What You Need to Know

Individualization of Insulin Therapy for Type 2 Diabetes Mellitus

Diabetes Treatments in the Pipeline

While we may have just experienced the "modern golden age" of insulins during which new insulin options became available, including longer acting insulin products like insulin degludec and concentrated forms of this and several established insulins (insulin glargine, insulin lispro), and advancements were made related to U-500 regular insulin administration (pen device, U-500 insulin syringe), a look into the pipeline provides a glimpse of developments that may provide new options for patients with diabetes in the future.

New technology that has been referred to as an "artificial pancreas" could revolutionize the use of insulin to manage diabetes mellitus. It involves a closed-loop system that incorporates continuous blood glucose monitoring with an insulin pump. Complex algorithms are then used for adjusting subcutaneous (s.c.) insulin therapy. This technology will enable the management of blood glucose concentrations with minimal patient input in patients with type 1 diabetes and some patients with type 2 diabetes.

The artificial pancreas is not a cure for diabetes but it has the potential to simplify insulin therapy for patients, maximize the time during which blood glucose concentrations are in the target range, and reduce the risk of severe hypoglycemia during the nighttime (a particularly dangerous time of day) as well as during the day. Some components already are available, and a hybrid closed-loop system for semi-automatically monitoring blood glucose concentrations and providing an appropriate basal insulin dose was approved by the Food and Drug Administration (FDA) in 2016 for patients 14 years of age or older with type 1 diabetes mellitus. A more automated artificial pancreas should become available within the next 5 years.

There has been considerable interest in developing formulations of glucagon-like peptide (GLP)-1 receptor agonists and insulin for oral administration. Semaglutide is a GLP-1 receptor agonist that is awaiting approval from the FDA for administration once weekly by s.c. injection in patients with type 2 diabetes. A once-daily oral formulation of semaglutide has entered phase 3 trials. In an open-label, placebo-controlled, dose-finding study comparing the oral formulation with the injectable formulation in 632 adults with type 2 diabetes, improvements in glycemic control were demonstrated over 26 weeks with both oral and s.c. semaglutide compared with placebo. Gastrointestinal adverse effects were reported with both oral and s.c. semaglutide. A placebo-controlled cardiovascular outcomes trial known as PIONEER 6 of oral semaglutide in patients with type 2 diabetes who are at high cardiovascular risk is underway, with results not expected until late 2018.

Attempts have been made for 10 years to develop an oral formulation of insulin but success has been elusive because of rapid destruction of the protein by gastric enzymes. Various strategies have been used to protect the protein from enzymatic degradation and increase its bioavailability and half-life, including pH-sensitive protective coatings, absorption enhancers that increase local pH, carrier technology that increases stability and promotes passage of insulin across the intestinal mucosa into the bloodstream, and modification of the insulin protein structure (e.g., acylation to add a side chain that increases the half-life). Clinical trials of oral insulin formulations with these features are in progress.

Drugs that improve mitochondrial function in patients with type 2 diabetes have been explored to overcome insulin resistance without the adverse effects associated with currently available diabetes therapies. The use of thiazolidinediones, which improve insulin sensitivity partly through their mitochondrial effects, is hindered by adverse effects. New drugs are in development that specifically

target mitochondrial function but lack thiazolidinedione-associated adverse effects. According to Initiative Chair Curtis Triplitt, one of these drugs probably will be the next blockbuster for managing type 2 diabetes.

More information

» DeFronzo RA, Triplitt CL, Abdul-Ghani M, Cersosimo E. Novel agents for the treatment of type 2 diabetes. *Diabetes Spectr.* 2014; 27:100-12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4522879/pdf/100.pdf (accessed 2017 Apr 12).

» Jabbour S, Pieber TR, Rosenstock J et al. Robust dose-dependent glucose lowering and body weight (bw) reductions with the novel oral formulation of semaglutide in patients with early type 2 diabetes (T2D). Presented at the 98th Annual Meeting of the Endocrine Society, Boston, MA: April 2, 2016. Abstract OR15-3. https://endo.confex.com/endo/2016endo/webprogram/Paper25706.html (accessed 2017 Apr 12).

» Voelker R. "Artificial pancreas" is approved. *JAMA.* 2016; 316:1957.

» Wajcberg E, Miyazaki Y, Triplitt C et al. Dose-response effect of a single administration of oral hexyl-insulin monoconjugate 2 in healthy nondiabetic subjects. *Diabetes Care.* 2004; 27:2868-73.

Insulin Stacking

Concerns have been raised about the potential for insulin stacking—the excessive accumulation of insulin in the bloodstream, which can result in hypoglycemia—from the newer long-acting basal insulins with a duration of action of 24 hours or longer. Insulin stacking has been described in patients receiving multiple daily insulin injections in whom rapid-acting insulin was given to correct hyperglycemia before the full effects of prandial doses were achieved. This phenomenon differs from the usual therapeutic (i.e., steady state) accumulation associated with repeated dosing of a longer-acting drug. It is attributed in part to the slight delay between insulin absorption from an s.c. depot and maximum glucose-lowering activity mediated by receptors in target tissues.

Basal insulins differ from rapid-acting insulins in their longer half-life and relatively flat pharmacokinetic profile, with a low steady state peak-to-trough ratio of insulin activity (measured using glucose clamp studies). The likelihood of hypoglycemia is lower when fluctuations in insulin activity are small. Pharmacokinetic and pharmacodynamic studies have demonstrated that insulin stacking is not a problem with long-acting basal insulins if appropriate starting doses and titration schedules are used.

Because long-acting insulins have long half-lives, the time required to reach steady-state levels is long. Therefore, dosage adjustments should not be made more often than once every three or four days with U-300 insulin glargine or insulin degludec to avoid overshooting the fasting blood glucose target. The glycemic impact of dosing errors (e.g., a missed dose or double dose) is smaller with long-acting basal insulins than rapid-acting insulins because of their longer half-life.

More information

» Heise T, Meneghini LF. Insulin stacking versus therapeutic accumulation: understanding the differences. *Endocr Pract.* 2014; 20:75-83.

Educational Opportunities in this Initiative

» Engaging the Experts faculty interview hosted by William A. Zellmer

» Discussion guide covering the role of insulin in managing type 2 diabetes (1.5 hr CPE)

» On-demand activity covering the basics of individualizing insulin therapy with a focus on new concentrated insulins (1.0 hr CPE)

» On-demand activity featuring application of concepts to clinical case vignettes (1.5 hr CPE)

» On-demand activity addressing advanced challenges in managing type 2 diabetes (1 hr CPE) – coming May 2017

» November 2016 and March 2017 e-newsletters

www.ashpadvantage.com/go/type2

Advice for Improving Patient Care

Here is some specific advice from your pharmacist colleagues who are experts in diabetes about how to improve the care of patients with type 2 diabetes.

From Dr. Andrew Bzowyckyj: Have a conversation with your patients about their perceptions of a "good glucose reading." While some patients may need help setting realistic expectations, most of the time their perceptions align reasonably well with guideline-recommended goals. I find many individuals either provide a range similar to those recommended within the ADA standards of care or a more general idea, such as "less than 150." Obtaining that information from the patient and documenting it within the medical record will allow you to personalize your conversations and dose adjustments to make sure you and the patient are on the same page.

From Dr. Susan Cornell: Ask patients specifically about how they take their medications and what medication-related problems they experience, which can facilitate early identification of and intervention to address adherence problems. Many newer insulins are available only in pens, and improper use of pens is a potential problem with consequences for glycemic control. Conduct a medication "check up" and review use of delivery devices on a repeated basis to ensure that patients understand how to optimize their use of insulin and other diabetes drug therapies.

From Dr. Joshua Neumiller: Recognize a patient's frustration with an apparent lack of improvement in health despite adherence to the treatment regimen by acknowledging small improvements and encouraging continued adherence to the treatment regimen. Celebrating small victories can make a world of difference in encouraging patients. Frequent patient reevaluation and modification of drug therapy often are needed to achieve and maintain therapeutic goals.

From Dr. Curtis Triplitt: Assume responsibility for advising prescribers about the availability of newer diabetes therapies to improve patient response and adherence. The choice of drug therapy for patients with type 2 diabetes often reflects prescriber familiarity with the agents, although newer medications or delivery devices might offer advantages for patients experiencing adverse effects or poor glycemic control from older therapies. The two biggest barriers to managing type 2 diabetes are starting insulin therapy and achieving glycemic goals. Treating to target (i.e., glycemic goals) is vital for optimizing outcomes.

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Other News

» An analysis of published reports on seven studies of cardiovascular outcomes from new therapies for type 2 diabetes revealed disproportionately low representation of black and African-American patients in five of the trials and inconsistent descriptions of race or ethnicity in five trials. Blacks or African Americans accounted for less than 5% of study subjects despite making up 12.6% of the U.S. population. Pharmacogenomic and pharmacokinetic differences among individuals receiving these medications could influence efficacy. Minority underrepresentation in clinical research has been attributed to barriers related to socieoeconomic status, lack of transportation, low health literacy, and limited knowledge of the research process. Strategies to increase enrollment of subjects from underrepresented minority populations are needed to realize the potential benefits of precision medicine in the treatment of type 2 diabetes.

» In January 2017, the American Diabetes Association (ADA) released a new position statement on diabetic neuropathy, updating its 2005 statement on the subject. The new position statement addresses the prevention, detection, diagnosis, and management of the disorder. The most common forms of diabetic neuropathy are distal symmetric polyneuropathy (often characterized by burning or stabbing pain, numbness, or tingling of the arms and legs) and diabetic autonomic neuropathy, which can affect the cardiovascular, gastrointestinal, and urogenital systems. ADA recommends lifestyle interventions (i.e., dietary modification and exercise) and optimization of blood glucose control to prevent or delay the progression of distal symmetric polyneuropathy in patients with or at risk for type 2 diabetes (e.g., patients with prediabetes or the metabolic syndrome). Lifestyle intervention as part of a multifactorial approach targeting glycemia (among other risk factors) to prevent cardiovascular autonomic neuropathy is recommended for patients with type 2 diabetes. For painful distal symmetric polyneuropathy, the guidelines recommend duloxetine, especially with coexisting depression, or pregabalin. Both are FDA approved for this indication, although because of cost gabapentin may also be considered.

One Pen One Patient Website Provides Additional Resources

For resources and a tool kit for facilitating the safe and appropriate use of insulin pens in the hospital setting, go to www.onepenonepatient.org. In addition, you will find two related educational activities:

» *AJHP* supplement, "Best Practices in Ensuring the Safe Use of Insulin Pens in the Hospital" (2.5 hours CPE)

» On-demand activity focused on the emerging role of newer concentrated insulins in managing diabetes and strategies for ensuring the safe use of concentrated insulins (1 hour CPE)

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