

New Diabetes Medications and Strategies to Improve Medication Adherence

Ericka B. Ridgeway, PharmD, BCACP, CDE, BC-ADM

November 12, 2015



Objectives

- Review 2015 hyperglycemia management guidelines and available agents
- Introduce new medication and insulin delivery options
- Discuss barriers and opportunities to individualizing drug therapy
- Review factors affecting medication adherence and analyze approaches to improve it

Let's Review¹...

Class	Available Agents	MOA/physiologic action
Biguanides	Metformin (Glucophage®, Riomet®)	Activates AMP-kinase, ↓ hepatic glucose production
Sulfonylureas (SU)	Glyburide (DiaBeta®, Micronase®) Glipizide (Glucotrol®, Glucotrol XL®) Glimepiride (Amaryl®)	Closes K _{ATP} channels, ↑ insulin secretion
Meglitinides (GLN)	Repaglinide (Prandin®), Nateglinide (Starlix®)	Closes K _{ATP} channels, ↑ insulin secretion
Thiazolidinidiones (TZD)	Pioglitazone (Actos®), Rosiglitazone (Avandia®)	Activates PPAR-γ, ↑ insulin sensitivity
α-Glucosidase inhibitors (AGi)	Acarbose (Precose®), Miglitol (Glyset®)	Inhibits α-glucosidase in the intestines, slows CHO absorption
DPP4 inhibitors (DPP-4i)	Sitagliptin (Januvia®), Saxagliptin (Onglyza®), Linagliptin (Tradjenta®), Alogliptin (Nesina®)	Inhibitors DPP-4 activity, increases incretin, ↑ insulin secretion, ↓ glucagon secretion
Bile acid sequestrants	Colesevelam (WelChol®)	Binds bile acids, ↓ hepatic glucose production?, ↑ incretin levels?

MOA = Mechanism of action

Let's Review¹...

Class	Available Agents	MOA/physiologic action
Dopamine-2 agonists	Bromocriptine QR (Cycloset®)	Activates dopaminergic receptors, ↑ insulin sensitivity
SGLT2 inhibitors (SGLT-2i)	Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), Empagliflozin (Jardiance®)	Inhibits SGLT2, blocks glucose reabsorption, increases urinary glucose excretion
GLP-1 receptor agonists (GLP-1 RA)	Exenatide (Byetta®, Bydureon®), Liraglutide (Victoza®), Albiglutide (Tanzeum®), Dulaglutide (Trulicity®)	Activates GLP-1 receptors, ↑ insulin secretion, ↓ glucagon secretion, slows gastric emptying, ↑ satiety
Amylin mimetics	Pramlintide (Symlin®)	Activates amylin receptors, ↓ glucagon secretion, slows gastric emptying, ↑ satiety

MOA = Mechanism of action



Let's Review¹...

Class	Available Agents	MOA/physiologic action
Insulin	<p>Rapid</p> <ul style="list-style-type: none"> • Lispro (Humalog®) • Aspart (Novolog®) • Glulisine (Apidra®) • Inhaled (Afrezza®) <p>Short-acting</p> <ul style="list-style-type: none"> • Regular (Humulin R®, Novolin R®) <p>Intermediate-acting</p> <ul style="list-style-type: none"> • NPH (Humulin N®, Novolin N®) <p>Long-acting</p> <ul style="list-style-type: none"> • Glargine (Lantus®, Toujeo®) • Detemir (Levemir®) • Degludec (Tresiba®) <p>Mixed</p> <ul style="list-style-type: none"> • NPH/regular (Humulin 70/30®, Novolin 70/30®) • NPL/lispro (Humalog Mix 75/25®) • NPA/aspart (Novolog Mix 70/30®) • NPL/lispro (Humalog Mix 50/50®) 	Activates insulin receptors, ↑ glucose disposal, ↓ hepatic glucose production

MOA = Mechanism of action; NPL = Neutral Protamine Lispro; NPA = Neutral Protamine Aspart ,

Glycemic Treatment^{1,2}



Glycemic Treatment^{1,2}

Lifestyle modification



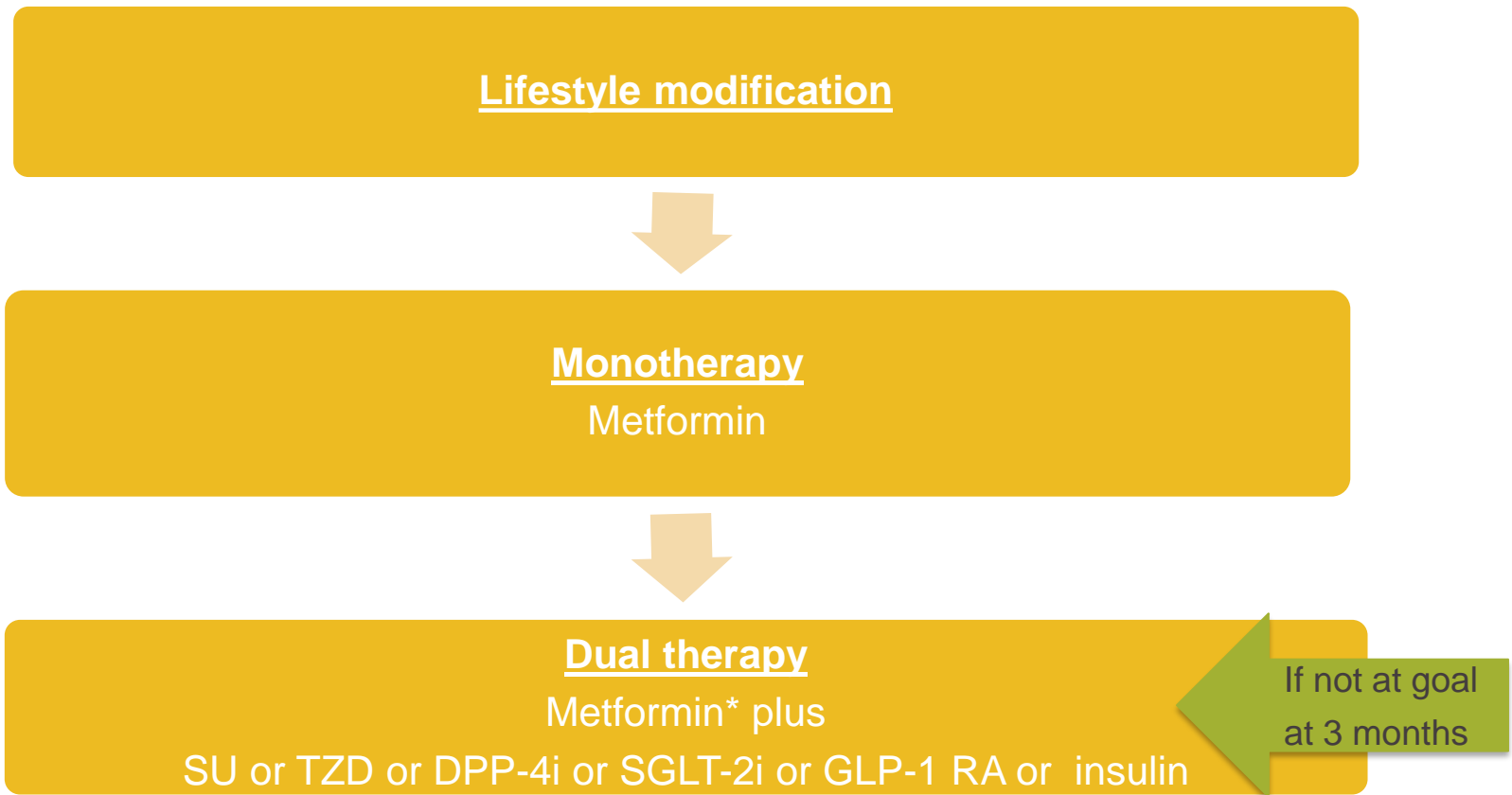
Monotherapy

Metformin*

If not at goal
at 3 months

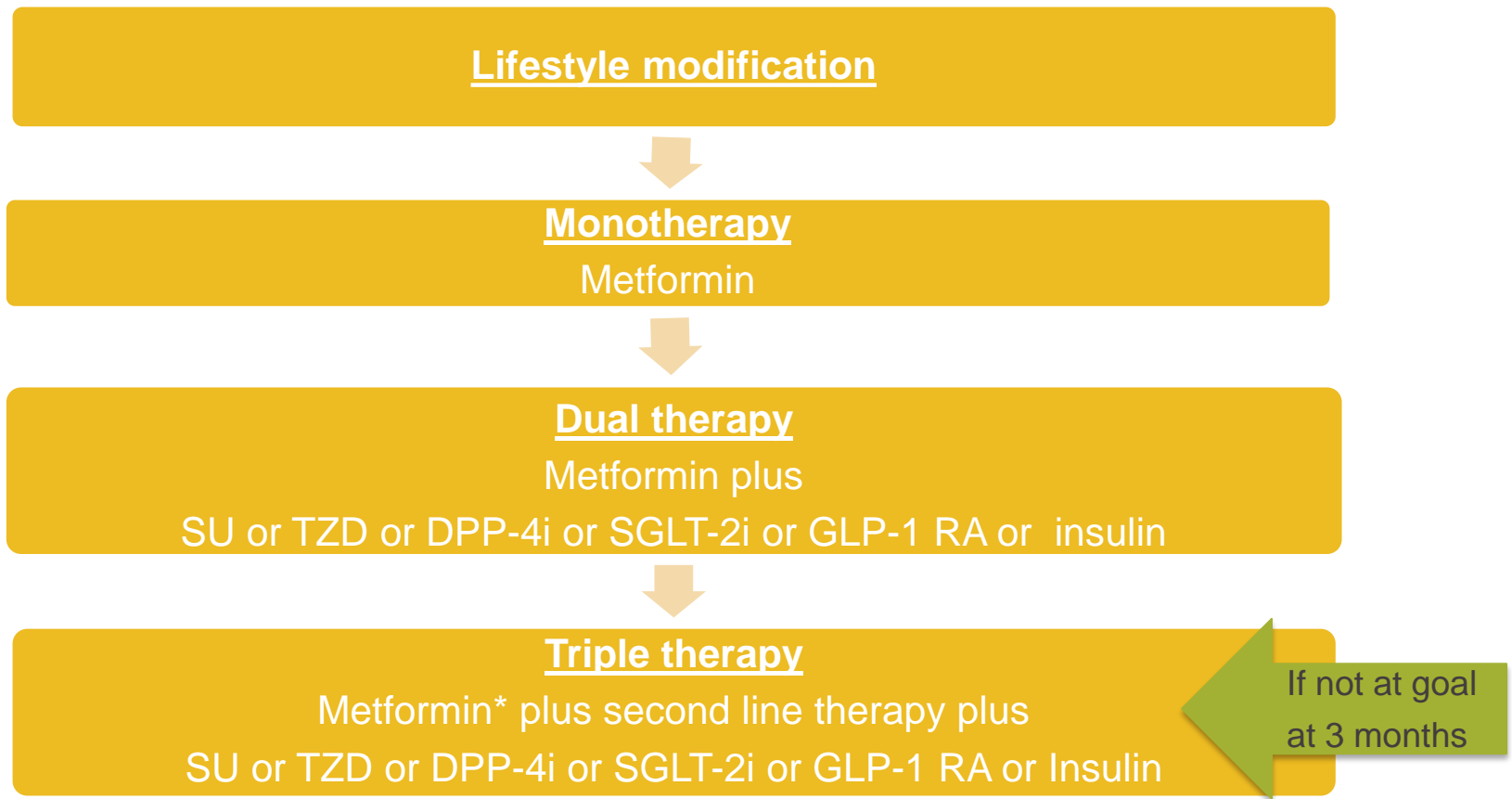
AACE Recommendation: Metformin or GLP-1 RA or SGLT-2i or DPP-4i or AGi (caution if TZD or SU/GLN)

Glycemic Treatment^{1,2}



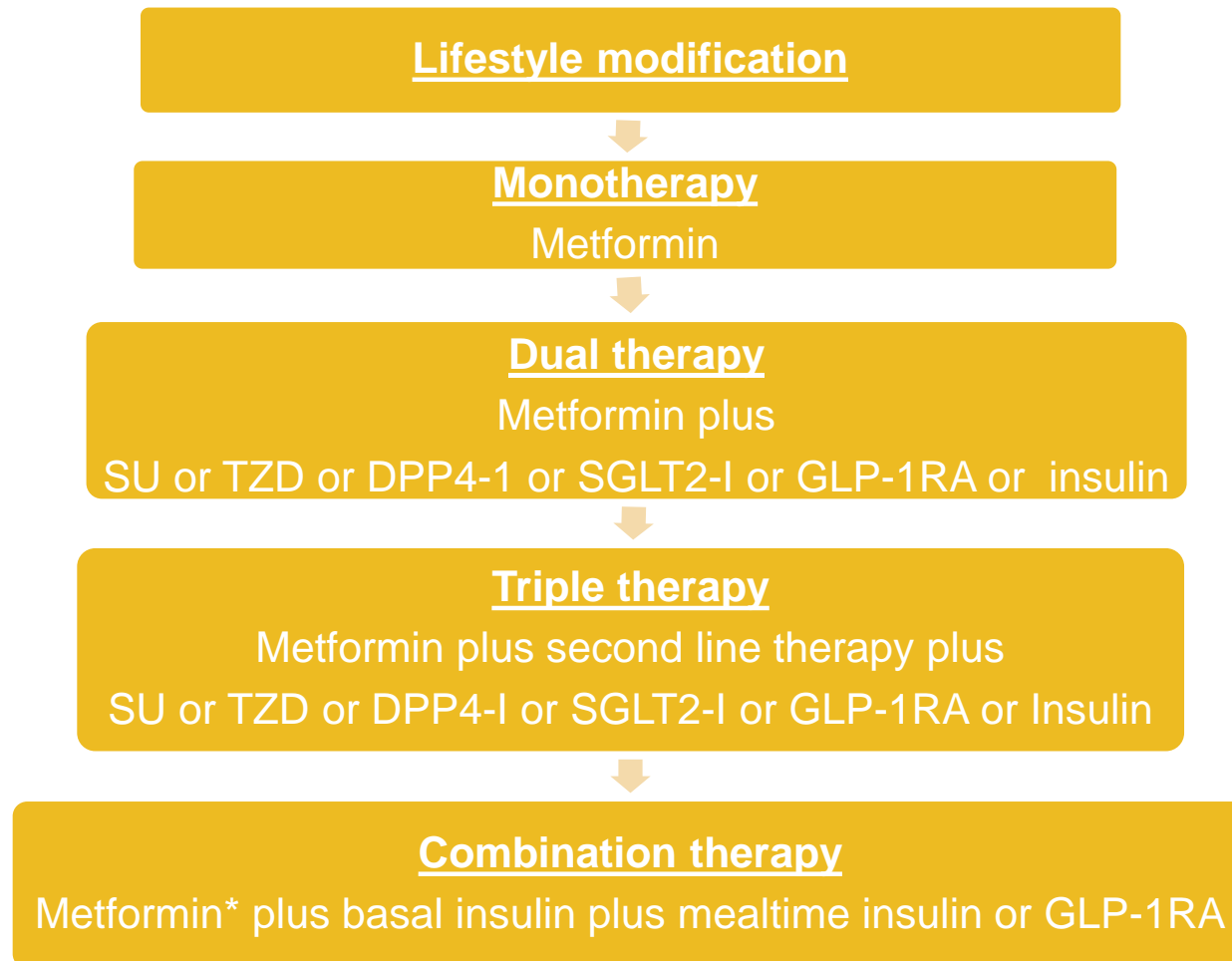
AACE Recommendation: Metformin or other 1st-line agent plus GLP-1 RA or SGLT-2i or DPP-4i or AGi or colesevelam or bromocriptine QR (caution if TZD, SU/GLN or basal insulin). If A1c $\geq 7.5\%$ start with dual therapy.

Glycemic Treatment^{1,2}



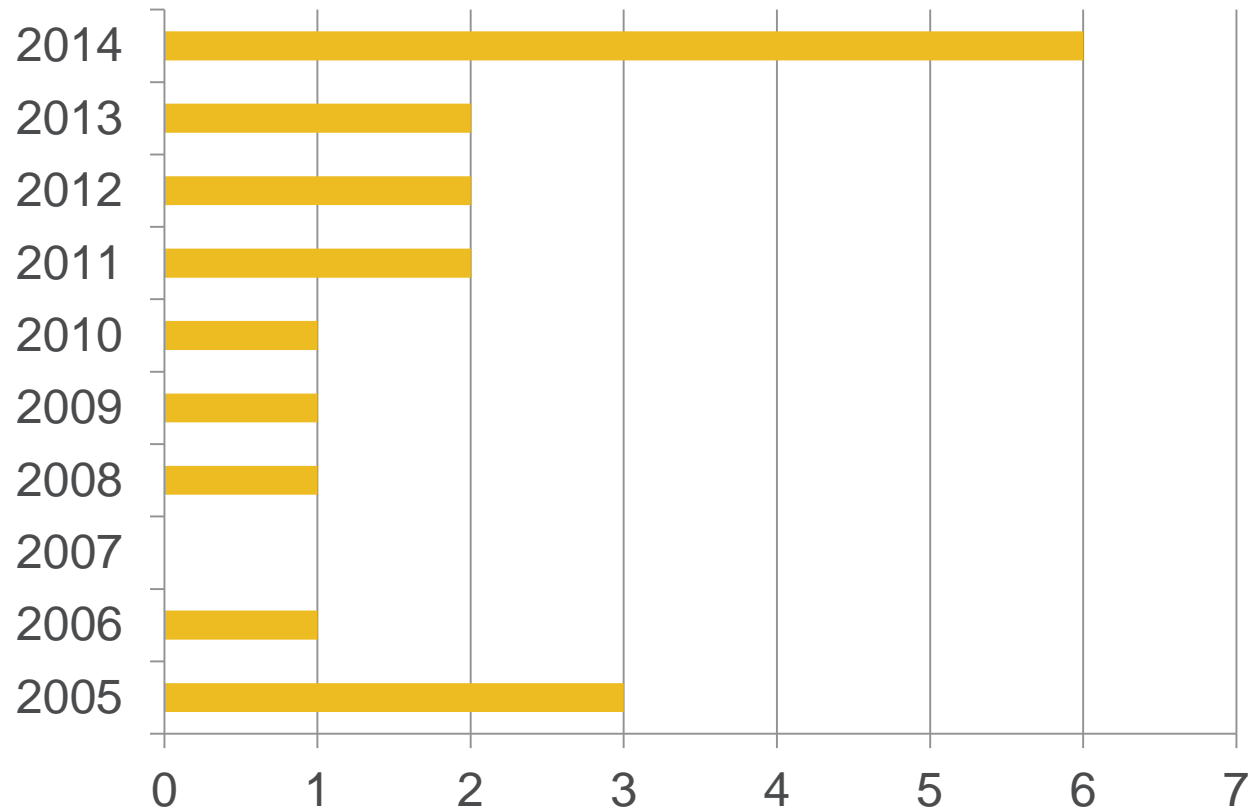
*AACE Recommendation: Metformin or other 1st-line agent plus 2nd-line agent plus GLP-1 RA or SGLT-2i or DPP-4i or AGi or colesevelam or bromocriptine QR (caution if TZD, SU/GLN or basal insulin). If A1c > 9% with symptoms, start with insulin +/- 1 other agents

Glycemic Treatment^{1,2}



*AACE Recommendation: Metformin or other 1st-line agent plus 2nd-line agent plus 3rd-line agent plus (or intensify) insulin. If A1c > 9% with symptoms, start with insulin +/- 1 other agents

Drug Approvals³

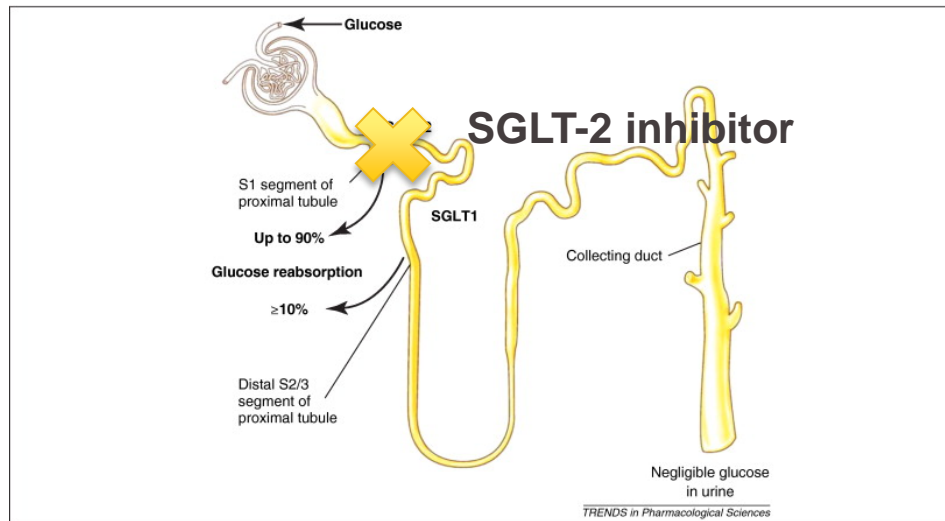


Newest Drug Approvals³

	Drug	Approval Month
2013	Alogliptin (Nesina®)	January
	Canagliflozin (Invokana®)	April
2014	Dapagliflozin (Farxiga®)	January
	Albiglutide (Tanzeum®)	April
	Empagliflozin (Jardiance®)	June
	Inhaled insulin (Afrezza®)	August
	Dulaglutide (Trulicity®)	September
	Dapagliflozin/metformin (Xigduo XR®)	October
2015	Glargine U-300 (Toujeo®)	February
	Empagliflozin/metformin (Synjardy®)	August
	Degludec (Tresiba®)	September

Canagliflozin (Invokana®), Dapagliflozin (Farxiga®), Empagliflozin (Jardiance®)^{4,5,6}

- SGLT-2 inhibitors
- Studied as monotherapy or in combination with other agents
- Lowers A1c by ~ 0.77-1%
- Caution with elderly
- Renal dose adjustment needed
- Patient instructions
 - Take in the morning



www.cell.com

Insulin Glycemic Effect⁷

Insulin Type	Onset (hr)	Peak (hr)	Duration (hr)
Lispro	0.25-0.5	0.5-2.5	≤5
Aspart	0.2-0.3	1-3	3-5
Glulisine	0.2-0.5	1.6-2.8	3-4
Oral inhalation	0.25	0.88	2.5-3
Regular	0.5	2.5-5	4-12
NPH	1-2	4-12	14-24
Detemir	3-4	None?	6-23
Glargine (U-100)	3-6	None	11-24+
Glargine (U-300)	3-6	None	24+
Degludec	3-6	None	42+
Mixed*	0.17-0.5	1-12	14-24

*kinetics varies based on type; hour (hr)

Afrezza®⁸

- Rapid-acting inhaled insulin
- Dose conversion table
- Contraindicated in those with chronic lung disease (i.e., asthma, COPD) secondary to risk of acute bronchospasm
 - Use spirometry, medical history and physical exam
- Side effects
 - Hypoglycemia, cough, throat pain/irritation, headache



www.mannkindcorp.com

Type 1 diabetes

- 24-week, open-label study of Afrezza in combination with basal insulin versus insulin aspart with basal insulin (n=344)
 - More patients in the aspart group achieved prespecified A1c target
 - Change from baseline A1c was -0.21 (Afrezza group) versus -0.4 (aspart group)

Type 2 diabetes

- 24-week, double-blind, placebo controlled study of patients inadequately controlled on optimal/maximally tolerated doses of metformin alone, or 2 or more oral diabetes medications (n=479)
 - Treatment with Afrezza versus placebo provided a statistically significantly greater mean reduction in A1c
 - Change from baseline A1c was -0.82 (Afrezza group) versus -0.42 (placebo group)

Afrezza®⁸

- 4, 8, 12 unit single-use cartridges, 3 cartridges per cavity of blister strip, 5 blister strips per card (total of 15 cartridges)
- Cartridges are color-coded
- Inhaler can be used for up to 15 days from date of first use
- Store in refrigerator
 - If not refrigerated, but sealed good for 10 days
 - Opened strips good for 3 days
 - Inhaler can be stored in refrigerator, but use at room temperature











Afrezza® Instructions⁸

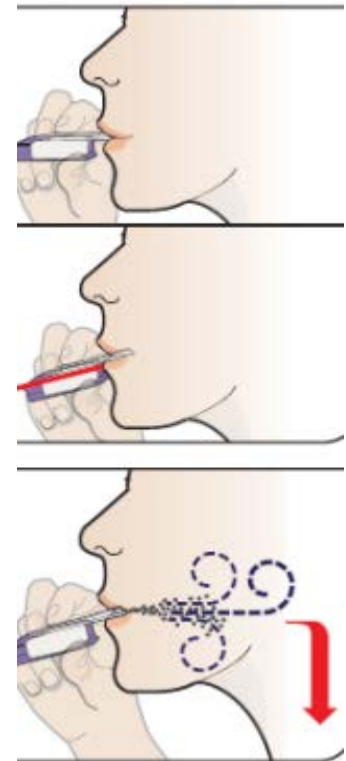
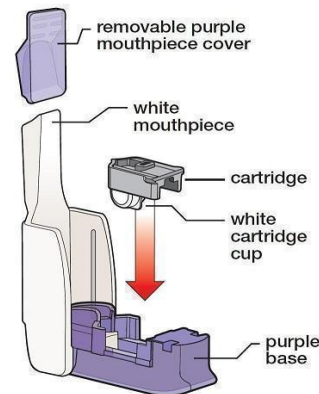
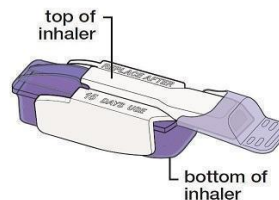
Step 1: Select cartridge
(see table)

Step 2: Load cartridge into
inhaler

Step 3: Inhale insulin

Step 4: Remove cartridge
and discard cartridge

Injected Mealtime Insulin Dose 	AFREZZA® Dose	# of cartridges needed			
		4 unit (blue)	8 unit (green)	12 unit (yellow)	
up to 4 units	4 units 				
5-8 units	8 units				
9-12 units	12 units				
13-16 units	16 units 		+		
17-20 units	20 units			+	
21-24 units	24 units				



www.afrezza.com; www.bharathtech.com

Insulin Glycemic Effect⁷

Insulin Type	Onset (hr)	Peak (hr)	Duration (hr)
Lispro	0.25-0.5	0.5-2.5	≤5
Aspart	0.2-0.3	1-3	3-5
Glulisine	0.2-0.5	1.6-2.8	3-4
Oral inhalation	0.25	0.88	2.5-3
Regular	0.5	2.5-5	4-12
NPH	1-2	4-12	14-24
Detemir	3-4	None?	6-23
Glargine (U-100)	3-6	None	11-24+
Glargine (U-300)	3-6	None	24+
Degludec	3-6	None	42+
Mixed*	0.17-0.5	1-12	14-24

*kinetics varies based on type; hour (hr)

Toujeo® (glargine U-300)^{9,10,11,12,13,14}

Long-acting insulin

Efficacy compared to glargine (Lantus®) in randomized, open-label trials

- Type 1 diabetes
 - In combination with mealtime insulin
- Type 2 diabetes
 - In combination with mealtime insulin with or without metformin
- No statistically significant difference compared to Lantus®, but higher doses of Toujeo® required for same effect

www.toujeo.com

Toujeo® (glargine U-300)⁹

300 units/mL in prefilled 1.5 mL Solostar® pen

- Package of 3 or 5

Patient education (especially if converting)

- Dose counter shows number of units, no re-calculation required
- Inject once daily at any time of day, but always at the same time every day
- Opened (in-use) pen good for 28 days



Insulin Glycemic Effect⁷

Insulin Type	Onset (hr)	Peak (hr)	Duration (hr)
Lispro	0.25-0.5	0.5-2.5	≤5
Aspart	0.2-0.3	1-3	3-5
Glulisine	0.2-0.5	1.6-2.8	3-4
Oral inhalation	0.25	0.88	2.5-3
Regular	0.5	2.5-5	4-12
NPH	1-2	4-12	14-24
Detemir	3-4	None?	6-23
Glargine (U-100)	3-6	None	11-24+
Glargine (U-300)	3-6	None	24+
Degludec	3-6	None	42+
Mixed*	0.17-0.5	1-12	14-24

*kinetics varies based on type; hour (hr)

Tresiba® (degludec U-100 and U-200)^{15,16,17,18,19}

- Long-acting insulin
- Efficacy compared to glargine (Lantus®) or detemir or sitagliptin in randomized, open-label trials
 - Three trials in patients with type 1 diabetes
 - In combination with mealtime insulin
 - Six trials in patients with type 2 diabetes
 - In combination with mealtime insulin or with oral anti-diabetic agents
 - Similar compared to Lantus and Levemir
 - Statistically significant improvements compared to sitagliptin

Tresiba® (degludec U-100 and U-200)¹⁵

100 units/mL and 200 units/mL prefilled 3 mL
FlexTouch® pen

- Package of 3 (U-200) or 5 (U-100)

Patient education FlexTouch® pen

- Dose counter shows number of units, no re-calculation is required
- Inject once-daily at any time of the day
- Opened (in-use) pen good for 56 days

Insulin Delivery Devices²⁰

Vial/syringe

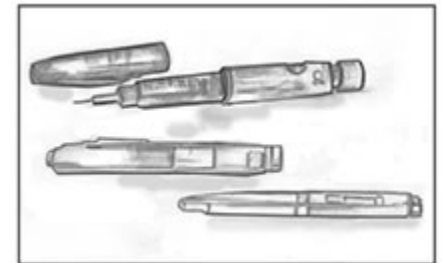
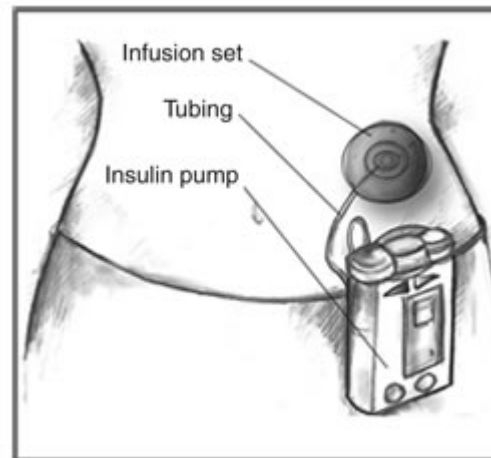
Pen

External pump

Internal pump

Port

V-go






www.niddk.nih.gov/health-information/healthalternative-devices-taking-insulin/pages/index.aspx

V-Go^{20,21}

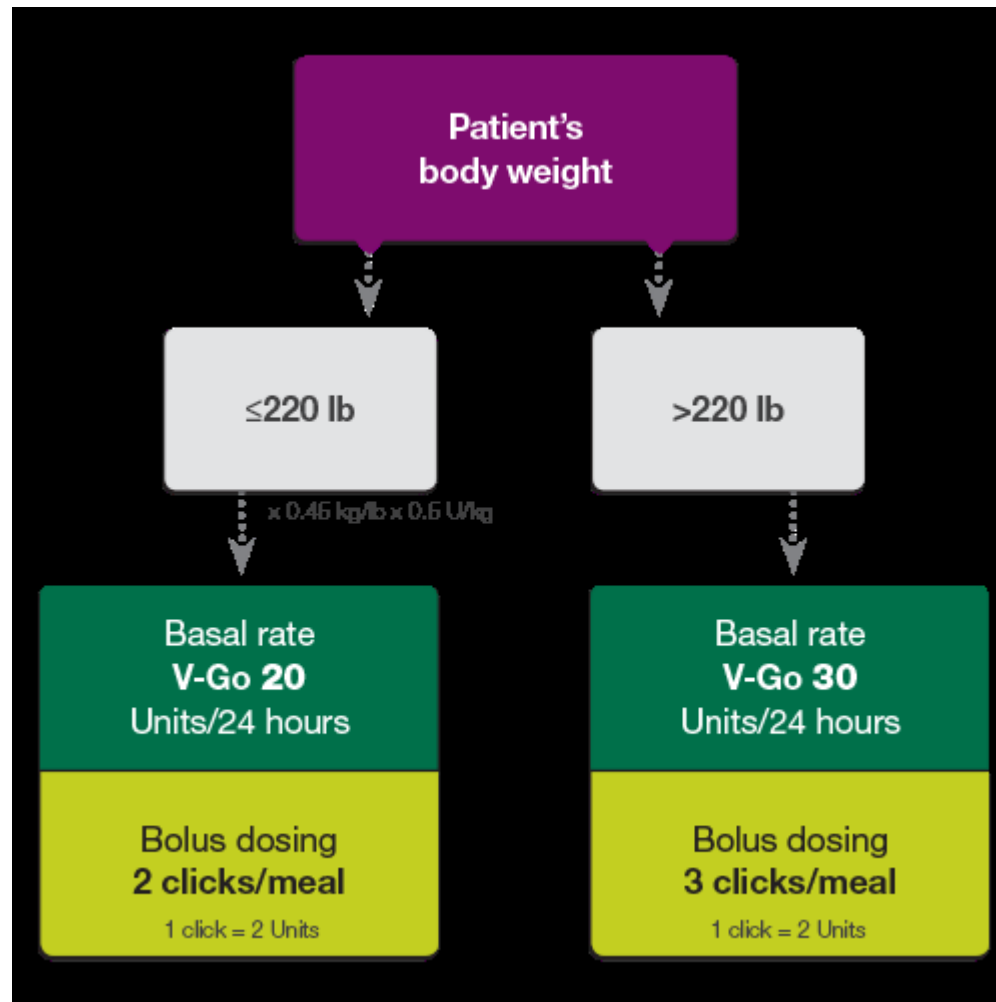
Disposable basal-bolus insulin delivery device Approved for patients with type 2 diabetes

- 3 simple steps
 - Fill
 - Wear
 - Go

V-Go option	Preset basal rate	+ On-demand bolus dosing	= Total available insulin
 DISPOSABLE INSULIN DELIVERY	20 Units/24 hr (0.83 U/hr)	+ Up to 36 Units in 2-Unit increments*	= 56 Units
 DISPOSABLE INSULIN DELIVERY	30 Units/24 hr (1.25 U/hr)	+ Up to 36 Units in 2-Unit increments*	= 66 Units
 DISPOSABLE INSULIN DELIVERY	40 Units/24 hr (1.67 U/hr)	+ Up to 36 Units in 2-Unit increments*	= 76 Units

www.go-vgo.com

V-Go²¹



www.go-vgo.com

Individualizing Drug Therapy

- Contraindications
- Medication characteristics
- Patient preference
- Medication adherence



Contraindications¹

Metformin

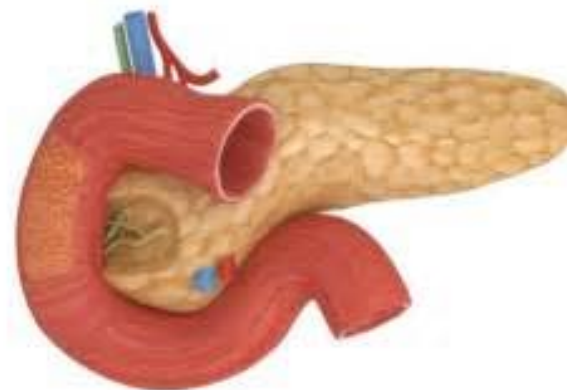
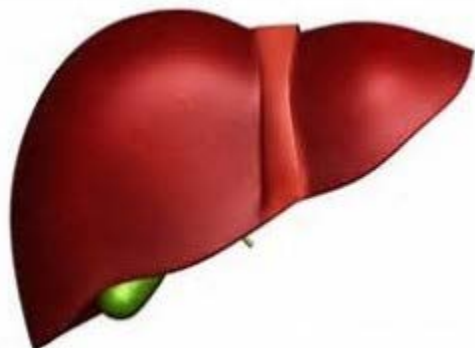
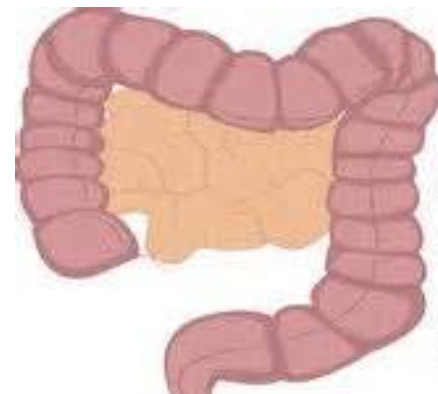
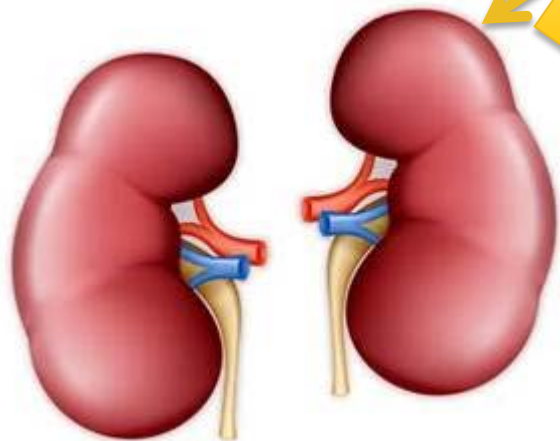
SU

DPP-4i

SGLT-2i

AGi

GLP-1 RA (Byetta)



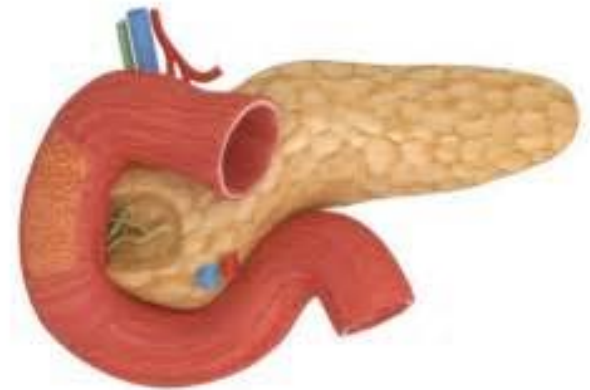
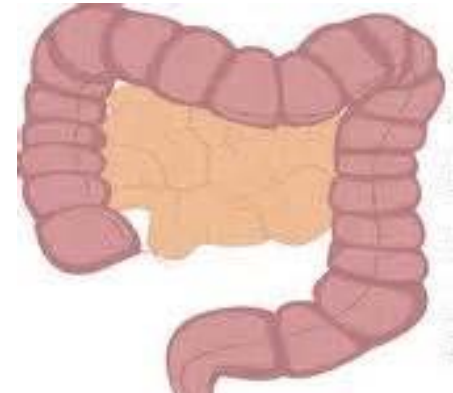
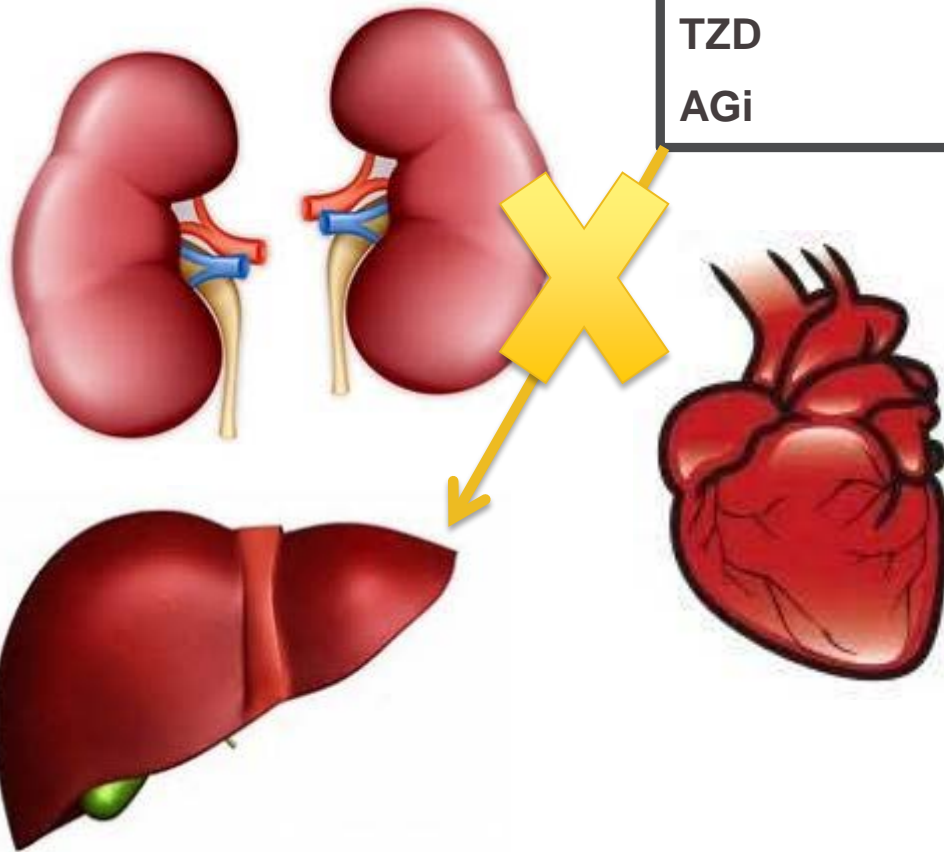
Contraindications¹

Metformin

SU

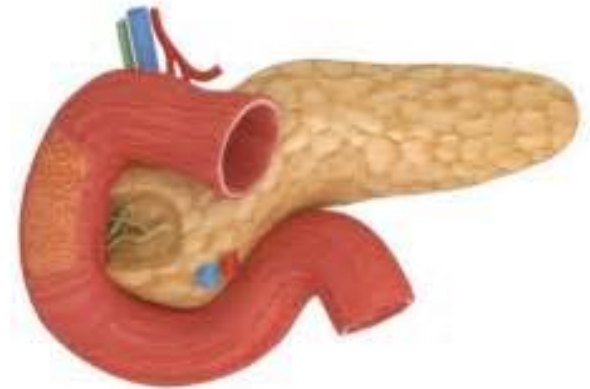
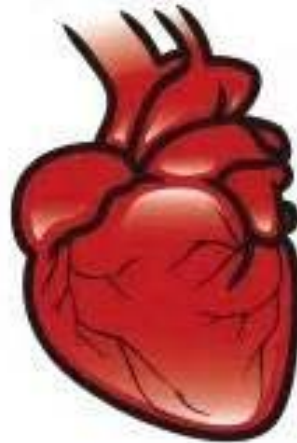
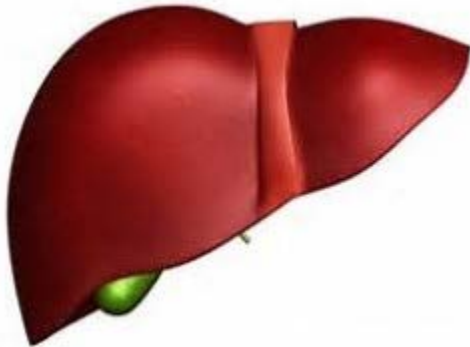
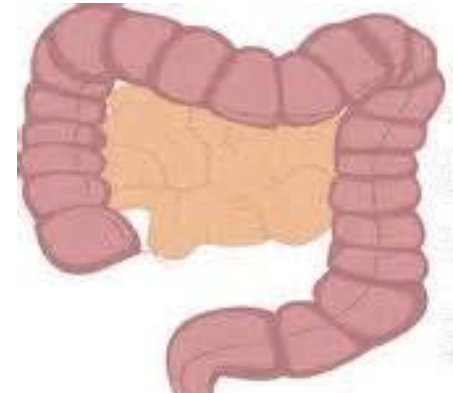
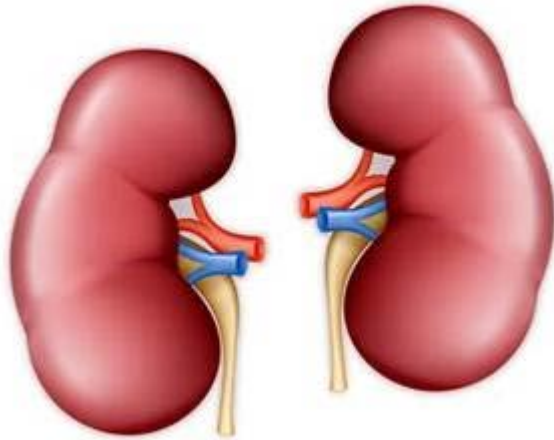
TZD

AGi



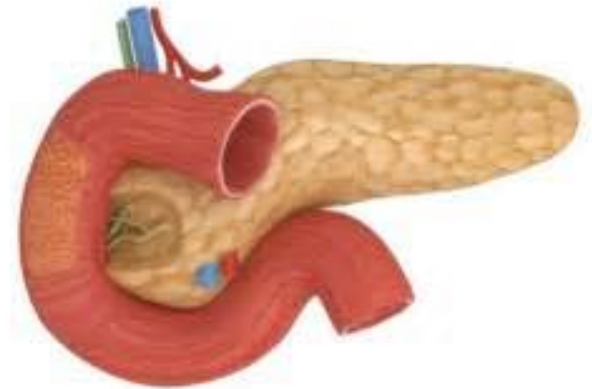
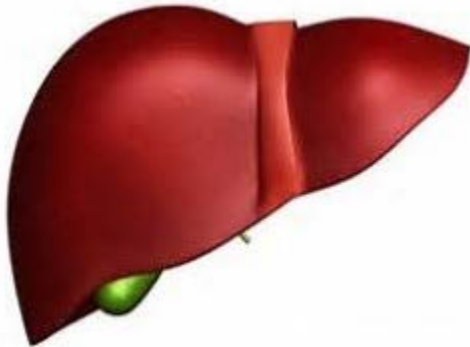
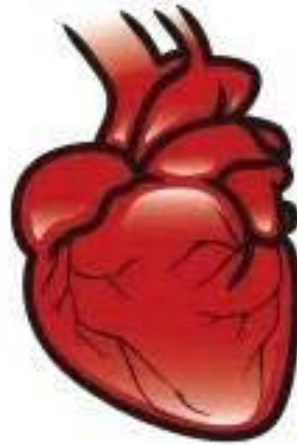
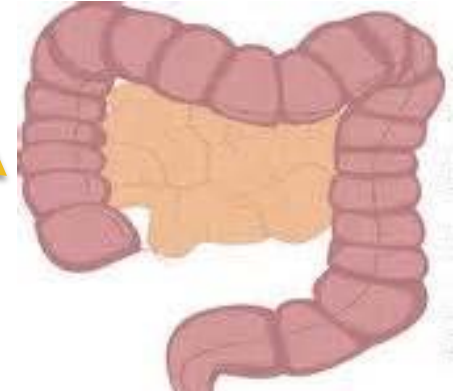
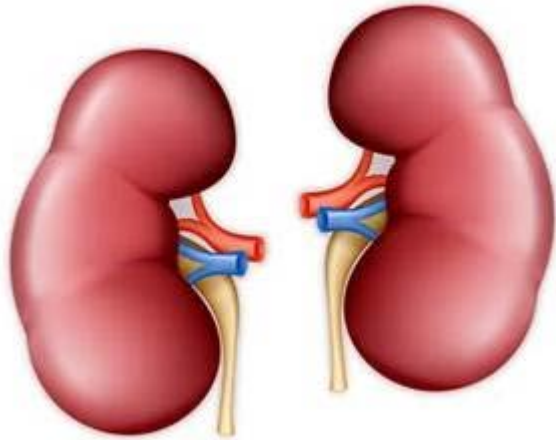
Contraindications¹

Metformin
TZD



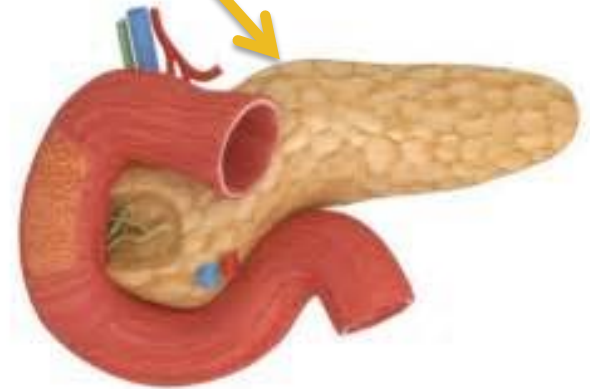
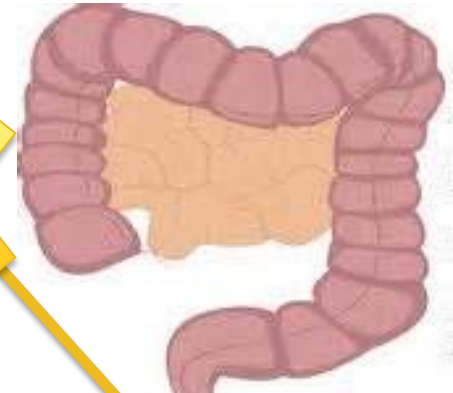
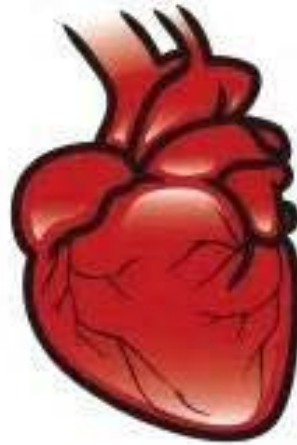
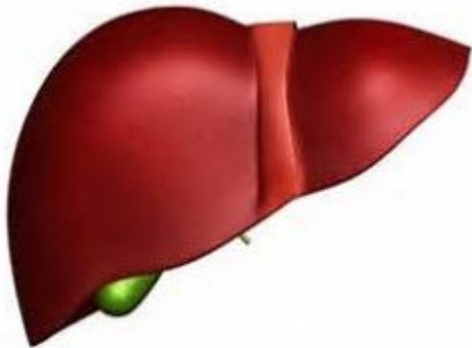
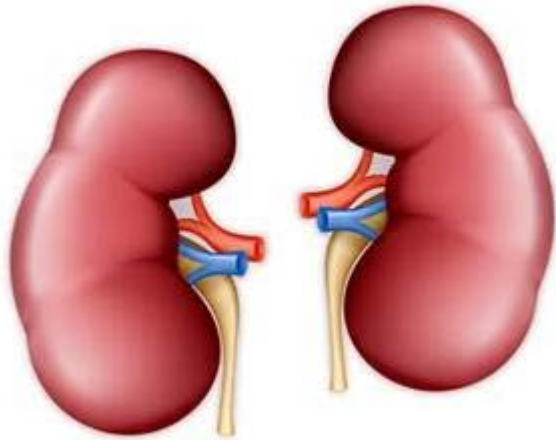
Contraindications¹

AGi



Contraindications¹

DPP-4i
GLP-1 RA



Medication Characteristics¹

Drug Class	Efficacy	Weight	Side Effects	Risk of Hypoglycemia	Cost
Biguanides	High	Neutral/loss	GI, lactic acidosis	Low	Low
SU	High	Gain	Hypoglycemia	Moderate	Low
GLN	Low	Gain	Hypoglycemia	Moderate	Moderate
TZDs	High	Gain	Edema, heart failure, fractures	Low	Low
AGi	Low	Neutral	GI	Low	Moderate
DPP-4i	Intermediate	Neutral	Rare?	Low	High
SGLT-2i	Intermediate	Loss	GU infections, hypotension, bone fractures	Low	High
GLP-1 RA	High	Loss	GI	Low	High
Amylin mimetics	Intermediate	Loss	GI, Hypoglycemia	High	High
Insulin	Highest	Gain	Hypoglycemia	High	Variable, high

Patient Preference

Pill burden

- Daily, BID, TID

Route of administration/dosage form

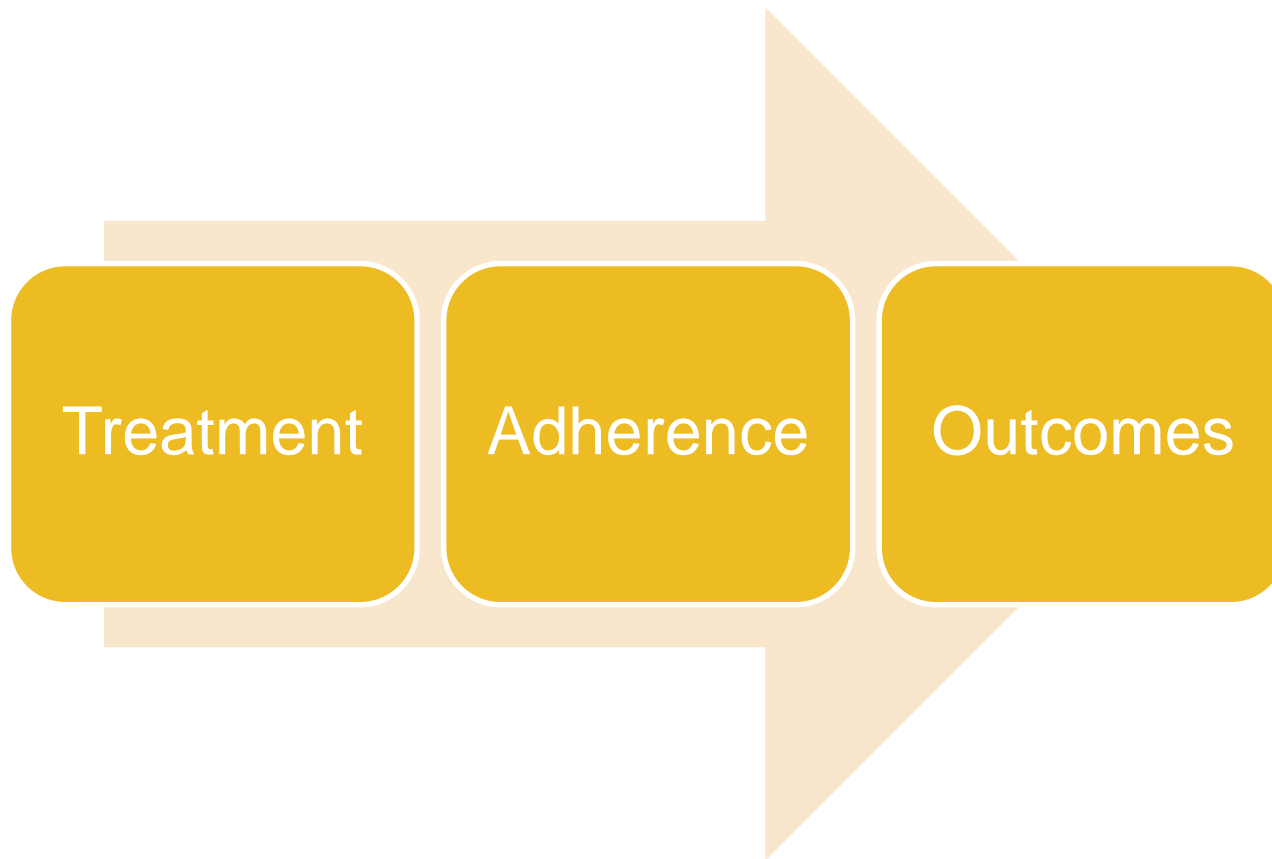
- Oral, injectable

Timing

- With or without meals

Other advantages?

Medication Adherence²²



Medication Adherence²³

The extent to which a person's behavior – taking medication, *following a diet, and/or executing lifestyle changes*, corresponds with agreed recommendations from a health care provider.

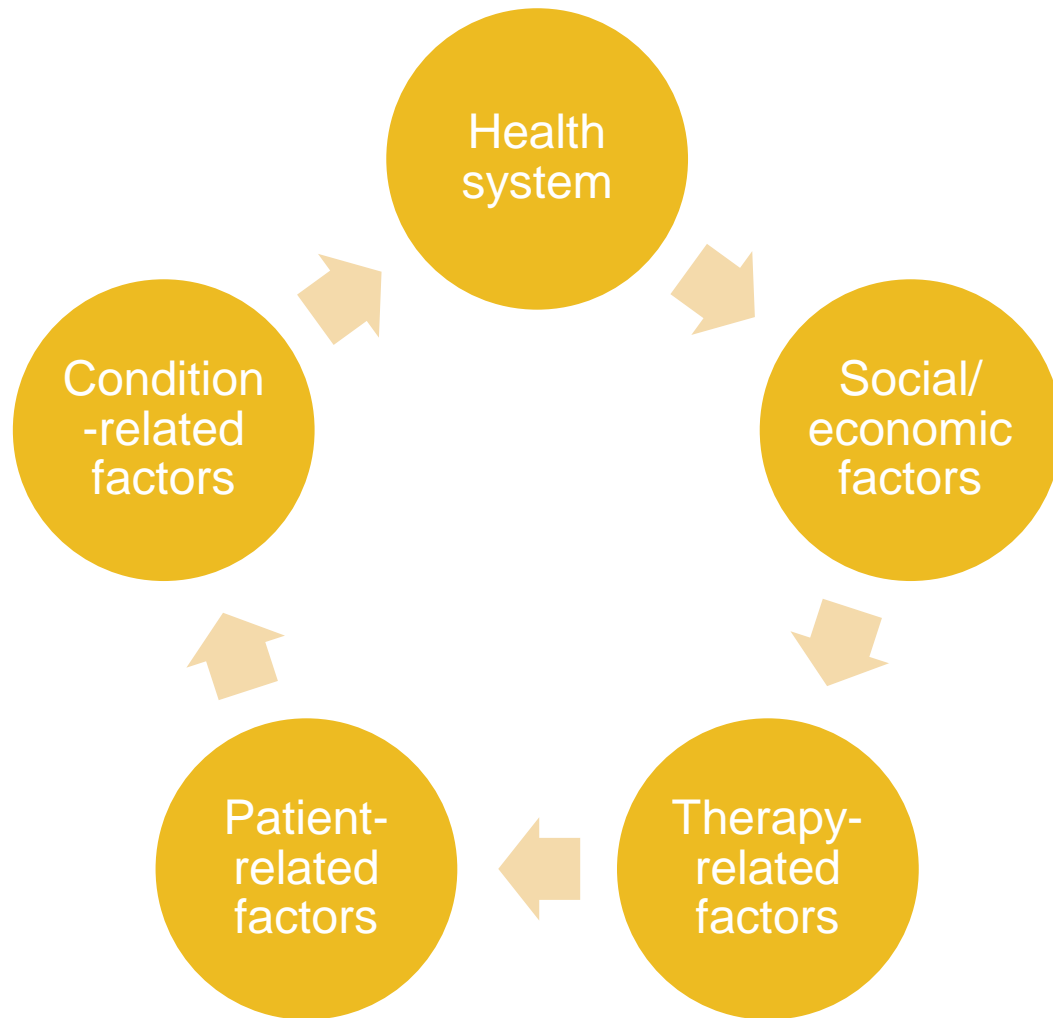
“Drugs don’t work in patients that don’t take them.”

Former Surgeon General C. Everett Koop, MD

Adherence Rates^{23,24}

- 51% in diabetics
- Range from 36 to 93% with oral hypoglycemic agents

Factors Affecting Adherence²³



Health System Factors²³

- Inadequate reimbursement by health insurance plans
- Lack of knowledge/training by health care providers (HCPs)
- Overworked HCPs
- Lack of incentives and feedback on performance
- Short consultations
- Lack of patient education and proper follow-up
- Inability to establish community support

Social/Economic Factors²³

- Poor socioeconomic status
- Poverty
- Illiteracy
- Low level of education
- Unemployment
- Lack of effective social support networks
- Long distance from treatment centers
- Transport costs
- Medication costs
- Culture and lay beliefs
- Family dysfunction
- Unstable living conditions

Therapy-Related Factors²³

- Complexity of regimen
- Duration of treatment
- Previous treatment failures
- Frequent changes to therapy
- How quickly the medication works
- Side effects

Patient-Related Factors²³

- Forgetfulness
- Psychosocial stress
- Anxiety about possible side effects
- Low motivation
- Lack of self-perceived need for treatment
- Negative beliefs regarding efficacy of treatment
- Denial about diagnosis
- Misunderstanding of treatment instructions
- Frustration with HCPs
- Fear of dependence
- Feeling stigmatized by the disease

Condition-Related Factors²³

- Severity of symptoms
- Level of disability
- Rate of progression and severity of disease
- Availability of effective treatments

Economic Cost of Non-Adherence²⁵

- \$100-300 billion annually
 - 3-10% of total U.S. health care costs
- Treatment failures, mortality, emergency department and hospital admissions

Improving Medication Adherence

- Education!
- Empowerment
- Prescription financial assistance
- Simplify regimens
- Patient-centered medical home
- Tools/technology



www.shop.diabetes.org.uk; rxtimercap.com; forgettingthepill.com; www.pillthing.com

Take home points, let's put it all together...

- The recommendations for the treatment of hyperglycemia provide guidance, but no two regimens need to be the same. Individualize, individualize, individualize!
- There are many new options available and likely many more on the way.
- There are many complex factors affecting medication adherence.
- Adherence will determine success; therefore, utilize all available resources.

References

1. American Diabetes Association. Approaches to Glycemic Treatment. In Standards of Medical Care in Diabetes – 2015. *Diabetes Care* 2015;38(1):S41-S48.
2. Abrahamson MJ, et al. AACE/ACE Comprehensive Diabetes Management Algorithm 2015. *Endocrine Practice*. 2015;21(4):e1-e9.
3. Food and Drug Administration. CenterWatch. Available at: <http://www.centerwatch.com/drug-information/fda-approvals/>. Accessed November 2, 2015.
4. Invokana® [Package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2015.
5. Farxiga® [Package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015.
6. Jardiance® [Package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015.
7. Insulin Products. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: <https://online.lexi.com>. Accessed November 5, 2015.
8. Afrezza® [Package insert]. Danbury, CT: Mannkind Corporation; 2015.
9. Toujeo® [Package insert]. Bridgewater, NJ; Sanofi-Aventis; 2015.
10. Becker RHA, et al. New Insulin Glargine 300 units/mL Provides a More Even Activity Profile and Prolonged Glycemic Control at Steady State Compared With Insulin Glargine 100 units/mL. *Diabetes Care*. 2015;38(4):637-643.
11. Riddle MC, et al. New Insulin Glargine 300 units/mL Versus Glargine 100 units/mL in People with Type 2 Diabetes Using Basal and Mealtime Insulin: Glucose Control and Hypoglycemia in a 6-month Randomized Controlled Trial (EDITION 1). *Diabetes Care*. 2014;37(10):2755-62.
12. Yki-Jarvinen, et al. New Insulin Glargine 300 units/mL Versus Glargine 100 units/mL in People with Type 2 Diabetes Using Oral Agents and Basal Insulin: Glucose Control and Hypoglycemia in a 6-month Randomized Controlled Trial (EDITION 2). *Diabetes Care*. 2014;37(12):3235-43.
13. Bolli GB, et al. New Insulin Glargine 300 units/mL Compared with Glargine 100 units/mL in Insulin-naïve People with Type 2 Diabetes on Oral Glucose-lowering Drugs: a Randomized Controlled Trial (EDITION 3). *Diabetes Obes Metab*. 2015;17(4):386-94.



References

14. Home PD, et al. New Insulin Glargine 300 units/mL Versus Glargine 100 units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). *Diabetes Care*. 2015;17:[Epub ahead of print].
15. Tresiba® [Package insert]. Plainsboro, NJ. Novo Nordisk Inc.; 2015.
16. Zinman B, et al. Insulin Degludec Versus Insulin Glargine in Insulin-naïve Patients with Type 2 Diabetes: a 1-year, Randomized, Treat-to-target Trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12):2464-2471.
17. Meneghini L, et al. The Efficacy and Safety of Insulin Degludec Given in Variable Once-daily Dosing Intervals Compared with Insulin Glargine and Insulin Degludec Dosed at the Same Time Daily: a 26-week, Randomized, Open-label, Parallel-group, Treat-to-target Trial in Individuals with Type 2 Diabetes. *Diabetes Care*. 2013;36(4):858-864.
18. Heller S, et al. Insulin Degludec, an Ultra-long-acting Basal Insulin, Versus Insulin Glargine in Basal-bolus Treatment with Mealtime Insulin Aspart in Type 1 Diabetes (BEGIN Basal-Bolus Type 1): a Phase 3, Randomised, Open-label, Treat-to-target Non-inferiority Trial. *Lancet*. 2012;379(9825):1489-1497.
19. Garber et al. Insulin Degludec, an Ultra-long-acting Basal Insulin, Versus Insulin Glargine in Basal-bolus Treatment With Mealtime Insulin Aspart in Type 2 Diabetes (BEGIN Basal-Bolus Type 2): a Phase 3, Randomised, Open-label, Treat-to-target Non-inferiority Trial. *Lancet*. 2012;379:1498-1507.
20. V-go Patient Information. Available at: <http://www.go-vgo.com/about-v-go>. Accessed November 2, 2015
21. V-go Dosing Information. Available at: <http://www.go-vgo.com/hcp/dosing-information>. Accessed November 2, 2015
22. Brown MT, Bussell JK. Medication Adherence: WHO Cares? *Mayo Clin Proc*. 2011;86(4):304-314.
23. *Adherence to Long-term Therapies*. Geneva, World Health Organization, 2003. 150 pages.
24. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. *Diabetes Care*. 2004;27(5):1218-24.
25. Iuga AO, McGuire MJ. Adherence and Health Care Costs. *Risk Management and Healthcare Policy*. 2014;7:35-44.





Questions?