

# 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

- ① 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
- ① Several different classes of orally active glucose-lowering drugs are available with varying actions on body tissues
- ① Not all oral glucose-lowering drugs cause hypoglycaemia in the absence of other anti-diabetic agents

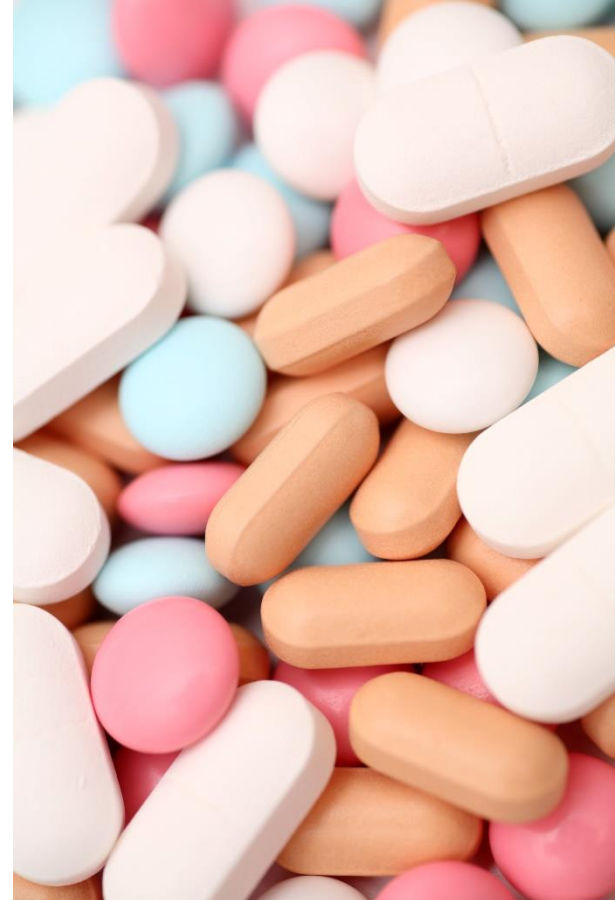


# Reasons for Treatment

- ① 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').
- ① Insulin is occasionally required soon after diagnosis of type 2 diabetes because of marked insulin deficiency suggesting that latent type 1 diabetes was present

# Actions of oral treatments

- ① Oral drugs for diabetes mainly work either by increasing insulin production or by making insulin more effective.
- ① Other agents with different actions are also available.
- ① The clinician should decide what is best for each individual and discuss these aspects with the resident with diabetes



# Starting oral glucose-lowering therapy

- ⊙ 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

- ① Other agents that are rarely used include:
  - acarbose (an  $\alpha$ -glucosidase inhibitor)
  - repaglinide or nateglinide (glinides).
- ① All glucose-lowering drugs have potential safety and tolerability issues that must be considered in choosing the most appropriate agent.
- ① If a drug is not tolerated or is ineffective, an alternative should be considered.

# Oral treatments for type 2 diabetes

Class	Examples	Advantages	Disadvantages	Comments
Biguanides	Metformin	Low hypo risk Low cost In widespread use	Can cause GI upset/weight loss May be contraindicated in renal impairment and CVD	Extended release formulation available Need to assess vitamin B12
Sulphonylureas (SUs)	Gliclazide Glimepiride Glipizide Glibenclamide	Low cost Can be used in certain grades of renal impairment	High risk of hypos Caution with glimepiride Avoid glibenclamide	Generally avoid in those with dementia, malignancy, frailty; consider discontinuing use in those on insulin
Meglitinides	Rapaglinide Nateglinide	Shorter duration of action than SUs – may be an advantage in those with erratic eating patterns	Limited evidence of use in older adults Hypoglycaemia	Can be withheld if meals are missed but otherwise limited roles in residents with diabetes
TZDs (Thiazolidinediones)	Pioglitazone	Low hypo risk Once daily dosing Can be used in certain grades of renal impairment	Contraindications in those with heart failure, fractures, leg oedema, anaemia Caution in use with insulin	May have limited roles in frail residents with diabetes
DPP-4 inhibitors	Sitagliptin Vildagliptin Saxagliptin	Low hypo risk Once daily dosing Can be used in various grades of renal impairment with dose adjustment (except linagliptin)	Higher cost Potential risk of heart failure in 'at-risk' individuals	Can be combined with insulin
SGLT-2 inhibitors	Canagliflozin Vildagliptin Dapagliflozin	Low hypo risk May be of benefit in high cardiovascular risk and reducing risk of hospitalisation due to heart failure	Higher cost May be associated with increased urinary frequency, genital infections, dehydration May increase risk of DKA	Stop SGLT-2 inhibitors in someone with covid-19 or acute illness Dose reductions in renal impairment
GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists)	Liraglutide Exenatide Semaglutide	Low hypo risk Once a day and once a week formulations available	Higher cost Requires sub-cutaneous injection GI side effects	Can be combined with insulin; be cautious in those with poor appetite, weight loss, frailty; advice required before use in renal impairment

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

## Key Steps

### 1<sup>st</sup> 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

### 2<sup>nd</sup> 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

### 3<sup>rd</sup> Step:

Add in basal insulin or a pre-mixed insulin, or a GLP-1 agonist

Sinclair AJ et al. EDWPOP 2011; Kirkman MS et al, AGS Consensus 2012; Sinclair AJ, Dunning, T, Colagiuri, IDF Global Guidance, 2013; Sinzocchi SE et al. ADA-EASD Consensus Statement, 2015, Diabetologia; Turnheim K, Exp Gerontol 2004; Neumiller JJ & Setter SM, Am J Pharmacother 2009; Heller SR, Pratley RE, Sinclair A et al, Diabetes Obes Metab 2018; Liu J, Wang LN, Cochrane database 2017; Schernthaner G, Schernthaner-Reiter MH, Diabetologia 2018

## Key Considerations

- ☉ Have a ‘risk to benefit’ conversation
- ☉ Estimate 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

# Starting oral glucose-lowering therapy

- ⊙ 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.

# Need for adjusting drug therapy



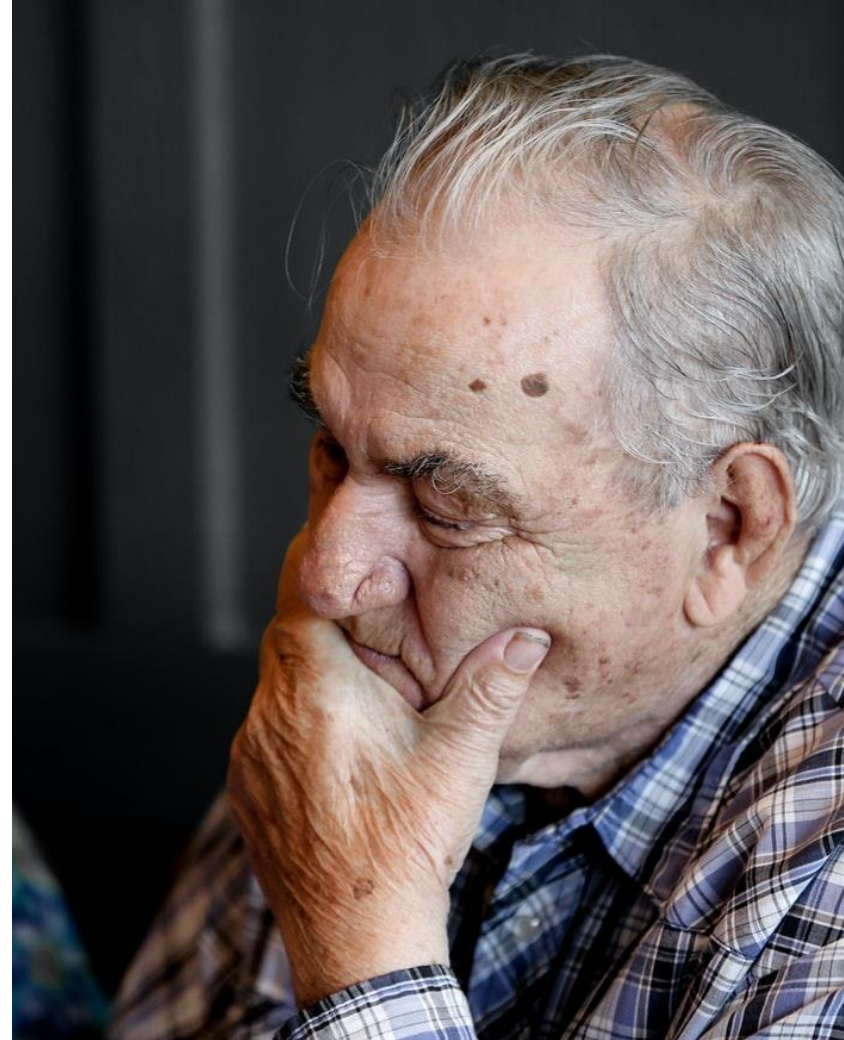
- ◎ Some people may fail to respond to a particular class of oral treatment, in which case an alternative from another class may need to be tried.
- ◎ Caution is needed when considering adding in another treatment as some may not be appropriate for a resident with diabetes, e.g. a sulphonylurea, pioglitazone, some SGLT-2 inhibitors and some GLP-1 receptor agonists

# Need for escalating drug therapy -1

- ① Following an initial response, blood glucose levels tend to rise again with time despite continuing treatment with an oral glucose-lowering agent.
- ① This is usually due to continuing loss of insulin production from the pancreas.
- ① However, other causes include a lapse of dietary control or the use of drugs which cause a rise in blood glucose, in particular corticosteroids.

# Need for escalating drug therapy -2

- © 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





# Identifying and tackling problems – SGLT-2 inhibitors

- ① An increased risk of genitourinary fungal infections is a side effect of the SGLT-2 inhibitors (a new group of oral agents – see Table).
- ① If this recurs, treatment will have to be stopped.
- ① 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

KM

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

KM

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

KM

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

KM

Remember, for many residents with diabetes, there is no need for very strict blood glucose control – see targets in Module A

# Question

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

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# Question

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

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- B. Sulphonylureas
- C. B alone and A and B together**
- D. DPP-4 inhibitors
- E. SGLT-2 inhibitors



# Question

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

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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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# Question

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

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- 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](https://care.diabetesjournals.org/content/43/Supplement_1/S1.full-text.pdf)
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- © Diabetes in Old Age 4<sup>th</sup> Edition (2017). See: <https://onlinelibrary.wiley.com/doi/book/10.1002/9781118954621>

Learning completed