DESG Teaching Letter

37 The use of oral hypoglycemic agents

1. Introduction/Aims

- Between 20% - 50% of people with type 2 diabetes can control their blood glucose levels by dietary modification alone. Diet therapy is tried in all patients for about the first 3 months following diagnosis. If dietary control of blood glucose is unsuccessful, pharmaceutical treatments are then considered.

  Within 2 years of diagnosis, 50% of patients with type 2 diabetes will have needed to progress to oral medication.
  This Teaching Letter aims to give you information about the oral hypoglycemic agents (OHAs) in current use in a form that you may find useful to pass on to people with diabetes. This information may form part of your education of patients when first prescribing OHAs, or when changing their present regimen.

  It may also help you to give answers to questions asked by patients about "their difficulties" when asked. The information is also in a form, and at a level, suitable for discussion between members of the multidisciplinary diabetes care team, when discussing an overall care strategy, eg, "Why do you recommend that particular OHA drug combination?" or "Is metformin alone the best OHA to use in a Type 2 DM patient of BMI 20-25".

This Teaching Letter is NOT:

- A detailed pharmacological description of these drugs
- A guide to drug dosage schedules and individual management
- A description of the evidence base behind prescribing and the comparative efficacy of various monotherapies and combinations

It is referenced, and these (key) references may lead the reader to a fuller understanding of the three bullet point comments given.

We are well aware of the new pharmacological agents for type 2 diabetes under development and trial. Finally, the opinions given here, alongside the facts, do reflect the editor's and authors' experiences in prescribing OHAs.

This DESG Teaching Letter was written by the DESG Executive commitee:

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The main reviser of the present letter is underlined. November 2007.

This Teaching Letter was written with the colaboration of Mr D. FSADNI, PharmD, *Malta*

MECHANISMS OF THE ORAL HYPOGLYCEMIC AGENTS

2. The pathogenetic mechanism of type 2 diabetes mellitus

Diabetes Mellitus (DM) is that level of abnormal glucose tolerance that produces persistent hyperglycemia (fasting plasma glucose [FPG] > 7.0 mmol/L and 2 hours post-prandial level more than 11.1 mmol/L) and thereby a characteristic set of "osmotic symptoms" eg, thirst, polyuria, weightloss, tiredness. Although Type 1 DM shows severe insulin deficiency at presentation requiring insulin treatment, and Type 2 DM is equated with insulin resistance, in fact, patients with Type 2 DM have a number of biochemical abnormalities leading to their condition. The three basic abnormalities are insulin resistance, insulin deficiency, and increased hepatic (liver) glucose output. Which of these abnormalities predominates in the pathogenesis of an individual person's DM, depends on a number of factors including body weight and activity level, family history, and duration of disease. Deciding which factor or factors are acting in an individual will determine which OHA or OHAs is/are used, and the likely duration of effective response to treatment. The fasting and post-meal glucose values will help determine which mechanisms are operative and will aid in adopting an optimal regimen. We have to keep in mind that since diet regimen is a constant factor in controlling blood sugar levels, whether receiving an OHA or insulin, it is recommended that each patient work with a dietitian to determine the best diet for their own individual body, lifestyle, and level of activity.

3. Summary of the mechanisms of action of the oral hypoglycemic agents

Figure 1. Mechanisms of action of different diabetes therapies

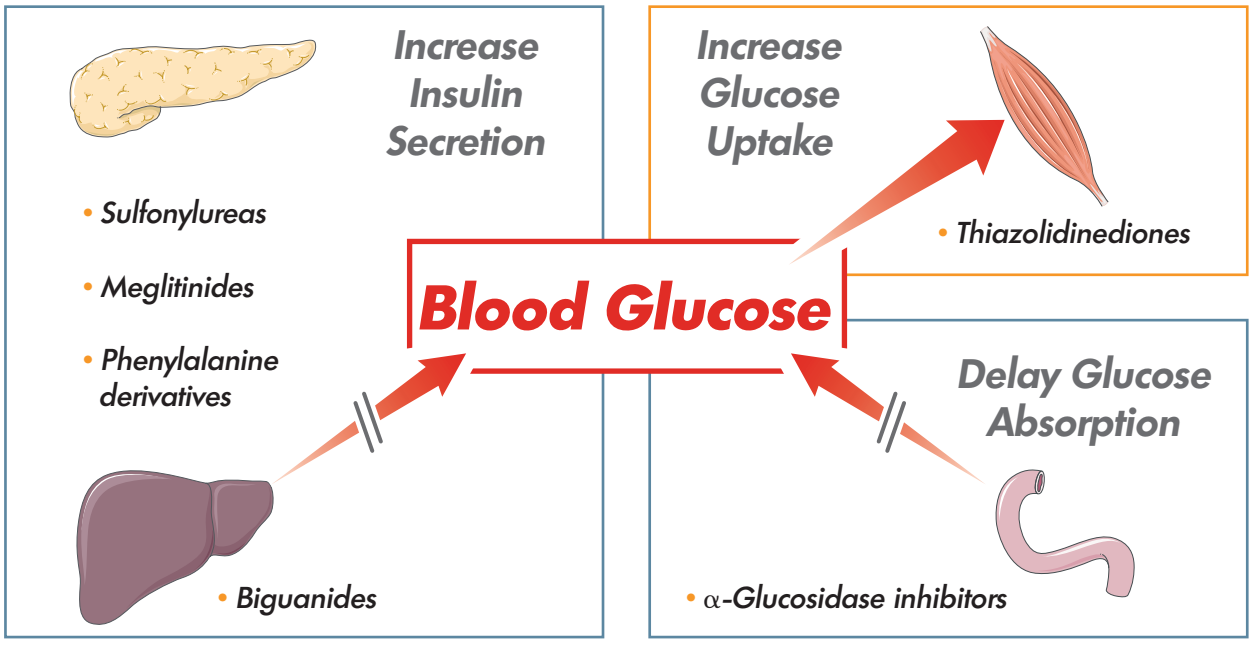

Figure 1 illustrates the likely sites of action of the currently available groups of OHAs. It emphasizes the importance of not just the pancreas and peripheral tissues (muscle and fat) in the pathogenesis of diabetes, but also the liver, gastrointestinal tract, and indeed fat tissue, in the abdominal cavity (visceral fat). When deciding which OHA or OHAs to use, full consideration should be given to which sites of action are the targets for treatment.

Currently, there are five distinct classes of OHAs available:

- Sulfonylureas/sulphonylureas (SUs)
- Meglitinides
- Biguanides
- Thiazolidinediones (TZDs)/glitazone
- α-glucosidase inhibitors

Each class displays unique pharmacological properties. Some of these will now be considered, again emphasizing that this Teaching Letter is not an exhaustive review.

4. Details of the five common classes of OHAs, divided by sites of action

a) Sulfonylureas/sulphonylureas (SUs)

Sulfonylureas/sulphonylureas mainly work by stimulating the release of insulin (secretagogue) from the remaining functional β-cell mass of the pancreas, by decreasing the potassium ion efflux at a "sulfonylurea receptor site." On average, this class reduces glycosylated hemoglobin (% HbA_{1c}) by 0.8% -2.0%, and FPG concentrations by 3.3 – 3.9 mmol/L (59-70 mg/dL), with the greatest reductions in patients with a higher FPG at initiation of treatment. These drugs also reduce post-meal glucose levels.

Hypoglycemia is the most troublesome side-effect, but less likely if a low dose is started, and uptitration is at 2-week intervals at least. Hypoglycemia is more likely in the presence of impaired renal function and in the underweight elderly patient. SUs may be used in combination with all other classes except the meglitinides, which are also insulin secretagogues. Difficulty losing weight, or weight gain, and hyponatremia may also occur.

There are several classes of sulfonylureas available on the market, with different potential. Their use should be adapted, when indicated; they must be used with caution in the elderly and in people with renal impairment (especially glibenclamide).

b) Meglitinides/Metaglinides

The metaglinides, currently repaglinide and nateglinide (a phenylalanine derivative) are also insulin secretagogues, binding to the ATP-sensitive potassium ion channels on β cells, but at a different site to SUs on the "sulfonylurea receptor." However, since they also need functioning β cells to work, there is no additive effect if taken with SUs. Time to onset of action is quicker than for SUs and duration of action is shorter. They may, therefore, reduce postprandial blood glucose peaks well, and overall HbA_{1c} by 0.5%-2.0%, and FG by 3.6-4.2 mmol/L. They are potentially a more flexible "lifestyle" drug, with variable meal time dosing. Hypoglycemia is significantly less common. This class of medication can be prescribed to patients with renal failure. Its high cost must be taken into consideration.

c) Biguanides

Biguanides work to reduce blood glucose by reducing liver (hepatic) gluconeogenesis and to some extent increasing peripheral tissue glucose uptake. They need insulin to work, do

not stimulate insulin release, and are not primarily insulin resistance–lowering agents. Overall they reduce HbA_{1c} by 1.5% -2.0%, and FG by 2.8-3.9 mmol/L. Metformin is the only available biguanide. Its gastrointestinal side effects are made worse usually by too large a dose initially, and increasing doses too quickly. Lactic acidosis, in patients without renal, cardiac, respiratory or hepatic failure, is rare. Metformin should not be initiated when serum creatinine is raised (120-150 by µmol/L) and should be withdrawn when serum creatinine exceeds 150-200 µmol/L. Metformin should also be stopped for 48 hours before and after imaging studies using contrast media, or longer if renal function has deteriorated. B12 deficiency, secondary to decreased absorption, rarely occurs.

d) Thiazolidinediones

The thiazolidinediones (TZDs), represented by rosiglitazone and pioglitazone, appear to truly reduce insulin resistance, also being called "insulin sensitizers." They therefore are in theory most useful in insulin resistance states, as may occur in most type 2 DM patients and especially in obese (greater than BMI >30kg/m^2) type 2 DM patients. Unfortunately, weight gain appears commonly on TZDs, sometimes due to fluid retention (edema), which must be distinguished from cardiac failure. This is more likely in the patient with ischemic heart disease (IHD) and high BP. TZDs have their action through intranuclear enzyme systems involved in transcription of insulin sensitive genes. This results from binding to the Peroxisome Proliferator Activated receptors, in particular the gamma type (PPARγ). This process is slow, and clinical and biochemical benefits may take 2-3 months, so initiation as monotherapy particularly in symptomatic new type 2 patients may be an issue. These drugs are indicated in monotherapy only when metformin is contraindicated or not tolerated.

Liver toxicity was a particular side effect with the first TZD, now withdrawn, so monitoring of liver function before, one month after, and during the treatment is needed, calling for good patient compliance and care by the professional. TZDs are usually withdrawn if serum transaminase levels (ALT) exceed 2.5 times normal. TZDs are better tolerated in cases of impaired renal function than metformin.

There are studies showing an increased risk of bone fractures in women. TZDs are not indicated in patients with coronary disease or heart failure, and there is currently increasing concern about their use in this context.

Combination preparations with metformin particularly assist patient adherence. Care with renal function is still needed. Weight gain and fluid retention are likely in patients on TZDs.

e) α-Glucosidase inhibitors

α-Glucosidase inhibitors, typified by Acarbose, competitively but reversibly inhibits small intestinal villi membrane bowel α-glucosidase hydrolase enzymes. These normally break oligosaccharides (small chain carbohydrates) into monomeric glucose for absorption. The theoretical result of taking an α-glucosidase dose with a meal is therefore to delay, but not stop, carbohydrate absorption. In practice this may result in reduction, by 1-2 mmol/L, of the post meal (1 or 2 hours post prandial) blood glucose peak. This should also work in theory in type 1 DM, but unfortunately there is a high rate of gastrointestinal intolerance to these drugs, perhaps related to prescribing too large a dose initially, not taking it with appropriate meals and increasing the dose too quickly. Care should be take in cases of renal impairment (creatinine >180micromol/L) and when there is coexisting bowel disease.

5. Possible uses of OHAs in the management of type 2 DM

The possible uses of the five classes of OHAs discussed here as MONOTHERAPY, or in COMBINATION THERAPY, are suggested below:

Options for monotherapy

Sulphonylureas	Meglitinides	Biguanides	Thiazolidinediones	α-glucosidase
Target population	**Target population**	**Target population**	**Target population**	**Target population**
• Normal weight	• Elevated PPG	• Overweight/Obese • Insulin resistant	• Insulin resistant • Overweight/Obese	• Elevated PPG
Advantages	**Advantages**	**Advantages**	**Advantages**	**Advantages**
• Effectiveness at reducing glycemia levels • Low cost	• ↓ risk of hypoglycemia • Short acting • Meal-adjusted dosing	• No weight gain • ↓ risk of hypoglycemia	• Hyperinsulinemia • ↓ risk of hypoglycemia	• ↓ risk of hypoglycemia
Disadvantages	**Disadvantages**	**Disadvantages**	**Disadvantages**	**Disadvantages**
• Weight gain • ↑ risk of hypoglycemia	• High cost	• GI side effects • Rare lactic acidosis	• Weight gain • Slow onset of action • Issue of liver toxicity • High cost • Risk of heart failure	• GI side effects • High cost

Initiate **combination therapy** if a single agent is inadequate, but tolerated

Options for combination therapy

Sulphonylurea + Biguanide or Thiazolidinedione or α-glucosidase inhibitor	Biguanide + Meglitinide	Biguanide + Thiazolidinedione	Biguanide + α-glucosidase inhibitor	Triple Combination Therapy
				Sulphonylurea + Biguanide + Thiazolidinedione or Sulphonylurea + Biguanide + α-glucosidase inhibitor

6. Notes/Practice points

- It is rational to start a recently or newly diagnosed type 2 DM patient, especially if symptomatic, on a single class of OHA, ie, monotherapy, determined by the likely pathogenetic mechanism predominating if not actively acting alone.
- Practically speaking this is usually determined by blood glucose profiles– predominately fasting versus predominately postprandial glucose elevation. In addition, obesity implies insulin resistance and increased hepatic glucose output.
- Beware of other factors that may be operating, like corticotherapy.
- Time to failure on monotherapy, ie, glycemic control judged inadequate, varies, but evidence is emerging that differences may be over 12 months in favor of some agents.
- Metformin has been considered, in most consensus statements, as the initial medication in all type 2 diabetics, but not when BMI under 25, and ketones are present.
- A common combination treatment is with an SU and metformin. Clinical experience suggests this controls most new patients, where diet alone is insufficient, and should be considered when BMI 20-25.
- Treatment changes and reasons for "failure" (usually the natural history of Type 2 DM) should always be explained to, and negotiated with, the person with diabetes.
- Early failure of monotherapy and then combined therapy should be carefully watched for and requires early treatment with insulin that it indicates. Type 2 DM is not only about insulin resistance, but insulin deficiency, which may sometimes dominate from the presentation.

7. The educational philosophy of OHA treatment

It is important when starting or changing OHA treatment, that both the responsible professional and person with diabetes share their views on why treatment is needed. Sharing a common agenda aids short term adherence to treatment, and therefore mid term evaluation of efficacy, and ultimately long term reduced risk of complications. The patient's perspective may include resolution of symptoms (although absence of these may work against adherence "I do not feel ill, so why do I need to take medication?"). They may also have previous knowledge of side-effects; apparent "failure" of tablets in a relative or friend; be on multiple medication already; or have concerns about compliance due to work or family commitments. The professional may be looking more at issues of the balance of pathogenetic mechanisms, eg, whether the patient needs a combination therapy early on; potential for weight gain where loss is needed or uncontrolled loss; drug toxicity, eg, renal impairment; drug interactions; and long-term benefits from long-term adherence rather than just short-term symptom relief – if there are any symptoms. In any case, a shared agenda between patient and professional is vital for successful treatment and monitoring of effects, both in the short term and long term.

8. Summary

OHAs are by definition the starting point of pharmalogical treatment of type 2 DM. The modes of action of the five classes described are different, and offer an opportunity to "tailor treatment" to

the likely pathogenetic mechanism or mechanisms in what is probably a heterogeneous condition. "Failure" of one level of treatment should be monitored for at all times by appropriate checks on well being, weight, fasting and post prandial blood glucose (self-monitoring) and % HbA_{1c}.

Some agents, biguanides and TZDs, may have a place in the prevention of or delay in onset of type 2 DM, in states of abnormal glucose tolerance detected in screening programmes. The discussion about TZDs still goes on.

9. References/appendix of.

References are not usually given in a Teaching Letter, but in this case as it is intended to be a high level guidance on the use of OHAs, and a source of further detailed information, an appendix of references is given. They support the opinions given here.

- WHO Sep 2006 Definition of Diabetes.
- *Am Fam Physician.* 2001;63:1747-1756, 1759-80.
- DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med.* 1999;131:281-303.
- Feinglos MN, Bethel MA. Treatment of type 2 diabetes mellitus. *Med Clin North Am.* 1998;82:757-790.
- Luina B, Hughes AT, Feinglos MN. The use of insulin secretagogues in the treatment of type 2 diabetes. *Prim Care.* 1999;26:895-915 .
- Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183-1197.
- DeDronzo RA, Goodman AM. The Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1995;333:541-549.
- Stumvoll M, Murjhan N, Perriello G, Dailey G, Gerich JE. The metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1995;333:550-554.
- Bailey CJ, Turner RC. Metformin. *N Engl J Med.* 1996;334:574-579.
- Nolan JJ, Jones NP, Patwardhan R, Deacon LF. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med.* 2000;17:287-294.
- Raskin P, Rappaport EB, Cole ST, Yan Y, Patwardhan R, Freed MI. Rosiglitazone short-term monotherapy lowers fasting and postprandial glucose in patients with type II diabetes. *Diabetologia.* 2000;43:278-284.
- Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes.* 1996;45:1661-1669.
- Dr. M. Ascoli Education Pharmacology: *Diabetes.* 2005; 71:180 Feb 7, 2005.
- Heine RJ, Diamant M., Mbanya JC, Nathan PM, Clinical Review. Management of hyperglycaemia in type 2 diabetes. *British Medical Journal.* 2006:333:1200-1204.
- Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2006;49:1711–1721.

These references do not include comparative efficacy or major randomized controlled trials deliberately, since this is not in the scope of this Teaching Letter.

The Diabetes Education Study Group would appreciate receiving comments, suggestions, and any documents developed after, or inspired by, this letter. Please send them to the DESG secretariat. E-mail diabetes.education@desg.org

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