

Introduction

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Diabetes mellitus is a major global health problem and is projected to affect 380 million people worldwide by 2025.¹ In the United States, 23.6 million adults (~8% of the population) have been diagnosed with diabetes, of whom 90–95% were found to have type 2 diabetes.^{2,3} For patients with diabetes, the therapeutic goal should be to achieve and maintain near normal glucose homeostasis. To this end, the American Diabetes Association and the American Association of Clinical Endocrinologists recommend target hemoglobin A_{1c} (A1C) levels of less than 7%, and 6.5% or lower, respectively.^{4,5}

Type 2 diabetes is a complex disease that progresses in stages—insulin resistance, hyperinsulinemia, impairment of β -cell function, and glucose intolerance—resulting in weight gain, high blood pressure, and deleterious cardiovascular effects. Many treatment strategies fail to address this multifaceted and progressive disease, and most patients with type 2 diabetes will require gradual intensification of treatment using different pharmacologic agents. It is important for health care professionals to be aware of newer therapies that provide effective glycemic control and have improved safety and tolerability profiles compared with traditional therapies.

Recent focus has been on developing therapies that target the incretin hormone system. The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), seem to be responsible for a variety of effects, including increase of insulin secretion in response to oral glucose ingestion,

inhibition of glucagon secretion, and delay of gastric emptying.^{6,7} Dipeptidyl peptidase-4 (DPP-4) is an enzyme that degrades native GLP-1 and GIP, resulting in relatively short half-lives of both molecules, thus reducing their overall insulinogenic activity.⁸ In patients with type 2 diabetes, incretin effects are greatly reduced as demonstrated by decreased secretion of GLP-1 and impaired insulinotropic action of GIP, which may contribute to the impaired insulin secretion observed in these patients.^{6,7}

Incretin-based therapies were developed to capitalize on the glucoregulatory effects observed within the native incretin pathways using two different strategies: GLP-1-receptor agonists that are resistant to degradation by DPP-4 (e.g., exenatide and liraglutide) and DPP-4 inhibitors (e.g., sitagliptin, vildagliptin and saxagliptin).⁹ These incretin-based therapies have demonstrated various clinical advantages, such as lack of weight gain and a reduced risk of hypoglycemia.

The overall purpose of this supplement is to provide information on incretin-based therapies, with a focus on the GLP-1-receptor agonist, liraglutide, recently approved in Europe and in late-stage review by the U.S. Food and Drug Administration, to help pharmacists place liraglutide within a therapeutic context. Pharmacists can play an important role in the treatment of patients with type 2 diabetes by remaining informed on the most currently available therapies. Understanding how to incorporate liraglutide and other incretin-based therapies within existing treatment regimens can make a significant difference in the management of type 2 diabetes.

The articles in this supplement, aimed at pharmacists, clinical pharmacologists, and other health care providers who treat patients with type 2 diabetes, represent a key reference on liraglutide's mechanism of action, its

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pharmacokinetics and pharmacodynamics, and its safety and efficacy as observed in clinical practice. In the first article, Dr. Samuel Grossman reviews the basic rationale for incretin-based therapies and discusses how to differentiate liraglutide from other incretin-based therapies. This article is followed by a detailed description by Jerry Meece of the pharmacokinetic and pharmacodynamic profiles of liraglutide. In the third article, I review experimental data demonstrating how liraglutide provides clinical benefit to patients with type 2 diabetes. In the final article, Drs. Barbara Zarowitz and Christopher Conner explore the potential benefits of liraglutide and other incretin-based therapies in decreasing the risk for two common adverse events, hypoglycemia and weight gain. Subsequent implications may be related to improved patient adherence and increases in overall clinical effectiveness associated with incretin-based therapies.

After reading this detailed review of liraglutide, readers should have a thorough appreciation of the physiologic and clinical data supporting the role of incretins in the control of glucose homeostasis. As some currently used therapies are limited by their inability to effectively control hyperglycemia over the long term, new treatment options, such as the incretin-based therapies, which provide improved glycemic control in addition to reducing the risk of hypoglycemia

and weight gain, may meet some of the unmet needs in glucose control.

References

1. **International Diabetes Federation.** Diabetes atlas, 3rd ed. Brussels, Belgium: International Diabetes Federation, 2007. Available from <http://www.eatlas.idf.org>.
2. **Centers for Disease Control and Prevention.** National diabetes fact sheet: general information and national estimates on diabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, 2007.
3. **National Institutes of Health.** National diabetes statistics 2007—prevalence of diagnosed and undiagnosed diabetes in the United States, all ages, 2007. Available from <http://diabetes.niddk.nih.gov/dm/pubs/statistics/#allages>. Accessed August 14, 2009.
4. **Nathan DM, Buse JB, Davidson MB, et al.** Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:1–11.
5. **American Association of Clinical Endocrinologists.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007;13:4–68.
6. **Drucker DJ, Nauck MA.** The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368:1696–705.
7. **Holst JJ, Gromada J.** Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab* 2004;287:E199–206.
8. **Deacon CF, Carr RD, Holst JJ.** DPP-4 inhibitor therapy: new directions in the treatment of type 2 diabetes. *Front Biosci* 2008;13:1780–94.
9. **Stonehouse A, Okerson T, Kendall D, Maggs D.** Emerging incretin based therapies for type 2 diabetes: incretin mimetics and DPP-4 inhibitors. *Curr Diabetes Rev* 2008;4:101–9.