Latest Update in Type 2 Diabetes Medications

Objectives

- Describe the current guidelines for the pharmacologic treatment of hyperglycemia
- Discuss medications available for treatment of type 2 diabetes
- Identify the availability, efficacy, and contraindications of new medication therapies for type 2 diabetes

CURRENT GUIDELINES

Patient Case

- MJ is a 52 year old hispanic female recently diagnosed with type 2 diabetes, who was initiated on metformin 1000mg BID

Type 2 Diabetes Guidelines

- American Diabetes Association
  - Updated in 2014
- American Association of Clinical Endocrinologists
  - Updated in 2013

ADA Recommendations

- Patient Centered Approach
- Goal HbA1c <7%
  - Pre-prandial BG <130mg/dl
  - Post-prandial BG <180mg/dl
  - Tighter targets (6.0-6.5%) – younger, healthier
  - Looser targets (7.5-8.0%+) older, comorbidities, hypoglycemia, prone, etc.

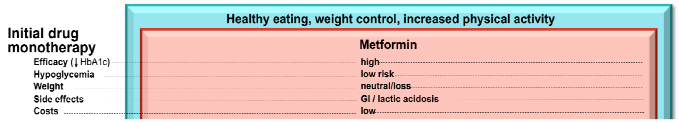


Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

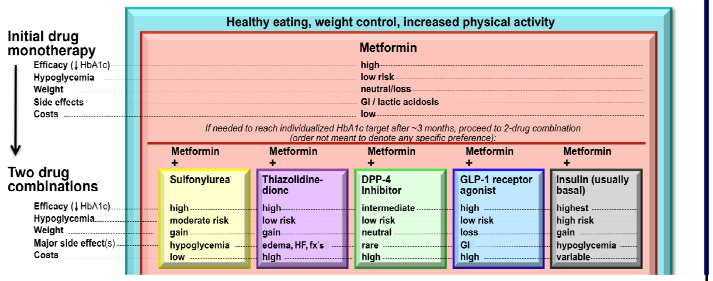


Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

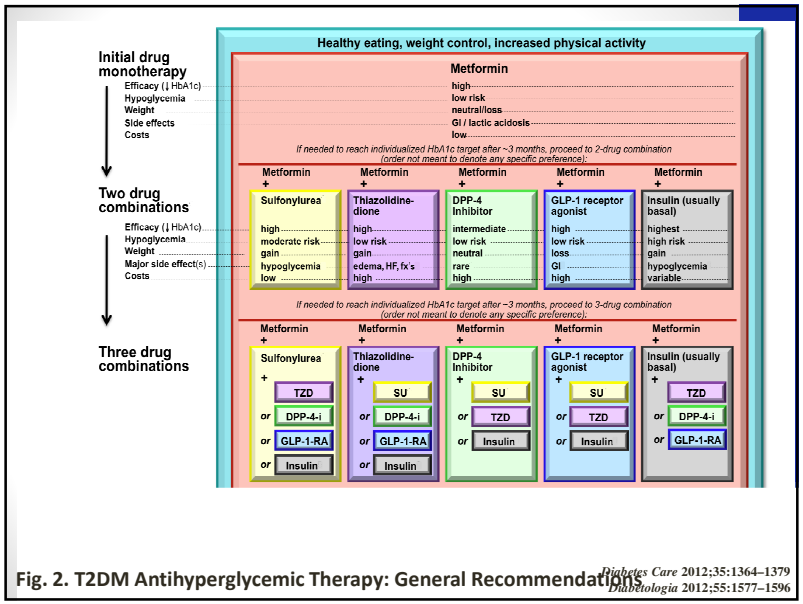
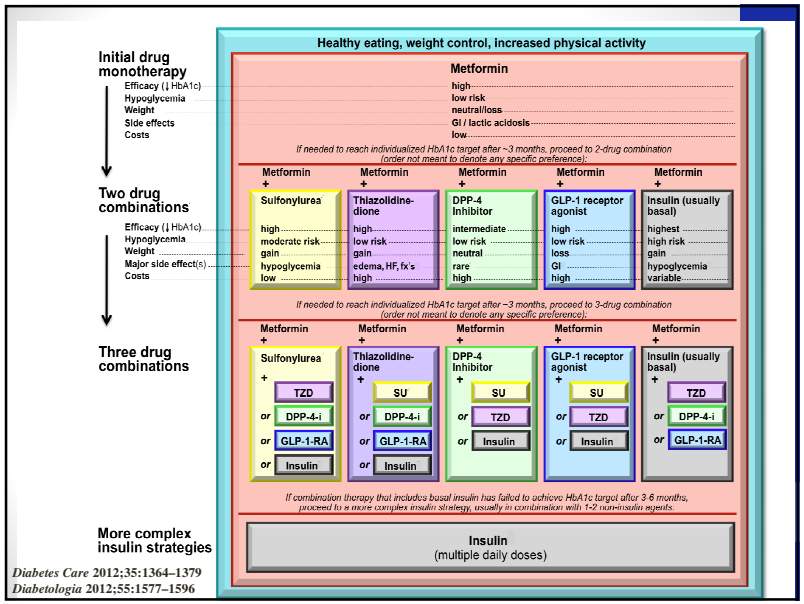


Fig. 2. T2DM Antihyperglycemic Therapy: General Recommendations

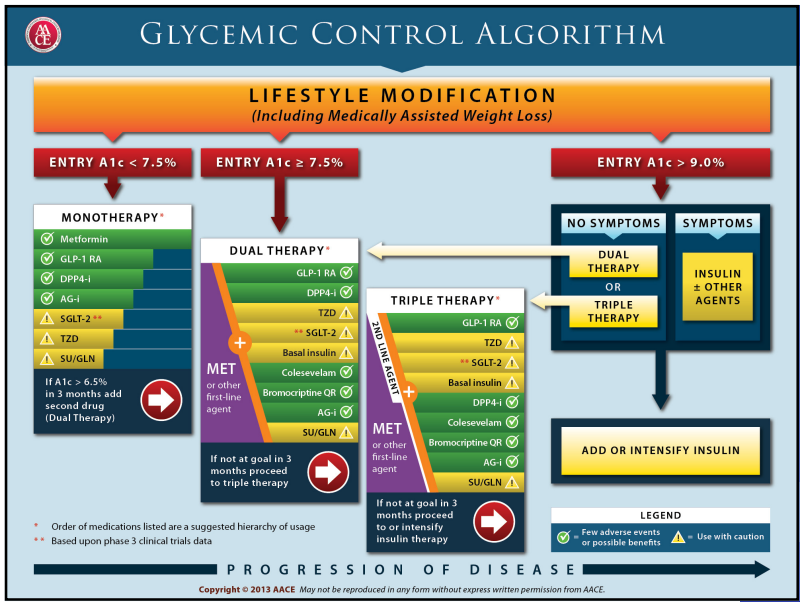
Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596



Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596

AACE Recommendations

- Lifestyle optimization is essential
- A1c target must be individualized
- Choice of therapies should be individualized
- Minimizing risk of hypoglycemia is a priority
- Minimizing risk of weight gain is a priority
- HbA1c goal < 6.5%

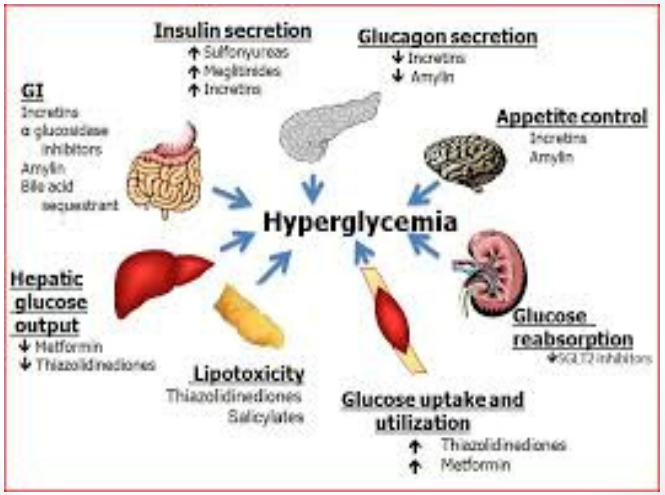


Other Factors to Consider

- Psychosocial factors
- Kidney function
- Comorbidities
- Lifestyle Modifications
- Blood Pressure
- Lipids
- Foot Care
- Vaccinations
- Socioeconomic status
- Health Literacy
- Culture

What about MJ???

MEDICATIONS AVAILABLE FOR TREATMENT



SUMMARY: DRUGS USED FOR DIABETES

Drugs Used for Diabetes

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INSULINS				
Rapid-acting: Lispro, aspart, glulisine Short-acting: Regular Intermediate-acting: NPH Long-acting: Detemir, glargine	Activate insulin receptor	Reduce circulating glucose • promote glucose transport and oxidation; glycogen, lipid, protein synthesis; and regulation of gene expression	Type 1 and type 2 diabetes	Parenteral (SC or IV) • duration varies (see text) • *Toxicity:* Hypoglycemia, weight gain, lipodystrophy (rare)
SULFONYLUREAS				
Glipizide Glyburide Glimepiride	Insulin secretagogues: Close K^+ channels in beta cells • increase insulin release	In patients with functioning beta cells, reduce circulating glucose • increase glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Orally active • duration 10–24 h • *Toxicity:* Hypoglycemia, weight gain
Tolazamide, tolbutamide, chlorpropamide: Older sulfonylureas, lower potency, greater toxicity; rarely used				

GLITINIDES				
Repaglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset of action • duration 5–8 h • *Toxicity:* Hypoglycemia
Nateglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset and short duration (< 4 h) • *Toxicity:* Hypoglycemia

BIGUANIDES				
Metformin	Obscure: Reduced hepatic and renal gluconeogenesis	Decreased endogenous glucose production	Type 2 diabetes	Oral • maximal plasma concentration in 2–3 h • *Toxicity:* Gastrointestinal symptoms, lactic acidosis (rare) • cannot use if impaired renal/hepatic function • congestive heart failure (CHF), hypoxic/acidotic states, alcoholism
ALPHA-GLUCOSIDASE INHIBITORS				
Acarbose, miglitol	Inhibit intestinal α -glucosidases	Reduce conversion of starch and disaccharides to monosaccharides • reduce postprandial hyperglycemia	Type 2 diabetes	Oral • rapid onset • *Toxicity:* Gastrointestinal symptoms • cannot use if impaired renal/hepatic function, intestinal disorders
THIAZOLIDINEDIONES				
Pioglitazone	Regulates gene expression by binding to PPAR-γ and PPAR-α	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease
Rosiglitazone	Regulates gene expression by binding to PPAR-γ	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease • may worsen heart disease

GLUCAGON-LIKE POLYPEPTIDE-1 (GLP-1) RECEPTOR AGONISTS				
Exenatide	Analog of GLP-1: Binds to GLP-1 receptors	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Parenteral (SC) • half-life ~2.4 h • *Toxicity:* Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis
Liraglutide: Similar to exenatide; duration up to 24 h; immune reactions, possible thyroid carcinoma risk				
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS				
Sitagliptin	DPP-4 inhibitor: Blocks degradation of GLP-1, raises circulating GLP-1 levels	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Oral • half-life ~12 h • 24-h duration of action • *Toxicity:* Rhinitis, upper respiratory infections, headaches, pancreatitis, rare allergic reactions
Saxagliptin, linagliptin: Similar to sitagliptin; longer duration of action				

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
AMYLIN ANALOG				
Pramlintide	Analog of amylin: Binds to amylin receptors	Reduces post-meal glucose excursions: Lowers glucagon levels, slows gastric emptying, decreases appetite	Type 1 and type 2 diabetes	Parenteral (SC) • rapid onset • half-life ~ 48 min • *Toxicity:* Nausea, anorexia, hypoglycemia, headache
BILE ACID SEQUESTRANT				
Colesevelam hydrochloride	Bile acid binder	Lowers glucose through unknown mechanisms	Type 2 diabetes	Oral • 24-h duration of action • *Toxicity:* Constipation, indigestion, flatulence

Combination Medications

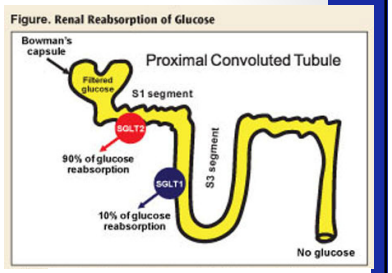
- TZD's + Metformin combinations
  - ✓ ACTO plus met® (pioglitazone/metformin)
  - ✓ ACTO plus met XR® (pioglitazone/metformin)
  - ✓ Avandamet® (rosiglitazone/metformin)
- Metformin + DPP IV-inhibitors
  - ✓ Janumet® (sitagliptin/metformin)
  - ✓ Jentadueto® (linagliptin/metformin)
  - ✓ Kombiglyze XR® (saxagliptin/metformin)
- Metformin + Sulfonylureas
  - ✓ Glucovance® (glyburide/metformin)
  - ✓ Metaglip® (glipizide/metformin)

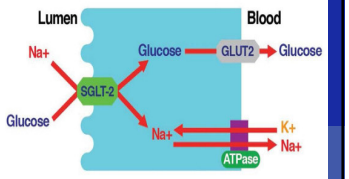
Combination Medications

- TZD's + Sulfonylureas
  - ✓ Avandaryl® (rosiglitazone/glimeperide)
  - ✓ Duetact® (pioglitazone/glimeperide)
- Metformin + Meglitinides
  - PrandiMet® (repaglinide/metformin)
- DPP-IV Inhibitors + Statins
  - Juvisync® (sitagliptin/simvastatin)

SGLT-2 Inhibitors

- Sodium-dependent glucose transporter (SGLT) 2 in proximal convoluted tubule
  - reabsorbs ~ 90% of filtered glucose
  - transport of glucose is linked to downhill sodium transport
    - Na^+ is then pumped out of the cell into the interstitium by active transport
    - Glucose exits by facilitated diffusion via glucose transporter (GLUT) 2 into the interstitial fluid.





http://www.endocrinetoday.com/pda.as

Glucose/Na Transport Genes

Transporter	Distribution
SGLT1	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	Kidney, brain, liver, thyroid, muscle, heart
SGLT4	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5	Kidney
SGLT6	Brain, kidney, intestine
SMIT1	Brain, heart, kidney, lung

Glucose Homeostasis

- Body glucose stores ≈ 450g
- Daily glucose turnover ≈ 250g
- Typical Western diet ≈ 180g/day
- Gluconeogensis (liver and kidney) bridges gap
- Brain consumes ≈ 125g/day
- Kidneys assist in homeostasis by reabosrbing glucose

Normal Renal Glucose Physiology

- 180g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules and reenters the circulation
- SGLT2 reabsorbs = 90% of the glucose
- SGLT1 reabsorbs – 10% of the glucose
- Virtually no glucose excreted in the urine

Effects of SGLT2 Inhibitors

- Inhibition of renal tubular sodium-glucose cotransporter → reversal of hyperglycemia → reversal of "glucotoxicity"
- ↑ Insulin sensitivity in muscle
  - ↑ GLUT4 translocation
  - ↑ Insulin signaling
- ↑ Insulin sensitivity in liver
  - ↓ Glucose-6-posphatase
- ↓ Gluconeogenesis
  - ↓ Cori Cycle
  - ↓ PEP carboxykinase
- ↑ Improved beta cell function

SGLT-2 Inhibitors

Canagliflozin (Invokana™) – 100mg and 300mg tablets
- Metformin IR + canagliflozin (Invokamet™)

Dapagliflozin (Forxiga™) – 5 and 10mg tablets
- Metformin XR + dapagliflozin (Xigduo™)

Empagliflozin (Jardiance™) – 10 and 25mg tablets

SGLT-2 Inhibitors

- In development:
  - Ertugliflozin – Phase II
  - Ipragliflozin – Phase III (approved in Japan 1/14)
  - Luseogliflozin – (approved in Japan 3/14)
  - Remogliflozin – Phase IIb
  - Sergliflozin – (stopped after Phase II)
  - Tofoliflozin – Phase III (approved in Japan 3/14)

SGLT-2 Inhibitors

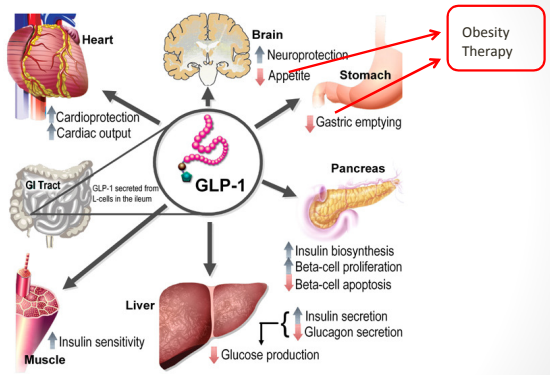
Benefits
- Insulin Independence
- Weight Reduction
- Low risk of hypoglycemia
- Blood pressure reductions

Limitations/Concerns
- Polyuria
- Electrolytes
- Urinary tract infections
  - Bacterial
  - Fungal
- Genital fungal infections
- Vulvovaginitis
- Bulanitis

GLP-1 Agonists
Glucagon Like Polypeptide -1

- Incretin hormone → stimulates post-prandial insulin secretion
- Other pancreatic effects:
  - Increases insulin production
  - Decreases glucagon secretion
  - Increases β-cell glucose sensitivity
- Extra-pancreatic effects → receptors located in the brain, heart, kidney, lung, and GI tract

Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues



GLP-1 decreases appetite and delays gastric emptying – therapeutic target for obesity

Richard E. Pratley, Matthew Gilbert; *Rev Diabet Stud, 2008, 5(2)*

GLP-1 Receptor Agonists

- Exenatide (Byetta®, Bydureon®) – 10mcg BID
- Liraglutide (Victoza®) - 1.2mg or 1.8mg daily
- Albiglutide (Tanzeum) – 30mg once weekly

GLP-1 Receptor Agonists

Benefits

- Increases satiety
- Slows gastric emptying
- Weight loss

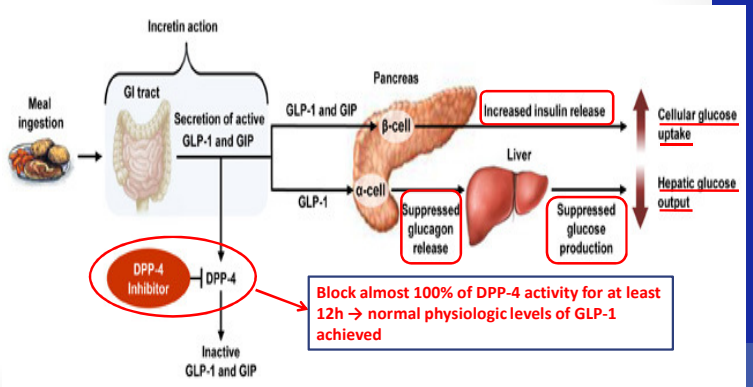
Limitations/Concerns

- Nausea, vomiting, diarrhea
- Hypoglycemia
- Delays absorption of other medications
- Thyroid cancer, pancreatitis - liraglutide

DPP-IV Inhibitors
Dipeptidyl Peptidase 4 Inhibitors

- Sitagliptin (Januvia®) – 100mg once daily
- Saxagliptin (Onglyza®) – 2.5-5mg once daily
- Linagliptin (Tradjenta®) – 5mg once daily

Mechanism of Glucose Control by DPP-4 Inhibitors



Michael Cobble, J Family Practice, 2009 · Vol. 58, No. 10

DPP-IV Inhibitors

Benefits

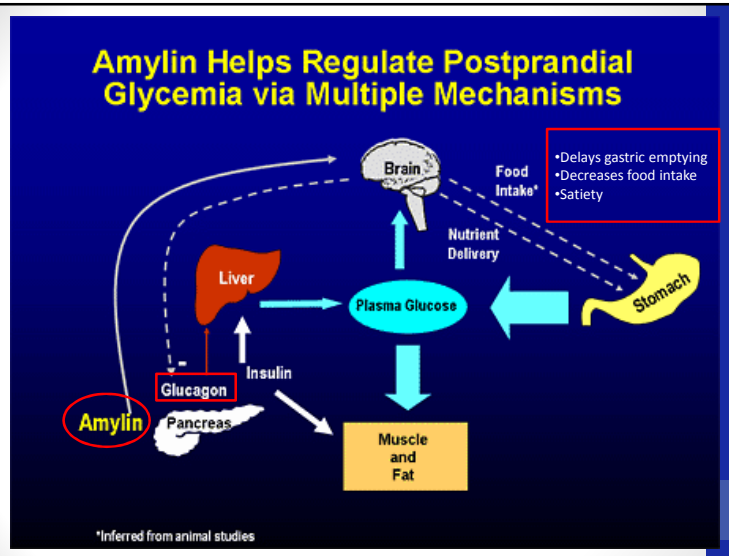
- Hypoglycemia is rare

Limitations/Concerns

- More effective in early stages of diabetes
- Increased URTIs
- Increased UTIs
- Headache
- Peripheral edema

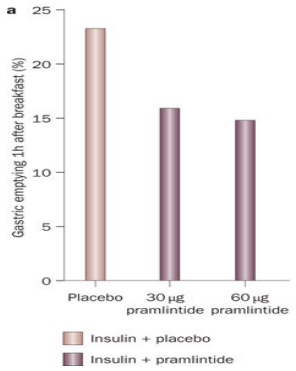
Amylin Mimetics

- Pramlintide (Symlin®) – 60-100mcg - a synthetic form of amylin with amino acid modifications to improve bioavailability



http://www.medscape.org/viewarticle/541702_2

Pramlintide Slows Gastric Emptying



Type-1 diabetes, n=11
99mTc-tin colloid (SnC) labeled pancake
% of radioactivity over stomach measured

Kong MF et al., Diabetologia , Volume 41, Number 5 (1998)

Amylin Mimetics

Benefits

- Weight loss
- Approved for Type 1 and Type 2

Limitations/Concerns

- Nausea
- Hypoglycemia
- Contraindicated in patients with gastropareiss or other disorders of motility

AVAILABILITY AND EFFICACY

Drug Name	Available Generic?	Cost without Insurance
Metformin	Yes	Free at Publix
Glipizide	Yes	$4.00
Pioglitazone	Yes	$193
Repaglinide	Yes	$73
Victoza	No	$720
Januvia	No	$177
Invokana	No	$400
Insulin	Yes	Variable

*Prices from GoodRX.com

Efficacy

Drug Class	Expected A1c lowering
Alpha-glucosidase inhibitor	0.5-1%
Amylin analog	0.5-1%
Biguanide	1-1.5%
DPP-IV Inhibitor	0.5-1%
GLP-1 agonist	1-1.5%
Insulin	1.5-3.5%
SGLT-2 Inhibitor	0.7-1%
Sulfonylurea	1-1.5%
Thiazolidinedione	1-1.5%

Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Diabetes Care 2012;35:1364-79.

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

Back to MJ…..

- A1c
- Home Glucose Readings
- Comorbidities
- Insured vs. Uninsured
- Side Effect Profile
- Medication Adherence
- Other Lab Values