Innovations in Diabetes Care and Management

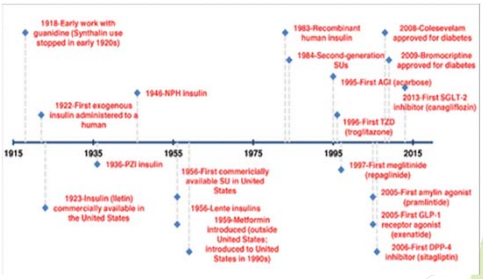
Barbara Walz, RN, BSN, CDE

April 26, 2018

Objectives

1. Briefly discuss the history of diabetes management over the past 100 years
2. Describe the impact of new technology and medical devices on the lives of People with Diabetes
3. Share the personal story of a Person with Diabetes and how they utilize the new hybrid insulin pump

We've come a LONG way, baby ……



The Problem

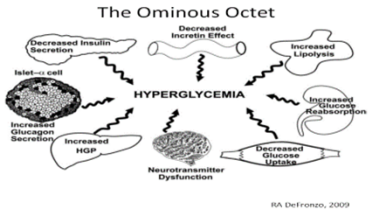
- 30.1 million Americans are affected by diabetes—this includes 23.1 million diagnosed and 7.2 million people who are unaware they have the disease. This computes to 23.8% of people are undiagnosed.
- One of the top 10 causes of death in the United States, diabetes has far-reaching implications for patients and their families and our health care system.
- According to the CDC, the number of Americans diagnosed with diabetes has more than tripled since 1980

  - www.diabetes.org/assests/pdfs/basics/CDC-statistics-report-2017

Treating Diabetes

- Healthy eating and exercise can help prevent and manage type 2 diabetes
- Medicines play a key role in helping reduce the risk of and treat the disease.
  - one medicine was found in studies to lower the risk by 31%.
  - In recent years, eight new classes of type 2 diabetes medicines have been approved by the Food and Drug Administration (FDA)
- 180 new medicines for type 1 and type 2 diabetes and diabetes-related conditions, such as chronic kidney failure due to diabetes and painful diabetic neuropathy are currently in development by America's biopharmaceutical research companies

Treating Diabetes



Innovations in DM Care

- New Medications

Goal – provide each person with diabetes an individualized tailored therapy

Non-insulin DM meds

- Sulfonylureas
- **Biguanides**
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- **Thiazolidinediones (TZDs)**
- DPP4 inhibitors
- **SGLT2 Inhibitors**
- Bile Acid Sequestrants
- Dopamine agonists

Non-insulin injectables

GLP-1 Receptor Agonists

Currently Available GLP-1 Products		
Brand name	**Generic**	**Dosing**
Once weekly		
Trulicity®	dulaglutide	0.75 mg weekly initially; may increase to 1.5 mg once weekly
Bydureon®	exenatide LAR	2 mg once weekly
Tanzeum®	albiglutide	30 mg once weekly initially; may increase to 50 mg once weekly
Once daily		
Victoza®	liraglutide	0.6 mg daily for 1 week then 1.2 mg daily; may increase to 1.8 mg daily
Adlyxin®	lixisenatide	10 mcg daily for 2 weeks then 20 mcg daily
Twice daily		
Byetta®	exenatide	5 mcg twice daily within 60 minutes prior to meal; may increase to 10 mcg daily after 1 month

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com. Accessed 11/17/2016.
Adlyxin® [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2016

GLP-1 Receptor Agonists

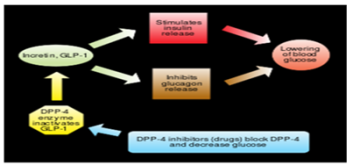
Benefits beyond BG reduction:

- ↓ CV Mortality
- Low risk of hypoglycemia
- Promote fullness and weight loss (1-5 kg)
- ↓ post-meal BG
- ↓ SBP (1-7 mmHg)
- ↓ TGs (12-40 mg/dL)
- Beta-cell preservation?

Marso SP, et al. *N Engl J Med* 2016;375:311-22.
Vilsbøll T, et al. *BMJ* 2012;344:d7771.
Shyangdan DS, et al. *Cochrane Database Syst Rev* 2011;10:1-112.
Schwartz SS, et al. Diabetes Care 2018;39:17986.
Sagal AR, et al. Endocrinol Metab Clin N Am 2016;45:845-874.
Diamant M, et al. Diabetes Care 2014;37(10):2765–73. 114.
Rosenstock J, Diabetes Care 2014;37(8):2253–25.
Nauck MA. *Diabetes Care* 2013;36(7):2126-2132.

GLP-1 and DPP-4

GLP-1



Insulin Update

TRESIBA® insulin degludec [rDNA origin] injection

RYZODEG 70% insulin degludec and 30% insulin aspart [rDNA-origin]injection

Humulin® R U-500 KwikPen® insulin human injection 500 units/mL

Xultophy® 100/3.6 (insulin degludec and liraglutide injection)

SOLIQUA™ insulin glargine & lixisenatide injection 100 Units/mL & 50 mcg/mL, 100 Units/mL & 33 mcg/mL

basaglar® insulin glargine injection 100 Units/mL

Humalog 200 U/mL KwikPen® insulin lispro injection [rDNA origin] 200 units/mL

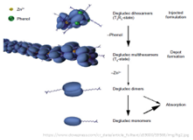
Toujeo® insulin glargine 300U/mL

New Insulin Products

- **Basal (long-acting)**
  - Tresiba® (insulin degludec)
  - Toujeo® (insulin glargine U-300)
  - Basaglar® (insulin glargine U-100)
- **Bolus (rapid; mealtime)**
  - Humalog® U-200 (insulin lispro U-200)
- **Other**
  - Humulin R® U-500 Kwikpen® and syringe
- **Combination Products**
  - Soliqua® (insulin glargine / lixisenatide)
  - Xultophy® (insulin degludec / liraglutide)
  - Ryzodeg® (insulin degludec / insulin aspart)

Tresiba® (insulin degludec)

- "Ultra-long" 42+ hour duration of action
- Available in 100 units/mL or 200 units/mL
  - No PK difference between U-100 and U-200
- Versus Levemir® or Lantus®:
  - Similar A1C reduction
  - ↓ within-day and within-subject variability
  - ↓ hypoglycemia and ↓nocturnal hypoglycemia



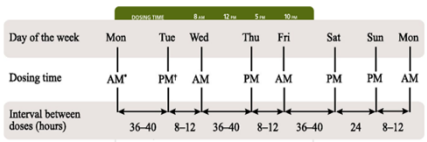
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4680830/bin/jdt-10-1077-g1.jpg

Segal AR, et al. *Endocrinol Metab Clin N Am* 2016;45:843-874
Woo VC. *Clinical Therapeutics* 2017;ePub ahead of print
Shirley M, et al. *Consult Pharm* 2017;32:42-46
Heller, et al. *J Diabet Med.* 2014;31:479-487.

Johnson et al. *J Diabet Sci Tech* 2016; DOI: 10.1177/1932296814680830.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed 11/27/2016.

Tresiba® (insulin degludec)

Insulin degludec "Flex" dosing

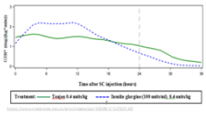


Insulin degludec can be administered anytime of the day as long as it is more at least 8 hours since previous dose and no more than 40 hours from last dose

Meneghini L, et al. Diabetes Care 2013;36:858-864.

Toujeo® (insulin glargine U-300)

- 30+ hour duration of action
- Versus Lantus®:
  - Similar A1C reduction
  - ↓ within-day and within-subject variability
  - ↓ hypoglycemia and nocturnal hypoglycemia
  - Slightly less weight gain (0.2-0.7 kg)



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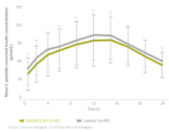
Johnson et al. *J Diabet Sci Tech* 2016; DOI: 10.1177/1932296814680830.
Toujeo Prescribing Information
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed 11/27/2016.
Owens DR. *Expert Opin Drug Metab Toxicol* 2016;12(8):977-987.

Basaglar® (insulin glargine U-100)

- First "follow-on" insulin
  - Lantus® patent recently expired
  - Biologic drugs: different FDA regulations, no "generics"
  - Basaglar®: "highly similar" to Lantus®
- Compared with Lantus®:
  - ≈ Equivalent PK/PD
  - Non-inferior efficacy and safety
  - Clinical trials too small/short to identify rare safety events



Segal AR, et al. Endocrinol Metab Clin N Am 2016;45:845-874.
Basaglar® [package insert]. Indianapolis, IN: Eli Lilly and Co., 2016.
Blevins TC, et al. Diabetes Obes Metab 2015;17(8):726-733.
Rosenstock J, et al. Diabetes Obes Metab 2015;17(8):754-741.
Grant JS, et al. Home Health: Now 2016;34(6):326-337.
Linnebjerg H, et al. Diabetes Care 2015;38(11):2226-33.
Pandya CL, et al. Med Clin (Barc) 2016;147(7):297-299.

U-500 Insulin Syringe

U-500 insulin syringe also now available!

Humulin-R U-500 Prescribing Information

Humulin-R® U-500 Kwikpen®

- **U-500 insulin now available in a pen!**
  - Same drug, less risk of confusion
  - Pen contains 1500 units of insulin
  - Dosed in 5 unit increments up to max 300 units per injection
- Crucial to ensure patient understanding of dose prior to switching

Johnson et al. J Diabet Sci Tech 2016; DOI: 10.1177/1932296816680833.
Segal AR, et al. Endocrinol Metab Clin N Am 2016;45:845-874.
Humulin-R U-500 Prescribing Information

Combination Products

- **Soliqua®** (insulin glargine and lixisenatide):
  - Dosed once daily without regard to food
  - Each dosing increment contains 1 unit of glargine and 0.33 mg of lixisenatide
  - Recommended starting doses:
    - Taking <30 units basal insulin or currently treated with lixisenatide: 15 units glargine / 5 mcg lixisenatide
    - Taking 30-60 units basal insulin: 30 units / 10 mcg
  - Max dose: 60 units / 20 mcg

Table 2: Recommended Titration of SOLIQUA 100/33 (Every Week)

Self-Monitored Fasting Plasma Glucose	SOLIQUA 100/33 Dosage Adjustment
Above target range	+2 units (2 units of insulin glargine and 0.66 mcg of lixisenatide) to +4 units (4 units insulin glargine and 1.32 mcg lixisenatide)
Within target range	0 units
Below target range	-2 units (2 units of insulin glargine and 0.66 mcg of lixisenatide) to -4 units (4 units of insulin glargine and 1.32 mcg lixisenatide)

*The recommended SOLIQUA 100/33 dosage is between 15 to 60 units (see Table 1).

Soliqua® Prescribing Information

Combination Products

- **Xultophy®** (insulin degludec and liraglutide)
  - Dosed once daily without regard to food
  - Each dosing increment contains 1 unit of degludec and 0.036 mg of liraglutide
  - Recommended starting dose: 16 units degludec / 0.58 mg liraglutide
  - Max dose: 50 units / 1.8 mg

Table 2: Recommended Titration of XULTOPHY 100/3.6 (Every Three to Four Days)[1]

Self-Monitored Fasting Plasma Glucose	XULTOPHY 100/3.6 Dosage Adjustment
Above target range	+ 2 units (2 units of insulin degludec and 0.072 mg of liraglutide)
Within target range	0 units
Below target range	- 2 units (2 units of insulin degludec and 0.072 mg of liraglutide)

[1] The recommended XULTOPHY 100/3.6 dosage is between 16 to 50 units (see Table 1)

Xultophy Prescribing Information

Summary Table 1 – New Insulin Products

Product	Concentration	Volume/pen	Units/pen	Max single-dose	Stability at room temp	Dosing increment	Duration	Minimum titration frequency
BASAL INSULIN								
INSULIN GLARGINE								
Basaglar®	100 units/mL	3 mL/pen	300 units/pen	80 units	4 weeks	1 unit/click	~24 hours	3-4 days
Toujeo®	300 units/mL	1.5 mL/pen	450 units/pen	80 units	8 weeks	1 unit/click	~30 hours	3-4 days
INSULIN DEGLUDEC								
Tresiba® U-100	100 units/mL	3 mL/pen	300 units/pen	80 units	8 weeks	1 unit/click	42 hours	3-4 days
Tresiba® U-200	200 units/mL	3 mL/pen	600 units/pen	160 units	8 weeks	2 units/click	42 hours	3-4 days
BOLUS INSULIN								
INSULIN LISPRO								
Humalog® U-200 KwikPen®	200 units/mL	3 mL/pen	600 units/pen	60 units	4 weeks	1 unit/click	≤5 hours	Individualize per patient
OTHER INSULIN								
REGULAR INSULIN								
Humulin®R U-500 KwikPen®	500 units/mL	3 mL/pen	1500 units/pen	300 units	4 weeks	5 units/click	~13-24 hours	Individualize per patient

Johnson et al. J Diabet Sci Tech 2016; DOI: 10.1177/1932296816630030.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at http://online.lexi.com. Accessed March 2017.
Basaglar, Toujeo, Tresiba, Humalog, and Humulin R U-500 Prescribing Information

Opportunities to Improve Insulin

Faster onset **Afrezza**	Longer duration **Toujeo, Tresiba**	Less variable PK **Toujeo, Tresiba**	More concentrated **Toujeo, Tresiba, Novolog U-200**
Less hypoglycemia and weight gain **Toujeo, Tresiba, Xultophy, Soliqua**	Improve administration safety **U-500 Kwikpen and Syringe**	More convenient / less injections **Toujeo, Tresiba, Ryzodeg, Xultophy, Soliqua, Afrezza**	Lower cost **Basaglar**

To learn more -

www.Drugs.com

Oral insulin

- Novo Nordisk was investigating a tablet formulation of insulin that is swallowed once daily and slowly absorbed into blood stream. Study to compare to injected basal glargine resulted in equally improved A1c. This was only an 8 week study on 50 people.
- Results were reported at ADA but development has been discontinued due to excessive cost.

Glucagon

- Nasal powder – Eli Lilly
- Patch – Zosano Pharma
- Pen – Xeris Pharmaceuticals

Treating Hypoglycemia

- Pills for prevention – looking for agents that could be taken in pill form to prevent hypos
- Micro-doses – currently being developed as a pen that person could carry with them at all times to treat mild hypoglycemia
- Dual-hormone artificial pancreas – used in a pump type delivery system. Major problem is developing glucagon that is stable in liquid form and effective for long term use.

Innovations in DM Management

- New Technologies
  - Intarcia Mini-Pump for GLP1 - stalled
  - Insulin Delivery Systems
    - V-Go Patch pump
    - Medtronic 670G – Hybrid Closed-Loop System
  - Continuous Glucose Monitoring Systems
    - Dexcom
    - Abbott FreeStyle Libre – personal
      - "wand style" intermittent glucose monitor

V-Go patch pump

- The V-Go is a simple-to-use, once-daily, disposable insulin delivery device. This spring-driven patch pump is worn on the skin to provide a preset basal rate and on-demand bolus dosing. Valeritas designed the device to be convenient and easy to use for people with Type 2 diabetes who use multiple daily injections.

OmniPod - tubeless insulin pump

2018 – projected launch of new DASH platform which send pump info to Glooko w/o patient intervention. Will lose phone connectivity.

Advantages of Continuous Subcutaneous Insulin Infusion (CSII) vs Multiple Dose Insulin Injections

- Programmable insulin delivery allows closer match with physiologic needs
- Uses only rapid-acting insulin, minimizing peaks and absorption-related variability
- Uses one injection site for up to 72 hr, thus reducing variations in absorption and treatment-related burden from multiple injections
- Reduction in glycemic variability and improved glycemic control
- Decreased risk of severe hypoglycemia and need for emergent medical attention
- Reduction in need for hospitalization and cost of care
- Improved quality of life and treatment satisfaction

Insulin Pump Issues

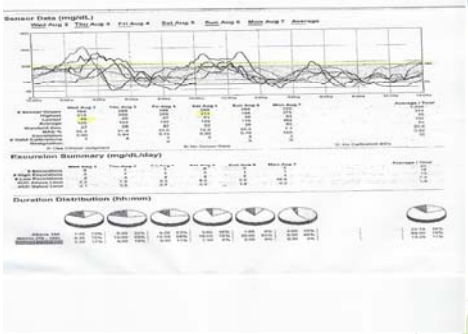
- Mechanical malfunction
- Insertion site issues such as inflammation or, rarely, skin infections
- Interruption of insulin supply due to kinking or blockage of the infusion set can lead to the rapid development of extreme hyperglycemia, especially in type 1 diabetes
- These factors may sometimes necessitate discontinuation of pump use and temporary reversion to insulin injections.
- Safeguards such as alarms that warn of delivery problems or low amounts of insulin in the reservoir are now standard features in insulin pumps.
- Psychological issues of being connected to a machine

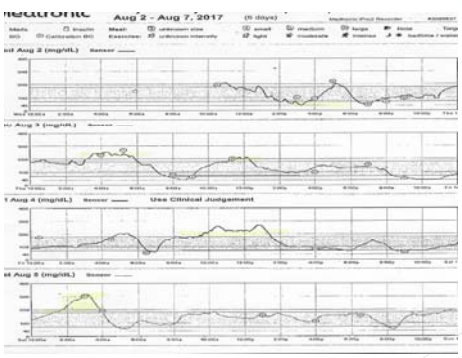
Medtronic Paradigm Insulin Pump

Medtronic 630G

Medtronic 630G – Smart Guard technology

- SMARTGUARD™ TECHNOLOGY - Lowers insulin based on glucose trends
  Only the MiniMed system has SmartGuard technology, which takes action if sensor glucose values go below a preset level. If the patient doesn't respond to alarms, SmartGuard technology can pause insulin delivery for up to two hours – giving time to recover.
- BOLUS WIZARD® CALCULATOR
  This feature automatically calculates and recommends precise bolus doses to help avoid insulin stacking if boluses are accidentally set too close together.
- PREDICTIVE ALERTS
  The pump alerts wearer up to 30 minutes ahead if they're trending high or low, so they can act sooner to keep glucose levels in proper range
- BUILT-IN CGM
  The sensor wirelessly sends glucose information to the pump every five minutes, so wearer can track how they are doing, spot trends and make adjustments.





Medtronic 670G -

Hybrid closed-loop insulin pump system

Closed Loop Insulin Delivery

- Recently approved by FDA
  - Consists of an insulin pump, a sensor and a blood glucose monitor
  - The sensor communicates with the pump, allowing it to adjust insulin administration based on glucose patterns.
  - The pump/sensor combo has to be calibrated two times a day with a separate blood glucose monitor. With proper calibration, the sensor keeps track of blood glucose values 24-hours a day.
- Utilizing glucose information, the pump changes or even "suspends" insulin delivery if the glucose level falls below a pre-set target.
- Alerts wearer to drops in glucose, allowing the wearer to verify the glucose value with a finger stick and to consume a snack to correct the low glucose if needed.
- Significantly decreases hypoglycemic events, especially during the night.
- Alerts the wearer to rapid rises in glucose while it modifies the insulin rate to correct the elevated glucoses.
- Provides newfound stability of blood glucoses.
- Essentially eliminates hypoglycemic events and reduces glucose excursions.

Artificial Intelligence in DM Management

- Moshe Vardi - professor at Rice University and expert on AI
- Machines can now rely on "learned" intuition
- Polanyi's Paradox
  - The paradox is described as "We can know more than we can tell, i.e. many of the tasks we perform rely on tacit, intuitive knowledge that is difficult to codify and automate."
- The paradox is in answer to the idea of computers, automation and AI replacing humans.
- HUGE impact on Diabetes Management

Medtronic 670G

- The **Suspend before low** option avoids lows and rebound highs proactively by automatically stopping insulin 30 minutes before reaching pre-selected low limits. The pump then automatically restarts insulin when glucose levels recover, without alerts.
- The **Auto Mode** option automatically adjusts basal insulin delivery every 5 minutes based on glucose levels to maintain target range, 24 hrs a day.
- Guardian® Sensor 3 continuous glucose monitoring sensor. Can wear up to 7 days. The FIRST and ONLY continuous glucose monitoring sensor FDA approved on which to base insulin dosing.
- Exclusive CONTOUR®NEXT LINK 2.4 meter provides easy and accurate CGM calibration, insulin dosing and remote bolusing

www.medtronicdiabetes.com

Tandem t:slimx2

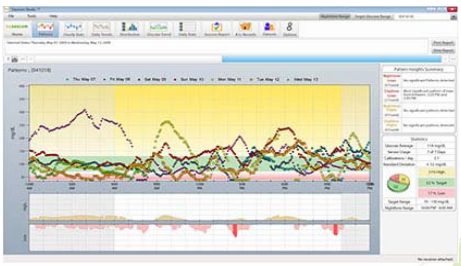
- Integrated with Dexcom G5 sensor
- Allows for remote software updates. Pts will be able to download updates w/o buying a new pump.

Dexcom G5 CGMS

Dexcom G5

- The first FDA-approved CGM System to make treatment decisions without fingersticks.
- Reads glucose every five minutes – and where it's heading – with just a glance at a compatible smart device or Dexcom Receiver
- At least 2 fingersticks required for calibration, or if symptoms or expectations do not match readings
- NOTE: Interacts with medications containing acetaminophen.

Sensor Data



Abbott FreeStyle Libre Pro

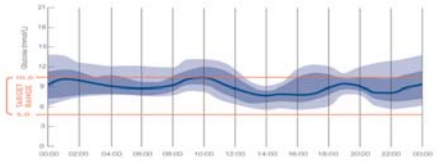
Continuous Glucose Monitoring System

FreeStyle Libre – FLASH Personal CGMS

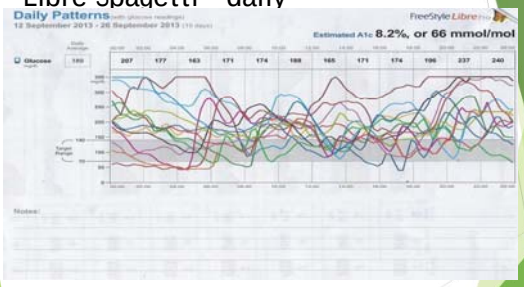
Approved by FDA to be used for treatment without calibration finger sticks

- Stays on the body for up to 10 days
- No fingerstick calibration required
- Automatically measures glucose every minute

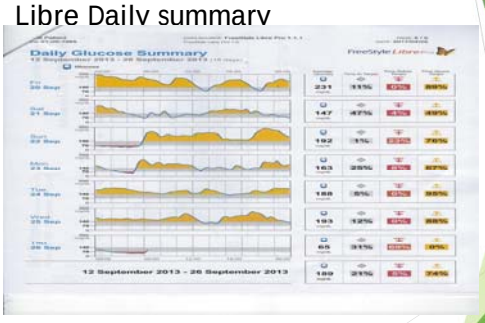
Libre graphs



Libre Spagetti - daily



Libre Daily summary



Gene transfer

- US Patent granted to Ralph A DeFronzo, MD and Bruno Doiron, PhD of UT Health San Antonio
- Plan is to alter other cells of the pancreas so that they secrete insulin in response to glucose.
- Utilizing gene transfer, a virus is used as a vector or carrier to introduce selected genes into the pancreas. These genes become incorporated and cause digestive enzymes and other cell types to make insulin.
- Gene transfer using a viral vector has been approved nearly 50 times by the FDA to treat other diseases.
- Replication of all beta cells (T1DM) is not needed. Only 20% of cell restoration is sufficient to cure T1DM.

New Technologies

- Websites
  - AmericanDiabetesAssociation.org
  - DiabetesEducator.org
  - NIDDK.nih.gov
  - dshs.texas.gov/TDCtoolkit.asp
  - CDC.gov/diabetes/NDEP
  - DiabetesResourcesGuide.com
    - Sponsored by Humana and the American Diabetes Association