PostScriptExtra

NHS Greater Glasgow and Clyde

PHARMACOLOGICAL MANAGEMENT OF ADULT PATIENTS WITH TYPE 2 DIABETES

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- This bulletin is an educational resource on the pharmacological management of type 2 diabetes. Refer to the full NHSGGC Diabetes guideline for further details and information on how to manage individual patients.[1]
- Appendix 1 provides a summary of licensed indications and formulary status for oral therapies and parenteral glucagon-like peptide-1 (GLP-1) agonists.
- Appendix 2 provides an overview of the different types of insulin, insulin devices and their formulary status.

Introduction

There are a number of oral therapies used in the management of type 2 diabetes. Some therapies are well established and have been used for many years such as metformin, sulfonylureas, acarbose, and the thiazolidinedione, pioglitazone. There are also a number of newer oral therapies including the dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) also known as 'gliptins' and the recently launched dapagliflozin which is first in a new class of medicine, a selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2).[2]

Insulin and the parenteral GLP-1 agonists, are licensed for the treatment of type 2 diabetes in combination with oral therapies in patients whose glycaemic control is not adequately maintained with oral therapies alone.[2]

Place in Therapy

(*Note that in addition to pharmacological therapies, lifestyle changes should be encouraged prior to therapy and continued throughout all the stages of management of type 2 diabetes.*)

Monotherapy

What agent should be used for monotherapy in the management of type 2 diabetes?

Metformin in combination with lifestyle changes should be considered as first line monotherapy in the management of type 2 diabetes in patients where lifestyle changes alone have failed and HbA1c is > 53 mmol/mol.[1]

The data for clinically relevant outcomes with metformin are limited, however, they are stronger than for any other available oral agent for the treatment of type 2 diabetes and it is therefore considered first line oral therapy.[3]

What are the main contra-indications with metformin?

The manufacturers' of metformin state it is contra-indicated in patients with renal impairment due to the risk of lactic acidosis.[4] Lactic acidosis is a rare but serious (and sometimes fatal) complication that can arise from metformin accumulation primarily in patients with renal impairment. In practice, local guidance suggests metformin should be avoided where eGFR is < 45 ml/min/1.73m^2.[5]

What about sulfonylureas?

A sulfonylurea should only be considered as first line monotherapy in the management of type 2 diabetes in patients where metformin is not tolerated or is contra-indicated. Sulfonylureas have no proven benefit on cardiovascular outcomes.[1] Gliclazide is the preferred sulfonylurea in NHSGGC.[6]

What cautions and contra-indications are associated with gliclazide?

Gliclazide is contra-indicated in severe renal or hepatic impairment.[7] Hypoglycaemia is an adverse effect of all sulfonylureas. Patients prescribed a sulfonylurea should be advised to have regular food intake. This is important due to the increased risk of hypoglycaemia if a meal is taken late, if an inadequate amount of food is consumed or if the food is low in carbohydrate. Gliclazide is normally taken twice daily with the last dose of the day usually at tea time. Hypoglycaemia is more likely to occur in people following weight reducing or low carbohydrate diets, during and after exercise, after alcohol consumption or if a sulfonylurea is combined with insulin, DPP-4 inhibitors, GLP-1 agonists or other oral antidiabetic agents. Weight gain is also associated with sulfonylurea use.[7]

Can pioglitazone be prescribed as monotherapy?

Pioglitazone would not normally be considered for monotherapy. Monotherapy with pioglitazone is restricted to patients in whom metformin or sulfonylureas are contra-indicated or not tolerated and in whom insulin therapy would be the next considered treatment option. It is not recommended as monotherapy in any other group of patients.[6] It should only be prescribed in patients without a history of heart failure or bladder cancer.

Can the gliptins (DPP-4 inhibitors) be prescribed as monotherapy?

The gliptins would not normally be considered for monotherapy. ***Sitagliptin, linagliptin*** or ***vildagliptin*** may be considered as monotherapy in patients whom both metformin and sulfonylureas are inappropriate due to contra-indications or intolerance.[6]

Dual Therapy

(Please note, compliance with therapy should be checked prior to prescribing an additional agent)

When should dual therapy be prescribed?

If adequate glycaemic control is not achieved by lifestyle measures and one agent and HbA1c remains > 53 mmol/mol, then dual therapy is necessary. The addition of a second oral agent is likely to improve HbA1c by no more than 9-16 mmol/mol.[1] Choice of agent depends on the individual patient and the relative indications and contra-indications of therapy and adverse effect profile.

What are the options for dual therapy in the management of type 2 diabetes?

If ***metformin*** therapy is used first line, consider the addition of a sulfonylurea or pioglitazone (only if sulfonylureas are contra-indicated or not tolerated).

If a ***sulfonylurea*** is used first line, consider the addition of pioglitazone (or metformin if not contra-indicated or tried previously).

What are the risks associated with pioglitazone?

Pioglitazone is contra-indicated in patients with heart failure or history of heart failure, hepatic impairment, current bladder cancer or a history of bladder cancer and uninvestigated macroscopic haematuria.[8]

In 2011, the European Medicines Agency (EMA), advised there is a small increased risk of bladder cancer associated with pioglitazone use. However, in patients who respond adequately to treatment, and who cannot be treated with other agents, the benefits continue to outweigh the risks.[9]

In 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) also issued an alert regarding the risks of cardiac failure with pioglitazone in combination with insulin. This combination is not normally used in practice, however, if used, patients should be monitored for signs and symptoms of cardiac failure, weight gain and oedema.[10]

Thiazolidinediones are also associated with fractures particularly in women, therefore, the risk of fracture should be considered in the long term care of female patients treated with pioglitazone.[3]

Other adverse effects of pioglitazone include weight gain and oedema.[8]

Are there any clinical outcome data for pioglitazone?

A Cochrane review reported there is insufficient evidence to draw conclusions on the effect of pioglitazone on outcomes such as mortality, morbidity, adverse events or health-related quality of life.[11]

Can I prescribe a gliptin (DPP-4 inhibitor) for dual therapy?

Gliptins should only be considered for dual therapy if there are major reservations with metformin, sulfonylureas or pioglitazone.[1]

A gliptin may be used in combination with:

- metformin if a sulfonylurea or pioglitazone are unsuitable,
- a sulfonylurea if metformin or pioglitazone are unsuitable, or
- pioglitazone if metformin or a sulfonylurea are unsuitable.

Only continue treatment with a gliptin after six months if HbA1c has decreased by 5.5 mmol/mol or more. If this reduction is not achieved then stop the gliptin.[1]

What are the risks and benefits associated with the gliptins (DPP-4 inhibitors)?

The MHRA published an alert on the risk of pancreatitis with gliptins. An increased risk of acute pancreatitis has been identified for all approved gliptins. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected the gliptin should be stopped.[12]

Advantages of the gliptins are that they are likely to be weight neutral and unlikely to cause hypoglycaemia.

The long term effects of the gliptins on microvascular complications, cardiovascular disease and mortality are unknown.[3]

What about the new agent dapagliflozin, when should it be used?

Dapagliflozin is the first in a new class of antidiabetic agents which increases the urinary excretion of glucose by inhibiting reabsorption in the kidney. It is a selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2).[13] Dapagliflozin should only be used in combination with metformin (as part of second line dual therapy), where a sulfonylurea is not suitable. It is not recommended for monotherapy, triple therapy, or for use in combination with insulin.[6]

What cautions and contra-indications are associated with dapagliflozin?

Dapagliflozin is not recommended for use if eGFR < 60 ml/min/1.73m^2.[2] The efficacy of dapagliflozin is dependent on renal function. Efficacy is reduced in patients who have moderate renal impairment and is likely to be absent in patients with severe renal impairment. Long term risks are unknown, however, some of the common documented adverse effects include urinary and genital infections. Due to the limited therapeutic experience in patients $\geq$ 75 years, initiation of dapagliflozin therapy is not recommended in this age group.[13]

While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.[13]

Triple Therapy

(Please note, compliance with therapy should be checked prior to prescribing an additional agent)

When should triple therapy be prescribed?

If HbA1c is > 59 mmol/mol on two oral hypoglycaemic agents, then the addition of a third agent can be considered. Oral agents and the parenteral GLP-1 analogues are unlikely to reduce HbA1c levels by more than 9-16 mmol/mol although the higher the initial level of HbA1c, the greater the subsequent drop with treatment. If HbA1c remains > 75 mmol/mol on two agents do not consider triple therapy and move directly to insulin treatment.[1]

What are the options for triple therapy?

The GLP-1 agonists, exenatide or liraglutide, should be considered in combination with other agents for triple therapy. If subcutaneous (SC) administration is unacceptable, a combination of three oral agents may be used (e.g. metformin, gliclazide and pioglitazone).

Lixisenatide, a new GLP-1 agonist which has recently been added to the NHSGGC Adult Formulary, may also be considered for triple therapy.[6] The GLP-1 agonists can be prescribed as an alternative to insulin in patients who have failed treatment on dual therapy and in whom insulin would be the next treatment option. GLP-1 analogues should only be considered in patients with a BMI > 30 kg/m^2.[1]

Exenatide is available as a twice daily SC injection and also as a modified release once a week SC injection.[2]
Liraglutide is administered once a day by SC injection.[2]
The maximum licensed dose of liraglutide (1.8 mg daily) should not be prescribed as it is not considered to be cost effective.[1] The maximum recommended dose of liraglutide in NHSGGC is 1.2 mg daily.[1]
Lixisenatide is administered once a day by SC injection.[2]

The GLP-1 agonists slow gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation and may reduce body weight by mechanisms involving reduced hunger and lowered energy intake.
The NHSGGC Diabetes guideline states if treatment targets of HbA1c reduction of at least 11 mmol/mol and loss of 3% of the initial body weight are not met by 6 months, treatment should be withdrawn. Treatment must be reviewed every 6 months and if efficacy is waning treatment should be changed to insulin therapy.[1]

What cautions and contra-indications are associated with GLP-1 agonists?

Once weekly exenatide should not be given if eGFR < 50ml/min/1.73m^2.[2] Twice daily exenatide and lixisenatide are not recommended for use in patients with end-stage renal disease or severe renal impairment (eGFR < 30 ml/min/1.73m^2).[2] The clinical experience in patients with moderate renal impairment is very limited and therefore, the manufacturer of liraglutide recommend avoiding its use in moderate renal impairment (eGFR < 60 ml/min/1.73m^2).[2]

Use of GLP-1 agonists has been associated with a risk of developing acute pancreatitis.[14,15,16] As with the gliptins, patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, the GLP-1 agonist should be stopped.

Is there any clinical outcome evidence for GLP-1 agonists?

A 2011 Cochrane review did not report any studies which investigated mortality or morbidity with the GLP-1 agonists.[17]

What about acarbose, when should it be used?

Acarbose is less effective than other oral hypoglycaemic agents but may be prescribed by specialists in addition to other agents for patients intolerant of metformin. Acarbose is contra-indicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, acarbose should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who suffer from states which may deteriorate as a result of increased gas formation in the intestine, e.g. larger hernias. Acarbose is also contra-indicated in patients with severe hepatic impairment.[18]

As acarbose has not been studied in patients with severe renal impairment, it should not be used in patients with an eGFR < 25 ml/min/1.73m^2.[18]

There are no peer reviewed data available on the long term effects of acarbose in terms of mortality, morbidity and quality of life.[3]

Refer to Appendix 1 for a summary of licensed indications and formulary status for oral therapies and the parenteral GLP-1 agonists.

Insulin

When should patients be initiated on insulin?

If there is suboptimal control with two (or three) oral hypoglycaemic agents or if dual therapy is contra-indicated then insulin should be introduced in combination with an oral hypoglycaemic agent (preferably metformin).[1] Patients should be warned about weight gain when commencing insulin.[1]

- Insulins include human insulin and recombinant insulin analogues (molecules similar to insulin but with slight differences in the amino acid sequence, which alter the pharmacokinetic properties).[19]
- The NHSGGC diabetes guideline recommends that all new patients who require insulin should be started on human insulins. There is no new evidence for improved diabetes control with insulin analogues in patients with type 2 diabetes.[1]
- Insulins vary in their onset of action and duration of action and are categorised as rapid-acting, short-acting, intermediate-acting and long-acting. Insulin mixes are also available which have different actions depending on their individual mix.
- Isophane insulin is recommended for use as a background insulin.
- The long-acting insulin analogues, insulin glargine and insulin detemir should only be considered in patients with type 2 diabetes who are troubled by night time hypoglycaemia.

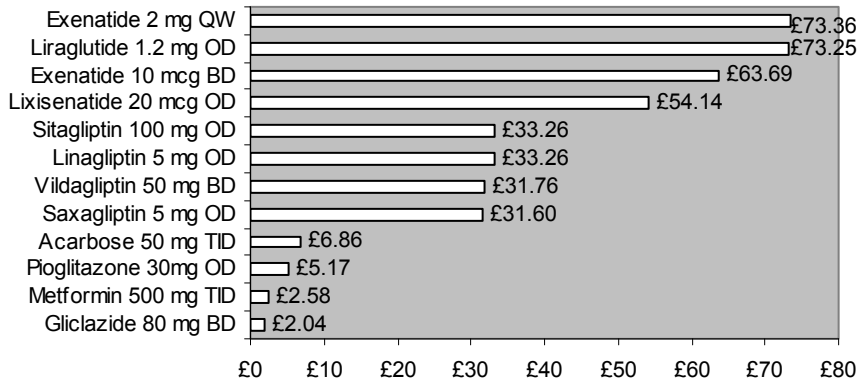
Refer to Appendix 2 for an overview on the different types of insulins and insulin devices.

E-learning modules on the safe use of insulin and non-insulin therapies in diabetes are available here

Please Note

Prescribing information can change, therefore, always refer to the latest version of the manufacturer's summary of product characteristics (SPC) at http://emc.medicines.org.uk for full prescribing information

Cost for 28 days treatment (Scottish drug tariff/eMIMS Oct 2013/BNF No. 66)



NB. **Doses shown are for general comparison only and do not imply therapeutic equivalence.**

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