement in total scale for assessment of positive symptoms score (P<0.0001). The study did not report data on weight.

Summary. The addition of aripiprazole to clozapine or olanzapine appears to be an effective strategy likely to result in a mean difference of weight loss of around 2 kg with aripiprazole compared to placebo. Data regarding effects on cholesterol, triglycerides and glucose were inconsistent across the trials, but there was a trend for measures of cholesterol and triglycerides to improve. Aripiprazole is unlikely to worsen psychotic symptoms.

Thus, adjunctive treatment with aripiprazole of people with psychosis on clozapine and olanzapine would appear to be a safe and potentially effective option to ameliorate weight gain without a detrimental effect on symptoms. There is no useful body of evidence regarding augmentation of other antipsychotics with aripiprazole for this purpose. It is also important to consider the possible disadvantages of polypharmacy versus the degree of benefit obtained.

The value of an augmentation strategy with an antipsychotic drug with low potential for weight gain may not be restricted to aripiprazole. There are reports that ziprasidone has some efficacy in this respect (e.g. Wang et al., 2011). The use of added amisulpride or lurasidone in ameliorating weight gain with antipsychotic treatment has not been explored.

Use of adjunctive metformin

Metformin hydrochloride is an oral glucose-lowering drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes in all national and international guidelines. Its main actions are to reduce hepatic glucose production and increase insulin sensitivity in muscle. In the management of diabetes, it has a neutral effect on body weight and reduces total cholesterol, LDL cholesterol and triglycerides.

As discussed above (*Antipsychotic medications and diabetes*), it appears that antipsychotic medications act to increase the risk of diabetes both through weight gain and independent mechanisms, with both of these influencing insulin resistance. The practical use of metformin in the management of 'pre-diabetes' and in diabetes is discussed later in this guideline (*Management of the increased risk for diabetes and CVD*). Here we review some of the evidence that metformin can reduce mortality, reduce the risk of progression to diabetes, and reduce weight in overweight and obese individuals at risk of the development of diabetes. We then review the clinical trial data relating to the use of metformin in overweight and obese people with psychosis.

First we summarise the results of two large clinical studies of the effects of metformin in the general population in the UK and the USA. In the United Kingdom Prospective Diabetes Study (UKPDS; n=753, with a median duration of 10.7 years in the trial), the use of metformin versus conventional treatment (primarily diet) was associated with reductions in all-cause mortality, myocardial infarction and microvascular complications (UK Prospective Diabetes Study Group, 1998). Although these results have recently been criticised (Boussageon et al., 2016), partly for lack of replication, other similar studies have been for shorter durations of follow-up and meta-analysis of these, together with UKPDS, supports the original conclusion (Holman et al., 2014).

A number of clinical trials have examined its effectiveness for the prevention of diabetes. The largest (n=3150) was undertaken in the USA. This was a multicentre RCT, which compared the effects of an intensive lifestyle intervention, metformin and placebo in adults in the general population at high risk of diabetes (Diabetes Prevention Program Research Group, 2002). This found that diabetes incidence rates during the 2.8 years of the Diabetes Prevention Program (DPP) were 4.8 cases per 100 person-years (95% CI 4.1 to 5.7) in the intensive lifestyle intervention group (58% risk reduction), 7.8 (6.8 to 8.8) in the metformin group (31% risk reduction) and 11.0 (9.8 to 12.3) in the placebo group. This trial was then continued into an open-label phase into which 88% of the original participants were recruited. During the 10-year (interquartile range 9.0 to 10.5) follow-up since randomisation to DPP, the original lifestyle group lost, then partly regained weight. The modest weight loss with metformin was maintained. Diabetes incidence rates in this follow-up study were similar between treatment groups: 5.9 per 100 person-years (5.1 to 6.8) for lifestyle, 4.9 (4.2 to 5.7) for metformin, and 5.6 (4.8 to 6.5) for placebo. Diabetes incidence in the 10 years since DPP randomisation was reduced by 34% (24 to 42) in the lifestyle group and 18% (7 to 28) in the metformin group compared with placebo. The research group's interpretation of these findings was that:

> during follow-up after DPP, incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.

Thus, in individuals at risk of developing diabetes, evidence suggests that metformin can reduce the risk of progression to diabetes, reduce mortality and reduce weight. Lifestyle interventions should be the first line of approach for those at high risk of diabetes. However, should these fail, metformin is an option in some clinical situations. This is reflected in recommendation 19 of the NICE public health guidance *Type 2 diabetes: prevention in people at high risk* (NICE, 2012). In this guidance a fasting plasma glucose (FPG) level of 5.5–6.9 mmol/l or an HbA_{1c} level of 42–47 mmol/mol (6.0–6.4%) is regarded as indicating a high risk and the use of metformin is suggested for:

- Adults at high risk whose blood glucose measure (FPG or HbA_{1c}) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme.
- Adults at high risk who are unable to participate in lifestyle-change programmes because of a disability or for medical reasons.

(For those at low risk of developing diabetes dietary and lifestyle advice are recommended with more specific brief lifestyle programmes for those at moderate risk. See later section.)

In relation to the effects of metformin on weight loss in the general population, a randomised, double-blind, placebo controlled RCT in France (Fontbonne et al., 1996), conducted in 457 people without diabetes with a high waist-to-hip ratio

(*n*=324 completers at one year), demonstrated weight loss in the metformin compared to the placebo group (respectively −2.0 kg (95% CI −3.0 to −1.1) vs. −0.8 kg (95% CI −1.6 to +0.1); *P*<0.06), but fell just short of being statistically significant. Weight loss with metformin in the DPP study was of similar magnitude and statistically significantly different from placebo (*P*<0.001). This benefit was directly related to degree of adherence with metformin treatment (Diabetes Prevention Program Research Group, 2012). A systematic review of studies in non-diabetic, obese young people aged 19 years or less identified five RCTs of metformin versus placebo (Park et al., 2009). Meta-analyses of the data from these indicated that compared with placebo metformin reduced BMI by 1.42 kg/m^2 (95% CI 0.83 to 2.02).

A recent meta-analysis of studies in which metformin was added to existing antipsychotic medication (most commonly clozapine, olanzapine or risperidone) identified 10 RCTs, of which four (three by the same author) were in people in their first episode of illness (Mizuno et al., 2014). Five of these studies were carried out in China or Taiwan, three in Venezuela, one in Iran and one in the USA, so the results may not be entirely generalisable to all populations. Furthermore, a funnel plot of these 10 studies suggested some possibility of publication bias for studies with smaller samples. The overall results of these studies favoured metformin over placebo with a mean difference of −3.17 kg (95% CI −4.44 to −1.90). In three studies there was no statistically significant difference between metformin and placebo. For the four trials in people with first-episode psychosis the mean difference was −5.01 kg (95% CI −6.41 to −3.62).

The largest study (Jarskog et al., 2013) was carried out across 17 sites in the USA and recruited 148 (*n*=116 completers) participants with schizophrenia or schizoaffective disorder who had been ill for at least 12 months and had a BMI of 27 kg/m^2 or greater. All participants received weekly diet and exercise counselling and either metformin or placebo for 16 weeks. The mean final daily dose of metformin was 1887 mg (SD 292), similar to everyday clinical use. At week 16 the mean weight change for the metformin group was −3.0 kg (95% CI −4.0 to −2.0) and that for the placebo group was −1.0 kg (95% CI −2.0 to 0.0), a statistically significantly difference (*P*=0.0065). Thirteen metformin and seven placebo participants achieved weight loss of 5% or more. BMI was changed by −1.0 kg/m^2 in the metformin group and −0.3 kg/m^2 in the placebo group. There was a statistically significant lowering of triglyceride levels and in HbA_{1c} at 16 weeks in the metformin group, but no significant difference between groups in total cholesterol, HDL or LDL cholesterol, fasting glucose or insulin levels. The only adverse effect reported that differed between metformin and placebo was diarrhoea. While this study indicates a positive effect of metformin for existing antipsychotic-related weight gain the effect is fairly modest, that is, a reduction of only one point in BMI. However, weight reduction was continuing up to the end of the 16 weeks and thus a longer trial might have revealed a larger improvement.

The longest study, lasting for 24 weeks, was at a single site in China and included people with first-episode psychosis. Wu and colleagues recruited 84 (*n*=76 completers) female patients within their first year of commencing antipsychotic treatment (mean duration 6.35 months) and who also experienced amenorrhoea (Wu et al., 2012). The metformin dose was 1000 mg/day. No information was given regarding other dietary or exercise programmes. The metformin group lost −2.3 kg and the placebo group gained +2.1 kg, with respective changes in BMI of −0.93 kg/m^2 and +0.85 kg/m^2. Insulin resistance decreased in the metformin group and significantly more of the metformin group resumed menstruation (66.7% vs. 4.8%). There were no differences in adverse effects between the two groups. In this Chinese population initial weight and BMI were lower than would be found in a western population (mean BMI at baseline was 22.5 kg/m^2) and thus the reduction in BMI with metformin represents a 4.1% change. Weight loss in the metformin group appeared to continue up to month 5 of the study, suggesting that any trial of adjunctive metformin treatment needs to be given a reasonable period in which to demonstrate maximum effect.

A 12-week RCT in 40 antipsychotic medication-naive patients in China (Wu et al., 2008) found that those receiving olanzapine plus metformin gained less weight than those receiving olanzapine plus placebo (respectively +1.9 kg (SD 2.72) vs. +6.87 kg (SD 4.23); *P*<0.02). However, these patients had a long mean pre-treatment duration of illness of 7.2 years and were inpatients with more limited access to food.

Klein and colleagues carried out a 16-week RCT in 39 (*n*=30 completers) service users aged 10–17 years who had gained more than 10% of their pre-antipsychotic body weight during less than 12 months of treatment with either olanzapine, risperidone or quetiapine (Klein et al., 2006). All participants and their families were offered regular dietetic advice. The participants on metformin (1700 mg/day) showed little change in weight over the treatment period (mean −0.13 kg, SD 2.88) while the placebo group continued to gain weight (mean +4.01 kg, SD 6.23). Differences between the mean values were significant at weeks 4, 8, 12 and 16. There was evidence that metformin treatment had an impact on the development of abnormal glucose tolerance. There were no differences in adverse effects between the treatment groups.

While adverse effects in the studies above did not appear to differ between metformin and placebo-treated participants it is important to remember that metformin can cause the serious effect of lactic acidosis, with a rate of around nine cases per 100,000 person years (often in the context of renal failure). For this reason, metformin is contraindicated in severe renal impairment (estimated glomerular filtration rate (eGFR) <30 ml/min), hepatic failure and heart failure. The risk may also be increased by alcohol consumption. Metformin can also decrease the absorption of vitamin B_{12} and 7% may develop deficiency of this over 4 years. The more common adverse effects are complaints of nausea, bloating, abdominal pain and diarrhoea in around 10–20% of patients, effects that often result in patients not being able to tolerate the drug. Thus, it is usually initiated at a low dose with gradual increase over 2–3 weeks.

Summary. These data would suggest that metformin can reverse existing antipsychotic-induced weight gain, with a difference from the effects of placebo treatment of approximately 3 kg. Four studies suggest it can help to attenuate weight gain in those commencing antipsychotics for the first time, but three of these are in Chinese populations and by the same author. There is evidence that metformin may improve abnormal glucose intolerance and some aspects of lipid profile. However, there is heterogeneity in the data from the available RCTs and many of the studies have included some aspect of lifestyle management. Most of the studies involve small numbers of participants and are of short

Table 3. Treatments that have been studied, or considered, for reduction of antipsychotic related weight gain (listed in alphabetical order and not order of importance).

Group	Evidence of efficacy for reducing weight gain and availability in the UK	Treatments given in alphabetical order within each group
A	Data available for these treatments from RCTs in antipsychotic treated patients. Treatments are available in the UK but are not necessarily licensed for the treatment of obesity.	Amantadine Melatonin Orlistat Topiramate Reboxetine Zonisamide
B	These treatments have evidence of efficacy in the general population but no trials in antipsychotic-treated patients. The last two drugs are not currently available for use in the UK.	Bariatric surgery GLP-1 analogues (liraglutide and exenatide) Lorcaserin Phenteramine/topiramate combination
C	For most of these treatments only a single (negative) clinical trial has been carried out in antipsychotic-treated patients. Treatments are available in the UK but are not licensed for the treatment of obesity.	Atomoxetine Dextroamphetamine Famotidine Fluoxetine Fluvoxamine Nizatidine
D	Had limited or no evidence of effectiveness in antipsychotic treated patients. Treatments no longer available in the UK.	D-fenfluramine Phenylpropanolamine Rimonabant Rosiglitazone Sibutramine

duration. No studies reported data on whether transition to diabetes was reduced in metformin versus placebo groups.

Metformin is not appropriate for people with comorbid harmful use of alcohol or alcohol dependence syndrome as alcohol enhances the hypoglycaemic effect of metformin and increases the risk of lactic acidosis. It is necessary to monitor renal function and vitamin B_{12} levels in those taking metformin.

Other interventions for overweight and obesity

A number of other treatments have been considered as possible adjunctive treatments and subject to clinical trials for weight reduction in the context of antipsychotic-induced weight gain. Some of these have been subject to clinical trials for weight gain and obesity in the general population but some have only been examined in the context of antipsychotic-induced weight gain. These various treatments are divided into four groups according to whether clinical trial evidence exists for their effects within antipsychotic-treated populations and their availability in the UK (Table 3).

The treatments listed in group A, above, are the only ones (aside from the possible use of bariatric surgery in more extreme cases) that currently merit significant review, and the evidence relating to these is summarised below. Less detailed discussion is provided for the treatments listed in groups B, C and D.

Treatments available in the UK with RCTs in antipsychotic-treated patients (group A)

Amantadine. Amantadine is an antiviral agent that has been shown to be effective for extrapyramidal adverse effects. Clinical trials for weight gain are based on its ability to modify dopaminergic and serotoninergic neurotransmission. Praharaj and Sharma (2012) identified six studies. Four were open-label trials or case series and only two double-blind, placebo controlled RCTs were identified that could be subject to meta-analysis. In Deberdt et al. (2005) 125 participants were recruited, of whom 111 completed a 16-week trial. In Graham et al. (2005) 21 participants were recruited, of whom 18 completed a 12-week trial. Both trials included participants with bipolar disorder as well as schizophrenia. All participants received amantadine or placebo in addition to olanzapine, but some participants were also on antidepressants or mood stabilisers. Both studies reported small, but statistically significant, weight loss in the amantadine group and weight gain in the placebo group. Meta-analysis suggested an overall beneficial effect for amantadine with a mean difference of −1.85 kg (95% CI −3.31 to −0.39). Only the smaller study reported changes in BMI (statistically significant). In the larger trial the difference in weight between the two groups was only 1.47 kg.

Note that amantadine is a weak dopamine agonist and has been reported to induce psychotic symptoms as an adverse effect.

Melatonin. Melatonin is a hormone involved in the entrainment of circadian rhythms. It has been shown to block olanzapine-induced weight gain and visceral adiposity in laboratory rats (Raskind et al, 2007), and a relationship has been described between nocturnal melatonin secretion and body weight in schizophrenia (Ferrier et al., 1982). Two double-blind RCTs have examined the effect of melatonin versus placebo. Romo-Nava and colleagues (2014) studied 44 participants with either schizophrenia or bipolar disorder for 8 weeks using melatonin 5 mg daily. The melatonin group showed attenuated weight gain versus

Table 4. RCTs of effect of topiramate versus placebo on weight in people with psychosis who are prescribed antipsychotic medications.

Trial	Drug naive	Antipsychotic	Length of trial	*n* (final *n*)	Results
Nickel et al. (2005)	No	Olanzapine	10 Weeks	49 (f) (43)	Only *n*=20 with psychosis. Difference in weight between the groups: 5.6 kg (95% CI –8.5 to –3.1; *P*<0.001)
Ko et al. (2005)	No	Clozapine, olanzapine, quetiapine, risperidone	12 Weeks	66 (53)	Difference in weight loss between groups: 100 mg vs. placebo: –1.68 kg vs. –0.3 kg (ns) 200 mg vs. placebo: –5.35 kg vs. –0.3 kg (F=5.52; *P*=0.008)
Afshar et al. (2009)	No	Clozapine	8 Weeks	32 (? 32)	Change in BMI (kg/m²): Topiramate: 24.1 to 23.2 (ns) Placebo: 25.2 to 25.4 (ns)
Narula et al. (2010)	Yes	Olanzapine	12 Weeks	72 (67)	Weight change significantly different between groups (*P*=0.05): Topiramate: –1.27 kg Placebo: +6.03 kg

placebo (1.5 kg vs. 2.2 kg; *P*=0.04) but effects on body fat mass were only seen in the bipolar patient group. Modabbernia and colleagues (2014) studied 48 participants in their first episode of psychosis who received either olanzapine plus melatonin 3 mg daily or olanzapine plus placebo. Weight gain was less in the melatonin group, with a mean difference of 3.2 kg (*P*=0.023).

Orlistat. Orlistat is an inhibitor of gastric and pancreatic lipase and prevents intestinal fat absorption. A meta-analysis of 16 placebo controlled RCTs in the general population (Rucker et al, 2007), showed that orlistat (120 mg three times daily) reduced weight by 2.9 kg (95% CI 2.5 to 3.2) after 1 year and more participants in the orlistat group achieved at least 5% weight loss. However, because of the adverse effects of orlistat (principally unpleasant steatorrhoea) only 70% of participants on average complete formal trials and long-term adherence is less than 2% at 2 years (Padwal et al., 2007).

Two studies in people with schizophrenia have demonstrated some effect on weight but in both studies the effect is only seen in male participants. Joffe and colleagues (2008) commenced 71 participants (63 completed the study) in a 16-week placebo controlled RCT of orlistat in addition to clozapine or olanzapine. Only men demonstrated weight loss (–2.36 kg vs. +0.62 kg; *P*=0.011). In what appears to be a separate study, the same research group (Tchoukhine et al., 2011) entered 44 participants on clozapine or olanzapine into a double-blind placebo controlled study of orlistat followed by a 16-week open-label phase. Again an effect was only seen in men and data from the open phase suggested that if patients do not achieve weight loss in the first 16 weeks continuation of treatment is not beneficial.

In one 8-week study, orlistat did not appear to have any clinically relevant effect on plasma concentrations of a number of psychotropic drugs, including haloperidol, clozapine and clomipramine (Hilger et al., 2002). Nevertheless, given that many psychotropic drugs are quite lipid soluble, the possibility of alterations in plasma drug concentrations should be considered.

Topiramate. Topiramate is a third generation anticonvulsant introduced to the UK in 1995 and used as a first-line treatment for focal and generalised seizures. Its anticonvulsant mechanism of action is thought to involve potentiation of GABA, inhibition of glutamate (AMPA) and Na^+ and Ca^+ channel blockade. The principal adverse effects are sedation, dizziness, cognitive effects, increased risk of renal lithiasis, paraesthesia and psychosis (reported as a low risk). Impairments of cognition have been observed across a number of domains (Thompson et al., 2000) and appear to be dose dependent (Loring et al., 2011). In one post-marketing surveillance study of people with epilepsy they were the most common reason for discontinuation of topiramate (Tatum et al., 2001). Trials of topiramate for reduction of obesity in the general population were halted due to the severity of adverse effects.

Weight loss has been reported in a proportion of people with epilepsy prescribed topiramate. A meta-analysis of studies of the effect of topiramate in overweight/obese people in the general population suggested a weight loss of 5.34 kg compared to placebo (Kramer et al, 2011). The proposed mechanism of action is a reduction in visceral fat associated with a decrease in plasma leptin concentrations.

Four double-blind, placebo controlled RCTs, ranging from 8 to 12 weeks in length, have examined the effect of topiramate on weight and/or BMI, when added to antipsychotic treatment (Table 4). Three studies found a statistically significant benefit compared to placebo. That of Narula et al. (2010) also reported improvements in favour of topiramate versus placebo in fasting glucose, total cholesterol and LDL cholesterol.

In addition, there have been a number of individual case reports and some case series suggesting beneficial effects on weight of topiramate added to existing antipsychotic treatment (e.g. Hahn et al., 2010; Khazaal et al., 2007). A 12-week non-blind, randomised, parallel group study (*n*=60), in which topiramate or placebo were added at the beginning of treatment with olanzapine, found attenuation of weight gain in those participants receiving topiramate (+2.3 kg) versus those receiving placebo (+4.1 kg) (Kim et al., 2006). In general, the starting dose used for topiramate has been around 25 mg twice a day with titration up to a final maximum dose of between 100 mg/day and 300 mg/day. Studies in which clinical symptom change was the primary outcome measure have tended to titrate up to maximum doses at the higher end of this range.

A further study examined longer term effects (Liang et al., 2014). Ten people with schizophrenia were commenced on topiramate for 4 months with a mean weight loss of 1.79 kg.

Topiramate was then discontinued with a further mean weight loss up to 4.32 kg reported at 12 months after discontinuation.

One meta-analysis (Mahmood et al., 2013), which included studies of people with schizophrenia but also autism and bipolar disorder, as well as studies in which weight change was not the primary outcome measure, concluded that augmentation of antipsychotic treatment with topiramate can prevent or reduce weight gain compared to control treatments, with a weighted mean difference of −2.83 kg (95% CI −4.62 to −1.03).

There has been some evidence for improvement in symptoms of schizophrenia (principally items from the general psychopathology sub-scale of the PANSS) from small, short-term trials of topiramate, added to existing antipsychotics, in people whose symptoms are relatively treatment resistant (e.g. Hahn et al., 2010; Tiihonen et al., 2005). Migliardi and colleagues (2007) did not find any effect of topiramate on the plasma concentration of a number of antipsychotic drugs.

Reboxetine. Reboxetine was the first selective noradrenaline reuptake inhibitor to be introduced for the treatment of depression and was approved for use in the UK in 1997. It binds to the noradrenaline transporter and potently inhibits reuptake of extracellular noradrenaline. There are very weak effects at histamine H_1 and serotonin $5HT_{2A}$ receptors and a very weak effect on serotonin reuptake.

There have been two studies examining the effect of reboxetine alone (Poyurovsky et al., 2003, 2007) and one study of a combination of reboxetine and betahistine (Poyurovsky et al., 2013) on olanzapine-related weight gain in people with schizophrenia. These studies are all from the same research group. They all suggest a significant attenuation of rise in BMI and weight gain by reboxetine as well as improvements in some related biochemical metabolic measures (triglyceride and leptin) but not others (glucose, HDL, LDL, insulin). Meta-analysis of these data shows a weighted mean difference between reboxetine and placebo of −1.90 kg (95% CI −3.07 to −0.72) (Mizuno et al., 2014).

Studies examining the effect of reboxetine on the clinical symptoms of schizophrenia find no significant effect on either positive or negative symptoms although improvement in mood has been reported in one. A study of its effects on plasma concentrations of clozapine and risperidone and their active metabolites did not find any interaction (Spina et al., 2001).

Zonisamide. Zonisamide is a sulfonamide anticonvulsant unrelated to other anticonvulsants. It was approved for use as an adjunctive therapy in adults with certain types of epilepsy in 2005 and has also been used 'off label' in bipolar disorder. It has been found to cause weight loss in overweight people with epilepsy (Wellmer et al., 2009) and in a 1-year, double-blind, placebo controlled RCT was shown to reduce weight in obese adults (Gadde et al., 2012). It has been shown to decrease weight in a small case series (n=3) of people with schizophrenia (Yang et al., 2010) and also in an open-label study, of rather complex design, of various medications, including zonisamide, added sequentially to olanzapine (Hoffmann et al., 2012).

Ghanizadeh and colleagues (2013) conducted a 10-week double-blind, placebo controlled RCT in 41 people with schizophrenia who were on a stable dose of their current antipsychotic agent, most commonly risperidone (n=23). BMI increased by 2.2 kg/m^2 in the placebo group and decreased by 0.3 kg/m^2 in the zonisamide group (P<0.0001) with parallel changes in weight (+1.9 kg vs. −1.1 kg; P<0.0001) and waist circumference. Frequencies of adverse effects were reported as no different between the groups, although there were two dropouts from the zonisamide group.

Treatments with evidence in general population studies but not in antipsychotic-treated patients (group B)

There are treatments with evidence for efficacy in inducing weight loss in the general population but that have no clinical trial data in patients with antipsychotic-related weight gain (Table 3, group B). Lorcaserin is a selective 5-HT_{2C} receptor agonist, available in the USA since 2012 for the treatment of obesity in adults with BMI of 30 kg/m^2 or greater or those with BMI greater than 27 kg/m^2 in the presence of one related comorbidity. A phenteramine and topiramate combination (Qsymia) has also been available in the USA since 2012 for the same indication. At the time of writing there were no trials of these two medications for antipsychotic-related weight gain and these medications were not approved for use in the UK.

The GLP-1 receptor agonists are an injectable class of drugs that have been approved for the treatment of type 2 diabetes since 2006. They are based on analogues of human GLP-1 (liraglutide, albiglutide, dualaglutide) or exendin (exenatide, lixisenatide), which has 53% homology to human GLP-1. Their use is associated with significant weight loss and this has led to clinical trials of their use in people with overweight or obesity, albeit at higher doses than are used to treat diabetes. Liraglutide has recently been approved for the treatment of obesity in the USA and Europe.

Studies of liraglutide have not been performed in people with psychosis. However, in laboratory animal studies, liraglutide has been shown to reverse olanzapine-induced weight gain (e.g. Lykkegaard et al., 2008) and in a case report appears to have assisted weight loss in an obese female patient with schizophrenia (Ishoy et al., 2013). A clinical trial of exenatide for olanzapine-induced weight gain is in progress in the USA.

Bariatric surgery has not yet been subject to any formal clinical trial in people with psychosis. However, there are reports of a number of case series, extracted retrospectively from cohorts of all cases subject to bariatric surgery in particular surgical centres (e.g. Hamoui et al., 2004; Fuchs et al., 2016; Shelby et al., 2015). The numbers of people with a diagnosis of schizophrenia reported within individual case series are usually less than 10, and make up much less than 1% of all bariatric surgical cases. Most of these case series also report people with a diagnosis of bipolar disorder, for whom this appears to be performed more commonly. However, comparisons and calculation of a mean percentage across centres are not possible due to variations in how some of the data are collected. People referred for bariatric surgery in these centres generally have BMI greater than 40 kg/m^2 and many have a BMI greater than 50 kg/m^2.

The general conclusion from such reports is that people with diagnoses of schizophrenia and bipolar disorder demonstrate the same post-surgical weight loss as others. Improvement is generally reported as the percentage of excess weight loss (i.e. percentage weight loss above ideal weight if BMI was 25 kg/m^2). For example, at 6 months Hamoui et al. (2004) found excess weight

loss was 39.5% (range 29.4–62.9%) in the schizophrenia group versus 46.9% (range 30.0–95.5%) in the control group (no statistically significant difference). Some reports describe deteriorations in mental state post-surgery in a proportion of people with psychosis, while others find little change. One matched cohort, follow-up study over 2 years, in people with bipolar disorder (n=144), did not find any difference in hospital admissions or utilisation of outpatient services in those who underwent surgery compared to those who did not (Ahmed et al., 2013).

Without an appropriate clinical trial, we cannot be certain that bariatric surgery will have the same persistence of effect for antipsychotic weight gain as for other forms of obesity, as mechanisms other than excessive food intake may be involved. Those referred for such intervention require to be able to cooperate with post-surgical follow-up, for example, possible dietary changes for micronutrient deficiencies (Moore et al., 2016). It is also unknown, and probably unpredictable for individual cases, whether absorption of antipsychotic medications will be affected. However, it may sometimes be appropriate to consider bariatric surgery within the requirements of NICE guidelines for the management of obesity.

Other treatments with trials in antipsychotic-treated patients (groups C and D)

There is a small number of other medications, with possible theoretical rationales for use in antipsychotic-related weight gain, which have been subject to clinical trials. We have summarised the data regarding these medications below, but have not reviewed all of these in detail. For most of these medications there is either very little data available and/or many are not currently available for use. Further information about these medications can be found in a number of systematic reviews and meta-analyses (Das et al., 2012; Maayan et al., 2010; Mizuno et al., 2014).

Six medications that are available for prescription in the UK have been studied (Table 3, group C). Atomoxetine and dextroamphetamine have each been subject to a single negative clinical trial in people on antipsychotic medications. Two selective serotonin reuptake inhibitor antidepressants, fluoxetine (two trials) and fluvoxamine (one trial), were found to be ineffective, suggesting that this class of drugs is not useful for antipsychotic-related weight gain. Famotidine (one trial) and nizatidine (five trials) are both histamine H_2 receptor antagonists and inhibit secretion of gastric acid. Trials of these were all negative suggesting that this class of drugs is also not useful.

Finally, there have been five other drugs considered for this indication before withdrawal of their approval for use in the UK (Table 3, group D). D-fenfluramine was an anorectic drug with a number of effects on the serotonin system. A double-blind, placebo controlled RCT (n=29) demonstrated greater weight loss in the D-fenfluramine group (Goodall et al., 1988). However, other clinical reports examining its effect on the core symptoms of schizophrenia varied as to whether or not these could be worsened. The drug was withdrawn from use in 1997 due to risks of valvular heart disease. Phenylpropanolamine was an ingredient used in many over-the-counter and prescription cough and cold medications as a decongestant but also, in some countries, as an anorectic. It was ineffective for antipsychotic-related weight gain in a single trial, but has been withdrawn from use due to evidence of increased risks of haemorrhagic stroke.

Rosiglitazone was introduced to the UK in 1999 as an antidiabetes drug and withdrawn in 2010 due to increased risk of myocardial infarction. Two studies in people with schizophrenia failed to find benefit for amelioration of weight gain. Clinical trials of sibutramine resulted in both positive and negative findings for antipsychotic-related weight gain, but in 2010 the drug was withdrawn from the UK due to cardiovascular risks. Rimonabant is an inverse agonist for the CB1 cannabinoid receptor and reduces appetite. It was introduced in the European Union in 2006 for the management of obesity but withdrawn in 2008 due to increases in suicidality and depression. A 16-week double-blind RCT in Maryland in people with schizophrenia, and BMI greater than 27 kg/m^2, was terminated early (because the drug was withdrawn from the European market) but data from 15 patients (seven on rimonabant, eight on placebo) did not demonstrate any significant weight loss (Kelly et al., 2011).

Summary (for groups A–D)

On the basis of currently available evidence, the treatments summarised here cannot be recommended in routine clinical practice. For some there may be exceptional circumstances in which their use might be considered.

Only topiramate has a modest amount of evidence from RCTs to suggest it may help to mitigate weight gain with the potential to induce weight loss. The weighted mean difference from one meta-analysis was 2.8 kg. However, the degree of difference between topiramate and placebo varies considerably between studies. This seems to be without significant risk of adverse effects on core symptoms of psychosis. The evidence base is limited and the adverse effects, particularly on cognition, would appear to outweigh any potential benefit for most people.

Zonisamide, another anticonvulsant, has thus far been tested in only a single RCT but appears worthy of further research for this indication. While three studies from one research group support the use of reboxetine, there is no replication from other research groups and the effect seems only to be attenuation of weight gain rather than weight loss.

The evidence base in favour of amantadine and melatonin is small and is insufficient to recommend these treatments for serious consideration. The effect of orlistat is limited to men but extremely poor tolerance of steatorrhoea is a huge limiting factor. In practice only a very small proportion of people will continue orlistat in the long term making it of little value on a routine basis. There may be a role for bariatric surgery in extreme cases although the long-term benefit of this for antipsychotic-induced weight gain requires further evaluation.

More recent medications, such as lorcaserin and liraglutide, which seem to be effective in the general population, may have a role in the future but are yet to be evaluated for antipsychotic-induced weight gain.

Interventions for tobacco smoking

In general, smoking cessation rates for people with schizophrenia are around 50% of those for the general population (Williams and Foulds, 2007). NRT is the most widely used treatment but there are no double-blind, placebo controlled RCTs of its use in schizophrenia. Seven studies (summarised by Tidey and Miller, 2015) report abstinence rates between 9% and 23% at periods varying from 6 months to 12 months. These studies were all open-label as

far as NRT was concerned but most provided some form of individual or group support in addition, which was allocated at random. In general, addition of such support improved abstinence rates. One study reported a 6-month period of single-blind, randomised allocation of nicotine patches versus placebo patches for maintenance of smoking cessation (achieved during an earlier open-label NRT phase) in 17 individuals with schizophrenia (Horst et al., 2005). All eight of those receiving active patches remained tobacco-free but only three of nine receiving placebo patches (P=0.009).

It is important to remember that a number of chemicals in cigarette smoke (not nicotine) induce the activity of cytochrome P450 1A2 and hence may reduce the plasma concentration of a number of psychotropic medications, particularly clozapine but also olanzapine, haloperidol and some antidepressants. Thus, it is ideal if smoking is reduced in a controlled fashion with monitoring of plasma clozapine levels as necessary and monitoring of indications of rising plasma drug levels (such as increased adverse effects) for all medications.

The use of e-cigarettes in the general population, for substitution or smoking cessation, is increasing. However, there are concerns about their use in adolescents and whether or not e-cigarettes may encourage some people to start smoking. To date there is only one uncontrolled study of these for inpatients with schizophrenia in Italy (Minutolo et al., 2013). Over 52 weeks 50% of 14 participants demonstrated at least a 50% reduction in the number of cigarettes per day smoked, without evidence of deterioration in core symptoms of psychosis.

Studies with buproprion, which attenuates withdrawal symptoms and nicotine reinforcement, find that buproprion assists initial smoking cessation but that relapse rates are high following discontinuation of buproprion. Individual results for the six RCTs of buproprion, alone or combined with NRT, found either no significant difference from placebo at the end of the initial treatment phase or no significant difference at the end of a 3–6-month follow-up period (Tidey and Miller, 2015). However, many of these studies have small numbers of participants. Meta-analysis suggests a significant effect of buproprion at follow-up.

Studies of varenicline (three RCTs; see Tidey and Miller, 2015) report improved abstinence following an initial treatment phase but only one of two reporting abstinence rates after 6 months or longer found a statistically significant effect. However, again a meta-analysis suggests that varenicline has a significant effect.

Bennett et al. (2013) reviewed 11 studies that investigated psychosocial/behavioural approaches in people with schizophrenia and concluded there were reasonable short-term abstinence rates but data were too variable to determine clear long-term effects. A recently reported UK pilot RCT of a bespoke smoking cessation programme for people with psychosis (SCIMITAR), compared to usual care, suggested that the bespoke programme resulted in greater effectiveness (Gilbody et al., 2015). This is being followed up by a full trial. No RCT data are available with regard to promotion of exercise for smoking cessation.

Thus, while NRT remains the treatment of initial choice there are no double-blind, placebo controlled RCTs to support this. NRT is usually prescribed as part of an overall smoking cessation programme, and evidence suggests improved outcomes if such other forms of support are provided. Meta-analysis of a modest number of studies of buproprion suggests some benefit. Evidence to support behavioural/psychosocial approaches on their own and varenicline remains limited. There have been concerns that both buproprion and varenicline may cause adverse psychological effects (including suicidal ideation), but the evidence is conflicting (Hartmann-Boyce and Aveyard, 2016).

Interventions for alcohol misuse

Despite how commonly alcohol misuse occurs in schizophrenia, there are limited empirical data to guide clinicians in managing this usually challenging situation (see Lingford-Hughes et al., 2012). A Cochrane systematic review of psychosocial interventions in comorbid schizophrenia and substance use disorder revealed that none of these interventions showed particular superiority over ‘treatment as usual’ in reducing substance use, retention in treatment or improvement in mental state in people with serious mental illnesses (Hunt et al., 2013). For alcohol misuse, one small RCT of motivational interviewing showed some promise (Hunt et al., 2013). Other studies have primarily focused on illicit drugs such as cannabis with no, or limited, data relating to alcohol.

One question is whether a particular antipsychotic medication is preferable in comorbidity? Evidence from older studies suggested that first generation antipsychotics did not reduce harmful substance use, abuse or dependence, and in fact might increase it (Siris et al., 1990). Subsequently studies of second generation antipsychotics are primarily retrospective surveys, open trials or case series, with very few prospective RCTs. In these studies, there is no robust evidence that any particular second generation antipsychotic is associated with improvements in alcohol misuse although the uncontrolled studies generally report some benefit (see Lingford-Hughes et al., 2012 for further details). The second generation drugs studied include olanzapine, risperidone and quetiapine. There have been several case reports and surveys suggesting clozapine results in improved substance misuse although no prospective or controlled trials. Open studies of flupenthixol and risperidone depot/long-acting injections have also reported improvements and a recent study suggested that risperidone long-acting injection may be a better choice than oral (Lingford-Hughes et al., 2012; Green et al., 2015a).

With regard to alcohol relapse prevention medication, there is again limited evidence on which to develop clinical guidance. For the non-comorbid alcohol dependent populations, NICE recommends that acamprosate or naltrexone be offered to all those with moderate to severe dependence, with disulfiram as second line (CG115) (NICE, 2011: section 1.3.5). Acamprosate and naltrexone have been used safely in patients with schizophrenia and no particular considerations are required (Lingford-Hughes et al., 2012).

However, psychosis is listed as a contraindication for disulfiram and due to its propensity to increase psychosis, through blockade of dopamine-β-hydroxylase, as well as risks when combined with alcohol, its use in schizophrenia is limited. However, there is a trial of disulfiram in psychotic patients (73% with bipolar disorder) demonstrating improved drinking outcomes, without adverse consequences (Petrakis et al., 2006). This trial also demonstrated that the use of naltrexone resulted in improved drinking outcomes. There are no studies of nalmefene, baclofen or topiramate for alcohol misuse in people with schizophrenia. For those with alcohol abuse, there is no robust evidence to support the use of such medication to improve drinking behaviours.

In summary, there is no evidence to support any specific form of psychosocial intervention over usual management. While optimisation of antipsychotic treatment is always important, there is no RCT evidence that any specific antipsychotic will be more or less beneficial with regard to alcohol misuse, but there is some preliminary evidence to suggest that clozapine may reduce levels of substance misuse in general. Acamprosate and naltrexone may be considered as per existing NICE guidelines.

Management of the increased risks for diabetes and CVD

How should we apply NICE guidelines on pre-diabetes and diabetes in those with schizophrenia?

Decisions regarding the management of impaired fasting glycaemia or impaired glucose tolerance or regarding the management of diabetes for any individual should be made by that person's general practitioner, or by a consultant physician, in consultation with the individual. Initial risk assessment and investigation may be by the mental health team or general practitioner.

'Pre-diabetes'. The identification of a person's degree of risk for developing diabetes is an important step in determining the level of preventative measures required. The current NICE public health guidance *Type 2 diabetes: prevention in people at high risk* (PH38) (NICE, 2012) provides detail on how to approach this. The associated flowchart provides a summary of the main points: available online at http://www.nice.org.uk/guidance/ph38/chapter/1-Recommendations#recommendation-1-risk-assessment or page 12 of NICE PH38 (NICE, 2012).

Stage 1 of the NICE diabetes risk identification process recommends that clinicians and their patients should be encouraged to make use of validated questionnaires or web-based risk tools to assess the level of risk for an individual (e.g. http://riskscore.diabetes.org.uk/results on the Diabetes UK website). The precise approach, and subsequent advice, depend on age and whether the person falls into a 'high risk group' – determined by ethnicity, family history and whether or not the person has a condition that increases the risk of type 2 diabetes. People with psychosis and on antipsychotic medications should be regarded as being in a 'high risk group'. In the context of weight gain related to the initiation of antipsychotic medication it is worth noting that, in the general population, for every 1 kg/m^2 increase in BMI the risk of developing new-onset type 2 diabetes increases by 8.4%.

NICE recommends that a blood test should be offered to individuals in the general population with a high risk assessment tool score and those who are in a 'high risk group'. This will include people with psychosis, to whom a blood test should be offered at least once annually and more often if weight is increasing or symptoms of possible diabetes develop (polyuria, nocturia, polydipsia, tiredness, visual disturbance and candida infection). This can be a FPG or HbA_{1c}, the latter now being regarded as an appropriate alternative to FPG by the World Health Organization.

While different levels of advice about exercise and diet are provided for those with different levels of risk, in reality all people with psychosis should be advised to take broad preventative measures such as: at least 150 minutes of moderate intensity physical activity per week; maintain their BMI within the healthy range; reduce dietary fat and increase consumption of whole grains, vegetables and fruit, while minimising the intake of highly calorie dense foods. This would be consistent with the NICE guideline on schizophrenia (CG178) (NICE, 2014a).

In stage 2 of the NICE diabetes risk identification process (PH38) (NICE, 2012), three levels of risk are described, with associated recommended management:

1. Moderate risk: FPG <5.5 mmol/l or HbA_{1c} <42 mmol/mol
   - Discuss the risk of developing diabetes
   - Help modify individual risk factors
   - Offer tailored support services
2. High risk: FPG 5.5–6.9 mmol/l or HbA_{1c} 42–47 mmol/mol
   - Offer an intensive lifestyle-change programme to increase physical activity
   - Achieve and maintain weight loss
   - Increase dietary fibre and reduce fat intake
3. Possible type 2 diabetes: FPG ⩾7.0 mmol/l or HbA_{1c} ⩾48 mmol/mol
   - If asymptomatic carry out a further blood test to confirm or reject the presence of diabetes

NICE PH38 suggests that individuals who are at high risk of developing diabetes and whose blood glucose shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme, or those who are unable to participate in an intensive lifestyle-change programme, should be considered for treatment with metformin. Background literature relating to the use of metformin to reduce the risk of progression to diabetes and to reduce weight gain has been discussed in an earlier section and will not be repeated here.

Diabetes. People with a psychotic illness who develop diabetes should receive the same standard of diabetes care as the rest of the general population. It is important to remember that all people require an individualised approach and should be encouraged to engage with the appropriate local diabetes services. For example: someone with persecutory delusions may find it more difficult to attend a public gym for an appropriate exercise programme or go to a public swimming pool.

The advice in previous sections, above, regarding management of weight gain should be revisited if an individual goes on to develop diabetes secondary to overweight or presents with diabetes after a period of non-engagement with services. Ideally, medications that may contribute to weight gain should be avoided but this is often very difficult or impossible in the case of antipsychotic treatment.

An updated version of the NICE clinical guideline on the management of type 2 diabetes was published in December 2015: *Obesity: identification, assessment and management* (NG28) (NICE, 2015a) provides guidance on management and is reflected in the NICE pathway for diabetes available online (pathway available at: http://pathways.nice.org.uk/pathways/diabetes. PDF available at: http://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood-glucose-lowering-therapy-in-adults-with-type-2-diabetes-2185604173). Key points for the management of type 2 diabetes, from NICE NG28, which will be the most common presentation in the context of antipsychotic treatment, are:

1. Education about diabetes, dietary advice and lifestyle programmes should be offered, especially if the person is overweight. This should continue at regular intervals following diagnosis.
2. The target for HbA_{1c} should normally be 48 mmol/mol (6.5% in old units) with the precise target being dependent on the clinical situation and agreement with the person.
3. HbA_{1c} should be monitored 3–6 monthly until stable on unchanging therapy. Thereafter monitoring should be every 6 months.
4. If, despite lifestyle interventions, HbA_{1c} remains $\geqslant$48 mmol/mol (6.5%) then drug therapy should be offered.
5. Initial drug treatment: Standard-release metformin should be the first-line medication but the dose must be reviewed if eGFR is <45 ml/minute/1.73 m^2 and should be stopped if eGFR is <30 ml/minute/1.73 m^2.
6. If metformin is contraindicated or not tolerated consider initial drug treatment with: a dipeptidyl peptidase-4 (DPP-4) inhibitor, or pioglitazone, or a sulfonylurea.
7. First intensification of drug treatment (if HbA_{1c} rises to 58 mmol/mol; 7.5%)
   (a) If initial drug treatment with metformin has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: metformin and a DPP-4 inhibitor, or metformin and pioglitazone, or metformin and a sulfonylurea. (In occasional situations metformin and an SGLT-2 inhibitor may be appropriate.)
   (b) If metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider dual therapy with: a DPP-4 inhibitor and pioglitazone, or a DPP-4 inhibitor and a sulfonylurea or pioglitazone and a sulfonylurea.
   (c) For any of the above regimens, support the person to aim for an HbA_{1c} level of 53 mmol/mol (7.0%).
8. Second intensification of drug treatment (if HbA_{1c} rises to 58 mmol/mol)
   (a) In adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA_{1c} to below the person's individually agreed threshold for intensification, consider either: triple therapy (metformin, a DPP-4 inhibitor and a sulfonylurea; or metformin, pioglitazone and a sulfonylurea); or starting insulin-based treatment.
   (b) If triple therapy with metformin and two other oral drugs is not effective, tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with type 2 diabetes who:
   - have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity; or
   - have a BMI lower than 35 kg/m^2 and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities.
9. Failure of these regimens will, in most cases, lead to insulin-based treatment.

(Note: the above is a summary of key points. The revised guideline itself should be consulted for details regarding recommendations for specific clinical situations.)

There are many potentially serious consequences of diabetes. The appropriate monitoring for these is described in NICE NG28 (NICE, 2015a). Given the high mortality from CVD among those with schizophrenia issues relating to this are expanded upon below.

Reducing cardiovascular risk in severe mental illness

Data from the Framingham Heart Study have identified a number of factors as useful in the prediction of future CVD, including: BMI greater than 27 kg/m^2, smoking, elevated total cholesterol, presence of diabetes and presence of hypertension. A number of predictive models have been developed and refined, each using similar, but sometimes slightly different, variables. However, it is clear that variables such as those above have additive effects and that the total risk is greater than the sum of the individual risk factors (Wilson et al, 1998).

A 10-year follow-up study of 1307 individuals (mean age 56 years) on general practice severe mental illness registers in Cheshire (UK) demonstrated the progression over time with respect to some of these problems (Heald et al., 2016). Mean baseline BMI increased from 28.6 kg/m^2 to 31.0 kg/m^2 (P=0.0002). The number known to have type 2 diabetes increased from 26 (1.9%) at baseline to 101 (7.7%) at the end of the follow-up. Over the period of the study there was increasing prescription of statins. At baseline 33 (2.5%) patients were on antihypertensive medication and by the end of follow-up a further 162 (12.4%) patients had been commenced on antihypertensive medication. These data suggest that progression may occur in BMI and the development of diabetes and hypertension within a relatively older population of individuals with psychosis, although the study is limited by not having a control group to account for overall population trends.

The results of the second round of the National Audit of Schizophrenia (Royal College of Psychiatrists, 2014) show that not all service users are adequately monitored for these problems and that even when problems are identified these are not always treated. For example, for diabetes, in mental health trust case records, only 57% had a measure of glucose control in the previous 12 months, and of those with evidence of abnormality only 36% had evidence of receiving intervention. Thus it is vital that clinicians, service users and carers maintain an active approach to regular assessment of appropriate risk factors for CVD: smoking, BMI, glucose control, lipid profile, blood pressure and family history of premature CVD (less than 55 years of age in men and less than 65 years in women).

A useful resource to support clinical decision making in relation to the above risk factors is the Lester UK adaptation of the 'positive cardiometabolic health resource' (Shiers et al., 2014), which was developed from the original Australian version (Curtis et al., 2012). This provides staff in mental health teams with a simple outline of which clinical measures should be monitored,

what the appropriate values are for each measure and what interventions should be considered if these measures are outside appropriate limits. (This resource is available through the Royal College of Psychiatrist's website: http://www.rcpsych.ac.uk/workinpsychiatry/qualityimprovement/nationalclinicalaudits/nationalschizophreniaaudit/nasresources.aspx). (Note: The monitoring and interventions suggested in the 'positive cardiometabolic health resource' are very similar to those suggested for the NHS Health Check (Public Health England, 2016). This is a 5-yearly review expected to be carried out for all eligible people between the ages of 40 and 74 years in the general population.)

The management of weight gain and abnormal glucose control, smoking and alcohol misuse have been described earlier. Promotion of exercise, to improve cardiovascular fitness, is appropriate and may be through the mental health team or local primary care services depending on local arrangements. Exercise may improve cardiovascular fitness even in the absence of weight loss. Service users with hypertension should be referred to their general practitioner for further investigation and management. Note that antipsychotic medications may enhance the hypotensive effect of the commonly prescribed antihypertensive medications.

Service users with dyslipidaemia should be referred to their general practitioner. Management will usually be as per current guidelines such as the NICE guideline on lipid modification (CG181) (NICE, 2014b) or the JBS2 Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice (British Cardiac Society, 2005). All people with dyslipidaemia should receive advice about diet, exercise, weight management and smoking cessation. Those with total cholesterol concentration of over 9.0 mmol/l or a non-HDL cholesterol concentration of more than 7.5 mmol/l or triglyceride concentration of more than 10 mmol/l should be referred for specialist advice.

Regarding the prescription of statins, NICE guidance is that if lifestyle advice is ineffective in normalising the lipid profile then a statin should be considered after screening for their risk of CVD, usually with QRISK2 in the UK. (Note that risk assessment may be different in certain circumstances, for example, people with type 1 diabetes, those with familial hypercholesterolaemia and other situations outlined in NICE CG181.) Initially offer atorvastatin for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Statins should also be offered for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Generally, people in these categories will be over 40 years of age.

For people with diabetes aged 18–39 years who have one of: diabetic complications; poor blood glucose control; hypertension; features of the metabolic syndrome; or family history of premature CVD in a first degree relative (at least one of which may often be present in a service user with psychosis), then the JBS2 guidelines suggest commencing a statin although the NICE guideline does not. The cost effectiveness and safety of prescribing statins before the age of 40 years is not clear, particularly for women of childbearing age.

Prescription of a statin requires monitoring, including monitoring of hepatic transaminase enzymes at baseline, 3 months and 12 months, but not thereafter unless clinically indicated. Statins are contraindicated in pregnancy and ideally should be stopped 3 months before conception.

Wider considerations in primary care and secondary care

The Government report *No Health Without Mental Health: A Cross-Government Mental Health Outcomes Strategy for People of All Ages* (Department of Health, 2011) gave a commitment to improve the physical health outcomes for those with mental illness as well as a more general commitment to improve access to mental health services. The NICE clinical guidelines referred to in earlier sections of this document provide guidance regarding the management of certain specific physical health problems relevant to issues surrounding obesity, diabetes and CVD in people with psychosis, including those receiving antipsychotic medications.

Informal feedback from trusts involved in relevant national audit programmes indicates that in many mental health trusts the physical resources necessary for doing this are often lacking. This and the poor performance of many trusts on aspects of monitoring physical health, in both the first and second rounds of the National Audit of Schizophrenia (Crawford et al., 2014; Patel et al., 2014; Royal College of Psychiatrists, 2012, 2014), has led to the introduction of relevant indicators as part of the national CQUIN programme (NHS England, 2015: indicators 4a and 4b), which incentivises NHS trusts to ensure that such care is provided. These cover aspects of the physical health care of people with psychotic illness in all types of inpatient units and those under the care of community based early intervention psychosis services.

In primary care the quality outcomes framework (QOF) provides voluntary incentives, through the general medical services contract, to improve care in certain specific domains. The guidance for the general medical services contract prior to 2015 provided specific indicators in the clinical domain related to physical health in this population. These were for maintaining an annual record of: blood pressure (MH003), cholesterol/HDL ratio (MH004), blood glucose or HbA_{1c} (MH005), BMI (MH006) and alcohol consumption (MH007). Two further indicators in the public health domain related to smoking (SMOK 002 and SMOK 005). Other indicators for diabetes, primary prevention of CVD and obesity in the general population were expected to be inclusive of service users with mental health problems.

However, for the periods 2014–2015 and 2015–2016 the QOF indicators were amended, removing the clinical domain indicators relating to the monitoring of cholesterol/HDL ratio, blood glucose/HbA_{1c} and BMI. Additional statements relating to these were added, as below, but without financial incentive:

- It is recommended that patients receive health promotion and prevention advice appropriate to their age, gender and health status.
- The NICE clinical guideline on schizophrenia recommends the components of a review and has separated them out to create a series of indicators. The NICE clinical guideline on bipolar disorder recommends that patients with bipolar affective disorder have a physical health review, normally in primary care, to ensure that the following are assessed:
    - lipid levels, including cholesterol in all patients aged 40 or over even if there is no other indication of risk
    - plasma glucose levels

    - weight
    - smoking status and alcohol use
    - blood pressure
- The QOF continues to incentivise annual monitoring of blood pressure, alcohol and smoking status for patients with schizophrenia, bipolar affective disorder and other psychoses. *Clinicians should use their professional judgement to decide when and how frequently checks of lipid levels, glucose levels and weight should be carried out, in accordance with the needs of each patient.* (Italicising and underlining here and below were provided by the authors of this guideline document.)

For the 2016–2017 QOF, NICE proposed, to NHS England and the general practitioner's committee, restoration of the indicators relating to lipids and glucose, as well as an expectation that these are carried out from age 18 years (40 years in the 2013/2014 QOF). An amendment to the obesity indicator, in the public health domain, would have required a register of all patients aged 18 years and over whose BMI is 25 kg/m^2 or greater in the previous year, rather than the existing BMI of 30 kg/m^2 or greater. If implemented, these changes would have returned the QOF to a situation in which it largely paralleled NICE CG178. Following discussions, however, it was reported in February 2016 that it was decided not to make changes to the QOF indicators for 2016/17 (http://www.nhsemployers.org/your-workforce/primary-care-contacts/general-medical-services/quality-and-outcomes-framework/changes-to-qof-2016-17). The QOF indicators, and associated additional statements, thus remain as per the arrangements for 2015/2016.

NICE CG178 (paragraph 1.3.6.5) recommends that: 'the secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements'. Thus, particularly for people in their first episode of psychosis, it is likely that trusts will need to provide programmes for the monitoring of physical health as significant weight gain commonly occurs in the early months of treatment. All members of mental health teams need to ensure they have a proper understanding of the issues surrounding weight gain, weight management and cardiovascular risk.

Paragraph 1.5.3.2 of CG178 recommends that 'GPs and other primary health care professionals should monitor the physical health of people with psychosis or schizophrenia when responsibility for monitoring is transferred from secondary care, *and then at least annually*'. This is inconsistent with aspects of the QOF statements italicised and underlined above and can lead to conflicting views between primary and secondary care regarding the frequency of monitoring in the longer term and whether it should be carried out in primary care or by the mental health team.

The CG178 guideline also places an onus on clinicians in both settings to ensure they are all fully aware of the results of assessments of physical health, irrespective of where the assessment was carried out. A further complication in this is that epidemiological data suggests that 31% of people with severe mental illness have only been seen by primary care services during the previous 12 months (Reilly et al., 2012). Within primary care it is also clear that it can be difficult to ensure engagement of some people with severe mental illness with physical health monitoring arrangements.

These are issues that require careful local discussions and negotiations between trusts and local general practitioners but are issues that it is essential to resolve to ensure adequate care. Probably the best solutions are going to involve joint working and shared care between primary care and local mental health teams. One recent example of this is a new service model provided across Newham clinical commissioning group's area: http://www.england.nhs.uk/2015/05/15/mental-health-scheme/.

There is also the question of how best to provide appropriate lifestyle-change programmes. Much of the resource for this type of programme for the general population has been transferred, through Public Health England, to local authority budgets, although clinical commissioning groups will also commission such services from local community trusts. Evidence suggests that targeted services (e.g. for smoking cessation) work best and it is likely that trusts and local authorities will have to work together to provide such services. It is essential that people with psychosis, particularly in their first episode of illness, are given access to lifestyle-change programmes.

Finally, it is clearly important to prevent an accumulation of physical health risk factors by any individual. Weight gain and the development of obesity are important risk factors for diabetes and CVD in people with schizophrenia. It is thus essential that proper arrangements for monitoring weight are in place for all those presenting with a first episode of psychosis, that systems are in place to recognise those individuals who are gaining weight at an early stage of treatment and that members of mental health teams are aware of the options for managing undue weight gain.

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Declarations of interest of the participants are held by the British Association for Psychopharmacology (BAP) office and are available for consultation. There has been no involvement of pharmaceutical companies at any stage of the development of these guidelines, from conception to publication.

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Appendix 1

Dyslipidaemia: This term is used frequently throughout the document. The following provides a definition of this term and some explanation of related terminology. Dyslipidaemia refers to an aberrant blood lipid profile and, in our context, to elevations of potentially harmful lipids with reductions of those that may be protective for CVD. Traditionally this was elevation of total cholesterol and/or triglycerides, high LDL levels and often low HDL levels. However, it is now regarded as more appropriate (NICE, 2014) to measure non-HDL cholesterol levels instead of LDL levels. This gives a measure of all of the lipids that may promote arterial plaque production: LDL cholesterol level and the levels of very LDL, intermediate-density lipoprotein and chylomicrons. Non-HDL cholesterol is calculated from 'total cholesterol minus HDL-cholesterol' and has the further advantage of not requiring a fasting blood sample for its measurement. Thus, the increased risk of CVD is related to high total cholesterol and/or triglycerides and high non-HDL cholesterol levels. Some of the studies quoted will refer to the traditional measures of lipid biochemistry and some to the more recent measures. We have not distinguished between these approaches in reviewing the available clinical trials but the use of non-HDL cholesterol applies to current NICE guidance.

Appendix 2

Children and young people: The scope for the development of these guidelines was adults with psychosis over the age of 18 years. Weight gain, and appropriate interventions for this, in children and young people with psychosis is clearly an important topic. One of the reasons for excluding this population in our evidence review was the paucity of good data and RCTs in relation to interventions for this group, from which evidence-based guidelines could be written. The purpose of this Appendix is to provide some link between these guidelines and parallel issues for younger people. However, it is not intended to be a definitive review of the subject.

A NICE guideline (CG155) has been published regarding the recognition and management of psychosis in children and young people (NICE, 2013). In relation to monitoring for weight gain, metabolic and cardiovascular risk factors, this takes a similar approach to that adopted in the subsequent NICE guideline for adults with psychosis (NICE, 2014a). For those individuals who develop significant weight gain CG155 advocates, as we have for adults, lifestyle interventions as the first line of approach. Our review of clinical trial data for lifestyle interventions includes studies of people experiencing a first episode of psychosis, some of whom are less than 18 years of age.

There are no specific recommendations in CG155 regarding which antipsychotic medications should or should not be considered for children and young people in their first episode of psychosis. However, a recent NICE evidence update (NICE, 2015c) suggests that, because of the magnitude of the metabolic effects caused by olanzapine, olanzapine may not be suitable as a first-line medication for young people in their first episode of psychosis.

One review of studies of weight gain and the metabolic risks associated with treatment with antipsychotic medications, in children and young people, collated evidence from four types of published studies: RCTs; indirect comparisons of drugs using data from individual trials versus placebo; naturalistic cohort studies and pharmacoepidemiological studies (Maayan and Correll, 2011). The majority of these studies included young people with other diagnoses as well as schizophrenia. Similar to the findings for adults, the available data demonstrate a hierarchy of risk for the development of significant weight gain. The order of drugs from high to low risk was essentially the same as for adults: olanzapine $\geqslant$ clozapine > risperidone $\geqslant$ quetiapine > aripiprazole = ziprasidone. This is clearly relevant for considerations of initial treatment as well as switching of antipsychotic medication.

Some authors suggest that weight gain with antipsychotic medications is disproportionately greater in young people compared to adults (e.g. Kryzhanovskaya et al., 2012). Others (e.g. Correll et al., 2009) have concluded that younger people are not more vulnerable to this than adults, and suggest that this may be an apparent effect because many studies of adults include people who have previously been prescribed antipsychotics, and are starting from a baseline at which they have already gained some weight, before being changed to an alternative drug.

However, it is important to remember that the risk of type 2 diabetes in children and young people using antipsychotics is increased three-fold, compared with the risk in a matched healthy cohort (Bobo et al., 2013), and that onset of diabetes at an early age is likely to have greater long-term consequences. Furthermore, current evidence shows that the decline in β-cell function is three

to four times faster in young people with type 2 diabetes than in adults and that therapeutic failure rates are higher (Hannon and Arslanian, 2015).

In our guideline, we have recommended two other interventions as worth consideration for weight gain in adults with psychosis: adjunctive aripiprazole and adjunctive metformin. There are no RCT data available in relation to adjunctive aripiprazole in young people. Maayan and Correll (2011) review two double-blind, placebo controlled RCTs of adjunctive metformin in young people. One of these demonstrated a statistically significant reduction in weight gain but the other did not, making it impossible to make any recommendation.

Some of the questions that cannot be answered adequately from current data may be resolved on the completion of a currently running, 6-month, open-label, randomised trial of metformin and healthy lifestyle education in antipsychotic-treated children and young people (aged 8–19 years), with significant weight gain, in the USA (Reeves et al., 2013).