NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18)

Surveillance report

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Surveillance decision

We will update the NICE guideline on diabetes (type 1 and type 2) in children and young people. The update will focus on additional medicines to metformin, for the treatment of type 2 diabetes mellitus (T2DM) in children and young people.

Reason for the exceptional review

To explore the impact of new evidence looking at the use of medicines for T2DM in children and young people following publication of a recent study: GLP-1 (glucagon like peptide-1) agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis (Chadda et al. 2021).

Methods

The exceptional surveillance process consisted of:

- Considering the new evidence that triggered the exceptional review.
- Literature searches to identify other relevant evidence.
- Feedback from topic experts.
- Assessing the new evidence and topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

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.

Information considered when developing the guideline

During development of the NICE guideline, due to the paucity of evidence on medicines for T2DM in children and young people, metformin was the only medicine considered.

When assessing the efficacy of metformin treatment, the critical outcome was HbA1c. The guideline development group considered that if the use of metformin resulted in a reduction in HbA1c by near to or greater than 0.5 percentage point (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 2 diabetes. This decision was based on research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group, 1993), which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications. Fasting plasma glucose was also an important outcome as it is a commonly used measure of glycaemic control in clinical practice. We have therefore placed the greatest emphasis on these measures when assessing the impact of new evidence in this exceptional surveillance review. Other outcomes prioritised for inclusion in the review were: number of participants needing rescue medication; number of dropouts; number of participants with any adverse events, including diabetic ketoacidosis (DKA); and changes in body mass index (BMI) standard deviation score.

Information considered in this exceptional surveillance review

New evidence that triggered the exceptional review

A recent systematic review and meta-analysis (Chadda et al. 2021) looked at the use of GLP-1 agonists in 2 different populations. These populations were children and young people with pre-diabetes (when blood sugar levels are higher than normal but not high enough to diagnose diabetes) together with children who had T2DM; and secondly in children with obesity without raised blood glucose measures.

For this study, PubMed and Scopus were searched with relevant terms, up until April 2020. Studies were included if they were randomised control trials (RCTs) of any GLP-1 agonist, either on its own, or in conjunction with any other drug, for the treatment of obesity, pre-diabetes and/or T2DM in children aged under 18 years old. Studies had to report at least 1 of the following outcomes: HbA1c, weight change, or BMI change. Nine studies matched the inclusion criteria, of which 2 were in children and young people withT2DM, 1 was in children and young people with pre-diabetes and 6 were in children with obesity without raised blood sugar measures. The effects of GLP-1 agonists on difference in change-from-baseline HbA1c, blood glucose concentration, and weight outcomes were assessed.

Within this meta-analysis subgroup analyses were conducted on the results for children

with T2DM and pre-diabetes combined, and for children with obesity.

Individual effect estimates, from a random effects model, can be extracted from the forest plots in the meta-analysis for the 2 studies looking solely at T2DM, and these found a mean reduction of -0.9% (95% confidence interval [CI] -1.32%, -0.48%) and -1.06% (95% CI -1.65%, -0.46%) in HbA1c levels.

2021 evidence review

As the Chadda et al. 2021 systematic review paper only searched 2 databases and we received feedback from topic experts that medication other than GLP-1 agonists are being used to treat T2DM in children, we decided to do a focused search for RCTs published since January 2011 for all medicines that have a license to treat T2DM in either adults or in children.

Search and selection strategy

Due to paucity of evidence in 2015, the review question in the NICE guideline only included metformin: 'What is the effectiveness of metformin in improving glycaemic control in children and young people with type 2 diabetes when compared with usual care or placebo?' As the evidence base has since increased, we expanded the search to include all licensed drugs used to treat T2DM in adults and/or children (see appendix A) and re-ran the original search strategy with additional search terms for those licensed drugs.

We found 1,480 studies in a search for RCTs published between January 2011 and October 2021.

For RCTs to be included they had to meet the guideline's original inclusion criteria (see appendix E: review protocols), except that the intervention was changed to the medicines listed in appendix A (of this surveillance report), and usual care included treatment with metformin. We considered 4 studies to be suitable for inclusion based on their abstracts, of which 2 were the original research papers on liraglutide (a GLP-1 agonist) identified in the Chadda et al systematic review. The other 2 studies were on insulin types, and linagliptin for the treatment of T2DM in children and young people.

Full papers were assessed. On full-text review, 1 of the papers looking at liraglutide that was included in the meta-analysis (Klein et al. 2014) was a phase 2 study and therefore excluded. Another study looking at linagliptin (Tamborlane et al. 2018) was also found to

be a phase 2 study that aimed to provide data to inform the appropriate dose of linagliptin for children with T2DM to be used in a phase 3 pivotal trial (registration trial) and was therefore excluded.

We also searched for relevant ongoing research in this area for any medicine for T2DM in children and young people. Ten studies were identified; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations rapidly following publication. These studies are:

- Diabetes study of linagliptin and empagliflozin in children and adolescents
- Phase 3 alogliptin pediatric study
- Study to evaluate safety and efficacy of dapagliflozin and saxagliptin in patients with type 2 diabetes mellitus aged 10 to below 18 years old
- A study to investigate the efficacy and safety of canagliflozin in children and adolescents aged 10 to below 18 years old with type 2 diabetes mellitus
- A study of dulaglutide in children and adolescents with type 2 diabetes
- Dulaglutide versus liraglutide in obese type 2 diabetic adolescents using metformin
- Liraglutide effects in obese youth with prediabetes/new onset type 2 diabetes and non-alcoholic fatty liver disease
- Safety and efficacy study of exenatide once weekly in adolescents with type 2 diabetes
- Afrezza INHALE-1 study in pediatrics
- Ertugliflozin type 2 diabetes mellitus pediatric study

Evidence summary

Studies were identified that looked at the medicines liraglutide, insulin detemir and neutral protamine Hagedorn (NPH) insulin.

One study of liraglutide that met the inclusion criteria was also identified in the Chadda et al meta-analysis. Liraglutide is currently licensed for the treatment of T2DM in adults and children aged 10 years and above in the UK. This study (Tamborlane et al. 2019) looked at

subcutaneous liraglutide (up to 1.8 mg per day; n=66) or placebo (n=68) in patients between 10 to 17 years of age. All the patients received metformin, with or without basal insulin during the trial, as per their normal treatment protocol. The study authors calculated that a minimum sample size of 47 per treatment group was needed to achieve 80% power to detect a difference in HbA1c between groups of 0.9 ± 1.2 percentage points. Blood glucose measures were taken after the 26 week double blind period ended, and after a 26 week open label period. After 26 weeks HbA1c had decreased by 0.64 percentage points with liraglutide and increased by 0.42 percentage points with placebo, for an estimated treatment difference of -1.06 percentage points ($p<0.001$). This difference increased to -1.30 percentage points by 52 weeks. This is a clinically significant change in HbA1c measures.

One study looked at different insulin regimes in combination with metformin. Wheeler et al. 2018 compared 2 different insulins: detemir versus NPH insulin in combination with metformin and lifestyle intervention. Insulin detemir is licensed for diabetes mellitus in both adults and children over 1 year of age. NPH insulin is licensed for diabetes mellitus in both adults and children. Patients aged 10 to 17 years old (n=42) already receiving metformin ± other oral antidiabetic drugs ± basal insulin were randomised to receive either insulin detemir or NPH insulin. Both groups also received the maximum tolerated dose of metformin, and lifestyle intervention, over 26 weeks. The initial recruitment target for this study was 358 participants, which would have allowed for 80% power in a per protocol analysis, however after 17 months recruitment was stopped at 42 participants. These participants were allowed to complete the study. At the end of the study period there was a median 0.61% reduction in HbA1c for those taking insulin detemir, and a 0.84% decrease in HbA1c for those taking NPH insulin.

Topic expert feedback

To understand whether the evidence presented in the systematic review that triggered the exceptional surveillance review was sufficient to reassess current prescribing practices of GLP-1 agonists for the treatment of T2DM in children and young people, 13 topic experts were contacted via an online survey and we received 5 responses. Responses were received from a paediatrician and diabetes professor, a pharmacist with speciality in diabetes, a paediatric diabetologist, and 2 consultant physicians with an interest in diabetes.

Three topic experts told us that they were aware of GLP-1 agonists being used to treat T2DM in children and young people, in a clinical context in the UK currently. One topic

expert stated that liraglutide was the chosen second line therapy in their diabetes clinic, if metformin was not effective in controlling T2DM in children and young people.

All 5 experts agreed that in light of this recent publication, the guideline should be updated to consider the evidence for the use of liraglutide to treat T2DM in children and young people. Topic experts highlighted the wealth of safety data available in adults for these drugs, and their concerns about the serious health implications of T2DM in children and young people, meant that they considered additional pharmaceutical treatments to be of considerable benefit. It was also raised that clinicians have already been prescribing these treatments, and that its use is likely to increase due to the publication of the Chadda et al. 2021 study. The limited number of T2DM specific studies, and therefore of patients included in the meta-analysis being assessed in this review was also raised, highlighting the need for a comprehensive review of the complete evidence base.

One topic expert also suggested looking at other potential pharmaceutical therapies, such as SGLT-2 (sodium-glucose co-transporter-2) inhibitors. This drug class was included in our focused search, but no studies that met our inclusion criteria were identified. Four of the identified ongoing clinical trials include SGLT-2 inhibitors, and the results of these will be assessed as they become available.

Other relevant NICE guidance

No other relevant NICE guidance was identified.

Equalities

Topic experts highlighted that lower socioeconomic status and Asian or South Asian family background play a key role in the incidence of T2DM in children and young people. Consideration has been given to these populations in adults in NICE's guideline on type 2 diabetes: prevention in people at high risk. This has been noted as a potential gap in NICE guidance on the prevention of type 2 diabetes.

Overall decision

This exceptional review was triggered by a recent systematic review and meta-analysis (Chadda et al. 2021) that looked at the use of a GLP-1 agonists for T2DM, pre-diabetes and obesity in children and young people. This led to a further focused search for new

evidence on medicines for T2DM in children and young people which identified 2 RCTs investigating the effectiveness of liraglutide, detemir insulin or NPH insulin at reducing HbA1c levels. These studies' findings indicate that these treatments may lead to clinically meaningful reductions in HbA1c in children and young people with T2DM. While this is a small body of evidence, the study on liraglutide is adequately powered. Although the study on insulin had only a small sample size, it is recommended that NICE's guideline on diabetes (type 1 and type 2) in children and young people is updated to ensure that all current evidence on medicines for children with T2DM is considered.

The search for ongoing research identified 10 trials looking at a range of pharmaceutical treatment options for T2DM in children and young people, indicating that this is a developing research field. We will continue to assess the outcomes of these clinical trials to ensure that our guidance considers this evidence.

Additionally, all topic experts indicated that they thought that these recommendations should be updated. They reported that prescribing of liraglutide to children with T2DM is happening in practice, and that a comprehensive review of the evidence by NICE would be welcomed in order to support best practice. We will therefore update the guideline to look at additional medicines to metformin, for the treatment of T2DM in children and young people.

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