The Primary Care Diabetes Society's response to NICE on the draft type 2 diabetes guideline

One of the many tasks undertaken by the Primary Care Diabetes Society (PCDS) Committee is responding to NICE as a stakeholder in consultations on relevant guidelines. This article presents an extract from the PCDS's recent response to NICE on the draft type 2 diabetes guideline. This response was informed by a survey of PCDS members. The text has been edited minimally, for journal style.

NICE guidelines have, to date, been generally well received and respected by the healthcare community both nationally and abroad. NICE guidelines offer the healthcare professional cost-effective, evidence-based direction for clinical practice. It is therefore regrettable that, in regard to the current draft guideline on type 2 diabetes, these notable characteristics of a respected guideline must be called into question. The PCDS is unable to support the new guideline as it stands, as it appears to be based solely on drug acquisition costs rather than a reflection of cost-effective and safe practice.

Metformin

- Metformin's use as a first-line agent has been established with cardiovascular data, effectiveness and long-term management of target attainment. We accept that this should remain the first choice following lifestyle management.
- It is estimated that 10–15% of the population are unable to tolerate metformin owing to gastrointestinal side effects. Rather than suggesting a trial of modified-release metformin, NICE has suggested that an alternative agent should be used. Metformin has significant cardiovascular outcome data and remains weight neutral. Accepting that there are limited data on metformin as a modified-release preparation, it is still felt that it should be considered for those patients who are unable to tolerate normal-release metformin before moving on to an alternative therapeutic group (Fujioka et al, 2003; Blonde et al, 2004; Fujioka et al, 2005; Feher et al, 2007; Donnelly et al, 2009).
- There is no advice in the guideline as to how fast to titrate the metformin and what maximum dose to use. Most studies have shown that 2 g daily appears to provide an optimal balance between achieving control and tolerability.
- We are pleased to see that NICE accepts the use of metformin down to an estimated glomerular filtration rate of 30 mL/min/1.73 m^2 with caution.

Repaglinide

- Repaglinide has been proposed as an alternative initial therapy in patients who are unable to tolerate metformin. This is a drug that will be unfamiliar to many clinicians and we must advise caution in its use.
- Repaglinide is a fast-acting secretagogue. This would suggest that it can be used to induce insulin production only at meal times and thereby treat prandial hyperglycaemia. It is suggested that this will reduce the risk of hypoglycaemia and weight gain associated with sulphonylurea therapies. Unfortunately, data suggest that there remains a significant risk of these complications (Phung et al, 2010).
- We advise against the consideration of repaglinide for the following reasons:
  - A significant risk of weight gain and hypoglycaemia that in the long-term would negate acquisition cost savings by the increased need for medical intervention, hospitalisation and development of morbidities associated with weight gain.
  - Multiple daily dosing – repaglinide requires pre-meal dosing that is likely to result in issues regarding adherence to the therapeutic regimen.

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Primary Care Diabetes Society

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On behalf of the PCDS Committee

"The PCDS feels that the use of repaglinide is a significant concern in the draft NICE guideline and will cause confusion in the management of patients, lead to failure to adequately achieve targets and place patients at risk from poor compliance, hypoglycaemia, weight gain and the difficulty that clinicians will experience in intensification of therapy."

  - Multiple levels of dose increments – often patients may require different doses at different meals, depending on the carbohydrate load of their food, and this can result in confusion and complicated regimens (Grant et al, 2003; World Health Organization, 2003).
  - Increased frequency of blood glucose monitoring to ensure the correct meal-time dose of therapy and to prevent the risk of hypoglycaemia.
  - The short duration of action of repaglinide means that it is a useful prandial glucose regulator but will be unable to influence fasting glucose levels. Therefore, its ability to help patients achieve their target HbA_{1c} is unlikely without additional agents. NICE has suggested that it should only be used as a monotherapy and, surprisingly, has not considered it as an add-on to metformin.
  - NICE has not commented on dose titration and at what level alternative agents should be considered.
  - At the point when repaglinide is seen as not sufficient for control of glucose levels, this agent will have to be discontinued before the addition of any other agent owing to its licence. This will place patients at an increased risk in the transition phase.
  - There is limited long-term outcome data and cardiovascular safety data on repaglinide.
- The PCDS feels that the use of repaglinide is a significant concern in the draft NICE guideline and will cause confusion in the management of patients, lead to failure to adequately achieve targets and place patients at risk from poor compliance, hypoglycaemia, weight gain and the difficulty that clinicians will experience in intensification of therapy.

Pioglitazone

- Following the recent concerns regarding pioglitazone, the PCDS is surprised that it features so prominently in the draft guideline.
- Pioglitazone is a useful therapy in a limited number of people with diabetes. It has proven that it is effective over the long term for controlling HbA_{1c} (Dormandy et al, 2005), but owing to side effects of this therapy, its use has been significantly reduced, becoming limited to only certain patient phenotypes.
- Pioglitazone carries a significant comorbidity of weight gain and fluid retention (Dormandy et al, 2005; Colbourn et al, 2012). As a large number of people with type 2 diabetes are overweight, have cardiovascular disease and are likely to be on anti-hypertensive therapies that will lead to oedema, many primary care clinicians will avoid prescribing this therapy.
- Pioglitazone has also been associated with increased fracture risk, macular degeneration deterioration and bladder cancer. Although that last association is now disputed, there remains caution in its prescribing. Furthermore, any association between pioglitazone and bladder cancer is strengthened by length of use and cumulative dose, raising further questions over its early adoptive use in a national guideline.
- In middle-aged or older people and in females, the concern of fracture risk is high, and there will be concern over possible deterioration in vision for reasons other than diabetes.
- The draft guideline implies that pioglitazone should be the second choice to metformin treatment. The PCDS is concerned that this may increase the use of pioglitazone in patients who may not be totally suitable. We agree that it should be suggested that it can be considered, but not emphasised as the primary second choice in intensification.

Sulphonylureas

- By the fact that sulphonylureas are no longer suitable to be considered as an alternative to metformin, it must be assumed that NICE has accepted the general medical opinion that these therapies carry a significant risk of weight gain and hypoglycaemia (UK Hypoglycaemia Study Group, 2007). We are therefore concerned that they remain as an alternative, as a second-line agent, when NICE appears to have concluded that short-acting secretagogues are safer. Their place in the guideline is confusing and suggests that this is due to cost and prescribing licence rather than patient safety. We would suggest appropriate emphasis is placed upon when the drugs should be considered, taking into account their risks.

Newer oral therapies

Dipeptidyl peptidase-4 (DPP-4) inhibitors

- The PCDS agrees that DPP-4 inhibitors should be considered as a second intensification step. We would also suggest that they may have a role as a first-line therapy in patients who are unable to take metformin and have significant concerns regarding hypoglycaemia. Recent publications have also suggested they may be useful therapies in people with cardiovascular disease.
- The PCDS feels that the most cost-effective DPP-4 inhibitor should be used, rather than solely considering the cheapest acquisition cost, and emphasis should be made regarding renal monitoring and dose adjustment depending on the DPP-4 inhibitor chosen.
- The recognised licence of these therapies is not uniform, and so awareness should be raised that they may have different efficacy and use may be limited when combining them with other therapies. We feel that this is important to address owing to the increased pressure on primary care with drug switches and prescribing incentives.

Sodium–glucose cotransporter 2 inhibitors

- Sodium–glucose cotransporter 2 inhibitors have become a useful therapeutic agent in the management of overweight and obese people with type 2 diabetes. It is appreciated that they remain outside the scope of the draft documentation, but as they are likely to become more prominent in diabetes management, the PCDS strongly recommends inclusion of their appropriate use in the guideline (with, perhaps, consideration of criteria to start and stop therapy). Owing to the benefits of blood pressure and weight improvement, their place should be before pioglitazone.

Glucagon-like peptide-1 (GLP-1) analogues

- GLP-1 analogue therapies have been useful in managing both weight and glycaemic control. Concerns remain regarding their high costs, and newer agents are entering the market. The GLP-1 analogues have differing characteristics that should result in individualised choice of preparation and device.
- The draft guideline offers no advice regarding daily or weekly dosing. We assume this is because costs are similar.
- The NICE draft guideline has kept the criteria for starting and stopping GLP-1 analogues the same as the previous NICE guideline and technology appraisals. We agree that there is a rationale for the starting criteria but would rather it include the obese group as well as the morbidly obese. We would also recommend much lower BMI-specified cut-points for black and minority ethnic groups, as per the NICE public health guidance PH46.
- We feel that the stopping criteria should be reviewed. Many patients can achieve a reduction in both HbA_{1c} and weight; however, some only achieve target in one parameter. We would argue that stopping therapy when the target has been achieved in weight or HbA_{1c} is inappropriate and not based on any clinical evidence. The next alternative is to switch to insulin, which will lead to further weight gain and comorbidities.
- There is now good evidence to support the use of GLP-1 analogues with insulin therapy. NICE suggests that this should only be used under diabetes specialist care. Primary care has been involved in both GLP-1 analogue initiation and insulin management for many years. If the individual practitioner's skill level includes the ability to manage such therapies, we feel the combined use should not be barred in primary care.

Insulin

- NPH insulin has remained the first choice of insulin within the draft guideline. NICE has advised that analogue insulin may be used in appropriate patients, subject to hypoglycaemia or where twice-daily dosing is needed. We would like to emphasise that when converting between insulin types, advice must be given that doses may not be the same and that regular blood glucose monitoring should be encouraged.

Safety and prescribing in fertile females

- We feel that this is an important footnote for this document, even though it is covered in the NICE pregnancy guideline published

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Box 1. Responses from a survey of PCDS members on the draft NICE guideline run in February 2015 (307 respondents).

- **84%** were happy to use **metformin** as a **first-line** therapy and **95%** would wish to change to a **modified-release preparation** before changing to an alternative drug class
- **70%** would be **unhappy to use repaglinide** (the main barriers were its **multiple daily dosing**, the **inability to use it with other agents**, and concerns relating to **hypoglycaemia**, **weight gain** and a **lack of familiarity with its use**)
- **57%** would be **unhappy to use pioglitazone**, citing concerns over **cardiac safety**, **weight gain**, **fluid retention**, **fracture risk** and **cancer concerns**
- **91%** supported a **change in the stopping criteria** for **glucagon-like peptide-1 analogues** to allow ongoing prescribing **if one of the targets is achieved**

in February 2015. Owing to the increased prevalence of type 2 diabetes at an earlier age, there is concern that women may become pregnant on therapies that are not licensed or safe for use during pregnancy. A list of therapies to avoid or use with caution in this group of patients would add to the clarity and safety benefits of the guideline.

Conclusion

As the leading representative organisation for the management of diabetes in primary care, we are unable to support this draft guideline as it stands. We appreciate the time and effort that has gone into this guideline and are fully aware that significant changes will have both a time impact and a monetary cost, but we feel that the draft guideline cannot be safely applied in clinical practice. It is not evidence based, is subject to misinterpretation and lacks clarity, leading to both confusion in patient care and risk of patient harm.

The PCDS asks that the draft be reviewed and the concerns we have expressed be duly noted. We propose that delaying the publication of the final guideline to ensure that this is a document that can be used and respected is far more important than publishing a guideline that will harm the reputation of NICE and possibly result in harm to people with diabetes. We believe that this guideline has been strongly influenced by drug acquisition costs rather than being based on the broader medico-economic evidence currently available for diabetes management.

The PCDS is the premier voice for clinicians who deal with diabetes in primary care. To help our members understand the draft guideline, we ask NICE to address some important questions.

1 While we agree that there is sparse prospective randomised controlled trial data on the tolerability of modified-release metformin, there are retrospective cohort data and pragmatic uncontrolled data pointing to better tolerance of the modified release preparation, *particularly in those patients switched from immediate release to modified release*. With this in mind, coupled with the prescribing experience both of the PCDS Committee and of a sample of a membership that responded to a recent survey we ran (both of which favour and regularly prescribe the modified-release version in plain metformin-intolerant patients: Could the Guideline Development Group (GDG) please explain why this option is currently not recommended in the draft guideline?
2 Given that the only sizeable head-to-head study of repaglinide versus a sulphonylurea (Derosa et al, 2003) shows no advantage, in terms of both glycaemic control and hypoglycaemia, could the GDG please explain the advantages of the former, considering that its multiple daily dosing and incremental dosing requirements will have a significant effect on adherence to the regimen?
3 Is the GDG not aware that there will be confusion and risk of significant deterioration in glycaemic control when intensifying therapy following repaglinide, and, if so, how is the impact of this to be minimised?
4 Following the information provided from the aforementioned survey of our members (see *Box 1*), is the GDG concerned that the guideline will not be followed and thereby have a detrimental effect on the standing of NICE as an organisation? ■

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