ANTIDIABETIC THERAPY 2016: PHARMACOLOGIC OPTIONS

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Disclosure

- Spouse works for GlaxoSmithKline as recruiter and owns GSK stock
A 58 yo male consults you for T2DM of 8 years duration and treated with maximum doses of Metformin and Glimepiride for the last 6 years. HBGM reveals FPG 180-200 and 2 hr postdinner 200-220 with no reported hypoglycemia. His BMI is 32 and he eats well and exercises 4x per week. His BP is normal and lipids well controlled by a statin. His A1c in the last year has run 8.0-8.6% and is now 8.7%. He is eager to achieve an A1c of 7% or lower. How might he be best managed at this point?
Diabetes Mellitus Is Associated with Multiple Complications

- A 2- to 4-fold increase in cardiovascular mortality
- Major cause of kidney failure
- Leading cause of new cases of blindness
- Leading cause of lower extremity amputations

Insulin Resistance: Associated Conditions

- Vascular inflammation
- Atherosclerosis
- Dyslipidemia
- Decreased fibrinolytic activity
- Acanthosis nigricans
- Hyperuricemia
- Polycystic ovary syndrome
- Insulin resistance
- Type 2 diabetes
- Endothelial dysfunction
- Hypertension
- Impaired fasting glucose and/or glucose tolerance
- Obesity (central)

Dual Defects of Type 2 Diabetes

Insulin resistance: receptor and postreceptor defects

Peripheral tissues

Increased glucose production

Insufficient glucose disposal

Causes of Hyperglycemia

Liver

Increased glucose production

Insufficient glucose disposal

Peripheral tissues (skeletal muscle)

Pancreas

Impaired insulin secretion

Glucose↑

Diabetes 1996; 45: 1661-1669
Factors that May Drive the Progressive Decline of β-Cell Function

- Insulin Resistance
- Glucose Toxicity (hyperglycemia)
- "Lipotoxicity" (elevated FFA, TG)
- β-Cell Dysfunction

FFA = free fatty acids; TG = triglycerides.
Kahn SE. J Clin Endocrinol Metab. 2001;86:4047-4058.
Peripheral insulin resistance

Hyperinsulinemia

Impaired glucose tolerance

Defective glucoregognition

Early diabetes

β-Cell failure

Late diabetes

Natural History of Type 2 Diabetes


[Graph showing the progression of glucose levels, relative function, and other variables over years of diabetes.]
Decline in β-Cell Function with Diabetes Progression: UKPDS

Only 50% of β-cells may still be functioning at time of diagnosis.

Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.

Alpha-Cell Dysfunction Contributes to Excess Hepatic Glucose Production

- Dysregulation of glucagon secretion during fasting
- Impaired suppression of glucagon secretion after a meal

Fasting and postprandial hyperglycemia in type 2 diabetes

Horm Metab Res 2004; 36: 775-781
Diabetes 1991; 40: 73-81
Categories of Non-insulin Agents 2016

1. Sulfonylureas (SU)
2. Biguanides
3. Thiazolidinediones (TZD)
4. Meglitinides
5. Alpha-glucosidase inhibitors
6. Dipeptidyl Peptidase-4 inhibitors (DPP-4 inh)
7. Glucagon-like Peptide-1 receptor agonists (GLP-RA)
8. Amylin analogs
9. Dopamine receptor agonists
10. Colesevelam
11. Na-glucose Transporter-2 inhibitors (SGLT-2 inh)
## Individual Insulin Products 2016

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<td>• Regular insulin</td>
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<td>• Aspart</td>
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<tr>
<td>• Glargine U-300</td>
<td>• Lispro</td>
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<tr>
<td>• Degludec</td>
<td>• Glulisine</td>
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<td>• Regular insulin U-500</td>
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<td>• 70/30</td>
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<tr>
<td>• Lispro protamine</td>
<td>• 50/50</td>
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<td></td>
<td>• 75/25</td>
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Sulfonylureas

**First generation**
- chlorpropamide
- tolazamide
- tolbutamide

**Second generation**
- glipizide (ER/XL)
- glimepiride
- glyburide
Sulfonylureas

- Stimulate beta cell insulin release
- True “oral hypoglycemic” agents
- first generation agents rarely used
- second-generation agents used regularly
- **Glyburide no longer favored**
- adverse affects mostly limited to hypoglycemia and weight gain
- ?concern re: use in those with sulfa allergy
- **Do not prevent secondary failure**
- A1c drop 1.0-1.5% depending on baseline

JAMA 2010; 303: 1410-1418
SU dosing issues

- Glipizide 2.5-40mg/d
- Glipizide ER/XL 5-20mg/d
- Glimepiride 0.5-8mg/d
- Glyburide: AVOID

Renal disease:
- Glipizide: No dose adjustment
- Glimepiride: start 1 mg daily
- Glyburide: AVOID

Remember: SUs have highest rate of major hypoglycemia of any noninsulin therapy and ? cardiac safety compared to MET*

**Biguanides**

- Metformin and discontinued Phenformin
- Metformin first line after lifestyle changes in all algorithms if nl eGFR
- True “anti-hyperglycemic” agent mostly suppressing hepatic glucose output with minimal insulin sensitization
- some mild weight reduction
- adverse effect: GI-related, B12 def (16% of users), lactic acidosis (mortality 50%) rare with proper patient selection
- A1c drop ~1.0-1.5%

Endocrine Practice 2016; 22(1): 89-90
Metformin dosing

- Metformin 500mg BID initial dose, increase to 1000mg BID or 850mg TID as tolerated
- Metformin ER 500-2000mg with dinner meal may have fewer GI effects
- Max dose 2550mg/d
- Avoid in significant liver disease
- Dose with food intake or after meal
- Liquid formulation available as needed
- *Did not prevent secondary failure in UKPDS (Lancet 1998)* (Like SU, lacks durability of effect but effect more durable than SU)
- No hypoglycemia generally unless combo tx with OHA/insulin

NEJM 1996; 334: 574-579
Metformin use expanded to those with mild renal impairment and some with moderate renal impairment—APRIL 2016

• Obtain eGFR prior to initiation
• Safe if eGFR>45cc/min
• Contraindicated if eGFR<30cc/min
• If eGFR< 30-45cc/min, starting Metformin not recommended
• Assess/reassess benefit if eGFR 30-45cc/min
• Contrast given: hold for 48 hrs in those with eGFR<60cc/min or hx of liver disease, alcoholism, CHF, or with intra-arterial contrast; recheck eGFR at 48hrs prior to restart

Medical Letter April 2016; 58: 51-52
TZDs

- **PPAR-gamma agonists**
- “glitazones”
- Delayed onset to action
- “True insulin sensitizers”
- Only agents to directly target insulin resistance
- Durable effect over time
- Troglitazone removed for idiosyncratic liver toxicity (marked enterohepatic circulation)
- Rosiglitazone 2-8mg/d
- Pioglitazone 15-45mg/d
- No dose adjustment for CKD/ESRD

NEJM 2006; 355: 2427-2443
TZD efficacy/toxicity

• May play a role in beta cell preservation
• May prevent DM2—DREAM and PIPOD trials
• Cause fluid retention—avoid in NYHA III/IV and use caution in any pt with CHF
• Weight gain with weight redistribution
• Lowers A1c 1.0-1.5%, raises LDL-cholesterol
• Lower TG (Pio only)
• Bone loss/unusual fractures (both)
• ?CAD risk (Rosi); ?bladder cancer risk (Pio)—probably neither
• No hypoglycemia usually unless combo tx with OHA/insulin

NEJM 2013; 369: 1285-1287
JAMA 2015; 314: 265-277
Meglitinides

- insulin secretagogues
- “glinides”
- essentially short-acting mealtime sulfonylureas
- Dosed with meals to target postprandial glucose excursion
- A1c effect variable and less than SU overall
- Hypoglycemia may occur but milder than SU

Endocrine Practice 2016; 22(1): 90-91
“Glinide” dosing

- Repaglinide 0.5-4mg 3x per day at meals
- Nateglinide 30-120mg 3x per day at meals
- *Can target “some meals”, not others*

Renal dosing:
If eGFR<30cc/min, favor lower dose:
- 0.5-1mg Repaglinide
- 30-60mg Nateglinide
Alpha-glucosidase inhibitors

- inhibits disaccharidase brush border enzyme
- No insulin secretion so no hypoglycemia
- Minimal A1c drop (~0.4-0.5%)
- Acarbose/Miglitol both 25-100mg TID at meals
- Renal dose: avoid if eGFR<30cc/min or sCr>2mg/dl
- Causes much colonic gas formation—limits clinical use
- Weight neutral
- May be useful in postprandial hypoglycemia following bariatric surgery (off label use)
Incretin Effect Is Diminished in Type 2 Diabetes

Control Subjects (n=8)

Normal Incretin Effect

Subjects With Type 2 Diabetes (n=14)

Diminished Incretin Effect

Diabetologia 1986; 29: 46-52
Glucoregulatory Role of Incretin Hormones

**Glucagon-like peptide 1 (GLP-1)**
- Is released from L cells in ileum and colon
- Stimulates insulin response from beta cells in a glucose-dependent manner
- Inhibits glucagon secretion from alpha cells in a glucose-dependent manner
- Inhibits gastric emptying
- Reduces food intake and body weight

**Glucose-dependent insulinotropic polypeptide (GIP)**
- Is released from K cells in duodenum
- Stimulates insulin response from beta cells in a glucose-dependent manner
- Does not affect gastric emptying
- Has no significant effects on satiety or body weight

Best Prac Res Clin Endocrinol Metab; 2004; 18: 587-606
Diabetes Care 2003; 26: 2929-2940
GLP-1 and GIP Are Degraded by the DPP-4 Enzyme

Meal

Intestinal GLP-1 and GIP release

DPP-4 enzyme

Active GLP-1 and GIP

Rapid inactivation

Inactive metabolites

Diabetes 2004; 53: 654-662
Relative Contribution of FPG and PPG to Overall Hyperglycemia Depending on A1C Quintiles

![Bar chart showing the relative contribution of Fasting and Postprandial glucose to overall hyperglycemia across different A1C quintiles.]

- **Diabetes Care** 2003; 26: 881-885

- A1C Quintiles:
  - <7.3
  - 7.3–8.4
  - 8.5–9.2
  - 9.3–10.2
  - >10.2

- Contribution:
  - Postprandial glucose
  - Fasting glucose

- **n = 58** for each quintile.
DPP-4 inhibitors

• True “incretin” oral agents
• “gliptins”
• Inhibit DPP-4 that degrades GLP-1 and GIP
• Potentiates glucose-dependent insulin secretion (beta) and suppresses glucose-dependent glucagon secretion (alpha)
• Mostly weight neutral
• No hypoglycemia as monotherapy
• Modest A1c drop, ~0.7-0.9% depending on baseline
• No meaningful effect on gastric emptying

Endocrine Practice 2016; 22(1): 89-90
“Gliptins”

- Sitagliptin 25-100mg/d
- Saxagliptin 2.5-5mg/d
- Linagliptin 5mg/d

*All gliptins are renally excreted except Linagliptin

Renal dosing:
Sitagliptin: eGFR>50: 100mg/d
  eGFR 30-50: 50mg/d
  eGFR <30: 25mg/d
Saxagliptin: eGFR>50: 5mg/d
  eGFR<50: 2.5mg/d
Linagliptin: no adjustment needed

*Diabetes Obes Metab 2011; 13: 7-18
Gliptin pearls

Adverse events

- Pancreatitis warning*
- ?pancreatic cancer—probably not
- Nasopharyngitis
- Headache
- Hypersensitivity
- Little or no GI upset

Clinical use:

- Targets postprandial rise in glucose
- Little effect on FPG
- Certain “niche” groups (elderly)

NEJM 2010; 362: 774-777
GLP-1 RA

- Injectable incretin agents with pharmacologic effects
- Daily and weekly formulations
- "tides"

**Mechanism of action:**
- glucose dependent stimulation of insulin secretion and suppression of glucagon
- Delayed gastric emptying
- Central inhibition of food intake
GLP-1 RA agents

**Daily use**

*Intense postprandial effect*
- Exenatide 5-10mcg sc BID
- Liraglutide 0.6-1.8mg sc qD

**Weekly use**

*Postprandial and fasting effects*
- Exenatide 2mg sc qweekly
- Albiglutide 30-50mg sc q weekly
- Dulaglutide 0.75-1.5mg sc q weekly

Endocrine Practice 2013; 19(4): 718-725
GLP-1 RA effects

• Appetite suppression
• Weight loss
• Improved A1c ~1.0-1.5%
• Improved meal-time control
• Little or no hypoglycemia unless paired with SU/insulin
• Liraglutide 0.6-3mg/d with weight loss indication in nondiabetics

Endocrine Practice 2013; 19(4): 718-725
GLP-1 RA safety issues

• Nausea
• Diarrhea
• Bloating
• Early satiety
• Injection site reactions
• *Pancreatitis*
• *Avoid if personal/family hx of MTC/MEN2*

*NEJM 2010; 362: 774-777*
**Incretin treatment comparisons**

**DPP4-inhibitors**
- Augments insulin release and suppresses glucagon release (glucose dependent)
- No effect on gastric emptying
- Weight neutral
- Little or no hypoglycemia
- Pancreatitis risk but otherwise few GI effects
- Headache, hypersensitivity

**GLP-1 RA**
- Augments insulin release and suppresses glucagon release (glucose dependent)
- Slows gastric emptying
- Modest weight loss
- Little or no hypoglycemia
- Pancreatitis risk with numerous GI side effects
- ?C-cell tumor risk
- Requires cold storage

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Endocrine Practice 2013; vol 19(4): 718-724
Pramlintide

• Analog of human amylin which is cosecreted with insulin by beta cell

Mechanism of action
1. suppression of glucagon at meals
2. delayed gastric emptying
3. central suppression of food intake

Pramlintide dosing issues

• indicated in patients on rapid-acting meal time insulin with poor postprandial control

• T1DM: 15 mcg sc TID at meals, increase to 30-60 mcg sc TID as tolerated and adjust rapid-acting insulin as needed

• T2DM: start 60 mcg sc TID at meals, increase to 120 mcg sc TID as needed

Pramlintide treatment issues

**desirable**
- Weight loss
- Appetite suppression
- Modest improvement in A1c
- No dose adjustment if CrCl>15cc/min
- Convenient “pen” use

**adverse**
- Nausea/vomiting
- Avoid in gastroparesis
- Headache
- Avoid if A1c>9%

Dopamine Agonist therapy

• Bromocriptine mesylate is an ergot alkaloid and fast acting dopamine D2 receptor agonist that promotes mild glucose lowering
• Indicated along with lifestyle changes in T2DM
• Dosed as 0.8mg/d, increasing up to max 4.8mg/d

Mechanism of action:
• Unknown. May have effect on circadian rhythms affecting weight regulation and insulin resistance

Diabetes Care 2010; 33(7): 1503-1508
DA agonists

May cause:

- Nausea
- Vomiting
- Nasal congestion
- Orthostatic lightheadedness
- Avoid with antipsychotics medications

Diabetes Care 2010; 33(7): 1503-1508
Colesevelam

- A bile acid sequestrant that may lower glucose mildly while improving LDL-cholesterol
- A1c effect very mild
- No hypoglycemia
- Weight neutral
- May elevate TG levels in those with pre-existing TG elevations
- Use limited by constipation and bloating and limited efficacy

Endocrine Practice 2016; 22(1): 90-91
SGLT-2 inhibitors

- “gliflozins”

**mechanism of action:**
Inhibition of nephron-based glucose transporter to promote glycosuria

- Modest to moderate A1c drop and improved FPG
- Osmotic diuresis promotes mild volume contraction with decreased SBP
- Weight loss from glycosuria
- No hypoglycemia
- No usual GI side effects

Endocrine Practice 2016; 22(1): 89-90
SGLT-2 inh adverse effects

- Urogenital fungal infections
- Increased rate of UTIs
- Mild increase in LDL-cholesterol
- Little efficacy if eGFR<45cc/min
- Potential dehydration/orthostasis
- Increased bone fractures in clinical trials with canagliflozin/dapagliflozin* (bone effect or fall risk)

*Drug Des Devel Ther 2014; 8: 1335-1380
Empagliflozin use associated with decreased all cause mortality and decreased cardiovascular death, mostly attribute to decrease in CHF-related mortality

Unclear if individual or class effect?
SGLT-2 inh DKA risk?

- DKA noted rarely in T1DM (off label)
- DKA noted rarely in T2DM (on label)
- DKA has occurred with lower than expected plasma glucose ("euglycemic DKA")
- Increased glucagon from SGLT-2 inh suspected
- *Infrequent and no drug labeling changes at this time*

Endocrine Practice 2016; 22(1):89-90
With so many choices for therapy, what is a clinician to do?

• Most guidelines call for advantageous lifestyle changes first
• After diet/exercise tried, Metformin universally advised *if not contraindicated*
• After that, well.....
A 58 yo male consults you for T2DM of 8 years duration and treated with maximum doses of Metformin and Glimepiride for the last 6 years. HBGM reveals FPG 180-200 and 2 hr postdinner 200-220 with no reported hypoglycemia. His BMI is 32 and he eats well and exercises 4x per week. His BP is normal and lipids well controlled by a statin. His A1c in the last year has run 8.0-8.6% and is now 8.7%. He is eager to achieve an A1c of 7% or lower. How might he be best managed at this point?
Suggested references

• AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm 2016 *(Endocrine Practice, January 2016 or www.aace.com)*

• American Diabetes Association Standards of Care 2016 *(Diabetes Care, January 2016 or www.diabetes.org)*