Choosing a Diabetes Strategy

Where to Start and Where to Go

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The choice of which oral antihyperglycemic agent to use in an individual patient has become more complicated in the past several years. There are now two new classes of medications available:

- thiazolinediones/glitazones, and
- nonsulfonylurea insulin secretagogues.

The increase in options is good for patients, but often confusing for physicians. There is greater emphasis on the importance of achieving near normal glucose levels in most patients; multiple agents are often required to achieve this.

How is the first drug selected?

When deciding on the first drug to use, there are several things to consider, including:

- contraindications to particular agents,
- risk of hypoglycemia,
- efficacy,
- physiologic sense,
- cost and drug plan coverage, and
- evidence of long-term benefit.

Diana's case

Diana, 43, presents for her annual physical exam. She has a history of polycystic ovary disease, for which she has declined therapy. Her weight has been increasing for the past 10 years. She has a strong family history of Type 2 diabetes.

On exam:

- Blood pressure: 132/85 mmHg
- Weight: 95 kg
- Body mass index: 30
- Waist circumference: 102 cm

Chest, cardiovascular, and abdominal exams are unremarkable. Breast exam is normal. She does have mild hirsutism, mild facial acne, and acanthosis nigricans.

Her fasting blood sugar is 9.0 mmol/L and, at repeat testing, it is 8.8 mmol/L.

After three months of dietary changes and increased exercise, her weight decreases 5 kg, but her capillary blood glucose is 8 mmol/L to 12 mmol/L at meals and her hemoglobin A1c is 0.083 g/L.

You decide to start her on an oral agent for her diabetes, but which one should you use?

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A followup on Diana

One unique issue with this woman is that she is of child-bearing age. With the age of onset of Type 2 diabetes decreasing and maternal age increasing, Type 2 diabetes is becoming increasingly prevalent in pregnant women. This may affect drug choice.

Practice guidelines recommend insulin for the treatment of Type 2 diabetes prior to conception to ensure adequate glycemic control in the first trimester. In addition, metformin, and possibly glitazones, may restore fertility and regular menses in women of child-bearing age.

This may or may not be a desired effect. The patient must be warned so appropriate contraceptive measures can be used if pregnancy is not desired or until excellent glycemic control (hemoglobin A1c < 7.0%) is achieved.

For almost all patients, the first question should be *"Why not metformin?"* If there is no reason, then it should be the first drug used. Reasons not to choose metformin include:

- severe hyperglycemia with symptoms,
- presence of significant renal insufficiency,
- risk of lactic acidosis, or
- risk of severe gastrointestinal (GI) side-effects.

If *metformin can't be used...*

...the choice becomes either an insulin secretagogue or a glitazone. This is a difficult choice unless there are clear contraindictations to one of these groups (Table 1). They have similar efficacy, although insulin secretagogues work much faster; thus, if you need to correct the blood glucose quickly, an insulin secretagogue is better.

Although long-term data with clinical end points are missing, there are potential added benefits of glitazones. They are insulin sensitizers and, thus, make physiologic sense when treating insulin resistance. There have also been some early studies suggesting improvement in lipid profile, reduction in microalbuminuria, and beta cell protection with glitazones.[1,2] However, these drugs are much more expensive and not always covered by government drug plans.

Insulin secretagogues do have the potential for causing hypoglycemia, especially if meals are erratic. This is particularly important in the elderly and in those with known coronary artery or cerebrovascular disease.

If *the decision to use an insulin secretagogue is made...*

...the choice then becomes a nonsulfonylurea versus a sulfonylurea.

Meglitinides are a new class of drugs that stimulate insulin secretion like sulfonylureas. They have a

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Table 1

Classification of antihyperglycemic oral agents for Type 2 diabetes

Class	Name	Usual dosage	More common side-effects	Relative contraindications
Insulin secretagogues	Glyburide (Diabeta®)	2.5-20 mg/day, once or twice daily before meals	Can cause low blood sugar (may occur if a meal is missed or late, if more activity than usual, or if medication is changed); less hypoglycemia with gliclazide and glimepiride than with glyburide; nausea, fullness, heartburn; Diamicron may cause GI symptoms, headache, or flushing if taken with alcohol	• Pregnancy, lactation • Liver or kidney impairment • Type 1 diabetes
	Gliclazide (Diamicron®)	80-320 mg/day in divided doses before meals; MR formulation 30-120 mg once daily		
	Glimepiride (Amaryl®)	1-4 mg once daily		
	Repaglinide (GlucoNorm®)	0.5-4 mg taken just before meals; titrate to desired response (max: 4 mg); wait 1 week before dose change	Low blood sugar possible, but less frequent than with Diabeta or Diamicron	• Pregnancy, lactation • Dose size and interval may need adjustment in renal or liver impairment • Type 1 diabetes
	Nateglinide (Starlix®)	120-180 mg just before main meals		
Biguanides	Metformin (Glucophage®)	500-2,500 mg/day in divided doses; may take up to 2 weeks to see full effect	Nausea, gas, abdominal pain, diarrhea; used alone, very unlikely to cause low blood sugar	• Kidney or liver impairment • Uncontrolled CHF • Acidosis • Type 1 diabetes • Discontinue before tests using contrast dye, surgery or if severe infection occurs
Alpha glucosidase inhibitors	Acarbose (Prandase®)	25-100 mg 3 times daily with meals (start low and increase dose slowly every 4-8 weeks)	Abdominal pain, gas; by itself, will not cause low blood sugar; if taken with other diabetes pills or insulin, low blood sugar could occur; treat lows with milk or glucose tablets, as candy, soft drinks, or fruit juices will not raise blood sugar quickly with this drug	• Inflammation or ulceration of the bowel • Partial bowel obstruction • Disease affecting digestion • Kidney impairment • Large hernia
Thiazolid-inediones/ Glitazones	Pioglitazone (Actos®)	15-45 mg once daily; may take 8-12 weeks to see effect	Low blood sugar very rare; side-effects not usual, but may promote weight gain, edema; monitor liver function tests	• Pregnancy • Significant liver impairment • Avoid use in CHF
	Rosiglitazone (Avandia®)	4 mg total daily dose taken once or twice daily; after 8-12 weeks, titrate to 8 mg/day, if needed		

Note: Do not use > 1 drug from each class

MR: Modified release GI: Gastrointestinal CHF: Congestive heart failure

*See Compendium of Pharmaceuticals and Specialties (CPS) for full information

Table 2

Principles for combining oral agents when glycemic targets are not met by a single agent

1. Add, don't replace.
2. Don't wait too long.
3. Add an agent with a different mechanism of action:
   - Not 2 insulin secretagogues
   - Can use glitazone and metformin because both increase insulin sensitivity, but work on different tissues

very "quick on"/"quick off" effect, so they must be taken with each meal. This is advantageous for a person who needs flexibility in mealtimes, but more frequent dosing may be viewed as a disadvantage for a person with regular mealtimes.

The meglitinides provide better postprandial blood glucose control because of their quick release of insulin. They also tend to reduce the risk of low blood sugar before the next meal, as their effect is gone by that point.

The sulfonylureas are the group we have the most experience with and there is long-term data available on their safety and efficacy.[3]

If the decision to use a sulfonylurea is made...

...then you need to choose which sulfonylurea. Sulfonylureas differ in duration of action, risk of hypoglycemia, and coverage by provincial drug benefit plans. In individuals at risk for hypoglycemia, agents other than glyburide should be considered.

For almost all patients, the first question should be "Why not metformin?"

Acarbose, an alpha-glucosidase inhibitor, is the least effective in lowering hemoglobin A1c and is frequently associated with GI side-effects. However, it has been show to reduce progression from impaired glucose tolerance to Type 2 diabetes and may be indicated to delay the development of diabetes.[4]

If there is inadequate glycemic control with one drug...

...then a second agent should be added (Table 2). All of the drug classes can be combined, but no more than one drug from each class should be used. Improvement in blood glucose could take days to

weeks, depending on what agent was initiated first.

Deciding what drug to choose second follows the same rationale as choosing the first agent. The Canadian Diabetes Association 2003 Clinical Practice Guidelines[5] emphasize the importance of adding a second agent early and recommend considering a second agent before maximizing the dose of the first. This may be difficult, depending on the patient's willingness to take a second or third agent and his/her ability to pay for medications.

There is currently a combination pill available which combines rosiglitazone and metformin in a single tablet in various dosages. This combination drug may help improve compliance.

***If** glycemic control is not achieved with oral agents...*

...it is essential to move to insulin therapy, either alone, or in combination with oral agents. Dx

Take-home message

Treating diabetes...

- If there is no contraindication, metformin should be the first drug used.
- If metformin cannot be used, choose between an insulin sectretagogue or a glitazone; insulin secretagogues work faster.
- If an insulin secretagogue is used, decide between a nonsulfonylureas and a sulfonylurea.
- If there is inadequate glycemic control with one drug, a second agent from another class should be added.
- If glycemic control is not achieved with oral agents, move to insulin therapy.

References
1. Inzucchi SE: Oral antihyperglycemic therapy for type 2 diabetes. JAMA 2002; 287(3):360-72.
2. Reasner CA: Where thiazolidinediones will fit. Diabetes Metab Res rev 2002; 18(Suppl 2):S30-5.
3. Gerstein HC, Hanna A, Rowe R, et al: CDA position statement regarding the UKPDS and revision of diabetes clinical practice guidelines according to the UKPDS results. www.diabetes.ca/Section_Professionals/cpg_ukpdsposition.asp.
4. Chiasson JL, Josse RG, Gomis R, et al: Acarbose for prevention of type 2 diabetes mellitus: The STOP NIDDM randomised trial. Lancet 2002; 359(9323):2072-7.
5. Canadian Diabetes Association Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada 2003. Canadian Journal of Diabetes 2003; 27(suppl 2). (www.diabetes.ca/cpg2003).