Module B
Treating Diabetes

1 Oral therapies
Learning aims

To understand the effects of oral glucose (sugar)-lowering drugs on blood glucose levels

To appreciate which drugs are most likely to cause hypoglycaemia

To appreciate which characteristics of older residents with diabetes may influence the actions of these drugs
Key initial points

- Orally active glucose-lowering drugs are meant to be started to complement the effects of any lifestyle interventions when blood glucose levels remain unsatisfactory or symptoms continue.

- Several different classes of orally active glucose-lowering drugs are available with varying actions on body tissues.

- Not all oral glucose-lowering drugs cause hypoglycaemia in the absence of other anti-diabetic agents.
Reasons for Treatment

- The great majority of patients with type 2 diabetes have a combination of insulin deficiency (the pancreas cannot produce enough insulin to cope with circulating glucose levels) plus impaired glucose-lowering effect of the insulin hormone (‘insulin resistance’).

- Insulin is occasionally required soon after diagnosis of type 2 diabetes because of marked insulin deficiency suggesting that latent type 1 diabetes was present.
Oral drugs for diabetes mainly work either by increasing insulin production or by making insulin more effective.

Other agents with different actions are also available.

The clinician should decide what is best for each individual and discuss these aspects with the resident with diabetes.
Please remember that as a member of the care home staff you are not expected to make decisions on what treatment to start the resident with diabetes on! However, the information in these slides will assist you to understand the background to decisions taken.

Metformin is usually the first oral agent to be used, except in cases of severe kidney failure.

If the maximum tolerated dose of metformin (usually no more than 2g/day) fails to achieve target levels of blood glucose, a second oral drug may be added.

The choice at this stage usually lies between:
- a sulphonylurea
- a dipeptidyl peptidase-4 (DDP-4) inhibitor
- pioglitazone (a thiazolidinedione)
- a sodium-glucose co-transporter-2 (SGLT-2 inhibitor).
Starting oral glucose-lowering therapy

Other agents that are rarely used include:
– acarbose (an α-glucosidase inhibitor)
– repaglinide or nateglinide (glinides).

All glucose-lowering drugs have potential safety and tolerability issues that must be considered in choosing the most appropriate agent.

If a drug is not tolerated or is ineffective, an alternative should be considered.
<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Low hypo risk</td>
<td>Can cause GI upset/weight loss</td>
<td>Extended release formulation available</td>
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<td></td>
<td></td>
<td>Low cost</td>
<td>May be contraindicated in renal impairment and CVD</td>
<td>Need to assess vitamin B12</td>
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<td>In widespread use</td>
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<td>Sulphonylureas (SUs)</td>
<td>Gliclazide</td>
<td>Low cost</td>
<td>High risk of hypos</td>
<td>Generally avoid in those with dementia, malignancy, frailty; consider</td>
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<td></td>
<td>Glimepiride</td>
<td>Can be used in certain grades of renal impairment</td>
<td>Caution with glimepiride</td>
<td>discontinuing use in those on insulin</td>
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<tr>
<td></td>
<td>Glipizide</td>
<td></td>
<td>Avoid glibenclamide</td>
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<tr>
<td></td>
<td>Glibenclamide</td>
<td></td>
<td>Generally avoid in those with dementia, malignancy, frailty; consider</td>
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<td>Meglitinides</td>
<td>Rapaglinide</td>
<td>Shorter duration of action than SUs – may be an advantage in those with erratic eating patterns</td>
<td>Limited evidence of use in older adults</td>
<td>Can be withheld if meals are missed but otherwise limited roles in</td>
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<td></td>
<td>Nateglinide</td>
<td></td>
<td>Hypoglycaemia</td>
<td>residents with diabetes</td>
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<td>TZDs (Thiazolidinediones)</td>
<td>Pioglitazone</td>
<td>Low hypo risk</td>
<td>Contraindications in those with heart failure, fractures, leg edema, anaemia</td>
<td>May have limited roles in frail residents with diabetes</td>
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<td></td>
<td></td>
<td>Once daily dosing</td>
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<td></td>
<td></td>
<td>Can be used in certain grades of renal impairment</td>
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<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>Low hypo risk</td>
<td>Higher cost</td>
<td>Can be combined with insulin</td>
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<td></td>
<td>Vildagliptin</td>
<td>Once daily dosing</td>
<td>Potential risk of heart failure in ‘at-risk’ individuals</td>
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<td>Saxagliptin</td>
<td>Can be used in various grades of renal impairment with dose adjustment (except linagliptin)</td>
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<tr>
<td>SGLT-2 inhibitors</td>
<td>Canagliflozin</td>
<td>Low hypo risk</td>
<td>Higher cost</td>
<td>Stop SGLT-2 inhibitors in someone with covid-19 or acute illness</td>
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<td></td>
<td>Vildagliflozin</td>
<td>May be of benefit in high cardiovascular risk and reducing risk of hospitalisation due to heart failure</td>
<td>May be associated with increased urinary frequency, genital infections, dehydration May increase risk of DKA</td>
<td>Dose reductions in renal impairment</td>
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<td>Dapagliflozin</td>
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<td>GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists)</td>
<td>Liraglutide</td>
<td>Low hypo risk</td>
<td>Higher cost</td>
<td>Can be combined with insulin; be cautious in those with poor appetite, weight loss, frailty; advice required before use in renal impairment</td>
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<td></td>
<td>Exenatide</td>
<td>Once a day and once a week formulations available</td>
<td>Requires sub-cutaneous injection GI side effects</td>
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<td></td>
<td>Semaglutide</td>
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Abbreviations: hypo: hypoglycaemia; CVD: cardiovascular disease; DKA: diabetic ketoacidosis; GI: gastrointestinal
Evidenced-Based Strategies for Glucose Lowering Treatment in Older People – a 3 step process

1st Step:
Metformin is the first line of treatment after lifestyle – caution in severe renal impairment; consider low hypo potential SU or DPP4 inhibitor if MF contraindicated

2nd Step:
All other oral agents can be used (e.g. DPP4-I or SU or SGLT2-Inhibitor) depending on clinician choice, renal function, frailty status, risk potential for hypoglycaemia, economic considerations (q.v. sulphonylureas – use of gliclazide); if patient is markedly obese (>35) consider GLP-1 agonist; if all OHAs are not tolerated consider long-acting basal insulin or GLP-1 agonist

3rd Step:
Add in basal insulin or a pre-mixed insulin, or a GLP-1 agonist

Key Considerations
- Have a ‘risk to benefit’ conversation
- Consider the likelihood of worsening renal or hepatic function
- Estimate risk of hypoglycaemia
- Try not to put HbA1c at the heart of your planning – consider quality of life and minimising vascular risk as your main priorities

Cautions in Moderate to Severe Frailty
- Consider a glinide if eating patterns are irregular (short duration/rapid onset of action) or cognitive impairment;
- Avoid a SGLT2-Inhibitor in view of weight loss, dehydration, toe amputations;
- Caution with a GLP-1 agonist (weight loss, anorexia) but as part of a glucose-dependent strategy may reduce hypoglycaemia rate;
- Pioglitazone: caution with side effects but may be of value in those with high stroke and macrovascular risk

Explanatory Note: this is the scheme for clinicians (FYI) for treating older people with diabetes and does not necessarily apply to residents with diabetes. It can be studied with the previous table on oral treatments. The third step here is often insulin treatment or a GLP-1 agonist

Not all oral glucose-lowering drugs cause hypoglycaemia (see Table). For this reason, oral agents are sometimes divided into ‘anti-hyperglycaemic’ (those not causing hypoglycaemia as monotherapy) and ‘hypoglycaemic agents’ (agents that may cause hypoglycaemia).

A drug which on its own will not cause hypoglycaemia, may of course do so if added to insulin or a hypoglycaemic agent.
Some people may fail to respond to a particular class of oral treatment, in which case an alternative from another class may need to be tried.

Caution is needed when considering adding in another treatment as some may not be appropriate for a resident with diabetes, e.g. a sulphonylurea, pioglitazone, some SGLT-2 inhibitors and some GLP-1 receptor agonists.
Following an initial response, blood glucose levels tend to rise again with time despite continuing treatment with an oral glucose-lowering agent.

This is usually due to continuing loss of insulin production from the pancreas.

However, other causes include a lapse of dietary control or the use of drugs which cause a rise in blood glucose, in particular corticosteroids.
The clinical state of the person with diabetes should always be taken into consideration when choosing an oral glucose-lowering drug.

For example, an older frail person in whom it is especially important to avoid hypoglycaemia might be better treated with a DDP-4 inhibitor than a sulphonylurea if metformin alone provides inadequate diabetes control.
Need for further drug therapy

- As a rule, the need is for a second and then a third agent to be added in order to achieve glucose targets. Various combinations of oral agents can be used before considering insulin.

- Various classes of oral treatments may be used with caution only or may be contraindicated – see previous table on classes and their adjoining information. An example might be the case of Pioglitazone – this can lead to fluid retention and should not be used in a patient with a history of heart failure.
Identifying and tackling problems with treatments used

- Some problems, notably hypoglycaemia (a hypo), require prompt recognition and treatment.
- After recovery from a hypo, it is important to take action to prevent a further event (see next slide)
- Other common drug side effects:
  - nausea and diarrhoea with metformin
  - ankle swelling with pioglitazone.
These should be acted upon, with medical help.
Further action after a ‘hypo’ has occurred

Review possible cause:

- Excess insulin/sulphonylurea
- Inadequate food
- Gap between meals
- Extra exercise/exertion
- Use of a long-acting sulphonylurea

If no obvious cause, consider reducing dose of insulin or stopping a sulphonylurea
An increased risk of genitourinary fungal infections is a side effect of the SGLT-2 inhibitors (a new group of oral agents – see Table).

If this recurs, treatment will have to be stopped.

The higher urine volume induced by these agents may also cause urinary symptoms, for example increased frequency or incontinence, and lower blood pressure in vulnerable patients.
Key Messages

1. Remember that oral treatments for diabetes are supposed to complement a healthy diet – however, in care homes, many residents who may be frail, unwell or undernourished may not be able to participate in dietary programmes.

2. In general, treatments that lower blood glucose should be part of a simplified approach, and not be part of a complex treatment regimen.

3. Hypoglycaemia is a real threat to the wellbeing of any resident with diabetes who may be taking certain treatments – see table.

4. Remember, for many residents with diabetes, there is no need for very strict blood glucose control – see targets in Module A.
Q1. Some oral drugs for diabetes can work by which mechanism:

- A. Increasing insulin production from the pancreas
- B. Improving the effects of insulin
- C. A and B
- D. None of the above
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Q2. Which is the drug that is usually started first?

- A. DDP-4 inhibitor
- B. A sulphonylurea
- C. Metformin
- D. Pioglitazone
- E. SGLT-2 inhibitor
- F. GLP-1 receptor agonist
Q2. Which is the drug that is usually started first?

- A. DDP-4 inhibitor
- B. A sulphonylurea
- C. Metformin
- D. Pioglitazone
- E. SGLT-2 inhibitor
- F. GLP-1 receptor agonist
Q3. Which of the following first step or second step oral glucose lowering drugs (or combinations) may cause hypoglycaemia?

- A. Metformin
- B. Sulphonylureas
- C. A and B together
- D. DPP-4 inhibitors
- E. SGLT-2 inhibitors
Q3. Which of the following first step or second step oral glucose lowering drugs (or combinations) may cause hypoglycaemia?

- A. Metformin
- B. Sulphonylureas
- C. B alone and A and B together
- D. DPP-4 inhibitors
- E. SGLT-2 inhibitors
Q4. Not all glucose lowering drugs cause hypoglycaemia; a patient is taking a drug which may cause hypoglycaemia – what happens if another drug is added?

- A. The risk of inducing hypoglycaemia will be decreased
- B. The risk of inducing hypoglycaemia depends on the class of drug added
- C. The risk of inducing hypoglycaemia will be increased
Q4. Not all glucose lowering drugs cause hypoglycaemia, a patient is taking a drug which may cause hypoglycaemia – what happens if another drug is added?

- A. The risk of inducing hypoglycaemia will be decreased
- B. The risk of inducing hypoglycaemia depends on the class of drug added
- C. The risk of inducing hypoglycaemia will be increased
Q5. Blood glucose levels tend to rise again with time despite continuing treatment with an oral glucose-lowering agent. What are the possible reasons for this?

- A. A continuing loss of insulin production from the pancreas
- B. Repeated dietary lapses
- C. Use of other drugs that can cause hyperglycaemia
- D. All of the above
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- B. Repeated dietary lapses
- C. Use of other drugs that can cause hyperglycaemia
- D. All of the above
Q6. The clinical characteristics of the patient should always be carefully considered when choosing an oral agent, as different agents have different side effects. *For example, risk of heart failure can be increased by which of the following:*

- A. Metformin
- B. Glipizide
- C. Pioglitazone
- D. A DPP4-inhibitor
- E. SGLT-2 inhibitor
Q6. The clinical characteristics of the patient should always be carefully considered when choosing an oral agent, as different agents have different side effects. *For example, risk of heart failure can be increased by which of the following:*

- A. Metformin
- B. Glipizide
- C. Pioglitazone
- D. A DPP-4 inhibitor *(e.g. saxagliptin but not all in this class)*
- SGLT-2 inhibitor
Some key references

- American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2020). Available at: https://care.diabetesjournals.org/content/43/Supplement_1/S1.full-text.pdf

- Sinclair AJ et al. 2019. Evidence-based Diabetes Care for Older People With Type 2 Diabetes: A Critical Review
  https://pubmed.ncbi.nlm.nih.gov/30411402/?from_term=sinclair+a&from_sort=date&from_page=10&from_pos=8

Learning completed