Sweet Success:
Expert Tips in Using New & Old Diabetes Medications

There’s MORE new stuff to know?

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Suffering from the conference coma?
My Industry Associations

• **Novo Nordisk** – advisor and speaker (obesity only)
• **Astra Zeneca** – T2DM advisor
• **Medtronic** – Insulin pumps and continuous glucose monitoring (outpatient and inpatient)
Objectives

• Analyze and compare AACE & ADA diabetes guidelines in light of the primary care setting.
• Identify appropriate glycemic target goals of patients.
• Describe appropriate use of the newest oral and injectable anti-hyperglycemic agents.
• Discuss how selected diabetes meds are more safely and effectively used together.
Recent Diabetes Rx Innovations

• Improving incretins
• New class: SGLT2 inhibitors
• New insulin varieties *
• Needless systems **
• TECHNOLOGY! **
There she is...she has diabetes, HLD, HTN, BMI 32 and BG 230, A1C 8.1...now what?
So may drug choices...

So many treatment algorithms
**LIFESTYLE MODIFICATION**
(Including Medically Assisted Weight Loss)

**Entry A1c < 7.5%**
- **MONOTHERAPY**
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - AGI
  - TZD
  - SU/GLN

  If not at goal in 3 months proceed to Double Therapy

**Entry A1c ≥ 7.5%**
- **DUAL THERAPY**
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - Basal Insulin
  - Colesevelam
  - Bromocriptine QR
  - AGI
  - SU/GLN

  If not at goal in 3 months proceed to Two Therapy

**Entry A1c > 9.0%**
- **TRIPLE THERAPY**
  - GLP-1 RA
  - SGLT-2i
  - TZD
  - Basal Insulin
  - DPP-4i
  - Colesevelam
  - Bromocriptine QR
  - AGI
  - SU/GLN

  If not at goal in 3 months proceed to or intensify insulin therapy

**SYMPTOMS**

**NO**
- DUAL Therapy

**YES**
- INSULIN ± Other Agents
- TRIPLE Therapy

**ADD OR INTENSIFY INSULIN**
Refer to Insulin Algorithm

**LEGEND**
- Few adverse events or possible benefits
- Use with caution

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*Order of medications listed represents a suggested hierarchy of usage*

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**PROGRESSION OF DISEASE**

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Bottom line: Metformin, GLP1, SGLT2
Kessler’s Diabetes Rx Points

- **Safety first**
  - Safe target, safe drug—*think co-morbidities*
  - Can’t treat blind—need pt to give you data

- **Timing is everything**

- **Does it cause weight gain??**

- **Always** think….BASAL *first* then Prandial sugar!!

- All diabetes agents will affect one or both of these
So what blood A1C levels should we aim at?

FLEX that A1C!!!!
Individualizing Glycemic Targets in Type 2 Diabetes Mellitus: Implications of Recent Clinical Trials

Faramarz Ismail-Beigi, MD, PhD; Etie Moghissi, MD; Margaret Tiktin, NP; Irl B. Hirsch, MD; Silvio E. Inzucchi, MD; and Saul Genuith, MD

- **Most Intensive**: 6.0%
- **Less Intensive**: 7.0%
- **Least Intensive**: 8.0%

**Psychosocioeconomic considerations**
- **Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems**
- **Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems**

**Hypoglycemia risk**
- **Low**
- **Moderate**
- **High**

**Patient age, y**
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

**Disease duration, y**
- 5
- 10
- 15
- 20

**Other comorbid conditions**
- None
- Few or mild
- Multiple or severe

**Established vascular complications**
- None
- None
- Cardiovascular disease
- Early microvascular
- Advanced microvascular

ADA 2015 Recommended A1C Goals

- History of severe hypoglycemia
- Advanced micro- or macrovascular complications
- Extensive comorbid conditions,
- Limited life expectancy, or
- Long-standing diabetes where the general goal is difficult to attain despite active management

ADA 2015 Recommended A1C Goals

- **< 7%**
  - Most non-pregnant adults

- **< 6.5%**
  - Without significant hypoglycemia or other high risk issues
  - Short duration of diabetes
  - T2DM treated with lifestyle or metformin only
  - Long life expectancy
  - **No significant CVD**

Why don’t patients attain their glycemic goals?
Reality Check

NOTE TO SELF
Take meds
Finding Diabetes Drugs To...

- Increase insulin output
- Decrease insulin resistance
- Decrease hepatic glucose output
- Improve GI glucose metabolism
- Increase glucose excretion


Organs Involved with Glucose Homeostasis

Liver
- Metformin
- TZDs

Pancreas
- Sulfonylureas
- Glinides, GLP-1RA
- DPP-4 Inhibitors

Brain
- GLP-1RA
- Bromocriptine

Adipose
- α-glucosidase inhibitors
- GLP-1RA, Colesevelam

Muscle
- TZDs
- Insulin

Kidneys
- SGLT2 Inhibitors

Gut

Courtesy: Lucia Novak NP
What Sugars Do We Attack?

• Basal sugars (hepatic/fasting)
• Prandial sugar (prandial)
Post-prandial sugars are a big target!
So What Do We Have?

- **Insulin sensitizers**
  - Biguanides
    - Metformin (short & long form)
  - Thiazolidinediones (TZDs) ....
    - Pioglitazone (Actos)
    - Rosiglitazone (Avandia)
Metformin

- Renal clearance—risk of lactic acidosis in CKD
- Reduction of GI problems with XR version
- *Can be used in low doses in patients with GFR 30-60 ml/min*
  - Avoid if GFR < 30 ml/min
  - But should we avoid if serum creatinine...?
    - >1.5 in men
    - >1.3 in women
    - Hmmmm....maybe not
Thiazolidinediones (TZDs)

- Bad raps?
  - Rosiglitazone - CV risk
  - Pioglitazone – bladder cancer
- Fine to use in CKD—no dose adjustment needed
- Associated with weight gain
- Associated with fluid retention (worry re: CHF)
- *Concern about increased bone fractures*
- *May potentiate CKD-related bone disease?*
- Can give 15 mg tri weekly only
So What Do We Have?

- Secretagogues—release insulin
  - Sulfonylureas
    - Glyburide (Glynase), glipizide (Glucotrol), glimeperide (Amaryl)*
    - Basal and prandial support
  - Meglitinide analogues (fast release)
    - Repaglinide (Prandin)*, nateglinide (Starlix)
    - Prandial support
**Insulin Secretagogues**

- **Sulfonylureas**
  - Vary in metabolism & elimination
    - Tips for use in CKD & ischemic heart disease
  - Hypoglycemia risk!! **Must feed!** *(prandial/basal)*
  - Avoid glyburide in ischemic heart & CKD
  - Decrease glimeperide to 1 mg in CKD 3-5
  - Less dose adjusting with glipizide

- **Combos (with metformin and pioglitazone)**
Insulin Secretagogues

• Meglitinides (pancreas *pops*)
  – Hypoglycemia risk
  – Rapaglinide (Prandin) best in CKD

• Tips for use

• HELPS PRANDIAL

So What Do We Have?

- Glucosidase inhibitors — starch blockers
  - Acarbose, miglitol
- Difficult to treat hypoglycemia PO
- Avoid if SCr > 2 mg/dl
New “Old” Drugs

• Bile-acid sequestrants (colesevelam, Whelcol)
• Dopamine Agonists (bromocryptine, Cycloset)
What About These DM Meds?

- Incretins
  - Glucagon-like peptide-1 (GLP-1)
  - DPP-4 antagonists

Works on the prandial glucose

- SGLT2 antagonists

  - Works on basal & prandial sugars

GLP-1

Cardioprotection
Cardiac output

Neuroprotection
Appetite

Gastric emptying

Insulin biosynthesis
β cell proliferation
β cell apoptosis

Insulin secretion
Glucagon secretion

Glucose production

Insulin sensitivity

Muscle

Liver

Heart

Brain

Stomach

Pancreas

GI Tract

(GLP-1 secreted from L cells in the ileum)
GLP-1 Secretion and Inactivation

Mixed meal → Intestinal GLP-1 release → GLP-1 (7-36) active → DPP-4 → GLP-1 (9-36) inactive (>80% of pool)

$T_{1/2} = 1$ to $2$ min

Adapted from Deacon CF, et al. *Diabetes*. 1995;44:1126-1131
What Are Our Incretins?

- **Exenatide (Byetta)**
  - meal timed….bid SC
  - 5 mcg bid daily for 1 month then 10 mcg Bid

- **Bydureon** once a week SC
  - 2 mg single syringe

- **Liraglutide (Victoza) Daily***
  - Weekly up-titr at e: 0.6 mg-1.2 mg- 1.8 mg SC

- **Albiglutide (Tanzeum)** Once a week 30 mg—50 mg

- **Dulaglutide (Trulicity)** Once a week 0.75 mg-1.5 mg

## GLP-1 Receptor Agonist Drugs

<table>
<thead>
<tr>
<th>FDA Approved Drugs</th>
<th>Short-Acting</th>
<th>Long-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approved Drugs</td>
<td>Exenatide (Byetta)</td>
<td>Liraglutide (Victoza)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exenatide-LAR (Bydureon)</td>
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<tr>
<td></td>
<td></td>
<td>Albglutide (Tanzeum)</td>
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<tr>
<td></td>
<td></td>
<td>Dulaglutide (Trulicity)</td>
</tr>
<tr>
<td>Half-life</td>
<td>2–5 h</td>
<td>12 h–several days</td>
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<tr>
<td>Fasting BG</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>A1C</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial hyperglycemia</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>No effect</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1–5 kg</td>
<td>2–5 kg</td>
</tr>
</tbody>
</table>

GLP-1 Products

What patients take
User Tips on GLP-1 agonists

- Weight (also think inches vs pounds)
- Caution in renal insufficiency (not use if GFR <30)
- Delayed gastric emptying issues…”pukey”
- Will need with basal drug if A1C > 9
- Pancreatitis a concern…?
- Thyroid medullary cancer: BLACK BOX
- 15% will not have good responses
More Tips

• Can use with basal insulin, and other oral diabetes meds
• Caution with secretagogues (cut their dose at least 50%)
• Timing

• New basal insulin/GLP-1 combo approved in Europe:
More Incretins

- DPP-4 antagonists
  - Sitagliptin (Januvia, Janumet)
  - Saxagliptin (Onglyza, Kombiglyze)
  - Linagliptin (Trajenta, Jentadueto)
  - Alogliptin (Nesina)
  - Vidalgliptin (Galvus)
Inhibition of DPP-4 Increases Active GLP-1

DPP-4 Inhibitor

- Blocks enzyme that down regulates GLP-1
- *Prandial support—great in elderly*
- Sitagliptin (Januvia)
  - Renal based dosing 25, 50, 100 mg
- Saxagliptin (Onglyza)
  - 2.5 or 5 mg (P450)
- Linagliptin (Tradjenta)
  - 5 mg
- Concerns: severe rhinitis, chronic inflammatory skin issues, pancreatitis? Others?
DPP4-antagonist Considerations

- Cost
- Safety
- Half-life
- Renal/liver issues
DPP-4 Antagonist Combos

• Januvia-metformin
  – Janumet
  – 50/500 or 50/1000 b.i.d. regular and XR
  – tips

• Linagliptin-metformin
  – Jentadueto
  – 2.5/500 and 2.5/1000 b.i.d
  – Wait and see—no head to head
  – Combo reportedly can drop a1c 1.5-1.7%

New combos with SGLT2 inhibitors
Glucose: From Blood to Urine

Glucose filtration (180 g/day) 

90% 
S1 segment of proximal tubule

SGLT2 

10% 
S3 segment of proximal tubule

SGLT1 

Glucose reabsorption 

Macula densa 
Collecting duct 

With SGLT2 Inhibitor: Blood glucose 260 mh/dl 
Urinary glucose excretion = 130-150 mg/dl

(0 g/day) Glucose excretion

SGLT2 Inhibitors (Gliflozins)

- What do we have?
- Canagliflozin (Invokana) (Invokamet)
- Dapagliflozin (Forxiga) (Xigduo)
- Empagliflozin (Jordiance)
- Use as add on med for type 2 DM (2\textsuperscript{nd} or 3\textsuperscript{rd})
- Promotes glucosuria & and secondary weight loss
- Low incidence of hypoglycemia
- A1C reduction of 0.5-1.5%
- Seen in combo
SGLT2 Inhibitors: Points to Consider

• Not as effective with GFR < 45
• Average 3 Kg weight loss

Adverse reactions:
• Increased genital mycotic infection
• Bacterial urinary tract infections
  • Infections were manageable (Prevention?....Kessler tips)
• Rare elevations in potassium
• FDA warns that SGLT2 inhibitors may lead to diabetic ketoacidosis....rare but should be alert to this...especially in T1DM

What about Empagliflozin?

- Similar to others
- FDA closely reviewed cardiovascular data-helps heart failure
- Pediatric trials on going ...

February 02, 2015
U.S. FDA approves first-in-class Glyxambi® (empagliflozin/linagliptin) tablets for adults with type 2 diabetes
## Comparative Considerations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Availability</th>
<th>~A1c Reduction</th>
<th>Cost/30 d Varies</th>
<th>Hypoglycemia Risk</th>
<th>Weight Change</th>
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</thead>
<tbody>
<tr>
<td>SFU/glinides</td>
<td>Generic*</td>
<td>~1.5%</td>
<td>$/$-$$$$</td>
<td>Yes</td>
<td>GAIN</td>
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<tr>
<td>Metformin</td>
<td>Generic</td>
<td>1.0 – 1.5%</td>
<td>$</td>
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<td>Neutral</td>
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<tr>
<td>TZD</td>
<td>Generic</td>
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<td>$$</td>
<td>No</td>
<td>GAIN</td>
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<tr>
<td>AGI</td>
<td>Generic*</td>
<td>0.5 – 1.0%</td>
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<td>No</td>
<td>Neutral</td>
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<tr>
<td>DPP4-Ils</td>
<td>Brand</td>
<td>0.5 – 0.8%</td>
<td>$$$$$</td>
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<td>Neutral</td>
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<td>GLP-1 RAs</td>
<td>Brand</td>
<td>0.4 – 1.5%</td>
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<tr>
<td>Colesevelam</td>
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<td>SGLT2 inhibitors</td>
<td>Brand</td>
<td>0.5 – 1.0%</td>
<td>$$$$$</td>
<td>No</td>
<td>LOSS</td>
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</tbody>
</table>

Adapted from D'Allesio DA and Hirsch IB. glycemic Management of Type 2 DM. *Translational Endocrinology & Metabolism*. 2011;2(1):75.
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
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<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
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<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
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<tr>
<td>RENAL/ GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Contraindicated CrCl &lt; 30</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>May Worsen Fluid Retention</td>
<td>More Hypo Risk</td>
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<td>Neutral</td>
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<td>More Hypo Risk &amp; Fluid Retention</td>
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<tr>
<td>GI Sx</td>
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<td>Increased LDL</td>
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<tr>
<td>BONE</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
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Legend:
- **Green**: Few adverse events or possible benefits
- **Yellow**: Use with caution
- **Orange**: Likelihood of adverse effects

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Then there is insulin
Algorithm for Adding/Intensifying Insulin

**START BASAL** (long-acting insulin)
- **A1c < 8%**
  - TDD 0.1–0.2 U/kg
- **A1c > 8%**
  - TDD 0.2–0.3 U/kg

**INTENSIFY** (prandial control)
- **Add GLP-1 RA or DPP4-i**
- **Add Prandial Insulin**
  - TDD: 0.3–0.5 U/kg
    - 50% Basal Analog
    - 50% Prandial Analog
    - Less desirable: NPH and regular insulin or premixed insulin

**Glycemic Control Not at Goal**

**Insulin titration every 2–3 days to reach glycemic goal:**
- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 4 U
  - FBG 140–180 mg/dL: add 2 U
  - FBG 110–139 mg/dL: add 1 U
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

**Glycemic Goal:**
- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

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FYI: New Insulin

• Long-acting Basal
  • U-300 Glargine (Trujeo)
  • Degludec (Tresiba)
    – Up to 42 hr duration – take daily
      » (OR 2-3- x week in some T2DM)
    – APPROVED September 2015
• Ryzodeg 70/30 (insulin degludec/insulin aspart injection)
• It will also come in combo with liraglutide (DegLira)
What would you do for these SWEET patients?
Josh

- 49 y/o male with known DM x 3 years refusing meds—now ready to talk to you.
- Sugar 300 mg/dl in office; no ketones
- A1C 10.2, Fructosamine 423; up urinating at night.
- BMI 29; HLD (stable), HTN (stable),
- Rx: atorvastatin, HCTZ, lisinopril, ASA
- Strong family Hx of DM
- What should you consider about this pt?
What Med(s) Would You Choose?

- Metformin
- TZD
- Sulfonylurea
- Glinide
- GLP-1 agonist
- DDP-4 antagonist
- SGLT2 inhibitor
- Basal insulin
Sam

- 60 y/o with DM x 8 years
- A1C 9; BG 220; c/o fatigue, weight gain & great hunger
- Hx: HTN, HLD, BPH, gout, hypothyroidism,
- Rx: metformin 2000 mg/d, glipizide XL 10 bid, allopurinol; levothyroxine; ceruvasstatin, ASA, Lisinopril, metoprolol
- BMI 35; renal & liver function normal
- What do you do next?
What Med(s) Would You Choose?

- TZD
- Glinide
- **GLP-1 agonist**
- DDP-4 antagonist
- SGLT2 inhibitor
- Basal insulin
- *What would you do with the metformin and SU?*
Minnie

- 56 y/o AA woman new onset DM
- A1C 11.2, BG in office 410mg/dl; 10 lb wgt loss past 3 months
- BMI: 38; HLD, HTN, fibromyalgia, carpal tunnel; CKD 3A (GFR 34); IBS
- On statin, HCTZ, ACEi, ASA
- What should you consider about this pt?
What Med(s) Would You Choose?

• Metformin
• TZD
• Sulfonylurea
• Glinide
• GLP-1 agonist
• DDP-4 antagonist
• SGLT2 inhibitor
• Basal insulin
How our patients live..

If you're crazy and you know it, shake your meds!
Had enough?

Death by PowerPoint