Novel Therapies for Type 2 Diabetes Management

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Type 2 diabetes is a major challenge of the 21st century. Its prevalence is growing rapidly, particularly in developing countries.[1] An estimated 285 million people worldwide are affected by diabetes. More than three million Canadians have diabetes and this number is expected to reach 3.7 million by 2020. It remains the leading cause of blindness, end-stage renal disease and nontraumatic lower-limb amputation and > 75% of patients die from CVD.[2] Because of its high morbidity and excess mortality, it remains a formidable burden on healthcare costs.[3]

Bernie's case

Bernie is a 58-year-old male who has had Type 2 diabetes for the past 8 years. He is fairly compliant with his dietary and exercise regime. He does not smoke. He has no history of micro- or macrovascular disease.

His BMI is 35 kg/m^2 and his BP is 132/78. He is presently on metformin 1 g b.i.d. for his blood glucose control. His most recent HBA1c is 7.8%.

What would be your next step in terms of pharmacotherapy?

Limitations of traditionally prescribed medications

- Hypoglycemia (sulphonylurea [SU], meglitinides [MG], insulin)
- Weight gain (SU, MG, insulin, thiazolidinedione [TZD])
- Deterioration of β-cell function (SU)
- CV concern (TZD)

What can we do to improve glycemic control?

Type 2 diabetes mellitus (T2DM) is a chronic progressive vascular disease with significant physical, economic and societal burden. However, < 50% of Type 2 diabetic patients in Canada are currently at target (HBA1c < 7%).[4] Recently, two new classes of antidiabetic drugs with novel mechanisms of action have become available—incretin mimetics/enhancers and Amylin analogues.

The incretin effect

The incretin effect is an augmentation of insulin secretion in response to oral glucose loading vs. parenteral administration. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are gut derived peptides that account for the majority of

Table 1
Comparison of DPP-4 inhibitors and GLP-1 analogues

Action	GLP-1 agonists	DPP-4 inhibitors
Route of administration	Injection	Orally
Gastric emptying	Delayed	No effect
β-cell function	Improved*	Improved*
Insulin secretion and glucagon suppression	Yes	Yes
HBA1c lowering	~0.8%-1.6%	0.7%
Effect on weight	Decrease	Neutral
GLP level	Marked increase	Slight increase
GI adverse effect	Nausea	No nausea

DPP-4: Dipeptidyl peptidase-4
GLP-1: Glucagon-like peptide-1
*animal model

the incretin effect after a meal. Although the incretin effect is blunted in T2DM, GLP-1 responsiveness is retained whilst the effect of GIP is attenuated.

Native GLP-1 is rapidly destroyed in the intestine by the enzyme dipeptidyl peptidase IV (DPP-4) and has a half-life of only one to two minutes. Two main classes of drugs have been developed to prolong the action of GLP-1—GLP-1 analogues or receptor agonists (incretin mimetics) and DPP-4 inhibitors (gliptins) (Table 1).

GLP-1 receptor agonist

Exenatide (not available in Canada)

Approved by the FDA for the treatment of T2DM in April 2005. The starting dose is 5 µg b.i.d. subcutaneously for four weeks increasing to 10 µg b.i.d. It reduces the HBA1c by 0.8% to 1.0% when used in patients who are poorly controlled on maximal doses of one or two oral agents[5,6] and also induces weight loss of 4 kg to 5 kg after 80 weeks of treatment.[7] Hypoglycemia is rare but nausea is a common side-effect.

T2DM is a chronic progressive vascular disease with significant physical, economic and societal burden.

Liraglutide (not available in Canada)

Long-acting GLP-1 analogue, which is chemically engineered with non-covalent binding to albumin. This configuration enables the molecule to be resistant to DPP-4, thus extending the half-life from 10 to 14 hours. It is administered as a once daily injection and reduces the HBA1c by 0.5% to 1.6%.[8,9] Liraglutide (monotherapy or added to metformin) significantly reduced fat mass and fat percentage vs. glimepiride in patients with T2DM.[10] Besides stimulating the secretion of insulin, both exenatide and liraglutide have other pancreatic and extrapancreatic effects (Figure 1).

DPP-4 inhibitors

Sitagliptin and saxagliptin (available in Canada)

Works by prolonging the action of GLP-1. In Canada, sitagliptin and saxagliptin are currently

Besides its action on insulin secretion, GLP-1 has been shown to:

- Pancreatic effects:
  - ↑ insulin synthesis
  - ↓ Glucagon secretion (glucose dependent)
  - ↑ β-cell mass (animal models only)
- Brain ↓ caloric intake
- Liver ↓ hepatic glucose output
- GI tract ↓ motility
- Cardiac function ↑

Figure 1. Pancreatic and extrapancreatic effects of GLP-1.

indicated for use as add-on therapy to either metformin or SU when diet and exercise prove ineffective.[11-13]

The Canadian Diabetes Association 2008 clinical practice guidelines recommend the use of DPP-4 inhibitors as add-on therapy if the glycemic target is not attained when a single antihyperglycemic agent is used and should be considered to lower postprandial blood glucose levels. There is a small risk of upper respiratory tract infections, skin rashes and headaches.

Amylin (not available in Canada)

Amylin is a 37-amino acid neuroendocrine hormone which is co-secreted with insulin from β-cells—equivalently deficient in Type 1 and long-standing T2DM. The half-life of native Amylin is short and hence the development of a synthetic analogue.

Pramlintide slows gastric emptying (do not use with other motility agents or with gastroparesis), suppresses postprandial glucagon secretion and increases satiety (weight loss).[14,15] It is indicated for poorly controlled patients with Type 1 or 2 diabetes who inject insulin at meal times. It is administered as a subcutaneous injection prior to major meals and cannot be mixed with insulin in the same syringe. Side-effects include nausea and vomiting, anorexia, hypoglycemia (with insulin), mean A1C reduction ≤ 0.62% and it is expensive (approximately $160 per month).

Take-home message

- Tight glycemic control is fundamental to the management of diabetes
- Incretin mimetics will initially be used at the stage of oral hypoglycemic failure whereas gliptins will be employed earlier as add-on or monotherapy
- The disadvantage of the subcutaneous administration of the incretin mimetics may be offset by significant weight loss and reduced need to monitor glucose levels (less hypoglycemia)
- The potential therapeutic role of Amylin remains to be determined
- It is still not clear whether the durability of glycemic control and safety of these agents will be sustained long-term

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