Individualised Treatment of Hyperglycaemia

Abstract and Introduction

Abstract
Hyperglycaemia is a significant contributor to the morbidity and premature mortality of type 2 diabetes. There are several glucose lowering agents, with each class having a different mechanisms of action, but their utilisation has to be considered within the context of disease pathogenesis; appropriateness of the agent for the patient, patient lifestyle and personal circumstance, and to some extent treatment costs. The most recent joint policy statement from the American Diabetes Association and the European Association for the Study of Diabetes addresses these issues and provides guidance on strategies for a patient centred approach to the implementation of evidence based medicine. Glycaemic targets are flexible, but early intervention, and therapy as intensive as individual circumstance dictates are recommended.

Introduction
In 2006 the ADA-EASD published a consensus algorithm for the management of hyperglycaemia in type 2 diabetes. This consensus recognised the importance of good glycaemic control in reducing the morbidity and premature mortality associated with type 2 diabetes and emphasised the benefits of early and intensive intervention from diagnosis with specialist input at treatment initiation. In particular the consensus deliberated the risks and benefits of aiming for glycaemic control as near normal as possible and how this might be achieved using the pharmacological agents then available.

It is interesting to recall that in Europe in 2006 metformin and sulphonylureas had been available for nearly 50 years and the TZDs were considered new drugs. In the UK the TZD troglitazone had been both introduced and withdrawn in 1997, due to idiosyncratic liver failure; pioglitazone and rosiglitazone were introduced in 2000 (and the latter was withdrawn in 2010 due to possibly increasing cardiovascular risk, but not death). Not all of the pharmacological agents in the diabetes armamentarium were included in the algorithm although the USA additionally had the amylin analogue pramlintide and the GLP-1 agonist exenatide, both of which were introduced in 2005.

It was agreed that if *HbA1c ≥ 7% then the patient should be moved to the next level of therapy unless individual circumstance strongly indicated otherwise. A summary diagram of the 2006 ADA-EASD algorithm is shown in figure 1. [1, 4]
Summary of 2006 ADA-EASD consensus algorithm for the management of hyperglycaemia in type 2 diabetes. If HbA1c < 7% maintain therapy. If HbA1c ≥ 7% move promptly to next level.1,4

**Key:** SU = sulphonylurea; TZD = thiazolidinedione

* TZD with insulin is off-label in the UK


Less than 18 months later a consensus statement update was presented online – in print 2008 - which addressed the use of thiazolidinediones, especially the issues surrounding rosiglitazone, and recommended greater caution when using these agents. In particular care was warranted in patients at risk of CHF, and in the USA in patients with CHF.5 In the interim the first in class DPP4 inhibitor sitagliptin had become available in the USA and Europe and was included in the listing of 'other drugs' with glucose-lowering efficacy.6

The subsequent consensus algorithm, available online in October 2008, stressed the role of lifestyle modification as an ongoing strategy in the management of type 2 diabetes and provided detailed discussion on the newer agents.6 It also introduced the concept of two tiers of treatment: tier 1 being the well validated core medications (metformin, sulphonylureas, insulin) and tier 2 including the addition of the less well-validated medications (the TZD pioglitazone and the GLP-1 agonist exenatide).6 Interestingly the consensus recommended against the use of rosiglitazone; but this agent is still available in the USA.

Since the 2006 consensus the diabetes therapeutics landscape has changed dramatically with the advent of further novel insulins and several agents which target the incretin system, whilst colesevelam (Welchol®) and a quick release formulation
of bromocriptine (Cycloset®) have been introduced as treatments for type 2 diabetes in the USA. In Europe colesevelam is indicated in the treatment of hypercholesterolaemia, and bromocriptine in Parkinson's disease and hyperprolactinaemic conditions, but neither agent is approved for diabetes. The actions and limitations of the glucose-lowering agents which are not used in Europe are summarised on .

Table 1. Actions and limitations of glucose-lowering agents available to treat diabetes in the USA but not Europe

<table>
<thead>
<tr>
<th>Agents administered orally</th>
<th>Main Mechanism of Action</th>
<th>↓ HbA&lt;sub&gt;1C&lt;/sub&gt; % (mmol/mol)</th>
<th>↓ FPGmmol/L(mg/dL)</th>
<th>Body Wt</th>
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<td><strong>a</strong>Dopamine-2 agonist (bromocriptine quick release)</td>
<td>• Regulation of metabolism via the hypothalamus</td>
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<td></td>
<td>• Activates dopaminergic receptors</td>
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| **b**Bile acid sequestrant (colesevelam) | • ? ↓ hepatic glucose production | ~0.5 (~5) | 0.9 (~14) | - | Any hypoglycaemic condition ↑ triacylglycerols Constipation Headache ? ↓ absorption of other medications and micronutrients |
|                                          | • ?↑ incretin levels |                                          |                  |         |                          |
|                                          | • ? activate farnesoid X receptor (FXR) in liver |                                          |                  |         |                          |
|                                          | • ↑ LDL-c |                                          |                  |         |                          |

<table>
<thead>
<tr>
<th>Agents administered by subcutaneous injection</th>
<th>Main Mechanism of Action</th>
<th>↓ HbA&lt;sub&gt;1C&lt;/sub&gt; % (mmol/mol)</th>
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*Most agents may rarely cause hypersensitivity reactions

aTake within 2 hours of waking; bTake with a well balanced meal; cTake at mealtimes↑ = increase; ↓ = decrease; – = no change; ~ = approximately; ? possibly; GI = gastrointestinal; LDL-c = low density lipoprotein cholesterol

However in the 2012 position statement the guiding principles of monotherapy, dual therapy and triple therapy and increasing complexity of insulin strategies, on a background of lifestyle modifications, remain in the quest for optimal glycaemic control.[7]

Drugs to Reduce Hyperglycaemia

Several drugs, with different modes of action, are available to reduce hyperglycaemia and they can be broadly divided into those which as monotherapy can cause hypoglycaemia and those which are not associated with neuroglycopenia ( and ).
### Table 2. Actions and limitations of current glucose-lowering agents available in the USA and Europe 8

<table>
<thead>
<tr>
<th><strong>Main Mechanism of Action</strong></th>
<th><strong>↓ HbA1c %</strong> (mmol/mol)</th>
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<tr>
<td><strong>Metformin</strong></td>
<td><em>↓ insulin resistance</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>~1–2% (~11–22)</td>
<td>1–4 (~18–72)</td>
<td>j/&lt;br&gt;GI intolerance&lt;br&gt;Lactic acidosis (rare)&lt;br&gt;Renal impairment, any hypoglycaemic condition</td>
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<tr>
<td></td>
<td><em>↓ hepatic glucose output</em></td>
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<td></td>
<td><em>↑ peripheral glucose utilisation</em></td>
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<td></td>
<td><em>↑ glucose turnover between intestine and liver</em></td>
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<tr>
<td><strong>Sulphonylureas</strong></td>
<td><em>Directly ↑ insulin secretion</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>~1–2 (~11–22)</td>
<td>2–4 (~36–72)</td>
<td>↑&lt;br&gt;Hypoglycaemia&lt;br&gt;Selection restricted by severe liver or renal disease, or porphyria</td>
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<td></td>
<td><em>Binds to SUR1 - stimulates β-cells by closure of K+-ATP channels</em></td>
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*Most agents may rarely cause hypersensitivity reactions*

**Dopamine-2 agonist** (bromocriptine quick release)
- Regulation of metabolism via the hypothalamus
  - ↑ insulin secretion
  - Activates dopaminergic receptors
- ~0.6–1.2 (~6–12)
- 0–1.3 (18–23)
- Any hypoglycaemic condition
  - Dizziness/syncope, nausea

**Bile acid sequestrant** (colesevelam)
- ?↓ hepatic glucose production
  - ?↑ incretin levels
  - ? activate farnesoid X receptor (FXR) in liver
  - ↓LDL-c
- ~0.5 (~5)
- 0.9 (~14)
- Any hypoglycaemic condition
  - ↑ triacylglycerols
  - Constipation
  - Headache
  - ?↓ absorption of other medications and micronutrients

**Amylin analogue** (pramlintide)
- ↓ glucagon secretion
  - Slows gastric emptying
  - ↑ satiety
- 0.5–1 (~5–11)
- -
- Any hypoglycaemic condition
  - GI side effects, nausea
| **Meglitinides** | • Directly ↑ insulin secretion<sup>b,c</sup>  
• Binds to benzamido site on SUR1 - stimulates β-cells by closure of K<sup>+</sup>-ATP channels  
• Rapid onset, short duration of action | ~0.5–1.5 (<5–16)  
1–3 (18–54) | ↑/– | Lesser risk of hypoglycaemia (fewer and less severe than with sulphonylureas)  
Liver or severe renal disease |
| **Gliptins (DPP-4 inhibitors)** | • ↑ insulin secretion<sup>b</sup>  
• Inhibition of DPP-4 allows increased t½ for incretins, which potentiate nutrient-induced insulin secretion | ~0.6–1.2 (<6–12)  
0.6–1.2 (10–22) | – | Small risk of hypoglycaemia (seldom severe), mostly when used with other glucose-lowering agents  
Substantial renal or liver disease |
| **Thiazolidinediones (glitazones)** | • ↑ insulin action<sup>a</sup>  
• Stimulate PPARγ  
• ↑ adipogenesis  
• Alter glucose-fatty acid cycle | ~0.6–2.0 (<0.6–22)  
2–3 (36–54) | ↑ | Heart failure, oedema, fluid retention, anaemia, fractures  
Cardiac disease, severe liver or renal disease |
| **α-glucosidase inhibitors** | • Slows carbohydrate digestion<sup>d</sup> | ~0.5–1 (<6–11)  
~0.5 (<9) | – | GI discomfort  
Intestinal diseases, severe kidney disease |

**Agents administered by subcutaneous injection**

| **GLP-1 receptor agonists** | • ↑ insulin secretion<sup>b</sup>  
• Resistant to degradation by DPP-4  
• Potentiate nutrient-induced insulin secretion | ~0.5–1.5 (<6–16)  
0.7–2.5 (13–45) | ↓ | Nausea  
Risk of hypoglycaemia when used with other glucose-lowering agents  
Do not use in severe renal or GI disease (eg, gastroparesis)  
Stop use if suspect pancreatitis |
| **Insulins** | • ↓ hepatic glucose output  
• ↑ peripheral glucose uptake, storage, and utilisation  
• ↓ lipolysis | Variable, as needed | ↑ | Hypoglycaemia  
Major lifestyle adjustments  
Glucose monitoring |

<sup>*Most agents may rarely cause hypersensitivity reactions</sup>

<sup>a</sup> requires presence of circulating insulin

<sup>b</sup> requires presence of a functional β-cell mass

<sup>c</sup> Take with meals, lessen risk and severity of hypoglycaemia
Hypoglycaemic Agents

The hypoglycaemic action of insulin is well established as is the glucose lowering efficacy of the sulphonylureas which act directly on the beta cell to stimulate insulin release. A range of sulphonylureas is available with differing onsets and durations of action as well as different pathways of metabolism and elimination, providing opportunities for selection of the sulphonylurea most suited to the individual patient.

Although the meglitinides (glinides), also directly stimulate insulin release they are less likely to cause hypoglycaemia as they have a very rapid onset and short duration of action. They are often termed prandial insulin releasers, as they should only be taken with food. Despite not being included in any of the algorithms the new consensus notes that it may be appropriate to use a meglitinide instead of a sulphonylurea.[7]

Antihyperglycaemic Agents

A particular benefit of antihyperglycaemic agents is that they are generally associated with weight loss or weight neutrality, unlike the hypoglycaemic agents which promote weight gain whilst improving glycaemia.

Metformin is the oldest antihyperglycaemic agent and it has a multiplicity of mechanisms and sites of action, the most notable of which is to reduce insulin resistance particularly in the liver whereby hepatic glucose production is decreased but not completely inhibited. The α-glucosidase inhibitors (eg acarbose in the UK) retard the rate of carbohydrate digestion in the small intestine, but are rarely used in the UK and USA - possibly due to patient intolerance of their GI side-effects – as well as limited glucose lowering efficacy. However as noted in the position statement the α-glucosidase inhibitors may be helpful as initial therapy in patients unsuited to metformin.[7]

The bile acid sequestrant colesvelam,[9] the dopamine agonist bromocriptine,[10] and the amylin analogue pramlintide[11] offer similar opportunity to enhance individualisation of therapy, but have not been included in the main algorithm ().

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The TZDs, of which only pioglitazone is now licensed in Europe, are PPARγ agonists which enhance insulin sensitivity - notably to increase glucose uptake into muscle and fat. Unlike the other antihyperglycaemic agents TZDs are associated with weight gain, but this may be partly due to an increase in fluid retention.

There are several DPP4-inhibitors (gliptins) which have varying pharmacokinetic profiles with differing routes of metabolism and elimination, but are all considered weight neutral and can assist weight loss in some patients. These agents enhance the availability of circulating incretins and offer increased opportunity to tailor the prescription to the patient. The GLP-1 receptor agonists/mimetics, which stimulate glucose dependent insulin release, are the antihyperglycaemic agents most strongly associated with weight gain – but the opportunity to use these agents may be compromised by local guidelines; for example the recommendation by NICE that patients have a BMI ≥ 35 kg/m² or a BMI < 35kg/m² plus a co-morbidity. This class of agent, which is an injectable, has been available in the USA since 2005, but only entered Europe in 2007.

**Algorithm Agents**

The number of glucose lowering agents included in the algorithm has increased with each iteration of the consensus, firstly with the addition of GLP-1 agonists, and now inclusion of DPP4 inhibitors; but those excluded continue to be the alpha-glucosidase inhibitors, meglitinides and pramlintide as well as the more recently introduced colesevelam and bromocriptine. This class of agent, which is an injectable, has been available in the USA since 2005, but only entered Europe in 2007.

Figure 2 summarises the therapeutic approaches elucidated in the 2012 position statement.
Algorithmic summary of 2012 ADA-EASD policy statement recommendations for the management of hyperglycaemia in type 2 diabetes. If individualised glycaemic target not achieved, or maintained, move promptly to next therapy level using a patient-centred approach to drug selection.

Key: DPP4i = dipeptidylpeptidase 4 inhibitor; GLP-1a = glucagon-like peptide-1 agonist; SU = sulphonylurea; TZD = thiazolidinedione Reproduced with permission from MedEd UK.

Individualisation of Therapy

Increasing recognition of the importance of the patient in the medical decision making has led to the 2012 consensus recommending a patient centred approach.[7] This is especially pertinent in diabetes where lifestyle choices have such an influence on outcomes that lifestyle is the fundamental and enduring treatment strategy to which pharmaceutical interventions are added. An holistic approach to therapeutic choice is required as the strategy selected has to fit within the constraints of known contraindications, co-medication for additional morbidities and within the diverse demands of a person’s life. Added to this is the benefit:risk assessment associated with each agent, including the debate surrounding macrovascular risk and glycaemic targets, all of which should be considered within the context of the individual.[13]

This recent policy statement raises these issues and helpfully indicates the main advantages and disadvantages of the different therapeutic classes, their main modes of action and cost implications. All the agents are noted as being of high cost, except the well established 2nd generation sulphonylureas and metformin which are viewed as low cost and the alpha-glucosidase inhibitors moderately priced, with insulin costs being variable – depending on type and dosage.[7] The influence of optimal glycaemic management is discussed - an HbA1c > 7% is still considered a ‘call to action’ - with emphasis being placed on the importance of altering this target as required by personal circumstance, for example an HbA1c ~8% may be appropriate in a person susceptible to severe hypoglycaemia or with limited life expectancy, but hyperglycaemic symptoms should be eliminated. An elemental approach to decision making in diagrammatic format provides a framework in which to
consider the practicalities and benefits of more or less stringent control in the individual management of hyperglycaemia.\cite{7,13,14}

**Adherence**

The role of the patient, particularly in the management of chronic conditions such as diabetes, is being recognised as a fundamental factor for the achievement of optimal outcomes, for it is patients who decide upon their lifestyle choices and extent of adherence to prescribed medication.\cite{15–17} Indeed it is variously estimated that 36–93% of patients with type 2 diabetes on oral therapy collect <80% of prescribed medication, and adherence declines as the number of antidiabetic medicines, dosing complexity and co-medications increase.\cite{16,17}

With regard to lifestyle changes and taking medications a greater mutual understanding between prescriber and patient is required. The building of such a therapeutic alliance requires an awareness of the pros and cons of treatment strategies as is necessary for that patient to discuss the strategies with the prescriber. The move towards concordance facilitates patient adherence to the strategy and increases prescriber confidence that the agreed action plan will be implemented.\cite{17}

When moving from monotherapy to dual therapy – and even triple therapy – the pill burden can be reduced by substituting the two dual therapy agents with a fixed dose single tablet antidiabetic combination – thereby aiding adherence by reducing the pill burden.\cite{16–18} This approach is not mentioned in the latest consensus although compared to Europe a wide selection of combinations and dosage strengths is available in the USA (mainly metformin + another agent).\cite{16}

**Conclusion**

The latest policy statement notes that lifestyle strategies alone may be successful in patients with near-target hyperglycaemia (eg HbA1c <7.5%) and suggests that this approach be offered to well motivated patients.\cite{7} However in those less likely to implement and adhere to lifestyle changes as well as those with moderate hyperglycaemia, initiation of metformin is recommended. If metformin is inappropriate for the patient then a 2nd line agent or an α-glucosidase inhibitor should be considered. Despite increased awareness, diabetes is often not diagnosed until later in the pathogenesis of the condition, thus initial therapeutic strategies may be those found at later stages in the treatment pathway. It is appreciated that the disease, not drug failure, necessitates moving to the next step, hence continuation of therapy and the adding of another agent or introduction of increasingly complex insulin regimens to prevent hyperglycaemia and its acute and chronic sequelae.

The recent approach to managing hyperglycaemia might be considered conservative, with the older established – and now less costly - agents being given prominence. This may be due in part to the lack of long-term clinical experience with the newer agents generating a cautious approach; discretion is the better part of valour.

Cardiovascular risk reduction is a major focus of therapy in type 2 diabetes and a considerable contributor to the polypharmacy onto which glucose lowering treatments are added. Type 2 diabetes is a moving target so guidance has to be flexible and adaptable with strategies that can be implemented by the patient. The modern mantra of individualisation is a key issue in the 2012 ADA-EASD policy statement with the focus being on an alliance between the patient and prescriber. The provision of bespoke treatment suited to the patient recognises the person as well as their medical situation. This patient-centred approach empowers patients and enables patient and prescriber to 'sing from the same hymn sheet', ideally facilitating patient adherence, which also supports the prescriber to provide optimal treatment.

Mandatory glycaemic targets are not included in the latest treatment algorithm, as this encourages individualisation of strategies; but guidance is supplied. For ongoing treatment in patients who are not achieving their target transfer to the next step should be implemented rapidly. Whilst tight glycaemic control is advocated, there is endorsement of less rigorous targets as demanded by individual circumstance.

**Sidebar**

**Key Messages**

- Lifestyle measures are the cornerstones of treatment
- Form a therapeutic alliance with the patient
- Individualise glycaemic targets
- Individualise glucose lowering strategies

**References**


Abbreviations and acronyms

ADA, American Diabetes Association; BMI, body mass index; CHF, congestive heart failure; DPP4, dipeptidylpeptidase 4; EASD, European Association for the Study of Diabetes; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin A1c; NICE, National Institute for Health and Clinical Excellence; PPARy, peroxisome proliferator activated receptor gamma; TZD, thiazolidinedione

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