Medicinal Guidelines for Treating Type 2 Diabetes

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AtlantiCare Provider Group
ENDOCRINOLOGY
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Objectives

• 1. Identify the AACE/ADA guidelines for medicinal management of diabetes Identify the AACE/ADA Guidelines for medicinal management of type 2 diabetes
• 2. Discuss application of the standards of care in the practice setting
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**Comprehensive Type 2 Diabetes Management Algorithm**

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<td>Principle</td>
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<tr>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Lifestyle modification underlies all therapy (e.g., weight control, physical activity, sleep, etc.)</td>
</tr>
<tr>
<td>2.</td>
<td>Avoid hypoglycemia</td>
</tr>
<tr>
<td>3.</td>
<td>Avoid weight gain</td>
</tr>
<tr>
<td>4.</td>
<td>Individualize all glycemic targets (A1C, FPG, PPG)</td>
</tr>
<tr>
<td>5.</td>
<td>Optimal A1C is ≤6.5%, or as close to normal as is safe and achievable</td>
</tr>
<tr>
<td>6.</td>
<td>Therapy choices are affected by initial A1C, duration of diabetes, and obesity status</td>
</tr>
<tr>
<td>7.</td>
<td>Choice of therapy reflects cardiac, cerebrovascular, and renal status</td>
</tr>
<tr>
<td>8.</td>
<td>Comorbidities must be managed for comprehensive care</td>
</tr>
<tr>
<td>9.</td>
<td>Get to goal as soon as possible—adjust at ≤3 months until at goal</td>
</tr>
<tr>
<td>10.</td>
<td>Choice of therapy includes ease of use and affordability</td>
</tr>
<tr>
<td>11.</td>
<td>A1C ≤6.5% for those on any insulin regimen as long as CGM is being used</td>
</tr>
</tbody>
</table>
LIFESTYLE THERAPY
RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

<table>
<thead>
<tr>
<th>Nutrition</th>
<th>Physical Activity</th>
<th>Sleep</th>
<th>Behavioral Support</th>
<th>Smoking Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maintain optimal weight</td>
<td>• 150 min/week moderate exertion</td>
<td>• About 7 hours per night</td>
<td>• Community engagement</td>
<td>• No tobacco products</td>
</tr>
<tr>
<td>• Calorie restriction (if BMI is increased)</td>
<td>(e.g., walking, stair climbing)</td>
<td>• Basic sleep hygiene</td>
<td>• Alcohol moderation</td>
<td></td>
</tr>
<tr>
<td>• Plant-based diet; high polyunsaturated and monounsaturated fatty acids</td>
<td>• Strength training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increase as tolerated</td>
<td>• Increase as tolerated</td>
<td></td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>• Avoid <em>trans</em> fatty acids; limit saturated fatty acids</td>
<td>• Structured program</td>
<td>• Medical evaluation/clearance</td>
<td>• Structured counseling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Wearable technologies</td>
<td>• Medical supervision</td>
<td>• Meal replacement</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td>+</td>
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<td>+</td>
</tr>
<tr>
<td></td>
<td>• Screen OSA</td>
<td>• Home sleep study</td>
<td>• Discuss mood with HCP</td>
<td>• Nicotine replacement therapy</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Medical supervision</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Referral to sleep lab</td>
</tr>
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<td></td>
<td>+</td>
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<td>+</td>
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</tr>
<tr>
<td></td>
<td>• Medical evaluation/clearance</td>
<td>• Medical supervision</td>
<td>• Formal behavioral therapy</td>
<td>• Referral to structured program</td>
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<tr>
<td></td>
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<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>• Referral to sleep lab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COMPLICATIONS-CENTRIC MODEL FOR CARE OF THE PATIENT WITH OVERWEIGHT/OBESEITY

**STEP 1**
EVALUATION FOR COMPLICATIONS AND STAGING

<table>
<thead>
<tr>
<th>CARDIOMETABOLIC DISEASE</th>
<th>BIOMECHANICAL COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25</td>
<td>NO COMPLICATIONS</td>
</tr>
<tr>
<td>NO OVERWEIGHT OR OBESITY</td>
<td>BMI ≥25</td>
</tr>
<tr>
<td></td>
<td>OVERWEIGHT OR OBESITY</td>
</tr>
<tr>
<td></td>
<td>STAGE 0</td>
</tr>
<tr>
<td></td>
<td>MILD TO MODERATE</td>
</tr>
<tr>
<td></td>
<td>BMI ≥25</td>
</tr>
<tr>
<td></td>
<td>SEVERE</td>
</tr>
</tbody>
</table>

**STEP 2**
SELECT:
Therapeutic targets for improvement in complications + Treatment modality + Treatment intensity based on staging

- **Lifestyle Therapy:**
  Physician/RD counseling, web/remote program, structured multidisciplinary program

- **Medical Therapy (BMI ≥27):**
  Individualize care by selecting one of the following based on efficacy, safety, and patients’ clinical profile: phentermine, orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg

- **Surgical Therapy (BMI ≥35):**
  Gastric banding, sleeve, or bypass

**STEP 3**
If therapeutic targets for complications not met, intensify lifestyle, medical, and/or surgical treatment modalities for greater weight loss. Obesity is a chronic progressive disease and requires commitment to long-term therapy and follow-up.

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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 (including Medically Assisted Weight Loss)

Entry A1C <7.5%
Entry A1C ≥7.5%
Entry A1C >9.0%

MONOTHERAPY

- Metformin
- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY

- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY

- GLP1-RA
- SGLT2i
- TZD
- Basal Insulin
- DPP4i
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

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

SYMPTOMS

NO

- DUAL Therapy
- TRIPLE Therapy

YES

- INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

✓ Few adverse events and/or possible benefits

⚠ Use with caution

PROGRESSION OF DISEASE

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CLASSIFICATION OF ANTIHYPERGLYCEMIC AGENTS IN T2DM

• 1) BIGUANIDES
• 2) SGLT2 INHIBITORS
• 3) INCRETIN MIMEMTICS GLP-RA and Pramlintides
• 4) DPP4 INHIBITORS
• 5) ANTIABSORPTIVE AGENTS Alpha glucosidase inhibitors and Bile acid sequestrants
• 6) THIAZOLIDINEDIONES TZD’S
• 7) INSULIN SECRETAGAUGS Sulfonylureas & Meglinitides
• 8) BROMOCRIPTINE
• 9) INSULIN
• Approved in US in 1995
• First line therapy of T2DM treatment
• ↓ Hepatic glucose production
• ↓ Intestinal absorption of glucose
• ↓ Glucose absorption from the gut
• Improves insulin sensitivity
• Cannot be used in patients with GFR <40 or advanced liver cirrhosis
• Lactic acidosis
SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

- Work by inhibiting SGLT2 in the PCT, to prevent reabsorption of glucose and facilitate its excretion in urine.
- Action is dependent on blood glucose levels.
- Minimal potential for hypoglycemia.
- Relies upon normal renal glomerular-tubular function of at least GFR of >45.
SGLT2 INHIBITORS

SGLT2 INHIBITORS THAT CAN BE USED IN GFR >45

• CANAGLIFLOZIN
• EMPAGLIFLOZIN

SGLT2 INHIBITORS INDICATED FOR GFR = 60 OR MORE

• DAPAGLIFLOZIN
• ERTUGLIFLOZIN
SGLT2 INHIBITORS

The first oral DM agent to show Cardiovascular benefit

- EMPA-REG (first landmark trial)
  - Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

- CANVAS study
  - Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

- DECLARE study
  - Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes
SGLT2 INHIBITORS
ADVERSE REACTIONS

- Genital Mycotic Infections
- Osmotic Diuresis
- DKA that can also happen as “EUGLYCEMIC DKA”
- Amputations
- Special Considerations in Older Patients
- Hypoglycemia ONLY IF USED WITH INSULIN OR INSULIN SECRETATGOGUES
INCRETIN MIMETICS

• Incretin mimetics are agents that act like incretin hormones such as glucagon-like peptide-1 (GLP-1)
• They bind to GLP-1 receptors and stimulate glucose dependent insulin release
• Incretin mimetics also suppress appetite and inhibit glucagon secretion
• Their secondary effects include increased insulin sensitivity in liver, muscle and fat
EXENATIDE available as **Byetta** bid injection and **Bydureon** as extended release weekly injection

LIRAGLUTIDE available as **Victoza** once daily injection or in combination with basal insulin degludec as **Xultophy**

DULAGLUTIDE available as **Trulicity** once weekly injection

SEMAGLUTIDE available as **Ozempic**, once weekly injection pen

LIXISENATIDE only available in combination with insulin glargine as a daily dose in pen as **Soliqia**

**NEW!** Oral GLP-1 **oral semaglutide**, the first noninjectable GLP-1 receptor agonist for the treatment of type 2 diabetes available **Rybelsus**
PRAMLIINTIDE

AMYLIN:

- Produced by beta cells
- Polypeptide co-secreted from pancreatic beta cell at a 1:100 ratio to insulin
- Deficient in all Type 1 DM patients
- Cardinal effects:
  - enhanced satiety, diminished glucagon secretion, and delayed gastric emptying
- To be used as an injection tid ac meals
DIPEPTIDYL PEPTIDASE 4 INHIBITORS
DPP-4 INHIBITORS

How do they work?

• block the DPP4 enzyme, that destroys the intrinsic GLP or incretin within 2 minutes
• increases the life of INCRETIN
• increases insulin secretion, decreases gastric emptying, & decreases blood glucose levels

Well tolerated class with very low or no risk of hypoglycemia except when combined with insulin or insulin secretagogues
DPP4 INHIBITORS

SITAGLIPTIN as Januvia

LINAGLIPTIN as Tradjenta

SAXAGLIPTIN as Onglyza

ALOGLIPTIN as Nessina

ALSO AVAILABLE IN COMBINATION WITH EITHER METFORMIN OR OTHER ORAL AGENTS
ANTI-ABSORPTIVE AGENTS
Alpha Glucosidase inhibitors

- **Agents:** Acarbose (Precose); Miglitol (Glyset)
- **Primary Action:** slow digestion of carbohydrates and complex sugars
- **Side Effects:** Increases flatulence and abdominal bloating especially with high carb meals
BILE ACID SEQUESTRANTS

- **Agents:** Colesevelam (Welchol)
- **Primary Action:** reduce serum cholesterol level & blood glucose in people with diabetes
THIAZOLIDINEDIONES
TZD’s (glitazones)

- **Agents**: Rosiglitazone (Avandia); Pioglitazone (Actos)
- **Primary Action**: activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor
  - “LIPID STEAL HYPOTHESIS”
  - enhance the ability to store consumed calories
- **Side effects**: increased adiposity and weight gain as well as fluid retention and increased risk of CHF
Sulfonylureas (SFU) still remain a mainstay of therapy for DM due to their proven efficacy and low cost

- **Primary Action**: induce glucose-independent insulin release from beta cells by inhibiting K+ flux through K-ATP channels, opening Ca channels leading to insulin release

- **Side effects**: high risk of hypoglycemia; Meglitinides - shorter duration of action than SFU, hence slightly lower risk of hypoglycemia
BROMOCRIPTINE

- **Agents**: Cycloset, Parlodel
- **Primary Action**: improves insulin sensitivity primarily in peripheral tissues, skeletal muscles and fat
- **Early morning administration**: SAFELY used in patients with CVD and CKD
# INSULINS

<table>
<thead>
<tr>
<th>BASAL INSULINS</th>
<th>INTERMEDIATE ACTING INSULIN AND MIXED INSULIN</th>
<th>RAPID ACTING INSULINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine (Lantus, Basaglar, Toujeo &amp; Toujeo Max)</td>
<td>NPH</td>
<td>Regular Insulin (U100)</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>NPH/R 70/30 (Humulin 70/30)</td>
<td>Lispro (Humalog U-100, U-200)</td>
</tr>
<tr>
<td>Degludec (Tresiba U-100&amp; U-200)</td>
<td>NPH/LISPRO 75/25 (Humalog75/25</td>
<td>Aspart (Novolog and Fiasp)</td>
</tr>
<tr>
<td>Regular insulin U-500 (Humulin-R 500).</td>
<td>NPH/LISPRO 50/50 (Humalog50/50</td>
<td>Glulisine (Apidra)</td>
</tr>
<tr>
<td></td>
<td>NPH/ASPART 70/30 (Novolog70/30</td>
<td>Regular inhaled insulin (Afrezza)</td>
</tr>
<tr>
<td>Glargine/Lixisenatide (Soliqua)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec/Liraglutide (Xultophy)</td>
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</tr>
</tbody>
</table>
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 GLP1-RA**
  - Or SGLT2i
  - Or DPP4i

- **Add Prandial Insulin**

### Glycemic Control Not at Goal*

- **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:

- **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

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[Geisinger National Quality Award Logo]

2019 Award Recipient
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP1-RA</th>
<th>SGLT2i</th>
<th>DPP4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPO</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
</tr>
<tr>
<td><strong>RENO / GU</strong></td>
<td>Contraindicated if eGFR &lt;30 mL/min/1.73 m²</td>
<td>Exenatide Not Indicated if CrCl &lt;30</td>
<td>Genital Mycotic Infections</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>See #1</td>
<td>See #2</td>
<td>See #3</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>CHF Risk</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Neutral</td>
<td>Safe</td>
<td>Safe</td>
<td>Safe</td>
<td>Neutral</td>
<td>Safe</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td><strong>ASCVD</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td><strong>BONE</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>KETOACIDOSIS</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Can Occur in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- Green: Few adverse events or possible benefits
- Yellow: Use with caution
- Orange: Likelihood of adverse effects

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.
Thank you!!