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 **College of Pharmacy**

 **Fourth year. Clinical Pharmacy**

 **Endocrine disorders**

 **Diabetes Mellitus**

**α-Glucosidase Inhibitors**

1-**Acarbose** and **miglitol** **delay the breakdown of sucrose and complex carbohydrates** in the small intestine, prolonging carbohydrate absorption.

2-Good candidates for these drugs are patients who are **near target A1C levels** with near-normal FPG but **high PPG levels**.

3-The most common side effects **are flatulence, abdominal pain, and diarrhea**, which can be reduced by slow dosage titration.

**Meglitinides**

1-**Nateglinide** and **repaglinide** stimulate insulin secretion from pancreatic β-cells by binding to a site adjacent to the sulfonylurea receptor.

2-They are similar to sulfonylureas except that they have **a faster onset and shorter duration** of action.

3-Similar to sulfonylureas, the main side effects **are hypoglycemia and weight gain**.

4-They may be a good option for patients **with erratic meal schedules**. However, **multiple** **daily dosing may decrease adherence**.

5-Meglitinides should be taken by mouth **with each meal**, initiated at a low dose, and titrated over time until glycemic control is achieved.

**Bile Acid Sequestrants**

1-**Colesevelam** binds bile acid in the intestinal lumen, decreasing the bile acid pool for reabsorption. Its mechanism in lowering plasma glucose levels is unknown, and its role in therapy is unclear.

2-It reduces LDL-C in patients with type 2 DM by 12%–16%. Colesevelam is weight neutral and has a low risk of hypoglycemia. Patients with type 2 DM **who need a small reduction in A1C as well as additional LDL-C lowering may be candidates for this agent.**

3-The most common side effects are **constipation and dyspepsia**; colesevelam should be taken with a large amount of water. Colesevelam has multiple **absorption-related drug–drug interactions.**

**Dopamine Agonists**

1-**Bromocriptine mesylate** is FDA approved for treatment of type 2 DM. The mechanisms by which it improves glycemic control are unknown but may involve improved hepatic insulin sensitivity and decreased hepatic glucose output.

2-Its role in the treatment of type 2 DM is unclear. **Common side effects include** nausea, vomiting, constipation, fatigue, headache, dizziness, and asthenia. Somnolence and orthostatic hypotension may also occur.

**Amylin Analogs**

1-**Pramlintide** is a synthetic amylin analog that reduces glucagon secretion, slows gastric emptying, and increases satiety. **It was the first noninsulin agent approved for patients with type 1 DM.**

2-It is used **primarily in type 1 DM as adjunctive therapy** for patients who are not achieving **PPG goals** despite maximizing mealtime insulin doses.

3-It can also **decrease weight** and may allow for lower mealtime insulin doses.

4-The **most common adverse effects are** nausea, vomiting, and anorexia. It does not cause hypoglycemia when used alone, but hypoglycemia can occur when used with insulin.

5-To minimize the risk of severe hypoglycemia, **empirically reduce the mealtime insulin dose by 30%–50% when pramlintide is initiated.**

**Treatment of Hyperglycemia in Type 2 Diabetes**

1-Upon diagnosis, **set a patient-specific A1C target**. **Implement comprehensive lifestyle modifications** with MNT, physical activity, weight loss if obese, smoking cessation, and psychologic support upon diagnosis and reinforce them at every visit.

2-**Initiate metformin as first-line therapy in patients without contraindications or tolerability issues**. Start with a low dose and titrate to the maximum effective dose over time to improve tolerability.

3-If the initial A1C is close to goal (eg, ≤7.5%) **consider initial treatment with lifestyle modifications alone** if the patient is motivated.

4-Consider **starting two medications** (metformin plus a second agent) if the initial A1C is >**1.5% higher than the target A1C.**

5-**Consider early introduction of basal insulin in patients with** very high A1C levels (>10%), symptoms of hyperglycemia, or evidence of catabolism (eg, weight loss).

6-**See patients at least every 3 months if they are not meeting their goals and at least every 6 months if they are meeting goals.** At those times, check an A1C level, assess medication adherence, and reinforce lifestyle recommendations. **Add additional therapy if glucose targets have not been met.**

7-For patients maximized on metformin therapy but with A1C levels above the target, add a **second-line antihyperglycemic agent**. The ADA Standards of Care identify six drug classes to consider:

(1) DPP-4 inhibitors, (2) GLP1-RAs, (3) SGLT-2 inhibitors, (4) sulfonylureas, (5) TZDs, and (6) basal insulin.

8-Patient-specific factors to consider in medication selection include the individualized A1C target and **presence of comorbidities** (eg, ASCVD, HF, CKD, obesity).

9-**Drug-specific factors to consider include** glucose-lowering efficacy, impact on comorbidities, effect on weight and hypoglycemia risk, side-effect profile, ease of use, and cost.

10-Recommendations based on patient-specific comorbidities and other factors include:

* **Established ASCVD or CKD**: SGLT-2 inhibitor (eg, empagliflozin) or GLP1-RA (eg, liraglutide) with proven CV benefit.
* **Established ASCVD and HF:** SGLT-2 inhibitor with proven benefit in reducing HF progression. Avoid TZDs in patients with HF.
* **CKD (with or without ASCVD):** SGLT-2 inhibitor with proven benefit in reducing CKD progression.
* **Need to minimize weight gain or promote weight loss in patients without ASCVD or CKD:** GLP1-RA or SGLT-2 inhibitor. If these agents cannot be used, use a weight-neutral medication such as a DPP-4 inhibitor. Avoid sulfonylureas, insulin, and TZDs due to weight gain.
* **Compelling need to minimize hypoglycemia**: DPP-4 inhibitor, GLP1-RA, SGLT-2 inhibitor, or TZD could be added to metformin.

11-If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug(s), **then triple therapy is warranted**, adding a drug from another class.

12-People with type 2 DM can often be managed with oral medications for years before injectable medications are needed.

13-Insulin is recommended for extreme (A1C >10%) or symptomatic hyperglycemia. Otherwise, **GLP-1 RAs are preferred over basal insulin** because they have equal or superior A1C lowering efficacy and lead to weight loss instead of weight gain with a low risk of hypoglycemia.

14-**Basal insulin can be initiated** if additional glucose lowering is needed after the GLP-1 RA dose has been maximized.

15**-If the A1C target is not reached by maximally titrating basal insulin**, PPG levels are likely elevated and **a GLP1-RA or SGLT-2 inhibitor should be considered** if the patient is not already taking one.

16-**Prandial insulin is also an option**. Titrate the dose over time to achieve target PPG levels <180 mg/dL. **A second or third injection can be added** to the other meals if needed.

**Treatment of Hyperglycemia in Type 1 Diabetes**

1-All patients with type 1 DM require exogenous insulin. Achieving adequate glycemic control usually requires **intensive insulin regimens designed to provide insulin in a manner that mimics normal physiologic insulin secretion**, with consistent secretion of insulin throughout the day to manage glucose levels overnight and in between meals (ie, basal insulin), and bursts of insulin in response to glucose rises after ingestion of carbohydrates (ie, prandial insulin).

2-**Intensive insulin regimens** can be given with either **multiple daily injections** (MDI) or use of **continuous subcutaneous insulin infusion** (CSII) via an **insulin pump.**

3-A common MDI approach is one injection of long-acting insulin (eg, insulin glargine) for the basal component and three injections of rapid acting insulin (eg, insulin lispro) for the prandial component.

4-**A less expensive option consists of two injections of intermediate-acting insulin (eg, NPH insulin) and two injections of short-acting insulin (eg, regular insulin).** However, the ADA Standards of Care recommend that most patients should use rapid-acting insulins rather than regular insulin to reduce the risk of hypoglycemia.

5-**Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs** . The pump infuses a basal rate constantly throughout the day and allows **the patient to give bolus doses using a bolus dose calculator** based on current glucose levels, carbohydrate intake, and insulin on board.

6-Insulin pump therapy can provide more precise glucose control and allow greater flexibility and fine-tune tailoring.

7-**The total daily insulin dose is divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals).** The insulin doses would then be adjusted based on SMBG data. Ideally, patients should learn to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake.

8-Patients should also **SMBG before each meal or use continuous glucose monitoring (CGM) to evaluate the insulin regimen and make treatment decisions**. Bolus insulin doses can be better individualized by using carbohydrate-to-insulin ratios (C:I ratios) and correction factors (CF).

9-**Pramlintide is indicated as adjunctive treatment** in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin.

10-**Pramlintide may improve glycemic control and minimize weight gain caused by insulin**, but its use is limited by adverse effects such as nausea and vomiting, modest glucose improvements, increased injections and cost, and increased risk of hypoglycemia.

11-**Assess patients every 3 months if uncontrolled and every 6 months if controlled**. Obtain an A1C and adjust treatment as needed. Patients on intensive insulin therapy should SMBG at least four times daily, before meals and at bedtime.

12-**Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur**. SMBG is crucial during times of intercurrent illness or stresses for early detection and prevention of DKA.

13-Current guidelines recommend **CGM in patients with type 1 DM who are not meeting glycemic goals.** They are also recommended in patients with **hypoglycemia unawareness** to better detect and prevent hypoglycemic events.

**Common insulin regimens.**

(A) Multiple-component insulin regimen consisting of **one injection of long-acting** insulin (detemir, glargine degludec) to provide basal glycemic coverage and **three injections of rapid-acting insulin** (aspart, lispro, glulisine) to provide glycemic coverage for each meal.

(B) Insulin regimen consisting of **two injections of intermediate-acting insulin** (NPH) and rapid-acting insulin (aspart, lispro, glulisine), or short-acting regular insulin. Only one formulation of short-acting insulin is used.

(C) **Insulin administration by insulin infusion device**. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump.

**Hypoglycemia**

1-**Hypoglycemia is a common complication** of some diabetes medications and is associated with falls, injury, motor vehicle accidents, decreased quality of life, and increased risk of developing dementia, CV events, arrhythmias, and death.

2-The severity of hypoglycemia is classified as follows:

* **Level 1** (hypoglycemia alert value; ≤70 mg/dL: May not cause symptoms but should be treated with a fast-acting carbohydrate and may need medication dose adjustment
* **Level 2** (clinically significant hypoglycemia; <54 mg/dL: Serious, clinically important hypoglycemia
* **Level 3** (severe hypoglycemia): Associated with cognitive impairment requiring external assistance for recovery and can be life threatening.

3-**Initial autonomic symptoms include** tachycardia, palpitations, sweating, tremors, and hunger. **Neuroglycopenic symptoms** often occur with BG <60 mg/dL and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness.

4-Some patients have **hypoglycemia unawareness** and are unable to detect the early warning symptoms of hypoglycemia; they are at increased risk for the serious sequelae associated with severe hypoglycemia.

5-**SMBG and CGM can be useful in preventing hypoglycemia**. Patients must be educated to understand situations that increase risk of hypoglycemia (eg, delaying meals, during or after exercising, or fasting).

6-**Treatment of hypoglycemia** requires ingestion of carbohydrates, preferably glucose. Patients should carry a source of fast-acting glucose with them at all times and use the **“rule of 15” f**or proper treatment:

* First use SMBG to confirm BG <70 mg/dL and then **ingest 15 g** of fast-acting carbohydrates such as 1/2 cup (4 oz or 125 mL) of milk, juice, or soda; 1 tablespoon of honey; hard candy; jelly beans; or glucose tablets.
* **Repeat SMBG in 15 minutes**; if the BG is <70 mg/dL, **repeat the process.**
* **Once the BG is normalized**, **eat a snack or meal that includes complex carbohydrates** and protein to prevent further hypoglycemic episodes.

7-If the patient is unc**o**nscious, **give IV glucose or glucagon injection**. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV glucose cannot be rapidly administered.

8-**A glucagon kit should be prescribed and readily available to all patients on insulin who have a history of or high risk for severe hypoglycemia**. It can take 10–15 minutes before glucose levels start to rise, and patients often **vomit**.

9-**Position the patient on the side with the head tilted slightly downward to avoid aspiration.**

10-Clinicians **should monitor hypoglycemia at every visit**. Ask the patient about the frequency, severity, and timing of hypoglycemic events, need for assistance by others, or the need to administer glucagon.

11-**Reevaluate the treatment regimen** of patients with frequent or severe hypoglycemia to minimize future episodes.

**Complications and Comorbidities**

**Diabetic Ketoacidosis (DKA)**

1-**In patients with type 1 DM, DKA is usually precipitated by** omitting insulin, infection, or acute illness with resultant increases in cortisol, catecholamines, glucagon, and growth hormone.

2-Patients may be alert, stuporous, or comatose at presentation. Diagnostic laboratory values include **hyperglycemia, anion gap acidosis, and large ketonemia or ketonuria**.

3-Patients have **fluid deficits** of several liters and significant sodium and potassium deficits. Treatment requires **restoration of intravascular volume** with normal saline followed by hypotonic saline to replace free water, **potassium supplements**, and **insulin** given by continuous IV infusion.

4-Constant infusion of a fixed insulin dose and administration of IV glucose when the BG level decreases to <250 mg/dL are preferred over titrating the insulin infusion based on the glucose level.

5-**Rapid correction of the glucose** (a decrease >75–100 mg/dL/hr) **is not recommended** because it has been associated with cerebral edema, especially in children. Continue the insulin infusion until the urine ketones clear and the anion gap closes.

6-Give **long-acting insulin 1–3 hours before discontinuing the insulin infusion**. Perform hourly bedside monitoring of glucose and frequent monitoring of potassium (every 2–4 hours).

7-**Treatment with bicarbonate** to correct the acidosis **is generally not needed and may be harmful.**

8-It is essential to **correct the underlying situation** **or medical condition** that precipitated DKA. Metabolic improvement is manifested by an increase in serum bicarbonate and pH.

**Hyperosmolar Hyperglycemic State (HHS)**

1-HHS is a **potentially life-threatening acute complication** of diabetes associated with very high glucose concentrations, typically >400 mg/dL.

2-It usually occurs in **older patients with type 2 DM or** in younger patients with prolonged hyperglycemia and dehydration or significant renal insufficiency.

3-The **patient presentation is similar to DKA**, but HHS patients usually **have much higher BG, elevated serum osmolality, and little to no ketonuria or ketonemia.**

4-HHS typically evolves over several days to weeks, whereas DKA evolves much faster.

5-Large ketonemia is not usually seen because residual insulin secretion suppresses lipolysis. Infection or another medical illness is the usual precipitant.

6-**Fluid deficits are often greater** and **BG levels higher** (sometimes >1000 mg/dl) in patients with HHS than in patients with DKA.

7-**BG should be lowered very gradually** with hypotonic fluids and low-dose insulin infusions (1–2 units/hr).

**Macrovascular Complications**

1-Macrovascular complications (eg, CHD, stroke) **are the leading causes of death in people with diabetes.**

2-The ADA recommends **low-dose aspirin therapy** (75–162 mg daily) **in all patients with established ASCVD.** Clopidogrel may be used in patients allergic to aspirin.

3-The role of antiplatelet therapy for primary CV prevention is unclear because the benefits may be offset by a higher risk of bleeding; **some practice guidelines recommend aspirin if the 10-year risk of a CV event is >20%.**

4-In patients with **established ASCVD**, use of a **GLP1-RA or an SGLT-2 inhibitor should be strongly considered.**

5-For all patients whose **BP exceeds 120/80 mm Hg,** the ADA recommends dietary changes, physical activity, and weight loss in overweight or obese patients.

6-Drug therapy using agents proven to reduce CV events should be started **for BP >140/90 mm Hg.** A combination of **two medications should be used for BP >160/100 mm Hg**.

7-Initiate **high-intensity statin** therapy in all patients with diabetes and preexisting ASCVD regardless of baseline lipid levels. In the absence of ASCVD, prescribe a **moderate-intensity statin t**o all patients with type 1 or type 2 DM over the age of 40.

8-In patients <40 years of age, a **moderate intensity statin** may be appropriate for patients with multiple CV risk factors.

9-A **fibrate** (eg, fenofibrate), **omega-3 fatty acid**, or **niacin** can be added for patients with marked **hypertriglyceridemia**.

10-**Peripheral arterial disease** can lead to claudication, nonhealing foot ulcers, and limb amputation. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies. **Cilostazol** may be useful in select patients to reduce symptoms. **Revascularization** surgery can be considered in some situations. Perform foot examinations during each face-to-face patient encounter and a yearly **monofilament test** to assess for loss of protective sensation to identify high-risk patients.

**Microvascular Complications**

Efforts to improve glucose control significantly reduce the risk of developing microvascular complications and slow their progression.

**Nephropathy:**

1-**Albuminuria is a marker of renal damage** and can be predictive of end-stage renal disease. The ADA recommends screening for albuminuria upon diagnosis in persons with type 2 DM.

2-Screening **with type 1 DM** should begin with puberty **and after 5-years’** disease duration.

3-**BP control is important for preventing and slowing progression of nephropathy**. ACE inhibitors and ARBs can slow the progression of renal disease in patients with diabetes.

4-**Diuretics** are often necessary due to volume expanded states and are recommended **second-line therapy**.

5-The ADA recommends a **BP goal <140/90 mm Hg in patients with nephropathy** but a **lower target** (eg, <130/80 mm Hg) **if it can be achieved without undue burden or side effects**. **Three or more antihypertensives are often needed to reach goal BP.**

**Retinopathy**:

1-Patients with diabetes should have **routine dilated eye examinations to fully evaluate the retina.**

2-**Early background retinopathy may reverse with improved glycemic control and optimal BP control**. More advanced retinopathy will not fully regress with improved glycemia, and aggressive BG reductions may acutely worsen retinopathy.

3-**Laser photocoagulation** has markedly improved sight preservation. **Intravitreal antivascular endothelial growth factor (VEGF) therapy** is also highly effective for sight preservation.

4-**Bevacizumab** (used off-label) and **ranibizumab** are **anti-VEGF monoclonal antibodies**, and **aflibercept** is a VEGF **decoy receptor**.

**Neuropathy:**

* **Peripheral neuropathy** is the most common complication in patients with type 2 DM. **Paresthesias,** **numbness**, or **pain** are **the predominant symptoms**. The feet are involved far more often than the hands. **Improved glycemic control is the primary treatment and may alleviate some symptoms.** Pharmacologic therapy is symptomatic and includes low-**dose tricyclic antidepressants** (nortriptyline or desipramine), **duloxetine**, **gabapentin**, **pregabalin**, **venlafaxine**, **topical capsaicin**, and **tramadol**.
* **Gastroparesis** can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of **metoclopramide** or **low-dose erythromycin** may be helpful.
* **Diabetic diarrhea** is often **nocturnal** and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.
* **Orthostatic hypotension** may require mineralocorticoids (eg, **fludrocortisone**) or adrenergic agonists (**midodrine**).
* **Erectile dysfunction** is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil**, **vardenafil**, or **tadalafil**).

**Evaluation of therapeutic outcomes**

1-**Measure A1C every 3–6 months to follow long-term glycemic control for the previous 2–3 months**.

2-**SMBG provides an opportunity to adjust** medications, food intake, or physical activity and enables patients to detect hypoglycemia.

3-For patients with type 1 DM, **SMBG is typically performed 4–6 times per day**—prior to food intake and physical activity and at bedtime.

4-The optimal **frequency of SMBG in patients with type 2 DM on oral agents is controversial**.

5-**At each visit**, ask patients with type 1 DM **about the frequency and severity of hypoglycemia**.

6-Screen for complications at the time of diagnosis and thereafter as follows:

* Obtain yearly dilated **eye exams** in type 2 DM and an initial exam in the first 5 years in type 1 DM, then yearly.
* Assess **BP at each visit**.
* **Examine the feet at each visit**. Screen for pedal sensory loss annually.
* **Screen for albuminuria** at the time of diagnosis in patients with type 2 DM and 5 years after diagnosis in type 1 DM. At least once a year, assess urinary albumin (urine albumin-to-creatinine ratio) and eGFR in all patients with type 2 DM and in patients with type 1 DM for at least 5 years.
* **Check fasting lipid panel annually** if the patient is on lipid-lowering therapy.

7-Administer an **annual influenza vaccine** and assess for administration of the **pneumococcal vaccine and hepatitis B vaccine** series along with management of other CV risk factors (eg, smoking).

**Reference**

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