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Exploring the Role of Incretin-Based Therapy in Type 2 Diabetes
AAFP November E-Newsletter
(Part 1 of 2)

A CME eNewsletter from: The Journal of Family Practice, PCMG Primary Care Metabolic Group, Illinois Academy of Family Physicians

Recognition of the incretin system as a key pathway in glucose homeostasis has led to the development of the glucagon-like peptide-1 receptor (GLP-1R) agonists (exenatide twice daily, exenatide once weekly, liraglutide) and dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, saxagliptin, sitagliptin). Approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM), the benefits of incretin-based therapy offer the ability to further individualize glucose-lowering therapy as illustrated in the following 2 case studies.

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Learning Objectives

- Provide an overview of the rationale and role of incretin-based therapy as described in current practice guidelines for the management of persons with T2DM
- Compare the efficacy, safety, and tolerability of the incretin-based therapies currently available

Target Audience

Family physicians and clinicians with an interest in diabetes treatment and management.

Sponsor Disclosure Statement

Dr. Edward Shahady discloses he is on the advisory board for Amylin, Novo Nordisk Inc., and Sanofi. He discloses he is on the speaker's bureau for Merck.

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Accreditation

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CASE 1

A 52 year-old African-American man was diagnosed with T2DM 3 years ago. He generally feels well, but experiences occasional fatigue.

- Past medical history: essential hypertension
- Social history: owner/operator of local hardware store; lives with his wife; occasional alcohol consumption
- Physical examination: blood pressure (BP), 135/78 mm Hg; pulse, 78/min; respiratory rate, 19/min; temperature, 36.8°C; weight, 248 lb; body mass index (BMI), 37 kg/m^2
- Current treatment
  - Medications: metformin 1000 mg twice daily; hydrochlorothiazide 12.5 mg once daily; atenolol 50 mg once daily
  - Exercise: 20 to 30 minute walk 2 to 4 times per week
  - Nutrition: eats 3 meals per day, but regularly eats after feeling full
- Laboratory
  - Triglyceride, 250 mg/dL (other lipids within normal limits)
  - Serum creatinine, 1.0 mg/dL (estimated glomerular filtration rate [GFR], 100 mL/minute); microalbumin:creatinine ratio, <30 mg/g
  - A1C levels:

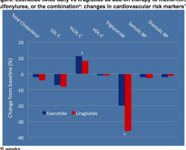
Lifestyle + metformin 500 mg twice daily, then metformin 1000 mg twice daily (at Diagnosis)

	Diagnosis	3 months	6 months	18 months	29 months	38 months
A1C (%)	9.1	7.7	7.6	7.7	7.9	8.3

Appropriateness of initial glucose-lowering therapy
The combination of lifestyle management (nutrition and exercise) and metformin is appropriate as initial therapy for many individuals with T2DM, including the patient in this case study. If metformin is not an option for a patient, a GLP-1R agonist can be considered if weight loss is a critical treatment goal.[1] In this patient, it is unlikely that the combination of lifestyle management and metformin would effectively lower his A1C level to less than 7.0%, which is the A1C level recommended by the American Diabetes Association for most people with T2DM.[2] In fact, the American Association of Clinical Endocrinologists/American College of Endocrinology recommend either insulin alone or with other agents, or metformin in combination with a GLP-1R agonist, DPP-4 inhibitor, or thiazolidinedione as initial therapy for individuals with an A1C >9.0%.[3] While the patient had a good response to his initial therapy as his A1C decreased to 7.7%, intensification of his glucose-lowering therapy at 3 months would have been appropriate unless he had experienced hypoglycemia.[3] Since his current A1C level is 8.3% and he has not experienced symptomatic hypoglycemia, further intensification of his glucose-lowering therapy is warranted.

Options for 2-drug glucose-lowering therapy
Several options are recommended for use in combination with metformin, including a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, GLP-1R agonist, or insulin (usually basal insulin).[1] With the possible exception of a DPP-4 inhibitor, the 4 other options would be expected to provide the approximately 1% reduction in the A1C level desired (0.5% to 1.0% for a DPP-4 inhibitor).[1] While transient nausea and occasional vomiting can occur, a GLP-1R agonist would be a good choice since there is a low incidence of hypoglycemia and weight loss is likely. Weight loss is especially important in this patient since his current BMI is 37 kg/m^2 and he regularly eats despite feeling full. The ability of the GLP-1R agonists to promote satiety may be helpful to address this latter point.[4-6] Losing weight with GLP-1R agonist therapy has been shown to improve patient quality of life[7] and may motivate this patient to intensify his lifestyle management, and possibly improve his overall self-management. A GLP-1R agonist would also be beneficial for 2 other reasons. First, GLP-1R agonist therapy is likely to provide a modest reduction of his triglyceride level in the range of 12 mg/dL to 40 mg/dL (Figure).[8-13] Second, a 1 mm Hg to 7 mm Hg reduction in BP is likely.[8,12,14]

Figure. Exenatide twice daily vs liraglutide as add-on therapy to metformin, sulfonylurea, or the combination[a]: changes in cardiovascular risk markers[13]



[a]26 weeks.
[b]*P* < .05.
BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.
Lipid values are reported as mg/dL; BP values are reported as mm Hg.

Appropriateness of initial antihypertensive therapy
Lowering BP to 130/80 mm Hg in individuals with diabetes is of unquestioned importance to reduce the risk of cardiovascular and kidney disease. Combination therapy with 2 or more drugs is recommended with options including a diuretic, beta-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB).[2,15] Among these, a cornerstone of antihypertensive therapy in people with diabetes is either an ACE-I or ARB.[1] A low-dose diuretic (eg, hydrochlorothiazide 12.5-25 mg/d) is also recommended as part of combination therapy. Since this patient is already taking hydrochlorothiazide and his systolic BP is above the goal of 130 mm Hg, a long-acting thiazide like chlorthalidone can be considered instead of hydrochlorothiazide.

CASE 2

A 78-year-old Caucasian woman, diagnosed with T2DM 8 years ago, has experienced 2 episodes of symptomatic hypoglycemia over the past 7 months.

- Past medical history: essential hypertension, renal dysfunction
- Social history: retired, lives alone; current smoker (56 pack-year history); drinks 1 glass of wine before dinner
- Physical examination: BP, 132/87 mm Hg; pulse, 70/min; respiratory rate 15/min; temperature, 37.2°C; weight, 194 lb; BMI, 30 kg/m^2
- Current treatment
  - Medications: metformin 750 mg twice daily; glimepiride 1 mg once daily; enalapril 20 mg once daily
  - Exercise: daily walk for 30 minutes
- Laboratory
  - Total cholesterol, 245 mg/dL; low-density lipoprotein cholesterol (LDL-C), 135 mg/dL; high-density lipoprotein cholesterol, 38 mg/dL; triglyceride, 350 mg/dL
  - Serum creatinine, 1.5 mg/dL (estimated GFR, 38 mL/minute); microalbumin:creatinine ratio, 75 mg/g
  - A1C levels:

Lifestyle management (at Diagnosis) — Metformin 500 mg twice daily, then metformin 750 mg twice daily (at 2 years) — Glimepiride 1 mg once daily (at 6.5 years)

	Diagnosis	2 years	3 years	5 years	6.5 years	8 years
A1C (%)	9.1	8.2	7.9	8.0	8.3	8.5

The hypoglycemia was attributed to the glimepiride, which was initiated 2 months prior to her first episode of hypoglycemia. Consequently, the glimepiride was discontinued at this visit.

Glycemic goal
Recent clinical trials such as ACCORD,[16] ADVANCE,[17] and VADT[18] are a reminder that a lower A1C level is not always appropriate and that treatment goals must be individualized. In this patient, rather than an A1C goal of <7%, a less stringent goal of <8% may be appropriate as she has dyslipidemia and evidence of nephropathy. Her age of 78 years would be a consideration if her life expectancy were short. Similarly, a less stringent A1C goal would be appropriate if her symptomatic hypoglycemic episodes were severe in nature. Among the glucose-lowering agents, the relative risk of hypoglycemia is greatest with insulin, sulfonylureas, and meglitinides.[1-3] The risk of hypoglycemia with the GLP-1R agonists and DPP-4 inhibitors is low, which is likely related to their glucose-dependent manner of stimulating insulin release and inhibiting glucagon secretion.[19,20]

Psychosocial factors might also be considered, particularly if the patient is depressed or distressed or is not confident about her self-management and has poor support. As this patient is retired and lives alone, investigation about psychosocial issues would be important.[21] Further discussion with the patient reveals that she has been increasingly depressed over the past year or so.

Chronic kidney disease
Diabetes is the most common cause of kidney failure, accounting for 44% of all new cases of kidney failure in 2008.[22] The estimated GFR of 38 mL/minute and microalbuminuria place this patient at stage 3B chronic kidney disease. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has been shown to more accurately calculate the GFR than the Modification of Diet in Renal Disease (MDRD) formula.[23] An application to calculate CKD-EPI is available from the National Kidney Foundation.

This patient's elevated BP and dyslipidemia, coupled with stage 3B chronic kidney disease and microalbuminuria, require intensification of treatment. Smoking cessation is also strongly recommended. In addition to the enalapril the patient is taking, a diuretic is recommended to lower BP to the target goal.[24] The target LDL-C in this patient is <100 mg/dL, or ideally, <70 mg/dL. A statin is recommended to lower LDL-C and a fibric acid derivative is recommended for hypertriglyceridemia.[24] Among the statins, atorvastatin, fluvastatin, lovastatin, rosuvastatin, and simvastatin can be used at this patient's current GFR.

The presence of kidney disease also requires reconsideration of her glucose-lowering therapy. A GFR <45 and ≥30 mL/minute/1.73 m^2 indicates that metformin should be used cautiously, at half-maximal dose, and with close monitoring of renal function.[25] Similarly, at this patient's estimated GFR of 38 mL/minute, repaglinide must be used cautiously and at a lower dose. Nateglinide, glimepiride, and pioglitazone can be used at normal doses.[26] Among the incretin-based therapies, liraglutide and linagliptin can be used at normal doses, exenatide twice daily and exenatide once weekly must be used with caution, and the dose of saxagliptin and sitagliptin reduced.[27-32]

Conclusion
The unique clinical pharmacology of the incretin-based therapies, and differences between the GLP-1R agonists and DPP-4 inhibitors, provides opportunities to individualize treatment for patients with T2DM.

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