5

Use of oral hypoglycaemic agents

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WHEN TO START AN ORAL AGENT

5.1 When should an oral hypoglycaemic agent be started?

Figure 3.1 shows the approach to glucose management in type 2 diabetes. First-line therapy should nearly always be dietary and lifestyle – the patient should not receive the message that the major treatment is tablets! In the UKPDS, dietary therapy was the sole intervention for the first 3 months and achieved a mean 2% reduction in HbA1c, more than that achieved by any single oral hypoglycaemic agent (OHA). Most of the latter will produce mean reductions of 1.0–1.5% in HbA1c, except for acarbose which is much less effective.

When the initial plasma glucose (PG) level is high, many clinicians are tempted to commence an OHA at diagnosis. Unless patients are highly symptomatic it is usually better to start with diet and exercise alone, except if there are important personal indications (e.g. forthcoming exams or foreign travel). People with newly diagnosed diabetes have often been drinking large quantities of sugary drinks such as lemonade, ‘Coke’ or fruit juices to quench their thirst. Just removing these and other simple sugars from the diet often leads to a rapid fall in PG and control of the symptoms. The consequent improvement demonstrates to the patient the importance of diet in diabetes treatment.

In general those patients with higher PG levels at diagnosis (once simple sugars are removed) are more likely to need OHAs in addition to diet. If there is concern about the initial PG level, it is prudent to review the patient in a few days to monitor their response and reassess the need for medication. If a sulphonylurea in particular is prescribed too early, some patients will develop problems with hypoglycaemia and weight gain within the first few weeks of treatment.

Usually use of an OHA is delayed until lifestyle measures alone have proved unsuccessful in achieving adequate control after a reasonable trial (see Q. 3.18). This will depend on the ‘target’ level of control that is desired, which may obviously be lower in HbA1c terms for some patients than for others, such as the elderly living alone. There is no hard evidence to base this on, but some data suggest that optimal control needs to be achieved within the first 6–12 months, as people frequently ‘track’ at that level thereafter.
5.2 What are the current options?
Despite some recent advances, there are still relatively few options, and the thiazolidinediones (TZDs) and meglitinides currently have restrictions on their usage (Table 5.1).

5.3 On what basis should I choose the initial oral agent?

**TABLE 5.1 Current drug treatment options in diabetes**

<table>
<thead>
<tr>
<th>Function</th>
<th>Name</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs decreasing insulin resistance&lt;sup&gt;1–5&lt;/sup&gt;</td>
<td>Metformin</td>
<td>Biguanide, detailed mechanism unclear</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinediones (TZDs, ‘glitazones’)</td>
<td>Work via PPAR-gamma receptors</td>
</tr>
<tr>
<td>Drugs increasing insulin secretion&lt;sup&gt;6–9&lt;/sup&gt;</td>
<td>Sulphonylureas</td>
<td>Stimulate insulin secretion, mainly second phase</td>
</tr>
<tr>
<td></td>
<td>Meglitinides</td>
<td>Stimulate insulin secretion, mainly first phase</td>
</tr>
<tr>
<td>Drugs reducing carbohydrate absorption&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>Acarbose</td>
<td>Inhibitor of intestinal alpha-glucosidase</td>
</tr>
</tbody>
</table>

5.4 Why the recent change from sulphonylurea to metformin as a first-line oral agent for most patients?
The main reason is the clinical trial data, though increasing obesity and recognition of the metabolic syndrome also play a part. Metformin targets the main problem of insulin resistance, and in the UKPDS the obese group treated with metformin showed a much greater drop in vascular events than the sulphonylurea/insulin groups.<sup>12</sup>
<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Name</th>
<th>Action</th>
<th>Common side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Reduces hepatic gluconeogenesis and increases peripheral glucose utilisation</td>
<td>Nausea, vomiting and diarrhoea</td>
<td>Renal failure (serum creatinine &gt; 150 µmol/l) Liver impairment Heart failure</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Glibenclamide</td>
<td>Stimulates insulin secretion by the pancreas</td>
<td>Weight gain Hypoglycaemia</td>
<td>In renal impairment glidazide, gliclazide and tolbutamide are safe but avoid glibenclamide and chlorpropamide, as hypoglycaemia can be a problem with drug accumulation</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Gliclazide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Gliquidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>Chlorpropamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Nateglinide</td>
<td>Stimulates insulin release</td>
<td>Hypoglycaemia</td>
<td>Renal or hepatic impairment Pregnancy</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Repaglinide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Pioglitazone</td>
<td>Increases insulin sensitivity</td>
<td>Fluid retention Weight gain Anaemia</td>
<td>Heart disease as can precipitate heart failure Hepatic or renal impairment</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Acarbose</td>
<td>Inhibits intestinal alpha-glucosidase delaying absorption of starch and sucrose</td>
<td>Flatulence, abdominal distension and diarrhoea</td>
<td>Inflammatory bowel disease</td>
</tr>
</tbody>
</table>
There are increasing numbers of combination tablets becoming available with two anti-diabetic agents of differing action. They offer the advantages of ease and probable improved adherence, but still await adequate long-term studies and should be used only when the doses are exactly what would otherwise be recommended. Examples are sulphonylurea/metformin, and metformin/rosiglitazone (Avandamet).

Metformin is not associated with weight gain whereas all other therapies are. What is not clear is the lowest level of BMI or waist circumference down to which metformin should be the first choice, or indeed if there is a lower limit.

5.5 What are the major side effects of metformin?

The main drawback of metformin is the high incidence of gastrointestinal side effects of nausea and diarrhoea, together with flatulence, abdominal pain and a metallic taste. Loose bowel movements can be an intermittent rather than a continuous problem.

These effects are usually dose-related and transient so it is always worth starting at low dose (e.g. 500 mg b.d. with meals) and gradually increasing (e.g. to 1 g b.d.) after 2 weeks or so. It is sensible to warn all patients about these side effects; approximately 15–25% of patients will report some initial gastrointestinal problems if questioned and it seems to be a more frequent problem with women than with men. For some patients (around 5%), the side effects are so persistent and severe that metformin has to be withdrawn. However, many patients will tolerate the drug despite some side effects, and it is worth exploring with the patient the highest tolerable dose. Even low-dose metformin 500 mg once or twice daily is valuable and can obviously be used in combination with other OHAs and with insulin in type 2 diabetes.

The recommended maximal dose is 2550 mg/day (850 mg × 3), though some clinicians go up to 3 g daily for very obese patients (e.g. > 100 kg).

Other less common side effects include lactic acidosis (see Q. 9.11) and decreased vitamin B12 absorption. A former biguanide – phenformin – was withdrawn some years ago because of the high risk of lactic acidosis.

5.6 How does metformin work?

Despite being in use for over 30 years, this still isn’t fully known at molecular level. Metformin decreases gluconeogenesis and enhances peripheral glucose utilisation.

5.7 When is metformin contraindicated?

This is controversial, the anxiety being the very rare lactic acidosis which carries a high mortality. The official list is outlined in Table 5.3, but evidence for most of these restrictions is almost entirely lacking. Despite wide
5.8 How is metformin best used in practice?

There are some simple rules for its best use:

- Always start with low dose (e.g. 500 mg b.d.), then increase some weeks later.
- Always take *during* a meal, never on an empty stomach.
- Warn patients about possible gastrointestinal side effects, stressing that most are transient.
- If side effects persist, halve the dose and then gradually increase more slowly; twice daily is often better for adherence than three times daily.
- Emphasise that it will take some days to weeks to become effective.
- For most patients a dose of 1 g b.d. should be the eventual target.
- It can be combined with other agents (*see Q. 5.17*).

*(See Case vignettes 5.1–5.3.)*

### USING SULPHONYLUREAS AND MEGLITINIDES

5.9 How do sulphonylureas work?

Sulphonylureas increase pancreatic insulin secretion. This is done through a calcium channel mechanism, and induces an increase in both first- and second-phase insulin release.
5.10 What are the major side effects and contraindications for sulphonylureas?

Hypoglycaemia is the main issue with sulphonylureas, but is hardly a side effect! Weight gain is common. They are otherwise well tolerated with occasional effects of rashes, nausea, vomiting, diarrhoea and constipation. They may rarely cause hepatic problems including cholestatic jaundice and eventual liver failure, as well as blood dyscrasias and severe skin reactions.7

They should not be used in severe hepatic disease and only a few are safe in renal impairment (see Q. 5.11). They should be avoided while breast feeding and in patients with porphyria.

These agents should be used with caution, especially in the elderly, those frail or living alone and in patients with renal failure as severe protracted hypoglycaemia can occur, especially with glibenclamide and chlorpropamide.

5.11 How are sulphonylureas best used?

Some useful advice can be summarised:

- Start with a low dose and increase at about 2-weekly intervals unless BG levels are initially very high.
- Sulphonylureas require residual beta-cell function in order to be effective.
- Some patients are very sensitive and need very small doses (e.g. glibenclamide or glipizide 2.5 mg daily, gliclazide 40 mg daily).
- Always warn and teach patients about hypoglycaemia.
- Weight gain in the first 3–6 months is to be expected, averaging around 3 kg.
- There is no benefit at all in exceeding maximum doses or using more than one sulphonylurea.
- Gliclazide, tolbutamide and gliquidone are the preferred agents in patients with renal impairment, but use with care.
- Severe hypoglycaemia with sulphonylureas is a medical emergency with a significant mortality and requires immediate hospital admission (see Ch. 7).

5.12 What is the difference with the newer agents like repaglinide?

The meglitinides (currently repaglinide and nateglinide) also stimulate insulin secretion but do so through a different mechanism and predominantly enhance first-phase insulin release, thus reducing immediate post-prandial hyperglycaemia.8,9

Had they been invented before sulphonylureas or were cheaper, they would probably be preferred as they cause less hypoglycaemia but are more expensive. Particular points are:
Start with a small dose.
Take up to 30 minutes before meals.
No meal – no tablet!
Side effects include gastrointestinal upsets and rashes as well as hypoglycaemia.

Case vignettes 5.1–5.3 illustrate circumstances in which a choice of OHAs can be made.

**CASE VIGNETTE 5.1**
A sedentary man aged 55 years has had type 2 diabetes for 5 months, BMI has fallen from 32 to 31 kg/m² on diet and exercise alone. Results are now steady, with fasting glucose 8.1 mmol/l, HbA1c 7.4% and creatinine 72 µmol/l.

*Comment*
Glycaemic control is suboptimal and, 5 months later, this is probably the best he will achieve with diet alone. You could continue with diet alone if he was still losing weight but commonly patients fail to sustain their initial good results. Metformin 500 mg twice daily is the next step, and may need doubling thereafter.

**CASE VIGNETTE 5.2**
A 68-year-old Afro-Caribbean woman was diagnosed on routine screening 8 months ago with a fasting BG of 9.8 mmol/l. Her BMI remains between 24 and 25 kg/m² on diet and exercise alone. The current fasting glucose is 7.7 mmol/l, HbA1c 6.9% and creatinine 64 µmol/l.

*Comment*
This patient has moderately good control but what is the appropriate target for a patient controlled by diet alone? The National Institute for Clinical Excellence (NICE) guidelines recommend a target for each person with diabetes in the range 6.5–7.5%, the decision to be made on individual circumstances. The UKPDS indicated that best outcomes in microvascular and macrovascular terms was in the group with lowest HbA1c: a mean of less than 6%. Thus, if she is well with no other health problems, a sensible target would be ≤ 6.5%. Diet alone is not achieving this target and control is likely to deteriorate with time.

The choice of OHA lies between metformin and a sulphonylurea. Whilst not overweight, she is likely to gain weight with a sulphonylurea. Metformin 500 mg twice daily is a reasonable choice, with low-dose sulphonylurea possible but carrying a risk of hypoglycaemia.

**CASE VIGNETTE 5.3**
A frail 79-year-old lady was recently diagnosed following the death of her husband; she now lives alone. She is overweight (70 kg) with a BMI of 29 kg/m² on diet only. Her latest results are fasting glucose 8.3 mmol/l, HbA1c 7.5% and creatinine 118 µmol/l.

*Comment*
This seems similar to Cases 5.1 and 5.2 but the decision here is not clear-cut, either scientifically or clinically. Firstly, the relevant studies did not include patients in this age group. Secondly, the recommendation to control glucose levels tightly is
on the basis of preventing long-term complications over 10–20 years. Realistically,
she may not live long enough to reap the benefits.

However, in an otherwise healthy woman, it would be reasonable to treat, but –
with her recent bereavement and living alone – waiting may be preferable.
Additionally she is overweight with mild renal impairment that would make you
hesitant to use metformin. In the elderly, glomerular filtration rate is significantly
impaired even though serum creatinine is only minimally raised. Her calculated
GFR is 39 ml/min (see Box 14.2).

A low-dose sulphonylurea such as gliclazide or glipizide could be considered
(though she may not be eating well or regularly) but not glibenclamide because of
the risk of prolonged hypoglycaemia while alone.

**THIAZOLIDINEDIONES – THE ‘GLITAZONES’**

5.13 What role is there for the ‘glitazones’ (thiazolidinediones, TZDs)?

These agents (rosiglitazone and pioglitazone) have recently been introduced
and work on the PPAR-gamma receptor to reduce insulin resistance.3,15
Unfortunately publication of data has been slow and outcome results are
not yet available.16 In general the TZDs produce similar glycaemic
improvements (1.0–1.5%) to other agents, both as monotherapy and as
combined therapy.

Currently TZDs are expensive and have no evidence of superiority though
there are reasonably plausible claims (but little hard evidence) that they:

- maintain effect in the long term and preserve beta-cell function
- have beneficial effects on lipids and many other cardiovascular risk factors.

Current use is limited by licensing and funding issues, together with
diminishing concerns about hepatic toxicity and their side effects, particularly
weight gain, oedema and heart failure. The hepatotoxicity anxiety is probably
unfounded, dating back to an earlier compound, troglitazone – indeed there
is increasing evidence that TZDs may benefit fatty liver (see Q. 18.2). Clinical
outcome trials are in progress but results are some years away.

Thiazolidinediones take several months to show their full effect so doses
should not be rapidly adjusted and patients must be warned to be patient!
Monitoring results is often helpful, but reviewing the HbA1c 3–6 months
after starting a thiazolidinedione is the most valuable assessment. Trials
with these drugs at full dosage suggest an approximate 1–1.5% reduction in
HbA1c: if the patient is highly symptomatic or has an HbA1c >10%, it would
usually be preferable to choose a faster-acting drug.

5.14 What are the side effects of the ‘glitazones’?

Though it is now clear that rosiglitazone and pioglitazone carry no major
risk of hepatic damage, manufacturers still advise performing 2-monthly
liver function tests for the first year. The remaining common side effects are weight gain (a mean of 2–5 kg in most studies), together with oedema and haemodilution. There is concern about precipitation of heart failure, especially in patients on insulin, though it is somewhat unclear if the oedema is being used as a diagnostic marker for this. Glitazones should not at present be used in patients with heart failure or at very high risk for it. Their use with insulin should also be limited to specialists until more trial data are available.

ACARBOSE

5.15 What role should acarbose play?
Acarbose is an inhibitor of alpha-glucosidase, thus limiting and delaying the absorption of starches. It has a mild hypoglycaemic effect, perhaps a mean HbA1c reduction of around 0.5% but at the expense of frequent gastrointestinal side effects including flatulence – these often cause patient withdrawal. It has a small role in patients unable to tolerate metformin and in combination therapy.

A recent study also showed a mild protective action in preventing conversion from impaired glucose tolerance (IGT) to diabetes.10

PRACTICAL ASPECTS OF USING ORAL HYPOGLYCAEMIC AGENTS

5.16 How quickly can the dose of OHAs be adjusted?
This depends on the drug, as shown in Figure 5.1. Remember also that HbA1c will take 6–8 weeks to reach a plateau once control is stable. Self-tested or laboratory glucoses may be more useful, though fasting BGs alone can be misleading.

In practice drug doses are often not titrated up to maximal effect; it is often useful to make clear to the patient and in clinical notes what the next step should be if a goal is not achieved within a set period.

5.17 Which combinations of oral agents work best together?
Classically this has been metformin or sulphonylurea or the reverse! There are now more options, though good clinical trial data are limited17,18 (Table 5.4). Triple therapy is currently being tested in trials and in the short term appears to be effective.19 It is important to recognise that sometimes insulin is a better option and has proven benefit. (See Case vignettes 5.4 and 5.5)
Table 5.4 Possible oral combination therapies\textsuperscript{17–19}

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin first, then sulphonylurea</td>
<td>Most commonly used combination</td>
</tr>
<tr>
<td></td>
<td>Some concerns about degree of benefit/safety</td>
</tr>
<tr>
<td>Sulphonylurea first, then metformin</td>
<td>Only likely to work if significant insulin resistance. Avoid if patient thin</td>
</tr>
<tr>
<td>Metformin plus TZD</td>
<td>Promising combination for insulin resistant/obese patients</td>
</tr>
<tr>
<td>Sulphonylurea plus TZD</td>
<td>Normally used when metformin not tolerated</td>
</tr>
<tr>
<td>‘Triple therapy’ (metformin, SU + TZD)</td>
<td>Untested in long term. Insulin an alternative. Trials in progress</td>
</tr>
<tr>
<td>Metformin plus meglitinide</td>
<td>Limited data – should be effective</td>
</tr>
<tr>
<td>Metformin plus acarbose</td>
<td>Limited data</td>
</tr>
<tr>
<td>Sulphonylurea + meglitinide</td>
<td>No real sense to combination</td>
</tr>
</tbody>
</table>

SU, sulphonylurea; TZD, thiazolidinedione.

Fig. 5.1 Schematic of approximate onset of action and time to stability for various hypoglycaemic interventions.
CASE VIGNETTE 5.4
A 48-year-old man has had type 2 diabetes for 3 years. BMI has fallen to 28.7 kg/m² while on treatment with metformin 850 mg twice daily. His fasting glucose is 8.5 mmol/l, HbA1c 7.8% and creatinine 94 µmol/l.

Comment
Glycaemic control here is not optimal, though not bad. For a patient on OHAs with no other serious illness, the target would usually be an HbA1c of 6.5–7.0%. The dose of metformin could be increased to 850 mg three times daily or 1 g twice daily assuming compliance. This may be insufficient to achieve optimal control, so the next step would be to add a sulphonylurea or a TZD.

CASE VIGNETTE 5.5
A very obese man (BMI 39 kg/m²), aged 57 years, with type 2 diabetes and hypertension for 3 years is on maximal metformin 850 mg t.d.s. Results: fasting PG 9.1 mmol/l, HbA1c 8.4%, creatinine 105 µmol/l.

Comment
This is above any recommended target for HbA1c but this man is markedly overweight and, with his hypertension, he is likely to have the metabolic syndrome and significant insulin resistance.

Encouraging weight loss and exercise is obviously important but usually unsuccessful after 3 years. If he were keen to lose weight and makes a good start with diet and exercise, then addition of orlistat could be considered and has been shown to improve glycaemic control in type 2 diabetes provided there is weight reduction.

However, an additional OHA is likely to be required. It is more logical to combine a TZD with metformin than to add a sulphonylurea. This should lead to improved glycaemic control through increasing insulin sensitivity. His liver function tests should be checked before starting TZDs and regularly for the first year: it may take 2–4 months to see the effect of TZDs, a full dose probably being required to reach the desired target.

5.18 After starting an OHA, the patient has complained of hypoglycaemic episodes. As glycaemic control is still not good enough, what is the next step?
First obtain a clear history of the symptoms, to be sure they are hypoglycaemic in character, their frequency and the time of day they occur. If they are happening infrequently with a clear precipitating event (e.g. spring-cleaning the house), then reassurance and advice about prevention is adequate. If they are occurring frequently, then treatment needs adjustment. Hypoglycaemic episodes need to be avoided since they are unpleasant, and lead to additional food intake and weight gain. A reduced dose of OHA with no need to snack is better than a higher dose with extra eating, especially if the patient is obese. Some patients need to reduce or omit sulphonylureas before vigorous work/exercise – self-tested BGs are helpful here.
For some people with recently diagnosed type 2 diabetes, the fall in PG levels can lead to hypoglycaemic symptoms at levels of 4–6 mmol/l. Before diagnosis they have become habituated to much higher PG levels and an abrupt fall can produce ‘hypoglycaemic’ symptoms. This is the probable explanation for such symptoms in people treated with metformin alone since this does not cause true ‘hypoglycaemia’. Reassurance and patience are required and, within a few weeks, the brain (which is the sensor for hypoglycaemia) becomes accustomed to the lower, normal, glucose levels.

The timing of tablet treatment can be adjusted to minimise hypoglycaemia. Medication is often given with breakfast, a relatively small meal, and many people are at their most active during the morning – thus hypoglycaemic symptoms mid- or late morning are common. It can be worth changing the timing of tablet treatment to later in the day with a main meal.

Finally, don’t expect maximal improvement too soon (see Q. 5.16): HbA1c targets should be achieved 6 months after diagnosis but not necessarily at 3 months, especially if weight loss and increased exercise programmes are continuing.

**5.19 How long should I persist with oral hypoglycaemic agents?**

In general, for as long as they are well tolerated and achieving glycaemic goals. Clearly most people with type 2 diabetes will eventually progress to needing insulin, if they live long enough. The rate of progression varies widely but appears to be fairly consistent within an individual. Over the years there will tend to be a relentless, if slow, trend to a need for escalating therapy, as shown in Figure 5.2.
Diagnosis

Response to dietary changes, exercise and weight loss
Gradual deterioration in control 3 years

Need for metformin, up to 1 g b.d.
Gradual deterioration in control 4 years

Addition of gliclazide, gradually up to 160 mg b.d.
Gradual deterioration in control 3 years

Nocturnal insulin added, metformin continued, gliclazide stopped
Increasing afternoon/evening BGs 2 years

Twice-daily insulin needed, with or without metformin

Fig. 5.2 A typical example of the rate of progression in type 2 diabetes from diagnosis to the need for insulin. Note progression of treatment escalation varies widely between people with type 2 diabetes.