

AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 07: Diabetes Mellitus

Potential High Impact Interventions Report

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI).

Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the 15 topics for which (1) preliminary phase III data for drugs, or phase II data for devices or procedures were available; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 52 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present five summaries on nine topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact.

Priority Area 07: Diabetes
1. *Artificial pancreas for treatment of diabetes
2. *Bariatric surgery for resolution of type 2 diabetes in patients with BMI <35 kg/m ² *
3. *Buccal insulin (Oral-lyn) for treatment of diabetes
4. D-tagatose for treatment of type 2 diabetes
5. *Exenatide extended-release (Bydureon) for treatment of diabetes
6. *Exenatide subcutaneous pump (Duros) for treatment of diabetes
7. GFT 505 for treatment of type 2 diabetes and pre-diabetes
8. Inhaled insulin (Technosphere) for treatment of insulin-dependent type 1 or 2 diabetes
9. InsuPatch for improving pump-infused insulin absorption
10. Off-label salsalate for treatment of type 2 diabetes
11. *SGLT2 inhibitor (ASP1941) for treatment of type 2 diabetes
12. *SGLT2 inhibitor (BI-10773) for treatment of type 2 diabetes
13. *SGLT2 inhibitor (dapagliflozin) for treatment of type 2 diabetes
14. *SGLT2 inhibitor (LX-4211) for treatment of type 2 diabetes
15. Ultra-long-acting insulin (degludec) for treatment of type 2 diabetes

Discussion

The U.S. Centers for Disease Control and Prevention (CDC) estimated that in 2007, 17.9 million Americans had some form of diagnosed diabetes, and an estimated 5.7 million had undiagnosed diabetes. About 5% to 10% of cases are type 1 diabetes mellitus (T1DM), and most of the other cases are type 2 diabetes mellitus (T2DM). The prevalence of T2DM is about 11% in the population aged 65 years or older and nearly 40% of those 80 years of age or older, but age of onset is trending younger. In 2007, CDC incidence statistics indicated that approximately 1.6 million new cases of diabetes were diagnosed that year for adults 20 years of age or older. The American Diabetes Association Task Force recently developed a revised classification system based on etiology rather than treatment mode. T1DM results from a chronic autoimmune condition in which the immune system attacks and destroys insulin-producing pancreatic beta cells leading to chronically elevated blood glucose levels. Without supplemental insulin intervention, the condition is fatal. Patients with T1DM take multiple daily insulin injections, or specially selected patients may use an external insulin pump for subcutaneous infusion.

After the disease is diagnosed, patients undergo a medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a plan for treatment, including establishing target blood glucose levels and glycated hemoglobin (HbA_{1C}) goals. The HbA_{1C} test measures how much hemoglobin has bonded to blood cells over a 3- or 4-month period and is the accepted standard for measuring successful diabetes management. Ongoing, patients follow a treatment plan and undergo education to learn how to self-manage their day-to-day care. Clinicians encourage patients to achieve an HbA_{1C} level of 7% because this value has been shown to reduce diabetes-associated complications. For T2DM, a variety of self-administered oral antidiabetes agents, alone or in combination, are generally tried as first-line medical therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase IV inhibitors. Many patients with T2DM fail to meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) agonist. Insulin supplementation has become increasingly common with T2DM.

New treatments in development for all types of diabetes focus on several aspects of prevention to delay onset in at-risk patients and on improving diabetes management. New drugs and drug-delivery modalities are intended to optimize efficacy to enable patients to meet and maintain near-normal glycemia without excursions high or low, to improve patient adherence to treatment regimens, and to reduce acute excursions (hyperglycemia, hypoglycemia), weight gain, and secondary complications (nephropathy, neuropathy, retinopathy).

Artificial Pancreas for Treatment of Diabetes

- **Key facts:** An artificial pancreas closed-loop system (CLS) (an external or implantable insulin pump, real-time continuous glucose monitor, and a small computing device with software and algorithms to detect glucose levels and coordinate with insulin delivery) is considered by many to be the ideal management strategy for patients on intensive insulin management. Researchers are developing two types of systems: reactive and predictive low-glucose suspend systems. In reactive systems, patients or clinicians preset a blood glucose threshold, and the pump automatically shuts off when that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level. While many proof-of-concept studies of CLSs have been performed, and while all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization because major advances in sensor technologies and artificial pancreas software algorithms

are needed, as is a developer that is able and willing to integrate the disparate components into a single CLS.

- **Key Expert Comments:** Overall, experts commented that a CLS has significant potential to simplify the way in which patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the T1DM population, and patients would need to be highly motivated and able to operate the system. Experts thought that patients would also need access to a highly trained multidisciplinary care team 24 hours a day, 7 days a week, to address any issues that might arise in the operation of a CLS.
- **Potential for High Impact:** High

Bariatric Surgery for Patients with Body Mass Index <35

- **Key facts:** Current guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI] $>40 \text{ kg/m}^2$) or individuals with a BMI $>35 \text{ kg/m}^2$ and an associated comorbidity. One such qualifying comorbidity is diabetes, which is highly correlated with obesity. Outcomes showing resolution of T2DM in patients who have undergone bariatric surgery has generated interest among clinicians and some patients in the potential of bariatric surgery to treat T2DM in less obese patients (i.e., BMI $<35 \text{ kg/m}^2$). The cost of the surgery would vary depending on the choice of procedure (e.g., Roux en Y; lap banding; sleeve gastrectomy). Currently, insurers generally do not cover bariatric surgery in patients at these BMIs and patients would bear the cost of treatment.
- **Key Expert Comments:** Overall, experts commenting on this topic believe that bariatric surgery has potential to lead to remission or cure of T2DM in mildly to moderately obese individuals, and its use in this patient population would significantly shift the care model and care setting. However, given the high risks associated with some forms of bariatric surgery and the long-term lifestyle changes mandated by the treatment, experts believe its use in this population would be highly controversial. They questioned whether patients would opt for surgery and whether clinicians would want to advise the surgery in this patient population. Given the large number of people with T2DM whose BMI is in the 30-to-35 kg/m^2 range, adoption of the procedure as a treatment for those who do not achieve adequate control of blood glucose with less drastic methods could have a very large impact on the health care system in terms of infrastructure (bariatric surgery services) and shifts in processes of care (from lifestyle changes and medication for diabetes to surgery).
- **Potential for High Impact:** High

Buccal Insulin (Oral-Lyn) for Treatment of Diabetes

- **Key facts:** Many patients who require exogenous insulin consider injections burdensome, yet continuous subcutaneous insulin pumps are appropriate for relatively few patients. Therefore, novel insulin delivery methods that do not involve injection are being sought. A noninjectable insulin in development, Oral-lyn™ (Generex Biotechnology Corp., Toronto, Ontario, Canada), is a liquid formulation of human insulin delivered as a buccal spray. It is administered by a proprietary inhaler similar to an asthma inhaler. Absorption is limited to the mouth with no entry into the lungs, and absorption is faster with a shorter total duration of activity because of the rich vascularity of the buccal mucosa, potentially making buccal insulin an ideal insulin to control glycemic excursions after meals. A phase III trial

comparing use of Oral-lyn as a prandial insulin to injected human insulin was expected to be completed in September 2011, but appears to be ongoing. Oral-lyn is currently available under a U.S. Food and Drug Administration (FDA) treatment investigational new drug program to patients in the U.S. with life-threatening diabetes and no other treatment options.

- **Key Expert Comments:** Overall, experts providing comments on this topic thought that buccal insulin has potential to improve diabetes treatment by providing a needleless alternative to injectable insulin, which could transition more patients to insulin therapy and potentially improve patient adherence to insulin dosing. However, experts noted that buccal insulin's efficacy has not yet been conclusively demonstrated and that trials of the drug were moving slowly. This may be due in part to the fact that this product is the only product of the company developing it, and funding to complete the required trials may be an issue.
- **Potential for High Impact:** Moderately high

New Exenatide Formulations to Improve Diabetes Treatment Adherence

- **Key facts:** Two therapies, extended-release exenatide (Bydureon™, Amylin Pharmaceuticals, Inc., San Diego, CA) injection and implanted continuous subcutaneously delivered exenatide (ITCA 650, Intarcia Therapeutics, Inc., Hayward, CA, via the Duros® pump system), are currently in development for treatment of T2DM to improve drug efficacy and tolerability as well as patient adherence.

Extended-release exenatide is a controlled-release once-weekly formulation delivered by subcutaneous injection. It is intended to mimic the function of GLP-1, a naturally occurring hormone that stimulates release of native insulin and inhibits glucagon release to lower blood glucose levels. GLP-1 also has been observed to promote a feeling of fullness and satiety, purportedly reducing intake of exogenous glucose. In August 2011, the manufacturers of Bydureon announced that FDA had acknowledged resubmission of their new drug application (NDA). In November 2011, Amylin Pharmaceuticals and Eli Lilly formally announced cessation of their partnership for development of exenatide, leaving sole development responsibility to Amylin Pharmaceuticals. An FDA action date was set for January 28, 2012.

ITCA 650 is a proprietary formulation of exenatide that remains stable at body temperature for extended periods of time and can be administered continuously using the Duros subcutaneous continuous delivery system. The Duros delivery system (which is also being evaluated for delivery of drugs for hepatitis and weight loss) is a semipermeable osmotic mini-pump that a physician or physician assistant inserts into the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. In mid-September 2011, the company announced plans for its phase III study after releasing final 48-week results from its phase II trial. The company reported that the drug resulted in improved glycemic control and was well tolerated at all doses, starting from 20 mcg/day and transitioning to 40, 60, or 80 mcg/day. The company also reported the drug led to reduced body weight after 24 and 48 weeks of treatment.

- **Key Expert Comments:** Experts commenting on these topics believe that both formulations have potential to improve diabetes treatment by improving availability of exenatide while reducing frequency of injection and nausea, thereby potentially improving patient adherence. However, experts noted that benefit might be incremental relative to existing forms of exenatide and other GLP-1 analogs.
- **Potential for High Impact:** Lower range of high impact

Sodium-glucose Cotransporter 2 Inhibitors

- **Key facts:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of drugs in development for T2DM. They are intended to reabsorb glucose from the glomerular filtrate of the kidney into the bloodstream and potentially reduce glucose reabsorption and increase glucose excretion through urine. In this way, SGLT2 inhibitors might reduce blood glucose without affecting insulin uptake and risking hypoglycemia, a common acute complication of diabetes. These agents can purportedly be used in conjunction with other oral antidiabetes agents and insulin without significant adverse effects and might help promote weight loss in overweight and obese patients. At least six SGLT2 inhibitors are in phase II and III trials. Furthest along in development is dapagliflozin (jointly developed by AstraZeneca, London, UK, and Bristol-Myers Squibb, New York, NY). With results from several phase III trials in hand, the companies submitted an NDA to FDA in December 2010. In July 2011, just after all expert comments had been received for this report, FDA Endocrinologic and Metabolic Drugs Advisory Committee voted against recommendation for approval of dapagliflozin for treatment of T2DM amid safety concerns and potential risk of adverse events. A formal decision was scheduled for October 28, 2011, but was to January 28, 2012. In light of this, the companies stated they would submit additional data from recently completed and ongoing phase III clinical trials as a major amendment to the original NDA submission.
- **Key Expert Comments:** Overall, experts commenting on SGLT2 inhibitors were optimistic about these drugs as a new alternative and/or adjunct for first-line pharmaceutical management of T2DM, given their potential impact on several key outcomes: weight loss, glucose control, and reduced hypoglycemic episodes. The AHRQ Healthcare Horizon Scanning System will seek additional expert comments about this topic in light of the pending FDA decision.
- **Potential for High Impact:** Moderately high

Diabetes Mellitus Interventions

Intervention

Artificial pancreas for treatment of diabetes

An artificial pancreas closed loop system (CLS; an external or implantable insulin pump, real-time continuous glucose monitor, and small computing device with software and algorithms to detect glucose levels and coordinate with insulin delivery) is considered by many to be the optimum strategy for diabetes management for patients on an intensive insulin management program who need daily exogenous insulin and are suitable candidates for insulin pumps. Literature indicates that patients with T1DM who experience hypoglycemia, or low blood sugar, are the most appropriate patients for CLSs.¹

For an implantable CLS, an endocrinologist administers local anesthesia and surgically implants the insulin pump and glucose monitor subcutaneously on opposite sides of the abdomen. The insulin reservoir is placed beneath the skin and is refilled every 2 to 3 months via transcutaneous injection. Patients typically spend 1 full day and night in the hospital for monitoring.²⁻⁴

Researchers are developing two types of devices: reactive and predictive low-glucose suspend systems.¹ In reactive systems, patients or clinicians preset a blood glucose threshold, and the pump automatically shuts off if that reading is reached. In predictive systems, the monitor uses control algorithms that predict when the patient's blood glucose is projected to decrease to a dangerously low level.

While many proof-of-concept studies of CLSs have been performed, and while all the necessary component parts of a CLS exist, a truly portable CLS for routine use is several years from realization because major advances in sensor technologies and artificial pancreas software algorithms are needed, as is a developer that is able and willing to integrate the disparate components into a single CLS.⁵ Another barrier to approval is U.S. Food and Drug Administration (FDA) guidelines set for CLS studies. In June 2011, FDA issued guidelines stating this intervention's sponsors would need to produce results showing use of these systems will "prevent or reduce the length and severity of hypoglycemia events better than conventional systems consisting of an infusion pump and continuous glucose monitoring system" to notify patients when blood glucose levels are not within normal range.⁶

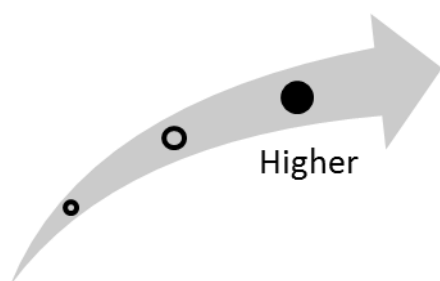
Zisser (2011) released an evaluation of the CLS artificial pancreas in 10 patients showing that this intervention can "safely regulate glycemia in patient with type 1 diabetes even following a meal challenge, without prior meal information."⁷ The controller successfully brought subjects back to the euglycemic range" and the CLS system "recognized all of the unannounced meals and gave appropriate meal boluses of insulin. The average percent time in the target glucose range (80 to 180 mg/dL) was 77% with one episode of mild hypoglycemia."⁷

Clinical Pathway at Point of This Intervention

After diabetes has been diagnosed, patients undergo a medical evaluation to classify the disease type, detect any complications, review glycemic control challenges, and establish a plan for treatment. Ongoing, patients follow a treatment plan and undergo education to learn how to self-manage their day-to-day care.⁸ For patients with T1DM, insulin therapy is required by either multiple daily self-injections or a subcutaneous external insulin pump. Patients with T2DM whose blood glucose is not adequately controlled by oral medication regimens and lifestyle changes can have injected insulin added to their regimens. Guidelines recommend that only specialized multidisciplinary teams initiate continuous subcutaneous insulin infusion in highly selected and motivated patients, and the therapy is not recommended for patients with T2DM.⁹

Figure 1. Overall High Impact Potential: Artificial pancreas for treatment of diabetes

Overall, experts commented that CLS has significant potential to simplify the way in which patients with T1DM manage the disease to achieve near-normal glycemia and avoid acute (hypoglycemia, hyperglycemia) and long-term complications (i.e., nephropathy, neuropathy, retinopathy). Such a system, they opined, would likely be indicated for only a subset of the population with T1DM, and patients would need to be highly motivated and able to operate the system. Experts thought that patients would also need access to a highly trained multi-disciplinary care team 24 hours a day, 7 days a week, to address any issues that might arise in the operation of a CLS. Development of disparate parts of a CLS has been ongoing for years; however, no single entity has taken on development and integration of the hardware and software required for a CLS. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.



Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.¹⁰⁻¹⁵ Experts agreed that a CLS that could link continuous glucose monitors and insulin pumps with seamless feedback to appropriately control patients' blood glucose levels in an automated fashion is a long-standing, significant unmet need in the diabetes treatment field. However, many experts noted that an off-the-shelf version of the artificial pancreas would most likely not be available for many years.

Experts observed that early versions of a CLS would likely be highly complicated to operate and, therefore, would be indicated only for a subset of patients who were highly motivated to learn to use the technology and who had access to a multidisciplinary diabetes care team trained in use of a CLS. Additionally, experts indicated that these systems would likely need significant upkeep by users and physicians to ensure their proper function. While experts envisioned that the initial use of these systems would be limited, they saw significant potential for these systems to become widely used after a period of refinement. If sufficient refinement of the systems should occur, experts believe, it could eventually simplify diabetes care for patients and physicians, because the CLS would automate a number of functions currently performed by the patient (e.g., blood glucose testing, insulin administration).

Relative to current treatments, experts envisioned small care-setting shifts, noting that patients would need to have the device implanted and, depending on the ultimate design of the system, might need to return to the physician's office to have the insulin pump reservoir filled.

Experts also suggested that use of the artificial pancreas could increase scientific understanding of diabetes, citing the significant amounts of data that such systems would generate.

Experts also envisioned that early versions of the artificial pancreas would be expensive and most likely lead to increased upfront costs for patients using the systems. However, experts believe that refinement of the systems and wider adoption would eventually reduce their upfront costs. Additionally, several experts noted that the high cost of the artificial pancreas system could be offset somewhat by improved glycemic control, which could result in fewer adverse health outcomes in these patients.

Intervention

Bariatric surgery for resolution of T2DM in patients with BMI <35 kg/m²

Current guidelines specify that bariatric surgery is indicated for individuals who are morbidly obese (i.e., body mass index [BMI] >40 kg/m²) or individuals who are obese with a BMI >35 kg/m² and an associated comorbidity that is expected to improve with weight loss. One such qualifying comorbidity is diabetes, which is highly correlated with obesity. Studies of outcomes of patients with T2DM who have undergone bariatric surgery have demonstrated that more than three-fourths of these patients are able to achieve glycemic control without the use of antidiabetes medications. Basing their opinions on this success, physicians have become interested in the potential of bariatric surgery to treat T2DM in obese patients with BMI <35 kg/m². Currently, insurers generally do not cover bariatric surgery in patients at a lower BMI, and patients would bear the cost, which would vary depending on the bariatric procedure selected.

Bariatric surgeries are classified as purely restrictive, mostly restrictive, or mostly malabsorptive.¹⁶ Restrictive procedures cause weight loss by limiting the amount of food that can be eaten at a meal. Malabsorptive procedures reduce the body's absorption of food.^{17,18} The most common form of bariatric surgery is Roux-en-Y gastric bypass (RYGB) surgery. RYGB has both restrictive and malabsorptive features. For restriction, the stomach is separated (using staples or another method) into a small upper portion and a large lower portion. Food enters only the upper portion (the gastric pouch). The small intestine is cut 15 to 50 cm distal to the ligament of Treitz. The distal small intestine is connected to the gastric pouch, permitting the emptying of food. This creates one limb (the "Roux," or alimentary limb) of a Y-shaped construction. Completion of the Y portion of the reconstruction involves performing an anastomosis (jejunojunction) to connect the proximal end to the side of the Roux limb at least 45 cm downstream to prevent reflux of bile and pancreatic juices into the proximal gastric pouch. The two limbs meet and form a common limb at the most distal section of the small intestine, where food and digestive fluids mix.¹⁶ The most common purely restrictive procedure is laparoscopic adjustable gastric banding (LAGB) in which a band is placed around the upper part of the stomach, which reduces the amount of food that can be ingested.¹⁶ Other less common procedures include the malabsorptive laparoscopic ileal interposition linked to a diverted sleeve gastrectomy, the malabsorptive biliopancreatic diversion, and the malabsorptive laparoscopic duodenojejunal bypass.^{16,18,19}

While bariatric procedures have been shown to be effective in managing T2DM, the procedures are not without serious risks; 10% to 20% of patients undergoing RYGB surgery experience serious complications (e.g., surgical leaks, hernia, wound infection, bowel obstruction), and 1% of patients die of complications. Additionally, RYGB is irreversible and results in permanent anatomic alterations. After surgery, patients require continual dietary supplements to avoid vitamin deficiency and malnutrition.²⁰

In 2010, Geloneze and colleagues presented data from a study in which 40 patients with T2DM and a BMI of 30 to 35 kg/m² were treated using RYGB.²¹ At 1 year postsurgery, patients exhibited improvement in multiple aspects of T2DM. Percent glycated hemoglobin (HbA_{1c}) went from a mean of 9.08% to a mean of 6.04% (66% of patients with HbA_{1c} less than 6%; 22% of patients with HbA_{1c} from 6% to 7%).²¹ Additionally, 50% of patients were able to discontinue use of antidiabetes medications for glycemic control.²¹

Also in 2010, DeMaria and colleagues published a retrospective analysis of outcomes from patients with T2DM and a BMI of 30 to 35 kg/m² whose data were in the Bariatric Outcomes Longitudinal

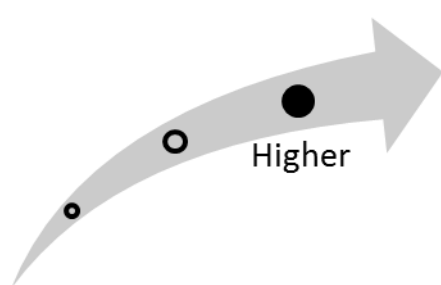
Database.²² The majority of these patients underwent RYGB (n = 109) or LAGB (n = 109), and data suggested early effectiveness of these surgical treatments for resolving T2DM.

In February 2011, FDA approved the use of the LAP-BAND adjustable gastric banding system (Allergan, Inc., Irvine, CA) in patients with a BMI of 30 to 34 kg/m² and an associated comorbidity.²³ Surgical procedures such as RYGB are not subject to FDA marketing approval; they may also be performed on patients with a BMI <35 kg/m², although the procedure is not covered by Medicare or most private third-party payers for BMI <35 kg/m².

Clinical Pathway at Point of This Intervention

Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood sugar levels. First-line treatment typically involves a single hypoglycemic agent (e.g., metformin, sulfonylurea derivative, DPP-4 inhibitor, glucagon-like peptide-1 [GLP-1] analog) and combination therapy if monotherapy is not sufficiently effective. The disease's progressive nature typically results in the need for a proportion of affected people to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually employ more intensive insulin regimens, which typically include a long-acting insulin once or twice per day (basal insulin) plus a short-acting insulin with meals (prandial insulin) to cover increases in glucose levels after meals.^{24,25} Bariatric surgery would provide another treatment option for T2DM in patients who are obese and not achieving adequate blood glucose control with medication or insulin.

Figure 2. Overall High Impact Potential: Bariatric surgery for resolution of T2DM in patients with BMI <35 kg/m²



Overall, experts commenting on this topic believe that bariatric surgery has potential to lead to remission or cure of T2DM in mildly to moderately obese individuals, and its use in this patient population would significantly shift the care model and care setting. However, given the high risks associated with some forms of bariatric surgery and the long-term lifestyle changes mandated by the treatment, experts believe its use in this population would be highly controversial. They questioned whether patients would opt for surgery and whether clinicians would want to advise the

surgery in this patient population. Given the large number of people with T2DM whose BMI is in the 30-to-35 kg/m² range, adoption of the procedure as a treatment for those who do not achieve adequate control of blood glucose with less drastic methods could have a very large impact on the health care system in terms of infrastructure (bariatric surgery services) and shifts in processes of care (from medication to surgery). Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.²⁶⁻³¹ Experts believe that there is a significant unmet need for novel treatments for T2DM, especially potentially curative treatments such as bariatric surgery. One clinical expert stated, "Although any weight loss and, therefore, any bariatric procedure may improve insulin resistance, the RYGBP does appear to improve diabetes by both weight dependent and weight independent mechanisms."³¹ The majority of experts also thought that the theory of using bariatric surgery to treat obese patients with T2DM who do not meet the current BMI limits is sound, citing the

effectiveness of bariatric surgery in resolving T2DM in morbidly obese patients. However, multiple experts noted the lack of studies of long-term outcomes for patients with BMI <35 kg/m².

Additionally, one expert with a research background noted that the mechanism of action by which bariatric surgery affects diabetes is unclear and, therefore, it might not be as efficacious in patients with lower BMIs as in those typically accepted for the surgery. In this vein, multiple experts observed that bariatric surgery in this patient population has significant potential to inform our scientific understanding of obesity, diabetes, and/or the metabolic syndrome.

Experts believe that use of bariatric surgery in this patient population would represent a significant shift in treatment models for this condition. Relative to current medical management of T2DM in the home setting, use of bariatric surgery would shift some of these patients to inpatient surgical procedures as well as increase the need for services involved in postsurgical management of bariatric surgery patients (e.g., dietary supplementation). One expert with a clinical perspective also noted that initiation of treatment with this therapy might be offered and commence sooner, ultimately reducing “the overall burden of disease on society.”³¹ Given the large number of potentially eligible patients in the U.S., widespread use of bariatric surgery to treat T2DM in mildly obese patients could necessitate increases in bariatric surgery infrastructure and staffing.

This shift in care model also has implications for the cost of T2DM treatment. Experts agreed that while use of bariatric surgery in this patient population would generate high upfront costs, it has the potential to reduce long-term costs through improved control of diabetes symptoms and/or reduced need for antidiabetes medications.

Experts suggested that there would be significant reluctance on the part of patients to opt for this treatment given its invasiveness, high adverse event rate, and the requirement for long-term changes in dietary intake. However, experts also cited the potential for bariatric surgery to resolve T2DM as one reason why some patients could opt for the treatment. Experts believe that considerable controversy would surround the risk-benefit ratio of the treatment and questioned whether physicians would be likely to recommend the treatment to patients.

Intervention

Buccal insulin (Oral-lyn) for treatment of diabetes

Diabetes is a class of diseases involving insufficient insulin secretion resulting in hyperglycemia that affects approximately 23.6 million Americans.³² Diabetes is often treated by providing the patient with exogenous insulin, which is typically administered by injection or continuous infusion using an insulin pump.³² However, many patients consider insulin injections burdensome, and not all patients are candidates for insulin pump use, which can reduce adoption of or adherence to insulin treatment by patients with diabetes who could benefit from it.³² Therefore, novel insulin delivery methods that do not involve injection are being sought.

One such noninjectable insulin in development is a liquid formulation of human insulin delivered as a buccal spray, called Oral-lyn™ (Generex Biotechnology Corp., Toronto, Ontario, Canada).³³ A buccal spray formulation requires transforming liquid insulin into an aerosol in combination with a pharmaceutical-grade chemical propellant. This process allows for delivery to the buccal mucosa by way of Generex's proprietary inhaler known as RapidMist™, which stores the liquid insulin. The patient puffs on the inhaler in a fashion similar to an asthma inhaler to administer the insulin; however, absorption is limited to the mouth with no entry into the lungs. This technology allows for much faster absorption of insulin and a shorter total duration of activity because of the rich vascularity of the buccal mucosa, potentially making buccal insulin an ideal insulin to control glycemic excursions after meals.³³

Twenty-five trials of buccal insulin have been completed since 1999. A recent review summarized the preliminary data as demonstrating that the amount of insulin absorbed by patients was directly proportional to the amount of buccal spray administered and that buccal insulin had a faster onset and shorter duration of action than injected insulin.³⁴ Additionally, administration of buccal insulin was generally reported as being well tolerated in the studies; however, some patients experienced mild transient dizziness during dosing.³⁴ A phase III trial comparing use of Oral-lyn as a prandial insulin to injected human insulin was initiated in April 2008.³⁵ The trial is tracking HbA_{1c} levels and rate of hypoglycemic episodes in 500 patients with T1DM who were using an intermediate-acting basal insulin and were randomly assigned to receive either Oral-lyn or injectable insulin as prandial insulin.³⁵ While the trial's estimated completion date was September 2011, it appears to be ongoing.³⁵

Oral-lyn is currently available in the U.S. to patients with life-threatening diabetes and no other treatment options, and it is approved under FDA's treatment investigational new drug (IND) program.³⁶

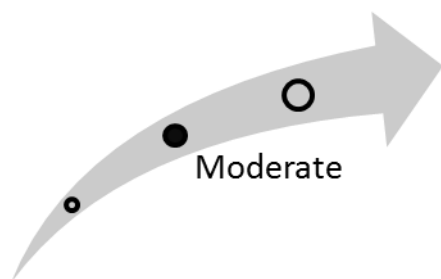
Clinical Pathway at Point of This Intervention

T1DM typically occurs early in life and results from a chronic autoimmune condition that leads to the destruction of pancreatic cells responsible for producing insulin.²⁵ Treatment for T1DM includes self-injection or infusion of insulin to maintain blood glucose levels. Frequent daily blood glucose monitoring, using fingerstick blood tests or electronic continuous glucose monitors, helps the individual with diabetes to self-administer the proper amount of insulin. Also essential to successful blood glucose management are diet, exercise, and lifestyle changes. Patients using insulin therapy generally use a long-acting insulin once or twice per day (basal insulin) plus a short-acting insulin with meals (prandial insulin) to cover postmeal increases in glucose levels.³⁷

T2DM typically occurs later in life (although incidence in a younger population has been growing as a result of obesity) and results from development of peripheral insulin resistance and an insulin-secretory defect. Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood

sugar levels. First-line treatment typically involves a single oral hypoglycemic agent; however, if adequate glycemic control is not achieved, a combination of hypoglycemic agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. The progressive nature of the disease typically results in the need for many people with T2DM to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually use insulin in the same manner as patients with T1DM.^{24,25}

Figure 3. Overall High Impact Potential: Buccal insulin (Oral-lyn) for treatment of diabetes



Overall, experts providing comments on this topic believe that buccal insulin has potential to improve diabetes treatment by providing a noninjectable alternative to injectable insulin, which could transition more patients to insulin therapy and potentially improve patient adherence to insulin dosing. However, experts noted that buccal insulin's efficacy has not yet been conclusively demonstrated and that trials of the drug were moving slowly. This may be due in part to the fact that this product is the only product of the company developing it, and funding to complete the

required trials may be an issue. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.³⁸⁻⁴³

Experts agreed that the current lack of a noninjectable insulin represents a significant unmet need. Experts suggested that many patients delay adoption of insulin therapy and/or have poor adherence to recommended insulin dosing because of their dislike of injections and that buccal insulin could improve these aspects of insulin therapy. However, multiple experts noted potential limitations of buccal insulin in meeting this unmet need. One clinical expert noted that buccal insulin was available only in a fast-acting form that could replace postprandial insulin injections, but not basal insulin injections, which use longer-acting insulin. Additionally, multiple experts noted the previous failure of an inhaled noninjectable insulin product (Exubera®, Pfizer, Inc., New York, NY) that FDA approved but was subsequently withdrawn from the market. Poor adoption of this inhaled insulin product was part of the reason for its withdrawal. Buccal insulin and the device used to administer it is very different from the inhaled insulin and device that comprised inhaled insulin, so these concerns are likely not very relevant to this product.

Experts generally believe that the principle of buccal insulin administration is sound and that preliminary data indicated its efficacy; however, several experts noted that results from large-scale trials comparing buccal insulin to existing insulin products would need to demonstrate equivalence before buccal insulin would be widely adopted. One clinical expert noted that while prior studies showed that buccal insulin's mechanism of action may be sound, absorption in patients may vary. One research expert noted that patients with life-threatening diabetes and no other treatment options have had access to buccal insulin through the FDA's treatment IND program for the past 2 years.

While several of the experts suggested that buccal insulin would have a small impact on diabetes treatment because it would replace only some of the injected insulin treatment, other experts envisioned significant impact in the way patients with T2DM who need insulin are treated. These experts cited the willingness of many patients to transition from injected insulin to an oral hypoglycemic medication and suggested that the availability of a noninjectable insulin could shift the

point in disease progression at which many patients with T2DM adopt insulin use. One clinical expert noted that patient quality of life would be significantly improved for those who prefer an oral hypoglycemic agent to insulin injection.

Experts commenting on this topic were divided on the issue of patient training. Some suggested that buccal insulin would require less patient training than current insulin administration modalities, citing the delivery system's purported similarity to an asthma inhaler. However, one clinical expert questioned how an asthma-inhaler-like delivery device would avoid lung exposure as Oral-lyn is purported to do and suggested that patients could require significant training to ensure consistent delivery of the appropriate insulin dose.

Experts were similarly divided on the potential impact of buccal insulin on costs. One expert with a research background suggested that buccal insulin would be only marginally more expensive than regular insulin, based on the cost of buccal insulin in the current treatment IND program. Conversely, one clinical expert suggested that buccal insulin would likely be significantly more expensive than regular insulin, drawing a parallel to the previous pricing of Exubera. Irrespective of the magnitude of cost increase relative to regular insulin, the increased cost of buccal insulin has the potential to be offset by improved treatment outcomes and less need to treat complications of poor glycemic control in patients with diabetes, experts noted. Lastly, several experts questioned whether use of buccal insulin would ultimately be covered by insurance, given the proven efficacy of injectable insulin, or suggested it might be used in a stepwise fashion after other regimens have failed to achieve desired effects. While the potential for increased costs and lack of insurance coverage could inhibit patient adoption of buccal insulin, experts believe that patients would be eager to adopt the technology.

Intervention

New exenatide formulations to improve diabetes treatment adherence

Injectable GLP-1 agonists available in the U.S. include Byetta®, a short-acting form of exenatide administered as a fixed-dose, subcutaneous injection, administered twice daily, and liraglutide (Victoza®), a longer-acting GLP-1 agonist developed by Novo Nordisk AS (Bagsvaerd, Denmark) that is injected once per day. Two therapies, extended-release exenatide (Bydureon™, Eli Lilly and Co., Indianapolis, IN, Amylin Pharmaceuticals, Inc., San Diego, CA, and Alkermes, Inc., Waltham, MA) and subcutaneously delivered exenatide (ITCA 650, Intarcia Therapeutics, Inc., Hayward, CA, via Duros® pump system) are currently in development for treatment of T2DM to improve drug efficacy and tolerability as well as patient adherence.

Bydureon is administered once weekly by subcutaneous injection.^{44,45} It is intended to achieve glycemic control in patients with T2DM for whom optimal glycemic control has not been achieved using other drugs such as metformin and/or sulfonylurea.⁴⁶ It mimics the function of GLP-1, a naturally occurring hormone that stimulates release of native insulin and inhibits glucagon release to lower blood glucose levels. GLP-1 also promotes a feeling of fullness and satiety to reduce continued intake of exogenous glucose.⁴⁶ Naturally occurring GLP-1 has a very short half-life and is not a viable therapeutic agent for long-term control. As a result, GLP-1 agonists such as exenatide that mimic the function of GLP-1, but have longer half-lives, are being investigated as therapeutic alternatives.⁴⁶

Blevins (2011) reported results from a phase III trial of extended-release exenatide. Patients received standard exenatide 5 mcg twice daily for 4 weeks followed by 10 mcg twice daily for 20 weeks or exenatide extended release 2 mg once weekly. At 24 weeks, the once weekly group produced significantly greater changes from baseline (least squares mean \pm se) in HbA_{1c} versus twice daily ($-1.6 \pm 0.1\%$ vs. $-0.9 \pm 0.1\%$; $p < 0.0001$) and fasting plasma glucose (-35 ± 5 mg/dL vs. -12 ± 5 mg/dL; $p = 0.0008$). Similar reductions in mean body weight from baseline to week 24 were observed in both groups (-2.3 ± 0.4 kg and -1.4 ± 0.4 kg). Both treatments were generally well tolerated. Transient and predominantly mild to moderate nausea, the most frequent adverse event, was less common with once-weekly administration (14%) than with twice daily (35%). Injection-site reactions were infrequent, but more common with once weekly dosing. No major hypoglycemia events occurred.⁴⁷

In July 2011, Amylin Pharmaceuticals, Eli Lilly, and Alkermes announced the formal submission of a reply to the complete letter response issued by FDA over potential safety concerns. Along with updates to safety information about ongoing or completed studies, included in the response were recent results showing that “exenatide, at and above therapeutic levels, did not prolong the corrected QT interval in healthy individuals as defined by the FDA’s published guidance.”⁴⁸ In August 2011, the companies announced that FDA had acknowledged resubmission of the application for extended-release exenatide. An action date has been set for January 28, 2012.⁴⁹ In November 2011, Amylin Pharmaceuticals and Eli Lilly formally announced cessation of their partnership for development of exenatide, leaving sole development responsibility to Amylin Pharmaceuticals.⁵⁰ Amylin stated plans to continue its commercialization pathway in the U.S.

ITCA 650 is another proprietary formulation of exenatide that remains stable at body temperature for extended periods of time and can, therefore, be administered as a continuous subcutaneous infusion. The Duros delivery system is a semipermeable osmotic mini-pump that a physician or physician assistant inserts into the patient’s arm or abdomen during an outpatient procedure that takes about 5 minutes. The matchstick-sized device delivers a continuous dose of exenatide over an extended period of time, which is intended to minimize the nausea associated with twice-daily dosing. Duros technology has been available since 2000 and is being tested for delivery of other types of drugs as well. The intervention ITCA 650 is a novel use of this stable formulation of exenatide with Duros.^{51,52}

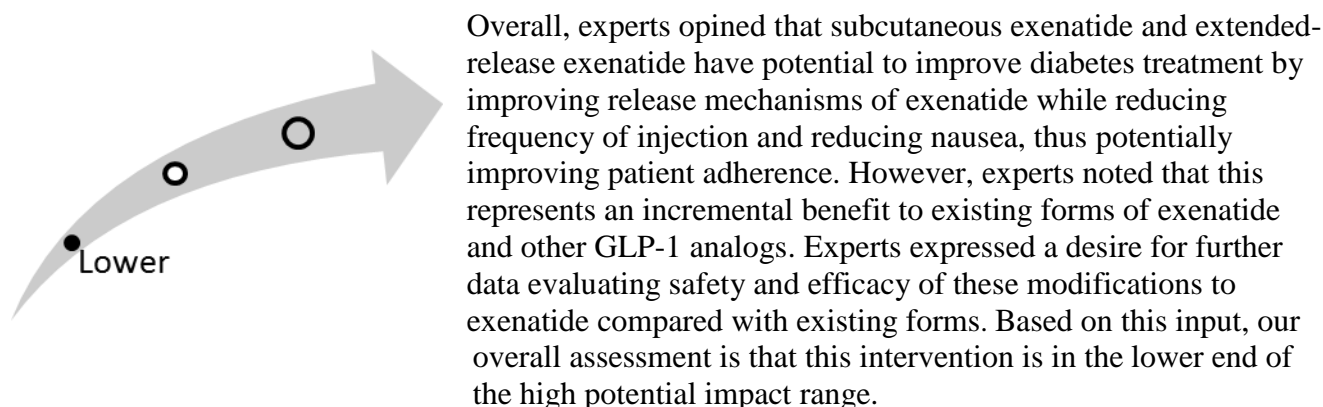
Intarcia reported final results from its phase II program on ITCA 650 in September 2011 and announced a collaboration with Quintiles to begin a phase III program of six trials by the end of 2011.^{53,54} After an initial 12-week treatment period comparing the drug (20 or 40 mcg/day 0 with twice-daily exenatide injections, treatment continued at one of four dosing levels: 20, 40, 60 or 80 mcg/day through week 24, and patients could continue for an additional 24 weeks, for a total of 48 weeks of treatment. Eighty-five percent of enrolled patients continued and the company reported in September 2011 that sustained reductions were observed in HbA_{1c}, fasting plasma glucose and weight across all treatment arms between 24 and 48 weeks. The greatest reductions were reported in the 60 and 80 mcg/day groups, but were not statistically different between those two groups.⁵⁵

Alza Corp., a unit of Johnson & Johnson, Inc. (New Brunswick, NJ), manufactures the Duros drug delivery technology that can be used for a range of indications. In 2000, the company received marketing approval from FDA for the Duros technology.^{8,8,8,51,56,57} Intarcia licensed exclusive rights for use of Duros from Alza Corp.

Clinical Pathway at Point of This Intervention

T2DM is a chronic disease that typically occurs later in life (although incidence in a younger population has been growing as a result of obesity) and results from development of peripheral insulin resistance and an insulin-secretory defect. Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood sugar levels. First-line treatment typically involves a single oral hypoglycemic agent; however, if adequate glycemic control is not achieved, a combination of hypoglycemic agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. The progressive nature of the disease typically results in the need for many people with T2DM to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually use insulin in the same manner as patients with T1DM.^{24,25}

Figure 4. Overall High Impact Potential: New exenatide formulations to improve diabetes treatment adherence



Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on subcutaneous exenatide using Duros.⁵⁸⁻⁶³ Perspectives on extended-release exenatide (Bydureon) were received from seven experts.⁶⁴⁻⁷⁰ Given that these two therapies are geared towards extending release and improving efficacy of exenatide, expert comments have been combined or synthesized to represent opinions on modifications to exenatide.

Experts agreed that while any new therapy for the treatment of diabetes would be welcome, these new modifications to exenatide may be incremental and minimally address the unmet need. In the case of subcutaneous exenatide, most experts said that exenatide is already available in the twice-daily injectable form. One expert with a clinical perspective believes that while continuous release of exenatide without injection may improve patient adherence, “long term efficacy is uncertain because tachyphylaxis may develop in response to constant exposure to exenatide.”⁷¹ In the case of once-weekly exenatide, most experts were optimistic about its potential to address the unmet need. While some experts referenced the existence of GLP-1 agonists on the market, they agreed that this therapy could “reduce HbA_{1c} levels” and promote weight loss.⁶⁹

Experts generally believe that the underlying mechanisms for both modifications to exenatide appear sound, in large part due to the existence of currently approved forms of exenatide and other GLP-1 analogs already on the market. One expert with a clinical perspective believes that the mechanism of action for subcutaneous infusion of exenatide would “deliver a constant dose over long periods, in contrast to sharp peaks resulting from twice daily injections.” The same expert noted that regardless of delivery system, subcutaneous exenatide would still induce nausea that is purportedly reduced, according to the manufacturer. Several experts noted that subcutaneous exenatide use would also result in effective weight loss. In regards to extended-release exenatide, one expert with a research perspective believes that while clinical studies show that this therapy “reduces HbA_{1c} levels, reduces weight, and has minimal short-term adverse events,” there are still concerns over long-term effects of extended-release exenatide, “particularly those associated with cardio-vascular health.”⁶⁵

Collectively, experts commenting on both modifications to exenatide believe that as long as these forms of exenatide therapy do not pose risk of serious adverse events (i.e., cardiac abnormalities, carcinomas), patient adherence and quality of life would improve with its use, thus improving patient health outcomes. Referring to subcutaneous exenatide, one expert with a clinical perspective was uncertain whether subcutaneous infusion of exenatide via the Duros osmotic pump would improve patient health outcomes when compared with twice-daily exenatide and other comparators. In regards to extended-release exenatide, one expert with a clinical perspective specifically referenced a study showing increased incidence of thyroid cancer in mice as a reason to question whether this therapy will improve health outcomes.

According to expert comments, extended-release exenatide and subcutaneous exenatide use would have minimal impact on clinical and patient learning curves. Experts believe that the previous existence of and exposure to injectable forms of exenatide and other GLP-1 analogs would minimize a patient’s learning curve with regards to extended-release exenatide. Most experts believe that in the case of subcutaneous exenatide, the learning curve for clinicians would be minimal based on the perceived simplicity of the procedure. One expert with a clinical perspective believes, “There would need to be some education on how to insert the device, but based on the information, it is not difficult.”⁶² Another expert stated that it would only take a few minutes to implant the Duros osmotic pump subcutaneously, implying that the level of difficulty regarding the procedure is relatively low.

Experts were divided with regard to the potential impact of these modifications to exenatide on costs. While some experts believe that per-patient costs would increase with both forms of exenatide, some experts noted that an increase in patient adherence and subsequent decrease in disease complications would lower long-term per-patient costs. Regarding extended-release exenatide, one expert stated, “Initially, the intervention may be more costly than some first-line agents currently used for T2DM. If the intervention is safe and effective, there would be a decrease cost to the patients, families, health care facilities, and third-party payers.”⁷⁰ Some experts are undecided on the potential impact on cost, making a case for an increase or decrease in per-patient cost. In regards to subcutaneous exenatide, one expert with a clinical perspective added, “Physicians may have to be

reimbursed for the procedure. However, it is possible that the long-term cost of miniosmotic pump insertion and subcutaneous exenatide infusion will be similar or cheaper than twice daily exenatide injections.”⁷¹

Intervention

SGLT2 inhibitors for treatment of T2DM

While many current treatments help control glucose levels, these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood sugar with current treatments. Therefore, novel treatments for T2DM are highly sought. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of drugs in development for T2DM. SGLT2 is a type of solute carrier predominantly found in the proximal convoluted tubule of the kidney cortex. Its function is to reabsorb glucose from the glomerular filtrate of the kidney into the bloodstream. Therefore, inhibition of SGLT2 activity has the potential to reduce glucose reabsorption and increase glucose excretion through urine, reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors can purportedly be used in conjunction with other oral agents and insulin without significant adverse effects. They may also help promote weight loss in overweight and obese patients. Multiple SGLT2 inhibitors are being tested for T2DM to regulate blood sugar levels, lower the risk of hyperglycemia, and decrease the risk of comorbidities associated with chronically increased levels of blood glucose.⁷²

The SGLT2 inhibitor furthest along in development is dapagliflozin (AstraZeneca, London, UK, in collaboration with Bristol-Myers Squibb, New York, NY).⁷³ Dapagliflozin has been studied in multiple phase III trials as a monotherapy and combination therapy (with oral hypoglycemic agents and insulin) and to assess its cardiovascular safety profile.⁷⁴ AstraZeneca and Bristol-Myers Squibb announced results from an extension of a phase III trial that showed the “investigational compound dapagliflozin plus metformin sustained greater mean reductions from baseline in blood sugar levels (glycosylated hemoglobin levels, or HbA_{1c}) in patients with type 2 diabetes inadequately controlled with metformin alone, as compared to placebo plus metformin over 102 weeks.”⁷⁵ Results from this study also showed reductions that “ranged from -0.48 percent in patients receiving dapagliflozin 2.5 mg plus metformin to -0.78 percent in patients receiving dapagliflozin 10 mg plus metformin, as compared to 0.02 percent in patients taking placebo plus metformin.”⁷⁵ Adverse events were reportedly balanced across treatment groups, with “events suggestive of genital infections and urinary tract infections more common in the dapagliflozin groups.”⁷⁵

Results from a phase III randomized controlled trial in 546 patients with T2DM with poorly controlled glucose after 24 weeks of treatment showed that reductions in HbA_{1c} levels were significantly higher in the dapagliflozin groups than placebo (2.5 mg: -0.67%; 5 mg: -0.70%; 10 mg: -0.84%; placebo: -0.3%, $p \leq 0.0002$ for all comparisons).⁷⁶ Patients treated with dapagliflozin also exhibited lower fasting plasma glucose levels, increased urinary glucose excretion, and greater declines in mean body weight. More patients in the dapagliflozin arms achieved HbA_{1c} levels of less than 7%.⁷⁶

Results from a phase III trial of dapagliflozin in 485 treatment-naïve patients with T2DM with baseline HbA_{1c} levels between 7% and 10% were also published in 2010.⁷⁶ After 24 weeks of treatment, a greater proportion of patients in the dapagliflozin arms achieved HbA_{1c} levels of less than 7% than in the placebo arm (2.5 mg: 41%; 5 mg: 44%; 10 mg: 51%; placebo: 32%). Dapagliflozin use also resulted in greater declines in fasting plasma glucose levels and increased urinary glucose excretion.⁷⁶ In these and other trials, dapagliflozin has been reported as well tolerated; however, reports of increased rates of genitourinary infections related to increased glucose levels in urine were reported in some trials.⁷⁶ Additionally, long-term safety data on renal function have not yet been reported.

Based on these and other trial results, the companies submitted a new drug application (NDA) to FDA in December 2010, and FDA's decision date was expected to be October 28, 2011.⁷⁴ However, in July 2011, the FDA Endocrinologic and Metabolic Drugs Advisory Committee voted against recommendation for approval of dapagliflozin for treatment of T2DM amid safety concerns and potential risk of adverse events associated with the SGLT2 inhibitor. The manufacturer is continuing with submission of additional data as amendments to the NDA, which include data from studies involving approximately 6,000 individuals in 40 clinical trials.⁷⁷ In October 2011, FDA extended the decision date for the dapagliflozin's NDA to January 28, 2012.⁷⁸

Additional SGLT2 inhibitors at earlier stages of development include the following:

Phase III trials

- Canagliflozin (Johnson & Johnson, Inc., New Brunswick, NJ)⁷⁹
- Tofogliflozin, also known as CSG-452 or RG7201 (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan, in collaboration with F. Hoffmann-La Roche, Ltd., Basel, Switzerland)⁸⁰
- BI-10773 (Boehringer Ingelheim GmbH, Ingelheim, Germany)⁸¹
- TS-071 (Taisho Pharmaceutical Holdings Co., Ltd., Tokyo, Japan)⁸²

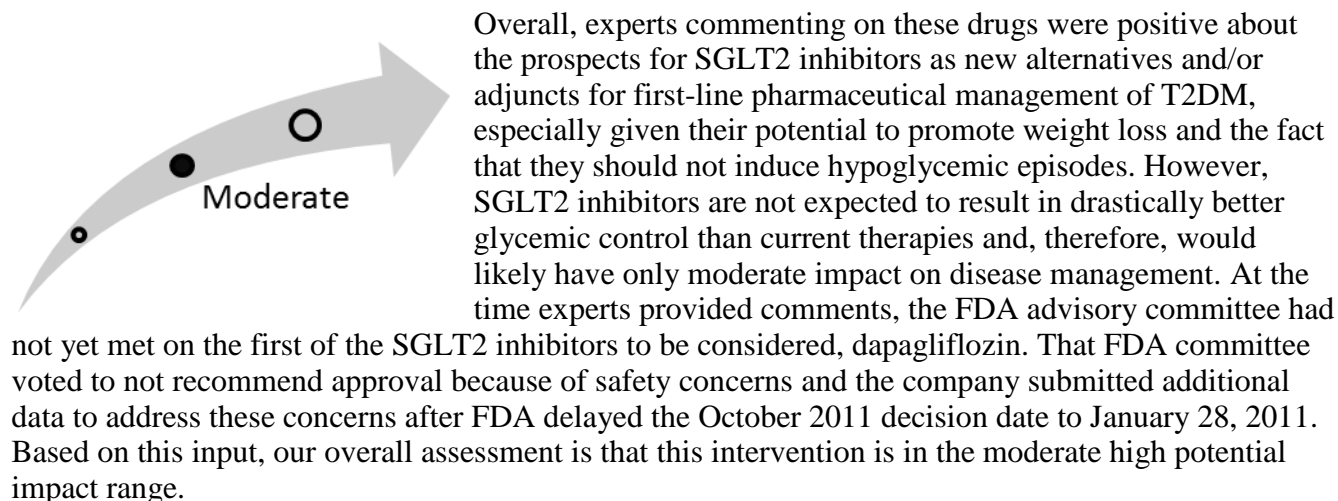
Phase II trials

- Ipragliflozin, also known as ASP1941 (Astellas Pharma, Inc., Tokyo, Japan)⁸³
- LX4211 (Lexicon Pharmaceuticals, Inc., The Woodlands, TX)⁸⁴

Clinical Pathway at Point of This Intervention

Initial treatment of T2DM includes diet control, exercise, and self-monitoring of blood glucose. If these measures are inadequate, physicians also prescribe medication to control blood sugar levels. First-line treatment typically involves a single hypoglycemic agent (e.g., metformin, sulfonylurea derivative, DPP-4 inhibitor, GLP-1 analog); however, if adequate glycemic control is not achieved, a combination of hypoglycemic agents with different mechanisms of action may have additive therapeutic effects and result in better glycemic control. The progressive nature of the disease typically results in the need for a proportion of people with T2DM to take insulin for adequate blood glucose control. Basal insulin may be added to existing hypoglycemic agents to achieve glycemic control; however, many patients with T2DM will eventually employ more intensive insulin regimens, which typically include a long-acting insulin one or two times per day (basal insulin) plus a short-acting insulin with meals (prandial insulin) to cover increases in glucose levels after meals.^{24,25}

Figure 5. Overall High Impact Potential: SGLT2 inhibitors for treatment of T2DM



Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on dapagliflozin.⁸⁵⁻⁹⁰ Perspectives on three additional SGLT2 inhibitors in slightly earlier development (BI 10773, ipragliflozin, LX4211) were received from a total of 18 experts—six per individual SGLT2 drug.⁹¹⁻¹⁰⁸ Given the similarity of these drugs to one another, experts' comments on the individual topics overlapped significantly when considered in aggregate. The synthesis of their opinions on dapagliflozin is representative of the class as a whole.

While several experts noted the current availability of multiple treatment options for T2DM, the majority indicated they believe that SGLT2 inhibitors have potential to meet a significant unmet need in T2DM treatment. The reasons they gave were as follows: the limited effectiveness of current therapies for all patients; the potential for hypoglycemic events with current therapies (which SGLT2 inhibitors are purported to avoid); and the role that SGLT2 inhibitors appear to play in weight loss to some extent, in addition to glycemic control.

Experts believe that the proposed mechanism of action of reducing blood glucose levels by preventing renal reabsorption of glucose through inhibition of SGLT2 is valid. However, one clinical expert expressed skepticism of SGLT2's purported ability to cause weight loss, noting the disappointing weight loss results of diabetes medications that have made this claim in the past. However, multiple experts noted SGLT2's novel mechanism of action (removal of glucose through the urine) and that initial trial results indicated that SGLT2s can induce some weight loss. One clinical expert expressed concern over adverse events associated with dapagliflozin. This same expert questioned whether patients would comply in light of data from a clinical study that revealed that the incidence of genitourinary infections increased in patients taking dapagliflozin. While experts deemed initial data on treatment efficacy promising, they expressed concerns regarding reports of urinary tract infections that would need to be examined in the larger set of ongoing clinical trials.

Many of the experts suggested that SGLT2 inhibitors would not change treatment models, citing the availability of multiple additional oral medications to aid in glycemic control. However, one clinical expert suggested that the potential for SGLT2 inhibitors to promote weight loss, in addition to aiding glycemic control, could alter the sequence in which some physicians prescribe T2DM drugs.

Experts expected that SGLT2s would encounter few barriers to adoption should they prove to be safe and effective. Further, they opined that patient and clinician preference for T2DM treatment would likely come down to side-effect profiles relative to other options. Lastly, experts expected that SGLT2 inhibitors would command a slight price premium relative to existing treatments.

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