NCCHTA

21 January 2009

Protocol, February 19th 2008.

1. Title
New drugs for diabetes: a technology assessment report in support of a NICE short guideline.

Commissioned by HTA Programme. Project reference 08/05/01

2. TAR team: Aberdeen HTA Group

Lead author and contact person;
Professor Norman Waugh
Dept of Public Health
Medical School Buildings
Foresterhill
Aberdeen AB25 2ZD 01224 555998 (direct) n.r.waugh@abdn.ac.uk
01224 554470 (secretary)

Co-authors (based in Aberdeen unless otherwise stated);
Pam Royle, information scientist and systematic reviewer
Bernd Richter, physician and coordinating editor, Cochrane Metabolic and Endocrine Disorders CRG, Duesseldorf
Ailsa Snaith, systematic reviewer
Christine Clar, systematic reviewer, Berlin
Ewen Cummins, health economist
Meg Marian, systematic reviewer

3. Background to review.

The NICE clinical guideline on Type 2 diabetes mellitus (T2DM) is being updated for release in 2008. Because of the number of new drugs for T2DM, an updating for release in 2009 is being produced as a short guideline. This TAR is being produced to assist with this process. The TAR remit is derived from the draft scope issued for consultation by NICE on January 14th.

Treatment of T2DM is initially with diet and exercise, with oral drugs being added if that is insufficient, or when the condition progresses, as is common. The UK Prospective Diabetes Study showed that in many patients, T2DM is a progressive disorder with diminishing beta cell function over time. Many patients progress from lifestyle changes to oral monotherapy, then to combinations of tablets, and in about a third of cases, to insulin therapy, with or without continued tablet treatment such as metformin.

Several new classes of drugs for diabetes have been introduced in recent years. These are listed below. The decision problems for the Guideline Development Group (GDG) will be where the new drugs fit into the treatment pathway. Our task in this review is to look at the evidence for their clinical and cost-effectiveness and to summarise that for the GDG.

4. New drugs for type 2 diabetes.

4.1 Two new classes of drugs for diabetes will be addressed in this review;

- The incretin mimetics, exenatide and liraglutide. These mimic the actions of endogenous glucagon-like peptide 1 (GLP1) and are known as the GLP1 agonists.

The first of these is exenatide, already licensed. Liraglutide does not yet have a license but one will be sought shortly.

- The inhibitors of the enzyme which inactivates naturally occurring GLP1, dipeptidyl peptidase 4, which are known as the DPP4 inhibitors. There are two of these at present, sitagliptin and vildagliptin.

The guideline will also update previous guidance on two other groups of drug;

- The glitazones, pioglitazone and rosiglitazone
- The long-acting insulin analogues. The previous guidance was issued when only glargine was available, but since then detemir has also been licensed and launched.

4.2 The number of drugs and comparators could lead to a large amount of work. The content of this review will have to be constrained by the resources available and the deadline for delivery, and so will focus on the key issues.

In order to limit the workload, the following approaches will be used;

- the GLP1 agonists are new, with evidence emerging all the time. A full systematic review will be produced in line with Cochrane methods (which will also be submitted to the Cochrane Metabolic and Endocrine Disorders CRG for publication in the Cochrane Library, and will go through the Cochrane quality assurance processes).
- the DPP IV inhibitors and also new. A Cochrane review is underway, by the CMED team in Duesseldorf, with some involvement from the Aberdeen team, and the findings of that review will be used to inform this TAR. The leader of CMED will be a co-author of the TAR.
- the glitazones are not new. We will review those systematic reviews which have been done since the NICE TA guidance (TA 63, which replaces TAs 9 and 21; HTA monograph 2004/8/13 is the associated TAR), but focussing on the recent concerns about cardiovascular side-effects, and whether these are a class effect or just seen with rosiglitazone.
- the long-acting insulin analogues are not new, though the current NICE guidance (TA 53) was done when only glargine was available. We will start by reviewing the reviews, and if necessary update these with any recent RCTs, including those which trial the insulins alone versus combination therapy with metformin.

4.3 Comparators – incretin mimetics

The standard practice in patients with type 2 diabetes, most of whom are overweight, is to start with metformin (if tolerated) and then add a sulphonylurea. (See existing NICE guideline on type 2 diabetes). If metformin was not tolerated, a glitazone could be used as the insulin sensitiser instead. So the incretin mimetics would be used as a third line in addition to those.

This gives the following comparisons;

1. metformin + sulphonylurea vs metformin + sulphonylurea + sitagliptin
2. metformin + sulphonylurea vs metformin + sulphonylurea + vildagliptin
3. sulphonylurea + glitazone vs sulphonylurea + glitazone + sitagliptin
4. sulphonylurea + glitazone vs sulphonylurea + glitazone + vildagliptin
5. metformin + sulphonylurea vs metformin + sulphonylurea + exenatide
6. metformin + sulphonylurea vs metformin + sulphonylurea + liraglutide
7. sulphonylurea vs sulphonylurea + exenatide
8. sulphonylurea + glitazone vs sulphonylurea + glitazone + exenatide
9. sulphonylurea + glitazone vs sulphonylurea + glitazone + liraglutide

Triple therapy,

10. metformin +sulphonylurea + glitazone vs metformin + sulphonylurea + sitagliptin

11. as for 10 but with vildagliptin

The 7th comparison reflects the licensed indications for exenatide, which do not include combination with a glitazone.

We will not examine any of the incretin mimetics as monotherapies. Nor will we review their use in impaired glucose tolerance, where there is some evidence, since this review only includes people with type 2 diabetes.

4.4 Comparators for long-acting insulin analogues

In Type 2 diabetes, insulin is started when control on a combination of oral drugs is unsatisfactory. So the comparators are other basal insulins, usually NPH but occasionally ultralente. Metformin will usually be continued. So comparisons will be;

12. glargine + metformin vs NPH + metformin
13. detemir + metformin vs NPH + metformin
14. glargine + metformin vs ultralente + metformin
15. detemir + metformin vs ultralente + metformin
16. glargine + metformin vs detemir + metformin

In patients unable to tolerate metformin, a glitazone might be used instead, but that would happen in both arms, so the key comparison remains glargine or detemir versus NPH, and the results of the trials including metformin can be extrapolated to those using a glitazone (if any).

We will review the evidence comparing glargine with detemir, but will not do any detailed comparison of one with the other.

Overweight people with type 2 diabetes often do not achieve good control after switching to insulin, partly because it can cause further weight gain. We will review one other option;

17. metformin + sulphonylurea + insulin vs metformin + sulphonylurea + lifestyle change

There are trials of the long-acting analogues against short-acting insulins at meal-times, for example once daily glargine versus thrice daily aspart. We will exclude such trials, because they are comparing different approaches to glycaemic control, rather than different basal insulins.

Since the main interest of the guideline group will be in routine care and everyday life, we will exclude studies comparing the different insulins in highly specialised situations such as after cardiac surgery.

4.5 The glitazones

We will review any systematic reviews of the clinical effectiveness of the glitazones which has emerged since the last of three NICE technology appraisals of glitazones (TA 63). We will review the considerable recent literature on the cardiac risks of the glitazones.

5. Methods

5.1 General approach

The clinical effectiveness, relative to the key comparators, will be assessed, in terms of difference in effect size. (The key question is not whether a drug is better than the comparator, but how much better.) Data on safety will also be sought.

The relative costs (taking into account all costs and savings over an appropriate period) will be estimated.

The effect size and costs will then be fed into an appropriate model and costs per quality adjusted life year estimated. Sensitivity analyses will explore uncertainties in important

parameters, and of the impact on quality of life of hypoglycaemic episodes and the fear of those.
In the clinical effectiveness analysis, we will not include any indirect comparisons, for two main reasons. Firstly, such comparisons are prone to bias due to confounding variables, which may not all be apparent. Secondly, they are used mainly in technology appraisals, when seeking to decide which of two or more options is better or best. We do not expect the guideline development group will wish to make any recommendations of whether one drug in each group is better than the other (for example, whether glargine should be used in preference to detemir, or exenatide in preference to liraglutide), because such comparisons would be based partly on cost, which may change. Having two drugs available in each group encourages competition on price.

5.2 Literature searches
Relevant literature will be found, and comprehensiveness checked, by;

- Searches of bibliographic databases, Medline, Cochrane Library, and Embase
- Checking reference lists of retrieved studies
- Obtaining lists of published studies from manufacturers
- Our peer review process

Searches will also be done to identify emerging evidence, from conference abstracts and trial registers. Studies available only in abstract may be used in the assessment of clinical effectiveness if there is a paucity of studies published in full in peer reviewed journals, and if this is necessary they will be reported with appropriate caution. Our default position is that studies available only in abstract will not be used.
Authors of previous studies will not be contacted.

Academic in confidence or commercial in confidence data, if available, would be used only if there was a lack of published data. In practice this will affect only liraglutide, and NICE will approach Novo Nordisk for unpublished data from the LEAD studies.

5.3 Inclusion criteria
For assessment of clinical effectiveness, only systematic reviews of RCTs, and RCTs will be used. Trials must be of sufficient duration, that being a minimum of 12 weeks, but preferably at least 24 weeks.
If a high quality review is available, searches for trials will be done only for studies published since the searches for that review were done. Trials must compare the drug against appropriate comparators, and will usually be in line with a licensed indication. However we may include some comparisons for indications not yet licensed.
Quality assessment of RCTs will use standard methods, for example as outlined in CRD Report 4.
Studies of other designs, such as long-term case series and open-label uncontrolled extensions, may be used for assessment of safety and acceptability.

5.4 Data extraction will be carried out by one researcher and checked by another. Any disagreements will be resolved through discussion, involving a third person if necessary.

5.5 Outcomes
Depending on data availability, the following outcomes will be included

- HbA1c
- Frequency of hypoglycaemia, especially if severe
- Glycaemic excursions, including post-prandial hyperglycaemia
- Weight gain or loss
- In those on only oral agents, progression to insulin therapy

- Complication rates – retinopathy, nephropathy, myocardial infarction, angina, heart failure, stroke, amputation, death.
- Adverse events
- Health-related quality of life
- Effects on employment (in those occupations where insulin treatment may not be allowed)

5.6 Cost-effectiveness
Assessment of cost-effectiveness will involve;

- A review of existing literature based on searches of bibliographic databases as listed above
- If necessary (if the existing literature is insufficient), economic modelling using an appropriate model for T2DM, such as the Oxford (UKPDS) one.
- *In the cost-effectiveness analysis, it may be necessary to draw on indirect comparisons for effect size, but if this is necessary, appropriate caveats will be included.*

5.7 Quality assurance.
This will be achieved by;

- using tried and tested HTA methods
- obtaining expert advice. The NICE Guidelines Development Group will be used as the advisory panel for this TAR.
- using the quality assurance procedures of the Cochrane CMED group for the reviews of the GLP1 agonists and the DPP IV inhibitors, with independent peer review at protocol and final draft stages.

6. Competing interests of authors.

None. Norman Waugh and Pam Royle are members of the Scottish Study Group for the Care of Diabetes in the Young, whose meetings have been sponsored by Novo Nordisk, but the company has no role in determining the content of the meetings.

7. Timetable/milestones

NICE would like to have the first meeting of the GDG on May 19th/20th 2008. We will try to have a draft of the clinical effectiveness ready by then.
Target for near-final draft report (including cost-effectiveness) – 28th July 2008. The GDG will then provide expert comment at its August meeting.
Final draft report to NCCHTA by end August.

NW 19/2/08