NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of psychosis and schizophrenia in children, young people and adults (NICE guidelines CG155 and CG178)

Surveillance report

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Contents

Surveillance proposals

We plan to update recommendation 1.1.3.2 and section 1.3.6 on how to use antipsychotic medication in NICE's guideline on psychosis and schizophrenia in adults: prevention and management to explore the role of metformin and liraglutide as add-on therapies to antipsychotics, for managing antipsychotic-induced weight gain (AIWG).

We also plan to update recommendations in section 1.3 about how to use oral antipsychotic medication in NICE's guideline on psychosis and schizophrenia in children and young people: recognition and management to explore the role of metformin as an add-on therapy to antipsychotics, for managing AIWG. Meanwhile recommendation for research 5 about weight management interventions will be removed from the NICE guideline on psychosis and schizophrenia in children and young people.

Reason for the proposal

We identified consistent new evidence from several systematic reviews and randomised controlled trials (RCTs) that metformin and liraglutide mitigate AIWG in adults with psychosis and schizophrenia. We identified a smaller volume of new evidence that metformin mitigates AIWG in children and young people with psychosis and schizophrenia. Currently both of NICE's guidelines do not contain weight management recommendations specifically for people with psychosis and schizophrenia.

Trigger for surveillance review

The 2022 surveillance of schizophrenia in children and young people identified 1 RCT (Correll et al. 2020) that reported metformin and switching antipsychotics are effective for mitigating AIWG. Additionally guidelines were identified from the Royal Australian and New Zealand College of Psychiatrists (2016) which cover children, young people and adults, that also recommend metformin for AIWG. It was also noted by NICE medicines advisers and clinical advisers that both of NICE's guidelines currently make very limited interventional recommendations about weight management for AIWG. New evidence identified in 2022 on its own was not enough to warrant updating recommendations at that time.

A decision was made to monitor the evidence base in real time for emerging evidence

about weight management interventions for people taking antipsychotics. The results of monitoring indicate that sufficient new evidence has accumulated to suggest recommendations about weight management in NICE's guidelines on psychosis and schizophrenia need to be updated.

Methods

The exceptional surveillance process consisted of:

- Literature searches of bibliographic databases of published new evidence and registries of ongoing trials at regular intervals between February 2022 and April 2023 for emerging evidence about weight management interventions for people receiving antipsychotics.
- Assessing the impact of evidence identified by previous surveillance reviews of NICE guidelines about schizophrenia, psychosis and bipolar disorder.
- Considering the evidence used to develop the NICE guidelines on psychosis and schizophrenia in children, young people and adults.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- The comments and opinions of a NICE consultant clinical adviser and NICE medicines adviser.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guidelines, or the whole guidelines.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Search and selection strategy

We conducted searches of bibliographic databases and registries of ongoing trials at regular intervals between February 2022 and April 2023 for emerging evidence about weight management interventions for people receiving antipsychotics. Search frequency was adjusted based on the number of relevant studies identified at each search timepoint.

Initially the search frequency was set to monthly (3 search timepoints), before being reduced to every 3 months (2 search timepoints) and a final search at a 6-month interval. Searches at the first timepoint (February 2022) were backdated to June 2016, the date of the last surveillance searches covering all aspects of psychosis and schizophrenia.

Studies were considered for inclusion using criteria defined by a review protocol (appendix A) adapted from review protocols for NICE's guidelines on psychosis and schizophrenia as well as NICE's guidelines on bipolar disorder, antisocial behaviour and conduct disorders in children and young people and obesity: identification, assessment and management.

The relevance of a study to children and young people is informed by review protocols on pages 163 and 219 in NICE's full guideline on psychosis and schizophrenia in children and young people. These include studies with people under 18 years of age and under and over 18 years of age, but with a mean age of under 25 years.

Evidence is summarised using study level data extracted from abstracts and the full text of studies as required. A brief overview of each study and its impact on recommendations is provided in the sections in this review on pharmacological weight management interventions and lifestyle, behavioural and nutritional interventions.

Information considered during this surveillance review

Overview of new evidence

We identified 51 studies (see appendix B) about weight management for AIWG mainly in adults with psychosis and schizophrenia. This comprised of 21 systematic reviews, 28 RCTs and 2 external guidelines. This new evidence covered pharmacological interventions used as add-on treatments to antipsychotics and lifestyle and behavioural interventions and nutritional supplements.

Pharmacological interventions identified included: metformin (14 studies), olanzapine/samidorphan fixed dose combination treatment (10 studies); the GLP1 receptor agonists liraglutide (4 studies) and exenatide (1 study); topiramate (6 studies), melatonin (2 studies); and amantadine, sitagliptin, betahistine, and ranitidine (1 study each). Note: 5 studies reported outcomes for several drugs.

Lifestyle, behavioural and nutritional supplement interventions identified included: nurse-lead interventions (4 studies); diet and nutrition (3 studies); online interventions (2 studies); use of probiotics and dietary fibre as antipsychotic add-on therapy (2 studies), structured education (2 studies) and behavioural weight management and motivational behaviour change to increase physical activity (1 study each).

Eight RCTs and 3 systematic reviews included only children and adolescents or contained a sufficient proportion of them for results to be relevant to recommendations in NICE's guideline on psychosis and schizophrenia in children and young people. See the section on studies relevant to children and young people.

Ongoing trials

We checked trials registries for relevant ongoing research; of the ongoing studies identified, 2 were assessed as having the potential to impact recommendations. We plan to regularly check whether these studies have published results and evaluate the impact of them on current recommendations as quickly as possible. These studies are:

- Home-based intervention with semaglutide treatment of neuroleptica-related prediabetes
- Does GLP-1RA prevent deterioration of metabolic state in prediabetic and diabetic patients treated with antipsychotic medication?

Following publication of this surveillance review, a stakeholder highlighted to us the ongoing RESOLVE realist review of non-pharmacological interventions for AIWG. We will also track this study and assess its impact on recommendations when it publishes.

Pharmacological weight management interventions

Metformin

We found new evidence from 13 systematic reviews (including those with children) suggesting a positive effect of metformin (compared to placebo) in attenuating AIWG when it is used as an add-on treatment to antipsychotics. These studies report a weight loss of about -3 kg (range -2.5 kg to -4 kg) in the intervention groups. This includes a Cochrane Review (Agarwal et al. 2022) with a meta-analysis of 4 RCTs that reports a weight loss of -4 kg compared with placebo. The authors concluded that 'there is

low-certainty evidence (allocation concealment, sample sizes) to suggest that metformin may be effective in preventing weight gain.'

Three meta-analyses comprising 23 RCTs in total: de Silva et al. 2016 (n=743), Siskind et al. 2016 (n=478) and Zimbron et al. 2016 (n=878) of adults receiving antipsychotics mainly for psychosis and schizophrenia reported statistically significant reductions in weight gain of about -3 kg for metformin (dose range 500 mg / day to 2,550 mg / day) over placebo (note: 2 out of 3 RCTs in Zimbron et al. 2016 are also meta-analysed by de Silva et al. 2016). There is some new evidence from these studies that metformin may be more effective in those with first episode compared with chronic psychosis and schizophrenia. Evidence from a meta-analysis, Zheng et al. 2019 (n=732) of 6 RCTs conducted in China reported that combining metformin with a lifestyle intervention may lead to greater weight reduction compared with metformin or lifestyle intervention alone. This study may be limited in its relevance to a UK population due to lower baseline weights in East Asian populations.

Two separate network meta-analyses (Zhuo et al. 2018 and Wang et al. 2021) that compared the effectiveness of several pharmacological interventions reported a weight loss attributable to metformin of -2.50 kg to -3 kg with reductions mirrored by BMI levels. Zhuo et al. 2018 (27 RCTs; 20 in people with schizophrenia; n=1,349) ranked interventions based on head-to-head efficacy for attenuation of body weight in the order of: sibutramine, topiramate, metformin, reboxetine and ranitidine. They report topiramate is associated with an increased risk of adverse events. They also noted that sibutramine, a serotonin-noradrenalin reuptake inhibitor that is not licensed in Europe, was not recommended due to concerns over safety resulting in its licensing being withdrawn by several countries (MHRA 2010 Sibutramine: suspension of EU licences recommended).

Wang et al. 2021 (n=3,467 adults), antipsychotic indication not stated, also ranked by order of efficacy for reducing body weight gain in the order of: topiramate, zonisamide, GLP1-receptor agonists, metformin and sibutramine. It reports topiramate tolerability is inferior to placebo, GLP1-receptor agonists and metformin. Additionally, a systematic review by Hiluy et al. (2018) that includes 14 studies about metformin also reports an attenuation of -3 kg although the meta-analysis is subject to high heterogeneity.

An RCT (Wang et al. 2020) with adults and adolescents (mean age 32 years, range 15 to 55) comparing topiramate and metformin reported superiority for topiramate for weight loss. However, the topiramate group were statistically significantly heavier at baseline compared with the metformin group and this is likely to have biased the results.

Additionally, this study was conducted in China and may be of limited generalisability to a UK population.

GLP-1 receptor agonists

We identified 4 RCTs and 1 systematic review on GLP1-RAs. One RCT on exenatide reported no superiority compared with placebo (Ishoy et al. 2017). Two RCTs and 1 systematic review with overweight or obese adults with schizophrenia and psychosis (Larsen et al. 2017; Whicher et al. 2021; Lee et al. 2022) reported that liraglutide in addition to antipsychotics resulted in weight loss between -5 kg to -6 kg compared with placebo.

An open label extension RCT (Svensson et al. 2019) reported that 9 months after stopping a course of 16 weeks' liraglutide treatment, people regained 1.5 kg of weight. A similar weight gain was seen in the placebo group. There was a higher risk of developing type 2 diabetes at 1 year in people who had been given placebo compared with liraglutide in the preceding RCT, but this was not statistically significant.

Olanzapine/samidorphan combination treatment

We identified 4 RCTs and 2 RCT extension studies that report a positive effect for olanzapine combined with samidorphan. Two RCTs (Correl et al. 2023, Kahn et al. 2021) report it can significantly reduce weight and the risk of clinically significant (defined as more than 7%) weight gain. Another RCT (Kahn et al. 2023) reports it reduces the risk of metabolic syndrome. An extension study (Yagoda et al. 2023) reports that weight is regained at 1 year following treatment discontinuation. Samidorphan/olanzapine combination treatment is not currently licensed for use in the UK for any indication.

Topiramate

Topiramate is as an anticonvulsant licensed for treatment of tonic-clonic seizures in adults and children, and for migraine prophylaxis in adults (BNF 2023). We identified 2 RCTs (Wang et al. 2020; Jamillian and Shayganfard 2018) and 4 systematic reviews, including a Cochrane Review (Agarwal et al. 2022; Wang et al. 2021; Hiluy et al. 2018; Zhuo et al. 2018) that report results for topiramate as an add-on to antipsychotics for AIWG. Several of these studies report weight losses of between -3.5 kg to -5 kg and head-to-head superiority over metformin. However the Cochrane Review (Agarwal et al. 2022) concludes that topiramate is probably not effective based on a meta-analysis of 3 RCTs for the

outcome of weight loss, although there is a small reduction in BMI. Zhuo et al. (2018) reports an association with adverse events and there are several MHRA safety advice notes associated with topiramate (BNF 2023).

Studies about other pharmacological interventions

Studies about melatonin, sitagliptin, betahistine, and ranitidine as add-ons to antipsychotic treatment reported no superiority over comparators for attenuating weight gain. One systematic review Zheng et al. 2017 (n=223) reported a small effect (-2 kg) for amantadine. Amantadine is licensed for Parkinson's, herpes zoster and influenza symptoms and use in this context seems highly experimental.

Intelligence gathering

An external 'evidence-based guideline' was identified (Fitzgerald et al. 2022) that recommends metformin for the management of AIWG. This external guideline has been produced by a coalition of clinicians based in the Republic of Ireland because 'no guideline exists that solely addresses AIWG management.' This external guideline includes a systematic review which reports metformin having the most consistent supporting evidence of a positive effect, a finding consistent with this surveillance review.

An MHRA drug safety update about metformin and reduced vitamin B12 levels (June 2022) was identified by NICE while this evidence summary was in progress. As a result of an assessment of new safety data, the MHRA now categorises vitamin B12 deficiency as a common metformin side-effect, especially in people with a longer treatment duration. As a result, the MHRA recommends monitoring B12 levels in people receiving metformin.

Lifestyle, behavioural and nutritional interventions

Thirteen studies involving behavioural lifestyle interventions report mixed results. Five systematic reviews reported superiority over care as usual for various behavioural and lifestyle interventions for different outcomes. Teasdale et al. (2017), 13/20 studies in people with schizophrenia and Sugawara et al. (2018), n=265, reported that interventions to improve people's nutrition were effective in reducing weight in people with schizophrenia and bipolar disorder. This included superiority for nutritional education delivered by a doctor or a nutritionist. Speyer et al. (2019), n=4,267, reported a positive effect for lifestyle interventions to enable people to better manage their weight; and Lee et

al. (2022), n=4,305, reported a positive effect for tailored weight management interventions offering regular contact that changed people's dietary and physical activity behaviour. Romain et al (2020), n=2,128, reported interventions based on motivational theory to increase physical activity had some positive effect on anthropometric outcomes.

Two nurse-led programmes: 1 community-based (Fernández Guijarro et al. 2019) and 1 integrating a physical health nurse into treatment as usual (O'Donoghue et al. 2022) had a limited effect on weight loss compared with treatment as usual. A theory-based structured education programme also had no impact on anthropometric outcomes and was not cost effective at an NHS willingness to pay threshold (Holt et al. 2019). A dietary intervention for people hospitalised with schizophrenia (Soric et al. 2019) and an online weight management intervention for adults with serious mental illness (Young et al. 2021) also had little effect on anthropometric outcomes in people who were not already obese.

Three RCTs in 2 studies (Huang et al. 2022 and Huang et al. 2022a) conducted in China investigated dietary fibre and probiotics as add-on therapies for adults with schizophrenia and bipolar disorder receiving antipsychotics. They report dietary fibre plus probiotics are superior to placebo for mitigating weight gain but not dietary fibre or probiotics alone in adults with psychosis or bipolar disorder taking atypical antipsychotics (n=136). They also report dietary fibre is superior to placebo in mitigating weight gain in adults with first episode psychosis who are antipsychotic naive. The latter study had a small sample size (n=58) and the relevance of both studies to a UK setting is questionable due to the low baseline BMIs of participants.

Studies relevant to children and young people

A systematic review, Ellul et al. 2018 (n=235, children and adolescents, 203 from the US and Canada, 32 from Iran) reports that when compared with placebo, metformin significantly reduces weight gain at 4-, 12- and 16-weeks (-1 kg, -1.8 kg and -3.2 kg, respectively) in children 12.7 to 14.3 years old receiving second generation antipsychotics. A systematic review, Mansuri et al. 2022 of children (n=213), 11 to 13 years taking second generation antipsychotics reports a reduction of weight of -2 kg in those using metformin but an increased risk of nausea and vomiting. Da Silva et al. (2016) includes a meta-analysis of 2 studies of children (n=62) and reports a weight reduction of -3.9 kg in children taking antipsychotics.

One RCT (O'Donoghue et al. 2022) found no difference between a physical health nurse integrated with care as usual versus care as usual alone for anthropometric outcomes in

young people with first episode psychosis.

Previous surveillance

The 2022 surveillance of schizophrenia in children and young people (see trigger for this surveillance review) identified 1 RCT (IMPACT trial) that reported metformin may be effective for mitigating AIWG in people with severe mental illness. The trial also reported that 'switching' antipsychotics, is effective in mitigating AIWG; a strategy accommodated in recommendation 1.3.18 in NICE's guideline on psychosis and schizophrenia in children and young people and recommendation 1.3.6.3 in NICE's guideline on psychosis and schizophrenia in adults, and explicitly described by recommendation 1.5.4 in NICE's guideline on bipolar disorder.

We identified external guidelines from the Royal Australian and New Zealand College of Psychiatrists for the management of schizophrenia and related disorders (2016) covering adults, children and young people that recommends metformin. A cohort study was identified by the 2015 evidence update (pages 16 to 17) on NICE's guideline on psychosis and schizophrenia in children and young people that reported metabolic changes caused by olanzapine are greater in magnitude in young people (12 to 18 years) compared with adults. This triggered an update to recommendations 1.3.14 and 1.3.15 about choice of antipsychotic medication in NICE's guideline on psychosis and schizophrenia in children and young people. An exceptional review of NICE's guidelines on bipolar disorder, psychosis and schizophrenia in adults, children and young people and antisocial behaviour and conduct disorders in children and young people, led to the relevant recommendations being updated in these guidelines, to clarify that tests of either glycosylated haemoglobin (HbA1c) or fasting blood glucose can be used to assess for diabetes in children, young people and adults who are treated with antipsychotics. This was triggered by an enquiry from a practitioner highlighting discrepancies in recommendations about monitoring for diabetes in the NICE guidelines on psychosis and bipolar disorder.

A 2017 surveillance review of NICE's guideline on psychosis and schizophrenia in adults identified evidence from a systematic review and 2 RCTs that showed positive effects in physical health outcomes in people treated with metformin who were on antipsychotic medication. Topic experts also indicated that the British Association for Psychopharmacology guidelines include some recommendations about the use of adjunctive metformin to reduce AIWG. This was assessed as supporting recommendation 1.1.3.2, which cross refers to NICE's guideline on preventing type 2 diabetes and

recommends metformin. Topic experts also highlighted the effectiveness of behavioural and lifestyle weight management, particularly yoga. This was assessed as broadly supportive of current recommendations. They also received intelligence from topic experts that recommendations about monitoring cardiovascular health could be better tailored to people with serious mental health conditions; and that adherence to recommendations about physical health monitoring was poor.

The 2017 surveillance of NICE's guideline on bipolar disorder identified a network meta-analysis that reported lurasidone was associated with less weight gain compared to quetiapine and olanzapine. This evidence was assessed as not being enough to impact recommendations.

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to weight management interventions for mitigating AIWG. We received 7 responses from topic experts, including: a consultant psychiatrist; a professor of psychiatry; a CAMHS psychiatrist specialising in the treatment of psychosis; a professor of general practice research; a former GP and specialist in the physical health of people experiencing severe mental illness; a mental health pharmacist; and an NHS national specialty adviser for mental health pharmacy.

Weight management for adults

In response to the question: 'Are you aware if metformin and liraglutide are being offered as an option to adults to attenuate antipsychotic-induced weight gain?', 6 of 7 respondents commented to say that these interventions were sometimes used, particularly metformin. One topic expert commented that they had not used metformin because they felt the evidence for its effectiveness was not yet strong enough. Another expert, a mental health pharmacist, who 'frequently recommends' metformin as an option for managing AIWG, felt there was a reluctance to use it in secondary mental health services and saw little evidence of its use in primary care. Three respondents commented that metformin is effective, although 1 caveated this by saying that their service only offers metformin when metabolic syndrome or prediabetes is present. They commented that it is not offered exclusively for AIWG mitigation, and it is not available for this indication on their local prescribing guidelines.

We asked: 'Under what circumstances do you think pharmacological interventions to attenuate antipsychotic-induced weight gain should be used?' Three respondents commented that they should be offered only when lifestyle interventions have not been successful. Three respondents commented that they should be used at the initiation of treatment when there is a risk of rapid weight gain. One expert noted that there is evidence that metformin leads to greater weight reduction in people with early psychosis, a comment consistent with evidence identified by this surveillance review.

One respondent commented that patients often refuse antipsychotic treatment because of weight gain risk. They responded to say that offering pharmacological therapies could act to address these concerns and influence a person's decision making about taking antipsychotics. They also felt that pharmacological interventions should be offered where there is a risk of metabolic disease and with olanzapine and clozapine which have a particular association with weight gain. Three respondents emphasised that pharmacological interventions should be 'offered', and not prescribed routinely. They noted pharmacological interventions should only be used following a process of shared decision making with a patient who is fully informed. One respondent commented that pharmacological interventions should not be offered until there is clear evidence of effectiveness, particularly from long-term trials.

Weight management for children and young people

We asked: 'Are you aware if metformin or other pharmacological interventions are currently being used with children and young people to attenuate antipsychotic-induced weight gain?' Two of 5 respondents to this question had direct experience of using or recommending use of pharmacological interventions. One noted that metformin was widely used with children and young people in some services but not others. Another topic expert felt that it should be an option for risk of severe weight gain but that not putting children at risk of severe weight gain was a preferable option. They commented that NICE's guideline on psychosis and schizophrenia in children and young people should be updated to recommend against using antipsychotics associated with rapid weight gain, for example olanzapine, except in exceptional circumstances where weight gain is a desired outcome.

Other respondents were aware that pharmacological treatments like metformin were used, that there was evidence for its use but that they had no direct experience of prescribing it. One of these topic experts noted that antipsychotics with a reduced risk of weight gain should be the first line treatment for psychosis. However, they commented that

pharmacological interventions for weight mitigation have a possible role in enabling successful treatment with antipsychotics that can induce rapid weight gain, for example, clozapine.

Six respondents offered further comments about the topic, with all noting the seriousness of AIWG and its impact on cardiovascular outcomes and long-term physical health. One respondent noted that AIWG also has a serious impact on wellbeing and self-esteem, particularly in young people, which can contribute to poor antipsychotic treatment adherence. One respondent noted that clinicians can be reluctant to switch antipsychotics from high-risk to low-risk of side-effects when a person's mental health has stabilised. They highlighted the ongoing iSWITCHED trial that is developing an educational switching intervention to: 'enable mental health professionals to implement evidence-based guidance on reviewing and switching high-risk antipsychotics.' We will track this trial and assess its impact when it publishes in October 2024. Another topic expert described AIWG as a 'massive and serious clinical problem' and commented that trials with newer pharmacological interventions for weight loss would be useful.

Validation about prioritisation of topic areas for active monitoring in the NICE mental health suite

We also considered responses from 5 topic experts (a subset of the experts described above) who also responded to NICE's validation about which key priority areas should be actively monitored in the mental health suite of guidelines. As part of this validation, we asked: 'Do you think metformin has a role in weight gain prevention and attenuation for adults and children receiving antipsychotics?' Additional issues that were raised in response to this question are reported in this section of the surveillance review. A topic expert responded that while there is a growing evidence base about metformin in adults there was an unanswered question about whether it is already being prescribed off-label for children. They commented that NICE should review whether there is sufficient evidence of effectiveness and safety in children to make recommendations in this area.

In relation to metformin's use in adults, all 5 respondents thought that it had a role to a greater or lesser extent, but 1 expert cautioned against the 'routine use' of metformin for AIWG.

Another expert commented that the outcomes of behavioural interventions including STEPWISE (assessed as part of a 2019 exceptional surveillance review of NICE's guideline on psychosis and schizophrenia in adults) had been disappointing. They added that GLP-1

receptor agonists should also be considered for AIWG in adults, an assertion supported by evidence identified by this monitoring review for liraglutide in adults. Another expert comment supported this by noting that pharmacological recommendations for weight gain should not necessarily be specifically about metformin.

Impact statement

Adults

We identified consistent new evidence that metformin mitigates the effects of weight gain in adults taking antipsychotics by approximately -3 kg compared with placebo. This included a Cochrane Review of 4 RCTs that concluded metformin may have a role within this group. However, it did caution that none of these RCTs reported on the key outcome reduction in the number of people with clinically significant weight gain (frequently defined by studies as 5% to 7% or more of baseline bodyweight). We also identified a smaller volume of consistent new evidence, that liraglutide mitigates weight gain in this group by approximately -5 kg. The new evidence is mainly from adults with schizophrenia and psychosis impacting NICE's guideline on psychosis and schizophrenia in adults. This adds to evidence identified about weight management interventions during the 2017 surveillance of NICE's guideline on psychosis and schizophrenia in adults.

Recommendation 1.1.3.2 in NICE's guideline on psychosis and schizophrenia in adults states that in the event of excessive weight gain to offer interventions in line with relevant NICE guidelines on obesity prevention, cardiovascular disease: risk assessment and reduction, including lipid modification and preventing type 2 diabetes). These guidelines include recommendations about metformin and liraglutide but considering new evidence, these cross-referrals seem inadequate. The guidelines cross-referred to do not contain recommendations about these drugs tailored to people with schizophrenia and psychosis taking antipsychotics. For example, section 1.19 in NICE's guideline on preventing type 2 diabetes, recommends metformin alongside lifestyle change interventions for obese people at risk of diabetes. Recommendation 1.19.1 specifically states to: 'offer metformin to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated if: this has happened despite their participation in intensive lifestyle-change programmes or they are unable to participate in an intensive lifestyle-change programme particularly if they have a BMI greater than 35'.

Recommendation 1.8.1 in NICE's guideline on obesity: identification, assessment and

management, states: 'consider pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated. Pharmacological treatments include liraglutide for people at least 35 kg/m^2 or at least 32.5 kg/m^2 for members of minority ethnic groups.'

While the rationale and impact section on intensive lifestyle-change programmes and metformin in NICE's guideline on preventing type 2 diabetes, notes that 'people with mental illness…have poorer physical health and would therefore benefit from …an intervention to reduce their risk of type 2 diabetes', both recommendations now seem inadequately nuanced for people with schizophrenia and psychosis. Topic experts have noted that people receiving antipsychotics may require pharmacological interventions at the initiation of treatment with antipsychotics to prevent rapid weight gain and to enable them to make a fully informed decision about the benefit-risk balance of antipsychotics. Although some topic experts were clear that pharmacological interventions should be used only after non-pharmacological interventions had been tried, evidence identified by this surveillance review for the positive effects of behavioural interventions on AIWG was mixed.

Metformin is licensed for the treatment of type 2 diabetes particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. It is also licensed for reduction in the risk or delay of the onset of type 2 diabetes in the same group. It is not licensed as a weight management intervention. Liraglutide is licensed for weight management in adults with BMIs as low as 27 kg/m^2 if they have at least 1 weight-related comorbidity (eMC).

It is noteworthy that liraglutide is also licensed as an adjunct to healthy nutrition and increased physical activity for weight management in adolescents over 12 years old, when certain conditions are met, and with obesity and a bodyweight above 60 kg. We did not identify evidence during monitoring for their effectiveness in mitigating AIWG in adolescents.

New evidence impacts recommendation 1.1.3.2 about excessive weight gain and section 1.3.6 on how to use antipsychotic medication in NICE's guideline on psychosis and schizophrenia in adults. The latter makes recommendations about monitoring physical health and antipsychotic side-effects including weight gain but currently contains no interventional recommendations about managing it.

Considering new evidence and the lack of interventional recommendations about AIWG

specific to people with schizophrenia and psychosis, recommendations in NICE's guideline on psychosis and schizophrenia in adults should be updated to explore the role of metformin and liraglutide for managing AIWG including their off-label use. Consideration should be given to:

- liraglutide's and metformin's side-effects profiles
- their role alongside non-pharmacological interventions for AIWG
- their potential to impact on patients' decisions to use antipsychotics
- their potential to impact treatment adherence
- the timing of their administration in relation to antipsychotic initiation.

Children

We identified a small but consistent volume of evidence that metformin may be effective in mitigating weight gain in children and young people by between -2 kg and -4 kg, compared with placebo. This evidence addresses recommendation for research 5 in NICE's guideline on psychosis and schizophrenia in children and young people on what is the most effective management strategy for preventing the development of excessive weight gain and metabolic syndrome associated with the use of antipsychotic medication in children and young people?

Recommendation 1.7.4 cross refers to NICE's guideline on diabetes (type 1 and type 2) in children and young people, which recommends metformin (recommendation 1.3.24) with the option of adding liraglutide (recommendation 1.3.26). Currently the NICE guideline on psychosis and schizophrenia in children and young people makes no recommendations about weight management interventions for non-diabetic children and young people, nor does it cross-refer to NICE's guideline on obesity: identification, assessment and management.

Topic experts commented that not exposing children to the risks of severe weight gain is preferable to managing its effects and suggested that there is scope to update NICE's guideline on psychosis and schizophrenia in children and young people to highlight those antipsychotics particularly associated with severe weight gain. This issue is addressed by recommendation 1.3.15 which notes discussing with the 'young person and their parents or carers the increased likelihood of greater weight gain with olanzapine' and by

recommendation 1.3.16, which advises that healthcare professionals should consult an antipsychotic's summary of product characteristics (SPC) before initiation.

The empirical evidence is smaller in volume than for adults for metformin's role in mitigating AIWG in children, but it consistently reports effectiveness for metformin for AIWG. Some topic expert responses suggest metformin is already being used with children in some services but that its use is patchy, this suggests variation in practice and a potential health inequality. Metformin is licensed for use in children with type 2 diabetes as a monotherapy or in combination with other antidiabetics, but not for prevention of diabetes or weight gain in children. Any use of it for weight management in children would therefore be off-label.

The original guideline development committee and topic experts responding to this surveillance review have respectively highlighted that metabolic responses to antipsychotics can be very severe in children (page 215 of NICE's full guideline on psychosis and schizophrenia in children and young people) and that weight gain can have a serious long-term impact on their physical and mental health. Considering this intelligence alongside the new evidence and taking into account the guideline's lack of interventional recommendations or cross-referrals addressing weight gain, the guideline should be updated to explore the role of metformin for managing AIWG. Consideration should be given to:

- metformin's side-effects profile
- its role alongside non-pharmacological interventions for AIWG
- its potential to impact on patients' and carers' decisions about using antipsychotics
- its potential to impact on treatment adherence
- the timing of metformin's administration in relation to antipsychotic initiation.

Equalities issues

People with serious mental illness are at greater risk of weight gain and associated cardiometabolic conditions. This can result from the use of antipsychotics and as a direct result of their illness. Recommendation 1.1.3.6 in NICE's guideline on psychosis and schizophrenia in adults states to: 'Routinely monitor weight, and cardiovascular and metabolic indicators of morbidity in people with psychosis and schizophrenia.'

Recommendation 1.7.2 in NICE's guideline on psychosis and schizophrenia in children and young people, states that: 'GPs and other primary healthcare professionals should monitor the physical health of children and young people with psychosis or schizophrenia at least once a year. They should bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population.'

Overall decision

NICE's guideline on psychosis and schizophrenia in adults will be updated to explore the role of metformin and liraglutide as add-on therapies to antipsychotics, for managing AIWG.

NICE's guideline on psychosis and schizophrenia in children and young people will be updated to explore the role of metformin as an add-on therapy to antipsychotics, for managing AIWG. Recommendation for research 5 about weight management interventions will be removed during the update.

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