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from the editor

We at diaTribe are grateful for quite a bit this Thanksgiving – several new diabetes devices and a couple of diabetes drugs approved by the FDA in recent months (and more by global regulatory authorities), the FDA coming in ON TIME (today!) with their advice for researchers and scientists and others developing the artificial pancreas, a grand World Diabetes Day celebration in San Francisco and around the world, and a great diaTribe family of writers, editors, and (most importantly) readers. A few more details on the newest news – as you might have heard, the FDA previously committed to release a draft guidance document on the artificial pancreas by December 1. Essentially, this draft guidance will tell companies and researchers what sorts of standards an artificial pancreas would need to meet in order to gain approval. Doctors, scientists, educators, advocacy groups, and patients were understandably eager to make suggestions to the FDA (and to encourage the agency to meet its self-established deadline), as we describe in this issue’s NewNowNext. We were very excited (and thankful!) to wake up today and see that all this pressure pushed the agency to come through and release the guidance document on December 1, as promised. For those interested in reading through it, visit http://1.usa.gov/shk3ox. Opinions about the document will likely emerge in the coming weeks, but in a conversation with Dr. Aaron Kowalski this afternoon, we learned that JDRF is encouraged after their initial review. Kudos to the nonprofit for so much work on behalf of so many patients.

Still, it will be several years until even hybrid “closed-loop” systems come to market, and even then diabetes management will remain a complex job that demands daily (and often hourly and sometimes minute-to-minute) focus. The upside is that companies have been putting a priority on making their devices and drugs as simple to use as possible. This month, we discuss some recent breakthroughs on this front, including the new t:sling insulin pump from Tandem. Additionally, the FDA has a lot on its plate in early 2012, including whether to approve a slew of new medicines that have promise to make life easier for patients, such as Bydureon, dapagliflozin, and Qnexa.

Simplicity is also the goal for Glooko, a new IT/social media diabetes company that seeks to remove some hassle out of downloading data from a blood glucose meter. Glooko’s system consists of a cord that quickly uploads data from any of six widely used meters to the Apple iPhone, iPad, and iPod touch. Once the data are on the devices, users can view it, make notes, and send summaries to their healthcare providers or families with a new app called Glooko Logbook. To do our part spreading the latest technologies (and to hear your thoughts about diabetes management on the web), we’re giving away free Glooko MeterSync Cables to the first 50 people who take a quick survey (see this month’s NewNowNext)! With that, onward – and thank you, as always, for your readership.

Yours,

Kelly L. Close
quotable quotes

“You can’t stare at your CGM 24 hours a day. A computer can.”
- Aaron Kowalski, PhD (Juvenile Diabetes Research Foundation, New York, NY) on the artificial pancreas on JDRF’s World Diabetes Day Webcast.

“I don’t think we’ll ever be perfect, but that shouldn’t be the enemy of the good.”
- Bruce Buckingham, MD (Stanford University, Palo Alto, CA) on the high expectations for the artificial pancreas at the Diabetes Technology Meeting, Burlingame, CA, October 29, 2011.

“I do think it’s getting better, but it’s still not right. I’m not overly optimistic, but the signs are there. We’ve gotten a few approvals in fewer than 30 days. It makes me encouraged.”
- Michael J. Billig (Experien Group, Sunnyvale, CA) on the improving regulatory environment at the JDRF Silicon Valley Panel, East Palo Alto, CA, November 18, 2011.

“In this environment, we need to shift from a mindset of ensuring drug safety to one of assuring a favorable risk benefit profile, where ... seriousness of events and patients’ views of acceptable risk drive benefit-risk tradeoffs.”
- Sanjay Kaul, MD (Cedars Sinai Medical Center, Los Angeles, CA) at the American Heart Association meeting, Orlando, FL, November 15, 2011.

“When you see that high number on the meter – it’s just a number. It’s not a statement of self esteem.”
- Bill Polonsky, PhD, CDE (Behavioral Diabetes Institute, San Diego, CA) at TEDx Del Mar, San Diego, CA, October 15, 2011.
FDA Approves Tandem’s t:slim Touchscreen Insulin Pump; Company Plans to Launch in the US in the First Half of 2012

Tandem Diabetes Care recently announced that its much anticipated t:slim insulin pump had received FDA clearance. This new pump features a color touchscreen and sleek software – innovations that we’ve come to expect in the consumer electronics space but are relatively new to the medical device space. The t:slim is up to 25% slimmer than the Animas Ping and Medtronic Paradigm insulin pumps, and also includes a rechargeable battery and a 300-unit insulin reservoir. For the data-driven, Tandem’s t:slim has USB connectivity for downloading 90 days of data to t:connect, a web-based application compatible with Macs and PCs. The t:slim insulin reservoir (what Tandem calls a ‘cartridge’) is also designed with a standard luer lock connection, allowing it to connect to all commercially available infusion sets with luer connectors (e.g., Comfort, Cleo, Inset, or Quick-set). We believe the t:slim will draw more people to insulin pumping. Currently, the t:slim is only approved for patients 12 years and older, although we believe Tandem will eventually conduct studies in younger children to expand this indication. Until that time, we suspect some doctors and educators may prescribe it “off-label” to patients younger than 12 years old.

We first saw the pump at last year’s AADE annual meeting (see NewNowNext in diaTribe #25) and had the opportunity to demo it in November right after it received clearance. We changed a reservoir cartridge, primed an infusion set, gave a bolus of saline, changed settings, and extensively navigated through the pump’s software interface. Holding the actual pump and leafing through the menus was a valuable experience for us; it feels more like using an iPhone than a traditional insulin pump. The influence of Steve Jobs is certainly apparent at first glance: the color touchscreen, the button at the top of the device to turn the screen off, and a single button push to return to the home screen. The demo left us more convinced that the t:slim is quite an innovative insulin pump.

Big picture, the pump’s user interface is a major highlight – it’s easy to use, intuitive, fast, sensitive to touch, and does both the obvious...and less obvious quite well. For example, we liked the insulin-on-board data on the home screen, the user confirmation screens and alarms, and the highly customizable profiles. As part of the development of the pump, Tandem gathered insights from over 4,000 people before deciding on the final design, paying particular attention to optimizing the pump’s software and user interface. For instance, the t:slim is said to significantly reduce the number of keystrokes to use advanced features compared to other pumps – we like that, since it means users will have to think about diabetes less, all else equal. Similar to the iPhone, returning to the home screen is possible at any time using a “bail out button.” Remarkably, in user studies, the majority of patients never referred to the instruction manual, and on average, the t:slim’s user interface is said to take about 90 minutes to learn. The screen was larger or comparable to other pumps on the market, and seemed clearer and more readable than other pumps we’ve seen.

Tandem’s t:slim also lived up to its name quite well, with a slim profile about the thickness of a deck of cards. The pump had a more durable feel than we expected, and it will be manufactured from Tandem’s headquarters in San Diego. The reservoir change process was pretty automated; on-screen messages guided the process, which centers on a Tandem-supplied, gum pack-sized cartridge that holds the insulin (up to 300 units) and contains the pump’s novel insulin delivery mechanism. Instead of conventional piston driven delivery, where a mechanical screw drives a syringe built into a reservoir (the way
a Medtronic or Animas or Roche pump works), the t:slim uses a micro-delivery technology. This means that very small amounts of insulin are shuttled from the reservoir to the infusion set, and the full insulin supply is never directly exposed to the patient’s body (as it is with other pumps). The t:slim also uses a volume-based technology to determine how much insulin has been pumped, unlike traditional syringe pumps that measure the action of the syringe but not how much fluid has actually been dispensed. Notably, the pump can deliver basal rates as low as 0.1 units per hour and in increments of as little as one one-thousandth of a unit of insulin (0.001 units). This may represent a higher level of accuracy from other pumps on the market, and we would be very interested to see pump comparison studies conducted. Of course, Tandem’s insulin delivery technology is completely new and unproven, so all eyes will certainly be on the company in the first few months after launch to ensure patient safety. While the FDA clearance carries significant weight on the safety front in particular, the new pump has not been used in large groups of patients over long periods of time yet.

As noted, we were initially concerned about the t:slim’s durability, but Tandem has reportedly tested the pump for both accidental drops and water. The pump is similar to an iPhone in that it is “drop resistant” — i.e., the screen can crack given a drop is significant enough, but as we understand it, warranty programs will be available. Typically, “the devil is in the details” with regard to such programs, so we hope it is one that is robust. Encouragingly, Tandem has informed us that if a user accidentally cracks the screen, the pump would be replaced under t:slim’s warranty. Tandem will also provide protective cases and screen covers in the pump’s starter kit, and other accessories will also be available for purchase. Unlike the Animas pumps and Insulet’s OmniPod, the t:slim is not waterproof, which is a detraction. According to the company, t:slim has been tested to function in three feet of water for 30 minutes (what’s known as an IPX7 rating, similar to Medtronic pumps). However, we know patients who have had water damage problems with Medtronic and other pumps despite this indication, so we look forward to greater clarity on t:slim’s durability in a more real world setting.

While the FDA has cleared the pump to be sold in the US, Tandem is still building its business operations and plans to launch the t:slim during the first half of 2012. Reimbursement information will be forthcoming. We’re very glad to finally see the t:slim approved after six months at FDA and we eagerly await giving it a real test drive in the near future. --AB/KC

Dexcom and Roche Announce Partnerships for Future-Generation Integrated Pump-CGM Systems, Selling Dexcom Seven Plus to Physicians for Short-Term Use with Their Patients

Self-monitoring of blood glucose (SMBG, i.e., fingersticks) and continuous glucose monitoring (CGM, i.e., wearing a sensor) sometimes seem like rival technologies in the world of diabetes management. However, that is not exactly true: people using CGM still take fingerstick measurements to calibrate the sensor and to confirm its accuracy when dosing insulin. The SMBG-CGM ‘rivalry’ is not necessarily true at a commercial level, either, as we saw in two recent partnerships between Roche (maker of Accu-Chek blood glucose meters and Accu-Chek pumps) and Dexcom (maker of the Seven Plus CGM system). One deal is about developing a handheld device that will communicate with Dexcom’s next generation CGM sensor and two different Roche pumps; one is about encouraging physicians to prescribe short-term “diagnostic” use of the Seven Plus, and both are detailed below.
One Handheld, Three Devices
Under a new research and development (R&D) agreement, Dexcom will help Roche develop a new handheld insulin-pump controller that also acts as a receiver for Dexcom’s fifth-generation sensor (note that the current Dexcom Seven Plus in the US is the third generation sensor). Interestingly, this CGM-integrated handheld will be able to operate two different kinds of Roche pumps: one that uses infusion sets (Roche’s traditional pump technology), and one that does not (i.e., a “patch” pump, Roche’s Solo technology). We anticipate that the former will be a new generation of the Accu-Chek Combo, which is an Accu-Chek Spirit pump integrated with an Aviva blood glucose meter. The Combo is available internationally and is currently under FDA review. As for the patch pump, we think it will be the Solo MicroPump, a sophisticated device that Roche has been developing since it acquired Medingo in 2010 (see NewNowNext in diaTribe #17 and NewNowNext in diaTribe #23). We think that probably only a few patients would own both pumps and switch off according to their activity schedules, unless Roche offers some sort of two-for-one deal. However, for patients who decide to permanently switch from a traditional Accu-Chek pump to the Solo (or vice versa), having the same handheld should make the transition much easier. Dexcom and Roche plan to submit the CGM-integrated handheld to the FDA before the end of 2013 as we understand it.

Integration Now and Tomorrow
This Roche partnership marks Dexcom’s third R&D agreement with a major pump manufacturer. Dexcom is also collaborating with Animas to develop the Animas Vibe (currently available in some European countries, with a potential US approval sometime in early 2013 at the earliest; see Conference Pearls in diaTribe #30 for background on the system), and it is also working with Insulet to develop a combination of the second-generation Omnipod and Dexcom’s fourth-generation sensor (now on a similar timeline to the Animas Vibe, which represents a delay from the timeline that had been established until recently (see NewNowNext of diaTribe #36). However, the Roche agreement is the first time we’ve heard about an integrated pump-CGM product that will use Dexcom’s fifth-generation system – something of a milestone, as the fifth-gen will have its data-processing “brains” in the CGM transmitter rather than the receiver. This means that the fifth-gen’s wireless signals could theoretically be displayed by a variety of devices, like a hospital monitor or even a smart phone. Pairing medical devices with smart phones still appears to be a sensitive issue for the FDA, so it might be many years before people are flipping between texting and tracking their glucose on the same screen. Fortunately, in the nearer term, the new generations of integrated diabetes technologies are getting only sleeker and user-friendlier, so we can’t wait to see the cutting-edge design that Roche and Dexcom have in store.

CGM Sampler
In another new agreement, Roche will begin selling Dexcom Seven Plus CGM systems to physicians, who can then make the systems available to patients for short-term use. Roche sales representatives will have financial incentives to sell Dexcom’s CGM. Additionally, Medtronic also had news on the short-term CGM front this month, announcing FDA approval of the iPro2. This is the newest version of Medtronic’s iPro CGM, which healthcare professionals can temporarily prescribe to patients to get a better idea of their glycemic control. We think both news items have the potential to benefit type 2 patients in particular, who can better assess with their doctor the progression of type 2 diabetes. For those patients (as well as for type 1 patients who don’t yet wear CGM), a short-term CGM stint should also help them get a better sense of their glucose patterns and how they can improve their diabetes management. Doctors have long been criticized for “inertia” in
moving patients to more optimal therapies and we believe just a week or two of CGM use should surely point out what is working and what isn’t. For other patients – those who have been wanting to try CGM, those who tried earlier versions of CGM and have been waiting for improvements, or those who have never even heard of continuous monitoring – short-term CGM use could be a segue into long-term adoption. --JPS

JDRF Puts Pressure on FDA to Encourage Faster Approval of an Artificial Pancreas

Recently, JDRF has ratcheted up the pressure on the FDA to encourage quicker development and approval of an artificial pancreas (AP) for type 1 diabetes. In late November, JDRF announced 110,000 individuals had signed a petition urging the FDA to avoid unnecessary delays in bringing an AP to market – impressively, the first 100,000 signatures were collected in just 23 days. The petition was focused on the FDA’s artificial pancreas draft guidance document, which it released (as promised) on December 1. The document represents the Agency’s current thinking on the AP, and it sets the stage for the regulatory requirements that artificial pancreas systems will need to adhere to. Examples include clinical trials, device characteristics, and safety provisions. Among other requests, JDRF has called for the FDA to allow short-term in-hospital evaluation of artificial pancreas systems followed by in-home trials of no more than three months. Following the publication of the guidance, JDRF released a statement that it is “encouraged” by the document and the agency has been responsive to many of the proposed recommendations.

Ultimately, JDRF is concerned that unnecessarily burdensome regulatory requirements will slow or even halt innovation and development of the artificial pancreas. A good example of such regulation is the much-delayed FDA approval of the Medtronic Veo insulin pump/CGM system. The device, which has been available in over 50 countries outside the US since 2009, is the first step toward an artificial pancreas but is still not accessible in America. As a reminder, the Veo can automatically suspend insulin delivery when the device senses (via CGM) that glucose levels have fallen below a threshold (e.g., 70 mg/dl). Recent data indicate that the Veo is particularly useful for reducing exposure to nocturnal hypoglycemia, a serious concern for anyone with type 1 diabetes and a frequent barrier to very tight glycemic control. As we understand it, the major trial to approve the Veo in the US, called the ASPIRE study, is expected to begin soon, meaning FDA approval won’t come until sometime in late 2012 or 2013 at the earliest. For more information on the Medtronic Veo, please see Conference Pearls in diaTribe #28. Fortunately, JDRF believes the recently released guidance lays out a rapid timetable to move from inpatient to outpatient trials – very good news considering the delays in getting the Veo approved.

The recent pressure on the FDA began to mount when JDRF helped organize a letter sent to FDA commissioner Dr. Margaret Hamburg from the American Diabetes Association (ADA), the American Association of Diabetes Educators (AADE), the Endocrine Society, and the American Association of Clinical Endocrinologists (AACE). The letter similarly focused on the AP draft guidance, urging the FDA to adopt recommendations previously put forth by the JDRF and leading clinicians. These recommendations included a call for greater flexibility, shorter trials, and a commitment to using CGM data to evaluate artificial pancreas systems (as opposed to more involved laboratory blood glucose measurements). We are glad to see these organizations working together to influence the FDA in the old grassroots sort of way, and based on early indications, it appears the FDA took the recommendations seriously in the the released guidance document.
JDRF also took out a full-page advertisement in the New York Times and Washington Post on November 2. The advertisement called attention to the dangers of fatal hypoglycemia and noted that the FDA’s AP guidance will play an important role in bringing a life-saving artificial pancreas to market. The advertisement was somewhat controversial, as it shows a picture of an eight-year-old with type 1 diabetes and asserts that one in twenty people like her will die from low blood sugar. We were initially surprised by the startling figure cited in the ad, but JDRF CEO Jeffrey Brewer clarified it’s based on studies by Dr. Phillip Cryer, a highly regarded hypoglycemia researcher and scholar. We think that the statistic could be misread to imply that one in twenty people with type 1 diabetes die of hypoglycemia every year or in childhood, rather than over the course of their lifetimes, during which time everyone will die of something. That said, we believe the ad was ultimately very valuable as it prompted many discussions about hypoglycemia and associated dangers and clearly raised the education level. We agree with the JDRF that any death that could be prevented with an artificial pancreas is unacceptable, and we look forward to greater awareness and collaboration now that the FDA guidance document has been released.

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Sanofi to Advance New Version of Lantus into Late-Stage Development in Early 2012

While Lantus (Sanofi’s insulin glargine) is the current standard for basal insulins, companies are still investing significant efforts to develop even better long-acting insulins. In clinical trials, Novo Nordisk’s new insulin called degludec provided similar improvements in blood glucose control as Lantus, with less hypoglycemia and more flexible dosing. Novo submitted degludec for regulatory review last month in the US and in Europe, placing potential approval in the second half of 2012 (see our NewNowNext in diaTribe #37). Lilly is developing its own version of insulin glargine and has hinted that it could potentially be safer and/or more effective than Lantus. In addition, Lilly is also developing a novel basal insulin of its own. The company is currently recruiting for two phase 3 trials for its insulin glargine product and intends to start phase 3 trials for its novel basal insulin by year end, placing approval for the two products as early as 2014 if everything goes as planned. Earlier this month, Sanofi announced that it will be advancing a new version of Lantus into phase 3 trials in early 2012, which by our estimates would place approval as early as 2014 if all goes accordingly – before Lantus’ patents expire in 2015 in the US. The company has disclosed very few details about the new formulation, but emphasized that it will have a different clinical profile than Lantus – whether this means it will have a longer duration of action, have improved stability or less hypoglycemia, enable more flexible dosing, or provide some other novel feature remains to be seen. Exciting times ahead for those using basal insulin – improved options appear to be well along their way.

--VW

Glooko Launches an Easy Way to Download Blood Glucose Meter Data to an iPhone, iPod Touch, or iPad; Enter Our Giveaway to Receive a Free Cable!

Although most blood glucose meters are theoretically able to upload test results to a computer, the reality can be a frustrating, time-consuming process. Different meters need different cords, uploading is sometimes time-consuming, and programs are often incompatible with Macs or not very user-friendly. This month, a company called Glooko launched what looks to be a less irritating way to download your meter’s blood glucose history. The crux of the system is a single cable that can plug in to any of six popular blood glucose meters: Bayer’s Contour, FreeStyle’s Lite and Freedom Lite, and One Touch’s Ultra2, UltraLink, and UltraMini meters. The other end of the cord plugs in to an
iPod touch (3rd and 4th generation), the iPhone (3GS and 4), or the iPad, allowing test results to be uploaded to the Apple device using the Glooko Logbook application (available free in the iTunes App Store). Generally, the process takes less than one minute, and the number of downloadable readings is only limited by the Apple device’s memory. Additionally, Glooko’s product can download multiple meters (e.g., meter in your car, meter at work, meter at home) and integrate the information based on date and time. We got a chance to try Glooko’s MeterSync Cable and the Glooko Logbook App, and we found it to be refreshingly straightforward.

Once downloaded, users can view the logbook on their Apple device, add notes (e.g., carb intake, insulin dose, activity level, pre/post meal tags), and share a 14-day summary report with their healthcare provider via email or eFax. While we do like the built-in communication features, we believe that many patients will find manually adding the notes time-consuming, if they even remember the data to share! For right now, the application is limited to displaying the test results in logbook format; to be able to show graphs or give statistics like averages, Glooko would need FDA approval. The company has informed us that future generations of the system will incorporate these features. Additionally, given Glooko’s notable investors who are associated with social media, we suspect next generation versions might even incorporate Facebook applications. Although it doesn’t have the most advanced data analysis capabilities, we really like that Glooko’s product simplifies blood glucose meter downloading, a problem that is real to many patients. The Glooko Logbook App is free on the iTunes App Store, although it must be used with the cord, which costs $40 and is available on Amazon. For a limited time, we are giving away free Glooko MeterSync Cables to the first 50 people who fill out a five-minute survey. If you are interested, please visit http://dqa.us.qualtrics.com/SE/?SID=SV_d59jtsarhWXmtsE. --AB

World Diabetes Day 2011: Hula Hooping in San Francisco’s Union Square and 531 Monuments Lit Blue Around the World

The diaTribe team had an outstanding evening in San Francisco for World Diabetes Day on November 14, which included blue hula hooping in Union Square. (For those who aren’t familiar, the blue circle is the International Diabetes Federation’s symbol for diabetes.) With the help of sponsors Abbott Diabetes Care and J&J LifeScan and co-organizers JDRF, ADA, the Diabetes Hands Foundation, DiabetesMine, UCSF, CPMC, and diaTribe, more than 200 people gathered in an attempt to beat the Guinness Book of World Records for largest hula-hoop workout at one time (the current record is 113 people). The festivities featured ample music, ice skating, and an amazing hula-hoop routine from professional Matt Plindle (to see a video of the routine, visit http://youtu.be/j8M4fBuFqww). We also enjoyed hearing from Manny Hernandez and taking part in the Big Blue Test along with 8,000 other people across the planet: (1) test your blood sugar; (2) get active for 14 minutes; (3) test your blood sugar again. Paul Madden’s inspirational words, wisdom, and humor were also valuable, coming from nearly 50 years with type 1 diabetes.

This year’s World Diabetes Day featured 531 monuments lit blue in 61 countries to raise global awareness about diabetes. Here in the US, 38 monuments were lit, including the Washington Monument and the Empire State Building. We always enjoy taking part in World Diabetes Day, not only to raise awareness of its global prevalence (now estimated at 366 million people around the world), but to remember that diabetes does not limit what any of us is capable of accomplishing. --AB
Takeda Submits DPP-4 Inhibitor Alogliptin and Combination Alogliptin/Actos and Alogliptin/Metformin Pill for Approval in the US

Recently, we learned that the Japan-based pharmaceutical company Takeda has submitted its type 2 diabetes therapy alogliptin for approval in the US. The therapy has been available in Japan since 2010 under the brand name Nesina. Alogliptin belongs to a class of drugs called DPP-4 inhibitors, which help the body secrete insulin only when blood glucose levels are high. Currently, there are three approved DPP-4 inhibitors in the US – Januvia (sitagliptin), Onglyza (saxagliptin), and Tradjenta (linagliptin). What distinguishes alogliptin from these other therapies, however, is that it may also become available in combination with the type 2 diabetes therapy Actos (pioglitazone) in a single pill. Actos, part of the class of medications known as TZDs, helps improve blood glucose control by increasing the body’s sensitivity to insulin. Thus, by targeting both insulin secretion (via a DPP-4 inhibitor) and insulin sensitivity (via a TZD), a combination alogliptin/Actos pill could form a very powerful (and convenient) therapy for people with type 2 diabetes. The FDA is expected to make a decision on whether or not to approve both alogliptin and the combination pill by April 25, 2012. We note that some studies have associated the use of Actos for more than one year with bladder cancer. In response, the FDA recently updated the medication’s label and will be looking for further clarity as more extensive trial data become available. For more information, please see the NewNowNext in diaTribe #34. In the last week of November, Takeda also submitted its combination alogliptin/metformin pill for approval in the US. For more information on other combination DPP-4 inhibitor/metformin pills, please see the NewNowNext in diaTribe #28. --BK

conference pearls

The 11th Annual Diabetes Technology Meeting

by Joseph Shivers

A few weeks ago we headed south from San Francisco to Burlingame, CA, where we saw one of the most exciting Diabetes Technology Meetings in recent memory. Below, we discuss some of the most notable topics, including: progress at every step toward the artificial pancreas, the extremely accurate performance of a new blood glucose meter that just launched in Europe, and a strong emphasis on wireless connectivity to other devices (and to the entire Internet).

A Refresher on Glucose (Cruise) Control

As we’ve written about before, one of the Holy Grails in diabetes technology is the development of an “artificial pancreas” – a product that could continuously monitor glucose levels and automatically deliver insulin in response (see the NewNowNext in diaTribe #31 and the Artificial Pancreas section of our free e-book, Targeting a Cure for Type 1 Diabetes). The long-term goal is to develop a “fully closed loop” – a system that requires no inputs from the person using it. Such a system would likely deliver additional hormones such as glucagon, which raises blood sugar in case of hypoglycemia.

In the nearer-term, researchers are working to wirelessly connect today’s insulin pumps and subcutaneous CGM sensors. Due to current insulin “lag time,” sensor inaccuracy, the difficulty of forecasting glucose control with today’s software, and other factors, such a system wouldn’t yet be able to give perfect, flat glycemic control all the time. However, it could reliably deliver insulin or glucagon when glucose is going especially high or low. In this way the system could dramatically decrease the amount of time that most patients
spend in hypoglycemia or hyperglycemia. Dr. Aaron Kowalski, JDRF’s Assistant Vice President of Treatment Therapies and diaTribe advisory board member, recently said that he expects this sort of “control-to-range” system to be commercially available by the end of 2016. (A “control-to-range” system would aim to keep blood glucose in a range, e.g., 80-180 mg/dl, instead of targeting a set value like 100 mg/dl.) Based on two demonstrations we saw at the Diabetes Technology Meeting, we are also optimistic about the strength of the technology, although early on, there will certainly be frustrations like with any new technology.

**Prototype Artificial Pancreas “Apps” in Action**

Dr. Patrick Keith-Hynes (University of Virginia, Charlottesville, VA) and Dr. Claudio Cobelli (University of Padova, Padova, Italy) led the first of two artificial pancreas demonstrations. Their research team has developed a way to wirelessly connect a Dexcom Seven Plus CGM, an Insulet OmniPod pump, and an Android cell phone application that runs the system. We note that the system is still a prototype and is designed for research, not commercial use. Still, it was cool to see, and it helped us get a sense of what upcoming commercialized devices might look like.

The home screen of the UVA research app features a traffic light icon that shows people whether their glucose is in the target range (green light), slightly too high or low (yellow light), or in more dangerous territory (red light) – a quick, intuitive, and cool-sounding way for someone to get a sense of things with one look at the phone. People can also tell the system when they are about to start exercising and they can manually dial in mealtime boluses (this is an example of a hybrid artificial pancreas, which provides automated basal glucose control but still requires mealtime dosing of insulin). On a positive note, the system is designed to work with a variety of different insulin pumps, CGM sensors, or software algorithms. Thus it can be widely used by researchers around the world. So far the system has been tested twice outside the hospital, once in Italy and once in France, and overall it performed well both times.

In the second artificial pancreas demonstration, Dr. Michael Kremliovsky (Medtronic Diabetes) showed off Medtronic’s own early-stage artificial pancreas system. The prototype consists of two CGM sensors, an insulin pump, and a mobile phone that controls it all (though for the version of the product that eventually comes to market, Medtronic plans to put all the software in the pump rather than using a phone). Both the UVA and the Medtronic systems connect to the Internet so that researchers can remotely monitor patients and see how the system is performing. Indeed, Dr. Kremliovsky displayed real-time CGM and insulin pump information from a patient testing the system in Australia!

**Medtronic Gets the Go-Ahead for US Trials of its New Pump and CGM Sensor**

As a reminder, the first step toward an artificial pancreas is called a “low glucose suspend” (LGS) system – a pump that stops dosing insulin when the glucose sensor reads hypoglycemia. Medtronic’s Veo – the first commercial LGS device – has been available internationally since 2009. However, because of a more conservative approach by the FDA, LGS still has not come to patients in the US. Although LGS systems have the potential to prevent coma or even death from low blood glucose, the FDA is concerned that they could also increase the risk of too-high glucose (for example, if the pump mistakenly suspended when blood sugar was actually in the normal or high range, a user’s blood sugar might go dangerously high). However, studies show that when the Veo suspends insulin delivery, blood sugar rises approximately 20-30 mg/dl/hour. Most researchers believe that the huge benefit such a device offers in terms of protection from severe hypoglycemia far out-
Fortunately, the FDA has now given Medtronic the green light to conduct ASPIRE, the first major outpatient trial of a low glucose suspend product in the US. Notably, the US version of the Veo will use Medtronic’s new Enlite sensor, which can be worn for six days at a time. (For reviews of the Enlite, see Test Drive in diaTribe #32 and Thinking Like a Pancreas in diaTribe #36.) As of this writing, Medtronic is still in the final planning stages of ASPIRE, which as we understand it will seek to enroll a minimum of 260 patients. However, the company did recently begin a large trial of the Enlite sensor, expected to complete in April 2012, according to Clinicaltrials.gov (for more information, see this issue’s TrialWatch). Medtronic has not announced its target timeline for launching the US version of the Veo; as always this will depend on how fast the studies enroll and how quickly the FDA reviews the regulatory submissions.

The next step after LGS systems (and before a hybrid or control-to-range product discussed above) will be predictive low-glucose suspend products. As their name suggests, predictive LGS devices can stop insulin delivery if their algorithms predict that hypoglycemia will occur within the next half-hour. In other words, these devices would hopefully avert hypoglycemia before it happens. A team of researchers from Stanford University and the University of Colorado, led by diaTribe advisory board member Dr. Bruce Buckingham, recently got FDA authorization to conduct the nation’s first outpatient study of a predictive LGS system. Dr. Buckingham showed at the meeting that the researchers’ prototype, which uses Medtronic technology, has performed solidly in controlled research settings. Thus, interest in this upcoming study is high.

**Early Looks at New Glucose-Monitoring Technologies**

In addition to sessions on the artificial pancreas, several presenters focused specifically on new approaches to CGM and fingerstick blood glucose meters (BGM). Two of the most powerful presentations we saw came from Dr. Richard Stadterman and Dr. David Simmons of Bayer, who discussed studies of the company’s novel BGM. Based on the data shown, the new Bayer meter would be by far among the most accurate on the market; we hope that its performance is borne out in the official trials required for US submission. Bayer has already launched the device (called Contour XT) in Italy, Spain, and Portugal, and we look forward to learning more about people’s experiences as it becomes more widely used.

Last but not least among new glucose monitoring technology at the meeting, Wireless Medical’s system attracted a good deal of attention. The firm is led by Dov Moran, better known as the inventor of the USB flash drive. Harnessing this expertise in miniature electronics, Mr. Moran and his team are working on a small chip that they say could enable any blood glucose meter or CGM to send data online without wires or even a cell phone. Mr. Moran did not say how far along in development this chip is or how the company would plan to introduce it. But at the very least, it is an intriguing example of today’s research environment and the new goals that scientists are targeting. As a reminder, Telcare received FDA approval in August for a related product: a wireless-enabled blood glucose meter (for more information, see NewNowNext in diaTribe #35). Wireless Medical’s technology would take Telcare’s technology a step further by enabling any meter or CGM to wirelessly upload data online.
SUM musings

PWD: Stand United
by Kerri Morrone Sparling

November was Diabetes Awareness Month, which encourages people to come together and raise awareness of diabetes. In that same vein, the annual World Diabetes Day in November is recognized by the United Nations. We, as a community of people living with diabetes, should be united with pride.

But instead, I see so much divisiveness in our pancreatically-challenged community.

In the beginning, the diabetes community was a beautiful thing. You couldn’t throw a URL without hitting a diabetes blogger, and the support was amazing. So many people, coming together to share best practices, admitting to worst practices, and everything in between. The personalities were diverse, but the common thread was diabetes, regardless of type. We were in this together, and everything truly felt warm, fuzzy, and holding steady at the emotional equivalent of a nice 104 mg/dl.

Now? Now, things have changed a bit. This community still has so much beauty, and limitless possibilities, but it is riddled with chasms, and I’m not sure of the cause.

We, as people with any kind of diabetes, have so much in common. Every single one of us knows the value, both emotionally and literally, of our A1c result. And whether we’re testing our blood sugar every few weeks or every few hours, we all know how that lancet feels when it pierces our fingertip. Everyone living with diabetes understands that their pancreas is compromised in one way or another, and that we need to adjust our lives, our medication, and our minds to manage that change.

But we also have so much that divides us as a community. I think that, even though we’re all categorized under the main heading of “diabetes,” it’s a very diverse and individualized disease. No matter how you slice it, all kinds of diabetes are complicated. Even though there are definitive types (type 1, type 2, LADA, MODY, gestational, pre-diabetes, and of course the caregivers and loved ones of people with diabetes), there are so many variables even within those categories. There’s no broad stroke definition of “diabetes” that suits us all. It’s like calling diabetes simply “a painting,” without taking into account the different canvases, paints, brushes, and styles. We’re all living with diabetes, and we manage it with a dizzying range of diversity.

Diversity is what makes our community strong, though. I’m not saying that we should all be the same, and that we should align our goals. It doesn’t matter what organization I’m supporting. It doesn’t matter where my fundraising dollars go or what walk I participate in or the color of the ribbon pinned to my shirt. Living with diabetes doesn’t mean we all have to be advocates, or that we even need to disclose our diabetes to anyone. What matters is being part of a community that, despite huge differences, rallies together to support one another when it counts.

Yet we battle. Sometimes our sides are chosen by our “type” of diabetes, despite the fact that we all are working toward the same goal of “good health.” We battle over which diet to follow, or which medication to take. We are divided over our loyalty to advocacy orga-
nizations or ribbon colors. We have heated discussions about pharmaceutical companies and cure research and what is or should be the “next big thing” in the diabetes world. We argue about who should lead and who should follow, and about “who has it worse.”

On top of that, we battle against insurance companies who deny us the tools and technology we need. We fight to cover items as sophisticated as continuous glucose monitors and as basic as test strips. And then we raise our voices to the companies creating these products, petitioning to make them more accurate, and more affordable. As people living with a chronic illness, we spend so much of our time making sure our diabetes doesn’t get the best of us that our efforts to achieve almost become efforts that fatigue.

Living with diabetes is not easy.

Which is why I become so frustrated, and disheartened, when I see people in the DOC (diabetes online community) picking one another apart instead of raising each other up. I personally have had people come after me for supporting the JDRF or the Diabetes Research Institute or the Joslin Diabetes Center, saying that I’m not focusing my efforts “the right way.” (These emails often come hot on the heels of other not-so-kind emails, saying I’m a bad person for deciding to have a child. I respect people’s opinions, but I stand by my decisions with confidence.) It’s not that we all have to agree, but we do need to re-educate ourselves about being supportive and respectful. Myself included. We don’t all need to agree. But being kinder goes a long way.

Diabetes is anything but predictable, and everyone has different agendas and goals – I understand that. Not everyone is waiting for a cure. Not everyone supports technological advances. This disease is unique to each diabetic and their loved ones, and the various communities and organizations reflect that. But I would love to see the diabetes communities mature and embrace one another instead of ostracizing and battling. We can’t lose sight of the most important aspect of these communities and organizations: support. Our strength is not found in what divides us. It’s in what unites us.

Kerri Morrone Sparling has been living with type 1 diabetes for almost twenty years. She writes a much-trafficked diabetes blog, Six Until Me (SUM), and is an active member of the diabetes community. She is known for her tagline, “Diabetes doesn’t define me, but it helps explain me.” Dexcom is currently a sponsor of SUM, and through that relationship, the company provides her Dexcom SEVEN PLUS sensors free of charge. For Kerri’s full disclosure, please visit http://sixuntilme.com/about/2010/03/disclosure.html.

learning curve

Hard to Lose Weight, Harder to Keep It Off – A Remarkable New Study Explains Why

by Mark Yarchoan

For years, studies have confirmed what is obvious to anybody who has tried to lose weight: weight loss is challenging, and keeping lost weight off is even harder. In 2005, a landmark study published in the *Journal of the American Medical Association* comparing a number of popular diets – Atkins (carbohydrate restriction), Zone (macronutrient balance), Weight Watchers (calorie restriction), and Ornish (fat restriction) – found that all of the most popular diets are similarly ineffective. At the end of one year, people
who had attempted to diet using any of these strategies lost an average of only about five pounds. Other studies have found that more than 90% of people who lose a lot of weight eventually gain the weight back.

These studies should not be considered a reason or excuse to avoid dieting. Even small amounts of weight loss and changes in lifestyle can have truly dramatic effects on health, including improved blood pressure and glucose control for people with diabetes. However, it is important to have realistic expectations about weight loss, because weight loss involves fighting a set of embedded forces in the body that are designed to prevent weight change. Although the conscious brain may be saying, “it’s time to lose weight”, a complex interplay of weight-related hormones may be saying something different.

The average American eats over 70 million calories in a lifetime, plus or minus a couple of million calories. Yet incredibly, for most people, body weight is kept within a relatively narrow range. Over the course of a decade, food intake and energy output is typically matched within 0.17%. This means that for almost everyone of any kind of build or weight, calories in and calories burnt are kept virtually equal. Working behind the scenes is a complex interplay of hormones and neuronal circuits that control hunger and metabolism so that both sides of this energy equation remain equal. This Learning Curve attempts to explain what these hormones are, how they work, and why their existence makes weight loss so challenging.

Leptin: A Long-Term Regulator of Fat
Originally discovered in 1994 by Dr. Jeffrey M. Friedman at the Rockefeller University, leptin is thought to be one of the most important regulators of weight. Children born with a rare genetic deficiency in leptin become morbidly obese at a young age, and their weight can be mostly normalized when leptin is administered to them. Leptin is secreted from fat cells and acts somewhat like a thermostat for weight. When a person gains weight, more leptin is produced, causing a decrease in appetite and an increase in energy metabolism. When weight is lost, the opposite happens.

It’s easy to understand why leptin makes successful dieting so difficult. When a person starts dieting, leptin levels fall dramatically even with modest weight loss. The fall in leptin is sensed by the brain, and the dieter begins to experience increased appetite. In addition, a fall in leptin levels makes high-calorie food taste better, and eating begins to feel more rewarding. As a result of low leptin levels, dieters may actually crave high calorie foods like potato chips. In addition to promoting increased calorie intake, the fall in leptin also decreases metabolism by making the body more efficient. Fewer calories are burned in muscle and other tissues at rest and while exercising. These converging effects of a fall in leptin – increased appetite and decreased energy metabolism – may explain why so many dieters regain weight that they worked so hard to lose.

A Hormonal Network Dedicated to Maintaining Weight
A number of other hormones effect whether a person feels hungry or full at any particular time of the day. Cholecystokinin (CCK), peptide YY (PYY), amylin, and glucagon-like peptide-1 (GLP-1) are hormones that are secreted by the gastrointestinal tract and pancreas in response to a meal and act on the brain to suppress appetite. A different hormone, ghrelin, is secreted from the stomach when it is empty, and causes hunger. Many of these hormones have been shown to interact with leptin and with each other, and so for example high levels of leptin plus amylin may cause more satiety than high levels of either hormone alone.
What happens to all of these weight-related hormones when a person loses weight? That question was recently answered in an important study conducted by a group of Australian researchers lead by Dr. Priya Sumithran that was published in the October 27 issue of the *New England Journal of Medicine*. The researchers recruited overweight people and put them on a strict diet (500 to 550 calories a day) that caused them to lose at least 10% of their body weight and kept them on a diet that would maintain the weight loss for one year. At the end of the year, the participants had significant changes in their obesity-related hormones. For example, leptin levels had fallen by about two-thirds when the subjects initially lost weight, and were still one-third lower at the end of the one-year study period even though participants had regained much of the lost weight. Other obesity-related hormones including those listed in the chart above were also changed. Going along with changes in hormone levels, participants were also found to have increased appetite and decreased metabolism. These results suggest that multiple hormones change in response to weight loss and they continue to encourage weight regain for at least a year after a person has lost weight.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Weight Effect Overview</th>
<th>Approved Medications Mimicking Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Fat Cells</td>
<td>Long-term regulator of weight, opposes weight change</td>
<td></td>
</tr>
<tr>
<td>GLP-1 (GLP-1)</td>
<td>Gut</td>
<td>Suppresses appetite following a meal</td>
<td>Byetta/Bydureon(exenatide), Victoza</td>
</tr>
<tr>
<td>Amylin</td>
<td>Pancreas</td>
<td>Suppresses appetite following a meal</td>
<td>Symlin (pramlintide)</td>
</tr>
<tr>
<td>PYY (PYY)</td>
<td>Gut</td>
<td>Suppresses appetite following a meal</td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin (CCK)</td>
<td>Gut</td>
<td>Suppresses appetite following a meal</td>
<td></td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Stomach</td>
<td>Causes hunger and promotes energy storage in fat</td>
<td></td>
</tr>
</tbody>
</table>

Taken together, all of this scientific evidence creates a compelling story of why weight loss is so challenging for most people. When weight is lost, multiple hormones controlling hunger and metabolism work together to cause weight regain.

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novel

trial watch

**A Performance Evaluation of the Enlite Glucose Sensor to Support a Full 144 Hours of Use**

ClinicalTrials.gov Identifier: NCT01464346

http://www.clinicaltrials.gov/ct2/show/NCT01464346

In April, Medtronic’s new Enlite sensor received CE Mark approval for six-day wear in Europe. Designed to be more comfortable and accurate that previous Medtronic sensors (see our NewNowNext in diaTribe #32), the Enlite sensor had been highly anticipated.
worldwide. While the sensor is now on the market in Europe, it remains unavailable in the United States. Importantly, data from this pivotal trial will be included in the US submission of the Enlite sensor for the FDA’s consideration. This study aims to characterize the performance of the Enlite sensor over an entire calibration and wear period of six days when used with Medtronic’s newest insulin pump. The study will take place at two locations – the AMCR Institute in Escondido, CA, and Rainier Clinical Research Center in Renton, WA. To be eligible, participants must be 18-75 years old, and have been clinically diagnosed with type 1 diabetes or type 2 diabetes. In addition, participants must not be pregnant, have had a hypoglycemic seizure within six months prior, or have a history of cardiovascular disease. If you are eligible and interested in participating, please contact Timothy Bailey (Escondido, CA) at 760-466-1530 or tbailey@amcrinstitute.com or Ronald Brazg (Renton, WA) at 425-271-1720 at rbrazg@rainier-research.com.

Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON)

As it currently stands, there are no treatments for chronic kidney disease (CKD; one of many unfortunate complications of diabetes) beyond controlling high blood pressure and blood sugar levels to prevent the development of irreversible kidney failure. Encouragingly, Reata Pharmaceuticals is developing a drug called bardoxolone that has in earlier studies been shown to improve kidney function in people with type 2 diabetes and CKD (see our NewNowNext in diaTribe #35). This study will assess the effectiveness of bardoxolone in delaying progression to end-stage renal disease (ESRD) and cardiovascular death for people with type 2 diabetes and CKD. If results from this study confirm that bardoxolone indeed improves kidney function, the drug could be approved as early as 2014. To be eligible, participants must be at least 18 years old, have type 2 diabetes, have a screening estimated glomerular filtration rate (eGFR; a measurement of kidney function) of between 15 and 30 ml/min/1.73 m2, and have been treated with an ACE inhibitor (e.g., Vasotec, Renitec, Altace, Accupril) or an ARB (e.g., Avapro, Micardis, Teveten, Benicar, Edarbi) for at least six weeks prior to and during screening. In addition, participants must not have known non-diabetic renal disease, history of a renal transplant, A1c >11.0%, or recent cardiovascular disease. The study is recruiting at 177 sites across the US and several international locations. --VW