Association of Diabetes Care & Education Specialists

**Activity/Session Title:**
**Diabetes for Health Care Professionals - Series**

# Pharmacologic Approaches to Glycemic Treatment

**Dian True RN, MA, CLSC, CDCES, FADCES**

April 2023

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## Disclosures to Participants

**Notice of Requirements for Successful Completion:**

Learners must participate in the full activity and complete the evaluation in order to claim continuing education credit/hours.

**Presenter has No - Conflicts of Interest/Financial Relationships Disclosures:**

**Dian True RN, CDCES, FADCES and Jen Steiner PharmD**

**Disclosure of Relevant Financial Relationships and Mechanism to Identify and Mitigate Conflicts of Interest:** No conflicts of interest

**Non-Endorsement of Products:** Accredited status does not imply endorsement by ADCES or Joint Accreditation of any commercial products displayed in conjunction with this educational activity

**Off-label Use: None**

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# Learning Objectives/Program Overview

- To identify and discuss the many classes of medications both oral and injectable for the treatment of diabetes.
- Identify biosimilar options to reduce medication expenses.



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## Today's presentation uses evidence-based research to best practice.

Research and data from the following organizations were used in developing this presentation:

American Diabetes Association

American Association of Clinical Endocrinologists

Continuing Education Credit available through the Wyoming Coordinating Body of the Association of Diabetes Care and Education Specialists.



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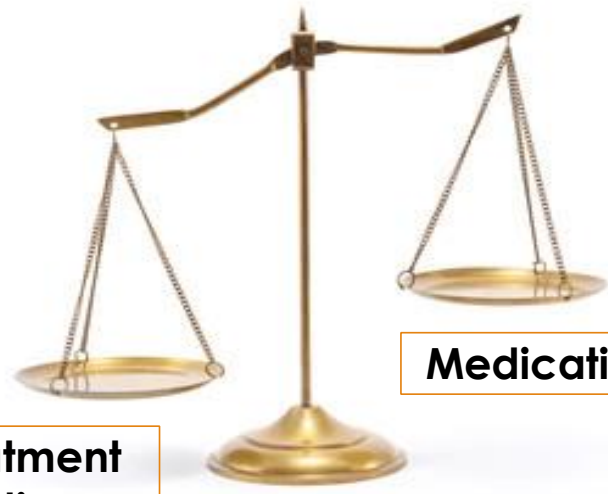
# Diabetes Medications



**Medications**

**Treatment Options**



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Automatic Zoom

## LIFESTYLE THERAPY

### RISK STRATIFICATION FOR DIABETES COMPLICATIONS

**INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS**

| | | | |
|---|---|---|---|
| **Nutrition** | • Maintain optimal weight<br>• Calorie restriction (manage increased weight)<br>• Plant-based diet; high polyunsaturated and monounsaturated fatty acids | • Avoid *trans* fatty acids; limit saturated fatty acids<br>• Technological aids | • Structured counseling<br>• Meal replacement |
| **Physical Activity** | • 150 min/week moderate exertion (e.g., walking, stair climbing)<br>• Strength training<br>• Increase as tolerated | • Structured program<br>• Wearable technologies | • Medical evaluation/ clearance<br>• Medical supervision |
| **Sleep** | • About 6-8 hours per night<br>• Basic sleep hygiene | • Screen sleep disturbances<br>• Home sleep study | • Referral to sleep study |
| **Behavioral Support** | • Community engagement<br>• Alcohol moderation | • Discuss mood with HCP | • Formal behavioral therapy |
| **Smoking Cessation** | • No tobacco products | • Nicotine replacement therapy and medications as tolerated | • Referral to structured program |



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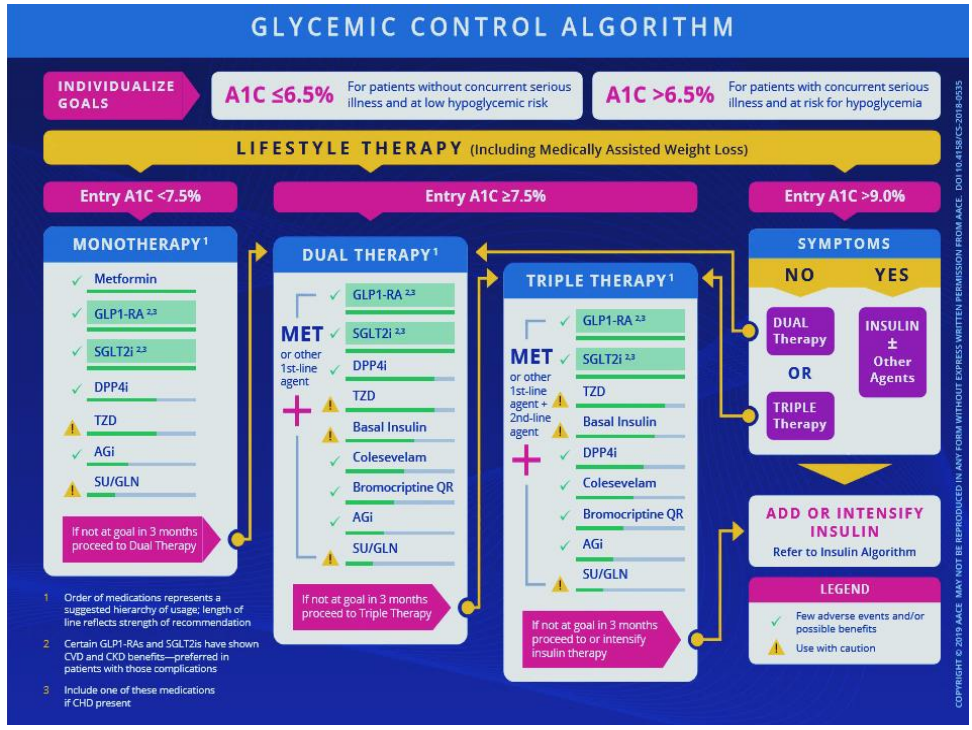


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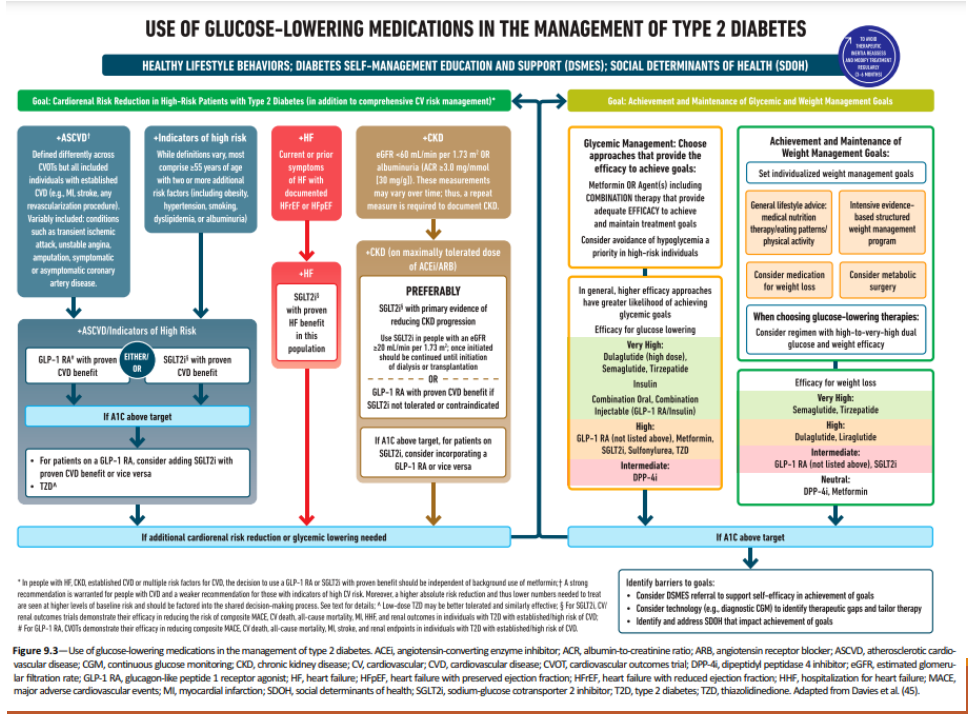


**Figure 9.3**—Use of glucose-lowering medications in the management of type 2 diabetes. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SDOH, social determinants of health; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2D, type 2 diabetes; TZD, thiazolidinedione. Adapted from Davies et al. (45).

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# Basic Physiology Review

**Beta Cells**

**Cells in the pancreas that produce, store, and release insulin**

**Alpha Cells**

**Secrete glucagon**

**Glucagon is released in response to low blood glucose levels**

- **Stimulating the liver to break down glycogen to be released into the blood as glucose**

**Incretin hormones**

**GIP (glucose-dependent insulinotropic peptide; also known as gastric inhibitory peptide) and GLP-1 (glucagon-like peptide-1)**

**Gut hormones secreted from enteroendocrine cells into the blood within minutes after eating**

**Incretin hormones work to increase insulin secretion**

An Overview of the Pancreas - Understanding Insulin and Diabetes
*https://www.endocrineweb.com/endocrinology/overview-pancreas*

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# Biguanide
## (metformin)

Mechanism of Action
- Helps to decrease the amount of glucose made by the liver
- Increases secretion of GLP-1 and reduces intestinal glucose absorption
- Increases insulin sensitivity making it easier for insulin to bring glucose from the blood and into muscles

Adverse Effects
- Nausea, diarrhea, upset stomach
- Weight neutral, low risk of hypoglycemia
- Vitamin B12 malabsorption with chronic use
- Lactic acidosis

**Efficacy:**
- **1-1.5% reduction in A1c**
- **Greater effect on FPG**
- **Effective on PPG**
- **Potential benefit on cardiovascular outcomes**

**Cautions & Key Points**
- **Caution for patients with moderate-severe renal impairment**
  - **Contraindicated in CrCl <30 mL/min**
- **Often stopped prior to radiology procedures where contrast dye is used**

https://aace.com/diabetesclinicalguidelines/resourcecenter2020

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# Biguanide Combinations (metformin)

**Multiple combinations (some examples):**
**-Alogliptin and metformin: Kazano**
**-Sitagliptin and metformin: Janumet**

**-Glipizide and metformin: Glipimet**

**-Pioglitazone and metformin: ActoPlus Met**

**-Canagliflozin and metformin: Invokamet**
**-Empagliflozin and metformin: Synjardy**





# Incretin Analogs (GLP-1 receptor agonists) Injectables

**Medications: Liraglutide (Victoza), dulaglutide (Trulicity), exenatide ER (Bydureon), semaglutide (Ozempic)**

**Mechanism of Action**
- **Synthetic analog of human GLP-1 that binds to GLP-1 receptors**
- **Helps pancreas make more insulin**
- **Helps decrease glucose made by liver**

**Advantages**
- **Preserved beta cell function**
- **Low risk of hypoglycemia**

**Disadvantages**
- **Cost and availability**
- **Injectable**
- **Nausea**
- **Avoid in:**
  - **History or family history of thyroid cancer**
  - **History of or those at risk for pancreatitis**

**Efficacy:**
- 0.5-1% reduction in A1c
- ↓FPG and PPG
- Weight loss ~3-5 kg

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# Incretin Analogs (GLP-1 receptor agonists) Oral Medication

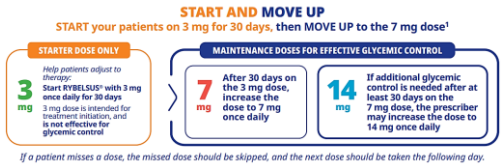
**Semaglutide (Rybelsus), Once a day oral GLP-1**

Mechanism of Action
- Helps to decrease the amount of glucose made by the liver
- Improves the way insulin works in muscles
- Increased muscle sensitivity makes it easier for insulin to bring glucose from the blood and into muscles - glucose can be used for energy

**Advantages**
- **Preserved beta cell function**
- **Low risk of hypoglycemia**

**Similar Class Effect as injectables**

**Disadvantages**
- **Cost and availability**
- **Nausea**
- **Avoid**
  - **History or family history of thyroid cancer**
  - **History of or those at risk for pancreatitis**

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# GLP-1 Agonists

**GLP-1 agonists with a demonstrated benefit on heart attack or stroke are recommended for patients with type 2 diabetes and established heart disease.**

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## SGLT-2 Inhibitors

**Medications: Canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro)**

**Medication:**
- Helps limit glucose from being reabsorbed into kidneys
  - Blocks ~50-80 grams of glucose per day from being reabsorbed

**Adverse effects:**
- Vaginal yeast infection, UTI
- Increased urination
- Hypoglycemia
- Dehydration
- Dizziness or fainting
- Hyperkalemia

**Positive effects:**
- A1c reduction up to 1%
- Reduction in body weight and systolic blood pressure
- Heart failure and CKD

**Caution:** Renal impairment, specific guidelines

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## SGLT-2 INHIBITORS

**SGLT-2 inhibitors have demonstrated a cardiovascular benefit and are recommended for patients with type 2 diabetes, heart disease (or multiple risk factors), or diabetic kidney disease to lower the risk of hospitalization due to heart failure and/or the risk of major events like a heart attack or stroke.**

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# Incretin Analogs (GLP-1 + GIP receptor agonists)

**Medication: Tirzepatide (Mounjaro)**

**Mechanism of Action**
- **Stimulate insulin release from the pancreatic islets**
- **Glucose dependent insulinotropi polypeptide receptor agonist**

**Advantages**
- **Preserved beta cell function**
- **Low risk of hypoglycemia**

**Efficacy:**
- Up to 1.5% reduction in A1c
- ↓FPG and PPG
- Weight loss

**Disadvantages**
- **Cost and availability**
- **Injectable**
- **Nausea**
- **Avoid in:**
  - **History or family history of thyroid cancer**
  - **History of or those at risk for pancreatitis**



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# DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS (-GLIPTIN)

**Medications: Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), Alogliptin (Nesina)**

**Administration**:
- Taken once daily without regard to meals

**Adverse Effects:**
- Pancreatitis
- Usually weight neutral
- Low risk of hypoglycemia

**Clinical Effects:**
- Inhibits breakdown of incretins (hormones) GLP-1 and GIP

**Cautions & Key Points:**
- Dose adjustment with renal impairment
- Expensive
- Has not been demonstrated to improve CV outcomes



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# Thiazolidinediones (TZDs)

**Medications: Pioglitazone (Actos), Rosiglitazone (Avandia)**

**Administration:**
- Taken once daily without regard to meals

**Adverse Effects:**
- Weight gain and edema are most common effects
- Worsening of congestive heart failure, especially when used with insulin
- Low risk of hypoglycemia

**Cautions and Key Points to consider:**
- Contraindicated in patients with NYHA Class III or IV heart failure
- Previous prescribing restrictions with Avandia
- Max effect may not be observed for 8-12 weeks

**Clinical Effects**
- Enhances insulin sensitivity on muscle and fat cells
- Decreases the amount of glucose made by liver



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# Sulfonylureas (not recommended)

**Medications: Glimeperide (Amaryl), Glipizide (Glucotrol), Glyburide (Glynase)**

**Clinical Effects**:
- Binds to receptors in beta cells, stimulating the pancreas to produce insulin
- May lose effectiveness over period of 2-3 years
  - "Beta-cell burnout"

**Adverse Effects:**
- Hypoglycemia
- Often associated with some weight gain

**Administration**:
- Taken once or twice daily, assess food intake
- Caution if patient is not eating

**Cautions & Key Points:**
- Associated with increased risk of hypoglycemia
- Avoid in poor renal function
- Glyburide least preferred sulfonylurea in elderly



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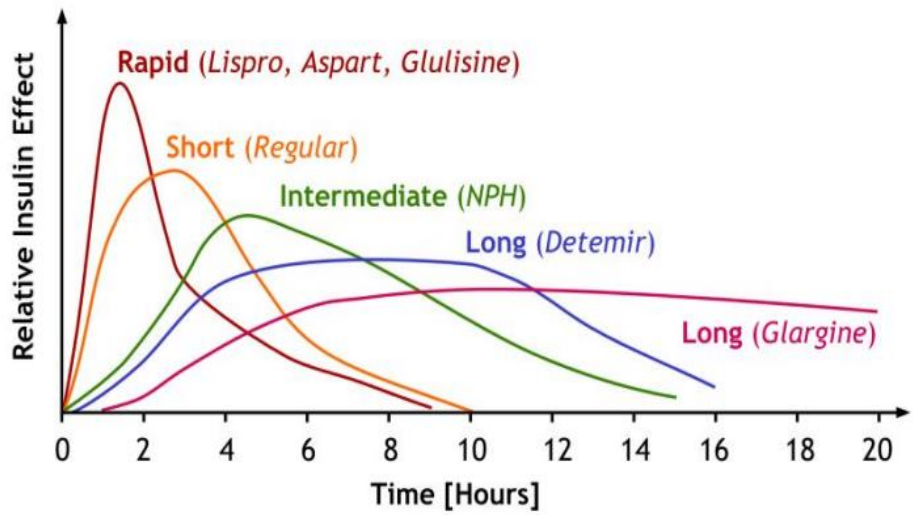
# Insulin Therapy

Tailored to meet Individual requirements

- Rapid Acting Insulins
- Short Acting Insulins
- Intermediate Acting Insulin
- Basal/Background Insulins
- Premixed Insulin
- Inhaled Insulin







# Rapid Acting Insulins Options

## Currently available insulin analogues

| | Generic name | Trade name | Manufacturer |
|---|---|---|---|
| Rapid-acting analogues | Insulin aspart | NovoRapid® | Novo Nordisk |
| | Insulin lispro | Humalog® | Eli Lilly |
| | Insulin glulisine | Apidra® | sanofi aventis |

**Insulin lispro available in U200 smart pen**

Insulin aspart (Fiasp) **100 U/mL** enters bloodstream in approximately 2 ½ minutes; can be taken at the start of a meal or up to 20 minutes onset of meal





# Short Acting Insulins Options

| Example Brand Names | Generic Name | Onset | Peak | Duration |
|---|---|---|---|---|
| Humulin R, Novolin R | insulin regular (human) | ~30 mins | 2 to 3 hours | 3 to 6 hours |

Regular (R) is also known as Soluble Insulin. Insulin regular used to be manufactured from beef and pork pancreas but is now available as human recombinant insulin. All brands of insulin from beef or pork origin have now been discontinued in the U.S.

# Intermediate Acting Insulins

| Example Brand Names | Generic Name | Onset | Peak | Duration |
|---|---|---|---|---|
| Humulin N, Novolin N | insulin isophane (human, NPH) | 2 to 4 hours | 4 to 12 hours | 12 to 18 hours |



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# Basal/ Background Insulin

| Brand Name | Generic Name | Onset | Peak | Duration |
|---|---|---|---|---|
| Lantus, Basaglar | insulin glargine | 1 to 3 hours | No peak | 20 to 24+ hours (steady state reached in 22 hours) |
| Levemir | insulin detemir | 1 to 3 hours | 3 to 9 hours | 6 to 24+ hours (steady state reached in 20 to 28 hours) |
| Toujeo | insulin glargine (Note: 300 units/mL) | 6 hours | No peak | Up to 36 hours (steady state reached at 2 to 3 days) |
| Tresiba | insulin degludec | 1 to 3 hours | No peak | 40+ hours (steady state reached in ~4 days) |

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# Basal/Background Insulin

- **All long-acting/basal or background insulins are usually dosed once per day. Long-acting insulins help to keep the blood sugar levels even throughout the day.**
- **It takes roughly 4 half-lives to reach steady state, and dose adjustments should be made with caution until a steady state is achieved.**



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# Biosimilar Insulins

A "follow on" insulin (also called a biosimilar for some products) are approved via an abbreviated FDA process in which the manufacturer demonstrates that the product is as safe and effective as the original insulin. Some of these insulins are now interchangeable and can be substituted for the reference product by the pharmacist without a separate prescription.

- Basaglar (insulin glargine) was approved in 2015 and is a follow-on insulin to Lantus.
- Admelog (insulin lispro) was approved as a follow-on for Humalog in 2017.
- Semglee (insulin glargine) was approved as a biosimilar to Lantus in 2020 - it is interchangeable with Lantus by the pharmacist
- Lyumjev (insulin lispro-aabc) was approved as a follow-on for Humalog in 2020.
- Rezvoglar Kwikpen (insulin glargine-aglr) was approved as a biosimilar for Lantus (but is not yet interchangeable with Lantus)



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# Premixed Insulins

**Premixed insulin** has two types of insulin mixed together in one vial. These are called biphasic insulins. This makes it easier to inject two different types of insulin at the same time.

The profile of the premixed insulin depends on the combination. Normally, one insulin will be rapid or short-acting and the other one has a longer duration of action.

Insulin lispro protamine and Insulin aspart protamine are suspensions of crystals produced from combining insulin lispro and protamine sulfate, and insulin aspart and protamine sulfate, respectively, under appropriate conditions for crystal formation. The addition of protamine makes insulin lispro and insulin aspart, which are rapid acting insulins, into intermediate acting insulin.

| Brand Name | Generic Name |
|---|---|
| Humalog Mix 50/50 | insulin lispro and insulin lispro protamine |
| Humalog Mix 75/25 | insulin lispro and insulin lispro protamine |
| Humalog Mix 50/50 | insulin lispro and insulin lispro protamine |
| Humulin 70/30 | insulin isophane and insulin regular |
| Novolin 70/30 | insulin isophane and insulin regular |
| Novolog Mix 70/30 | insulin aspart and insulin aspart protamine |
| Novolog Mix 70/30 Flexpen | insulin aspart and insulin aspart protamine |



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# Inhaled Insulin

Afrezza (insulin human) Inhalation Powder was approved by the FDA in June 2014. Afrezza is an ultra rapid acting inhaled insulin indicated to improve blood sugar control in adult patients with diabetes. It is given through an inhaler at meals and helps to control blood sugar spikes due to mealtime insulin.

It can be used in either type 1 or type 2 diabetes. In type 1 diabetes, it is given with injectable insulin.

| Brand Name | Generic Name | Onset | Peak | Duration |
|---|---|---|---|---|
| Afrezza | insulin inhalation | 12 to 15 minutes | About 1 hour | About 2 to 3 hours |

Exubera, also a rapid-acting inhaled insulin product, is no longer available on the US market. It was withdrawn from the U.S. market in 2007 due to lack of consumer demand for the product. No drug safety concerns were cited in this withdrawal, although there may have been a possible association with an increased risk of lung cancer.

Overall, success with inhaled insulins has been limited. This dosage form of insulin is not as effective as other treatments in helping patients to meet their blood sugar goal (A1C level less than 7%), and sales have been weak.



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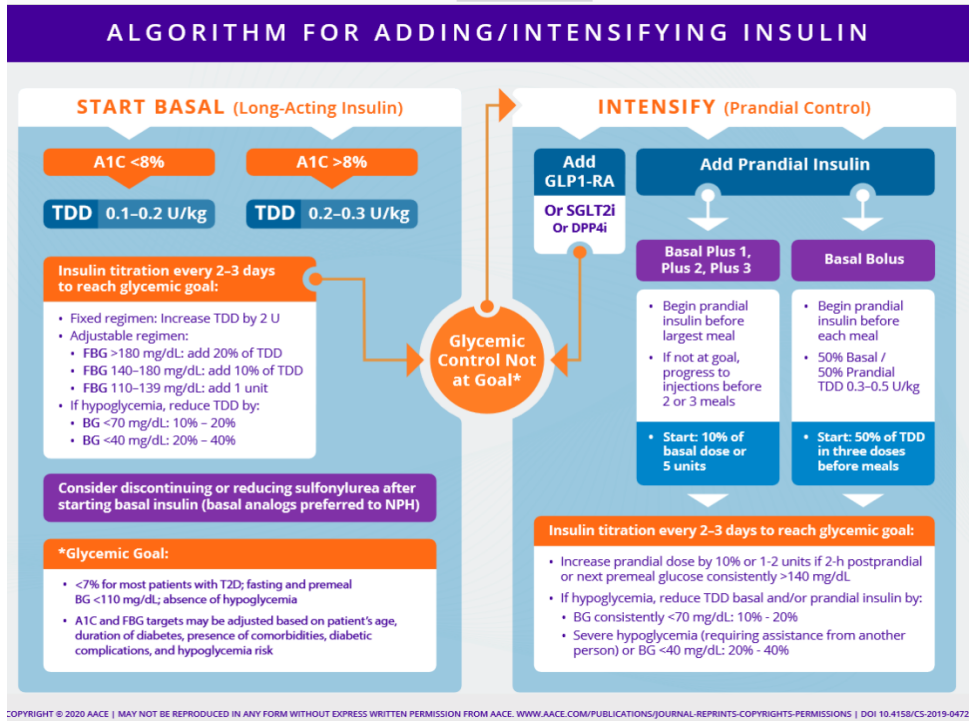
ALGORITHM FOR ADDING/INTENSIFYING INSULIN
START BASAL (Long-Acting Insulin)
A1C <8%
TDD 0.1–0.2 U/kg
A1C >8%
TDD 0.2–0.3 U/kg
Insulin titration every 2–3 days to reach glycemic goal:
• Fixed regimen: Increase TDD by 2 U
• Adjustable regimen:
• FBG >180 mg/dL: add 20% of TDD
• FBG 140–180 mg/dL: add 10% of TDD
• FBG 110–139 mg/dL: add 1 unit
• If hypoglycemia, reduce TDD by:
• BG <70 mg/dL: 10% – 20%
• BG <40 mg/dL: 20% – 40%
Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)
*Glycemic Goal:
• <7% for most patients with T2D; fasting and premeal BG <110 mg/dL; 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
Glycemic Control Not at Goal*
INTENSIFY (Prandial Control)
Add GLP1-RA
Or SGLT2i
Or DPP4i
Add Prandial Insulin
Basal Plus 1, Plus 2, Plus 3
• Begin prandial insulin before largest meal
• If not at goal, progress to injections before 2 or 3 meals
• Start: 10% of basal dose or 5 units
Basal Bolus
• Begin prandial insulin before each meal
• 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
• Start: 50% of TDD in three doses before meals
Insulin titration every 2–3 days to reach glycemic goal:
• Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL
• If hypoglycemia, reduce TDD basal and/or prandial insulin by:
• BG consistently <70 mg/dL: 10% - 20%
• Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20% - 40%
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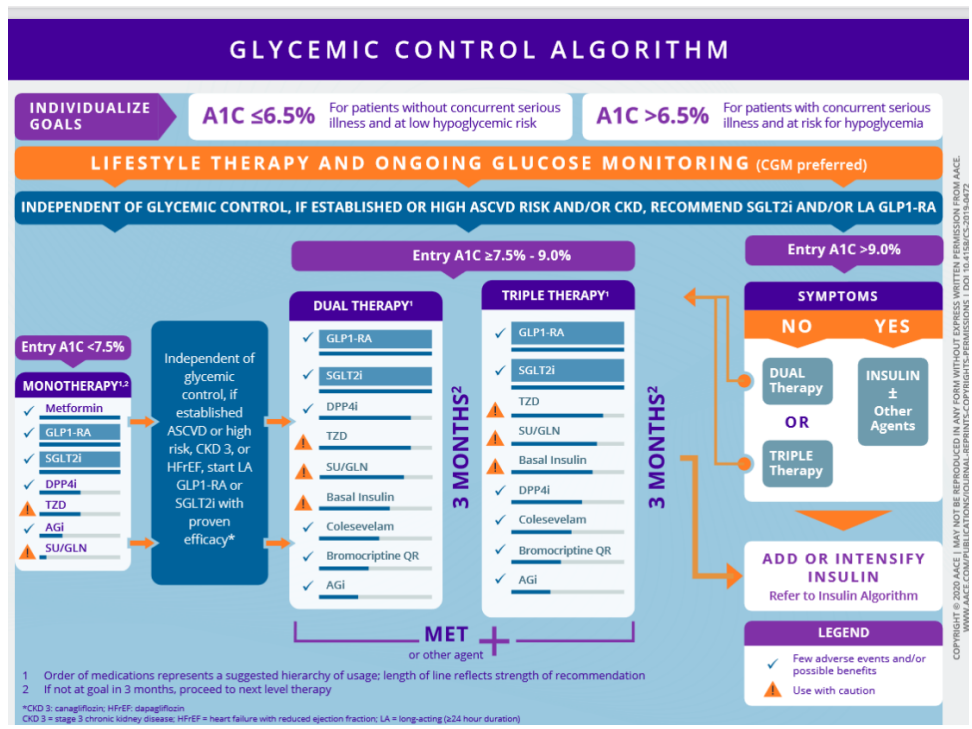
GLYCEMIC CONTROL ALGORITHM
INDIVIDUALIZE GOALS
A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemic risk
A1C >6.5% For patients with concurrent serious illness and at risk for hypoglycemia
LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING (CGM preferred)
INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2i AND/OR LA GLP1-RA
Entry A1C <7.5%
MONOTHERAPY1,2
Metformin
GLP1-RA
SGLT2i
DPP4i
TZD
AGi
SU/GLN
Independent of glycemic control, if established ASCVD or high risk, CKD 3, or HFrEF, start LA GLP1-RA or SGLT2i with proven efficacy*
Entry A1C ≥7.5% - 9.0%
DUAL THERAPY1
GLP1-RA
SGLT2i
DPP4i
TZD
SU/GLN
Basal Insulin
Colesevelam
Bromocriptine QR
AGi
3 MONTHS2
TRIPLE THERAPY1
GLP1-RA
SGLT2i
TZD
SU/GLN
Basal Insulin
DPP4i
Colesevelam
Bromocriptine QR
AGi
3 MONTHS2
MET + or other agent
Entry A1C >9.0%
SYMPTOMS
NO
YES
DUAL Therapy
OR
TRIPLE Therapy
INSULIN ± Other Agents
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm
LEGEND
Few adverse events and/or possible benefits
Use with caution
1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
2 If not at goal in 3 months, proceed to next level therapy
*CKD 3: canagliflozin; HFrEF: dapagliflozin
CKD 3 = stage 3 chronic kidney disease; HFrEF = heart failure with reduced ejection fraction; LA = long-acting (≥24 hour duration)
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# Combination Therapy

| GLP1 receptor agonist + | Basal insulin | Available as |
|---|---|---|
| Liraglutide + | Degludec | Xultophy |
| Lixisenatide + | Glargine | Soliqua |





# QUIZ

***You must double check all dosing and spelling before administration to ensure correct medication and dose***

- **True**

***Many medications come as combination therapy***

- **True**

***Biguanides (metformin products) must be held for all radiology studies with contrast dye.***

- **True**

***All oral agents can cause hypoglycemia***

- **True**

## Resources:

https://pro.aace.com/pdfs/diabetes/AACE_2019_Diabetes_Algorithm_03.2021.pdf

https://pro.aace.com/disease-state-resources/diabetes/clinical-practice-guidelines/2022-aace-clinical-practice-guideline

https://diabetesjournals.org/care/issue/46/Supplement_1

https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment

https://www.drugs.com/diabetes-treatment.html



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*Thank you for participating!*

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