



Diabetes and the Audiological Monitoring of Ototoxic/Vestibulotoxic Medications

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UNIVERSITY OF
GEORGIA
College of Pharmacy

UGA College of Pharmacy + Athens Neighborhood Health

- Community partnership
- Federally Qualified Health Center
- Diabetes Clinic
- Introductory Pharmacy Practice Experience Site



About Us



Objectives

- Pathophysiology of Diabetes induced complications
- Diabetes treatment
- Medication management

A person wearing a white lab coat is shown from the chest down, pointing their right index finger towards the right side of the frame. The background is a plain, light-colored wall.

What is Diabetes?

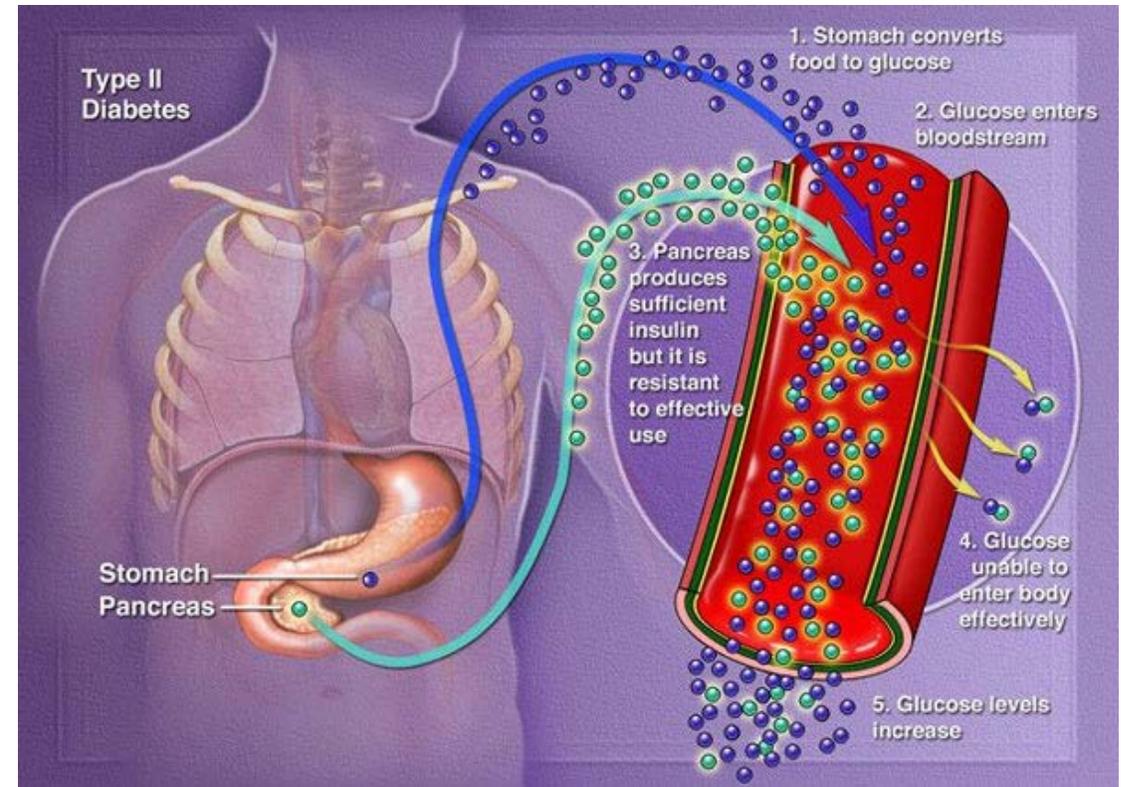
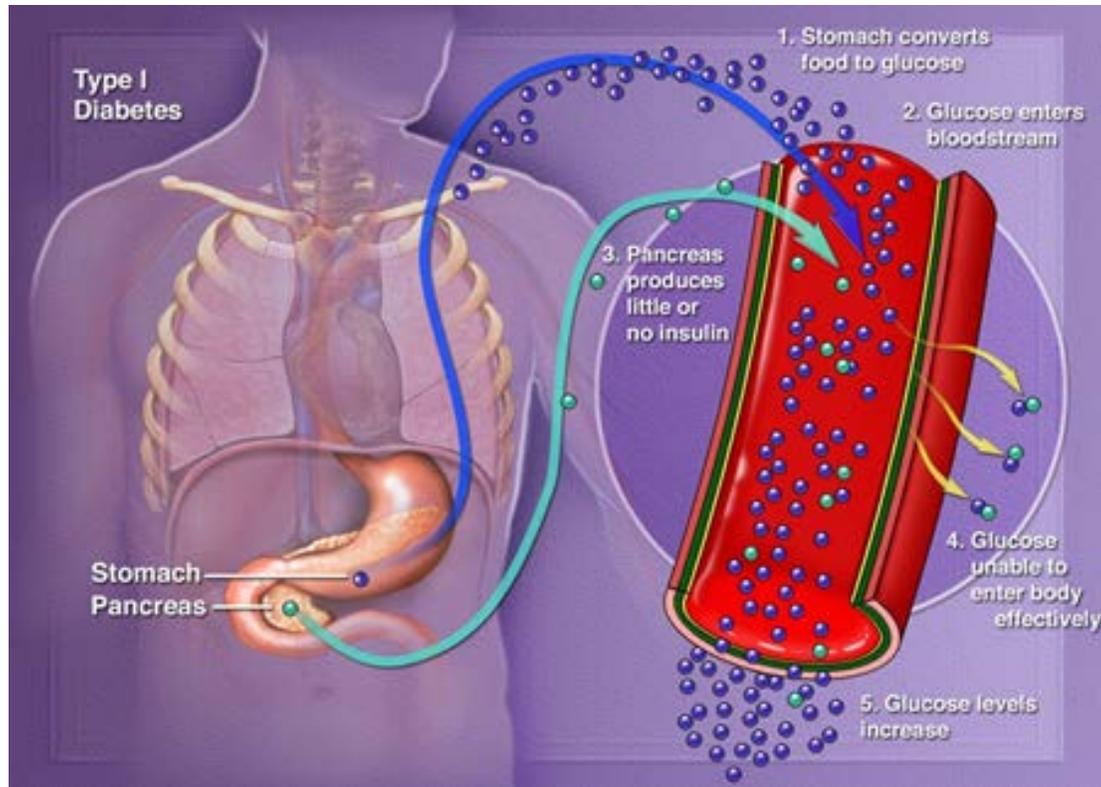
An open-ended question!



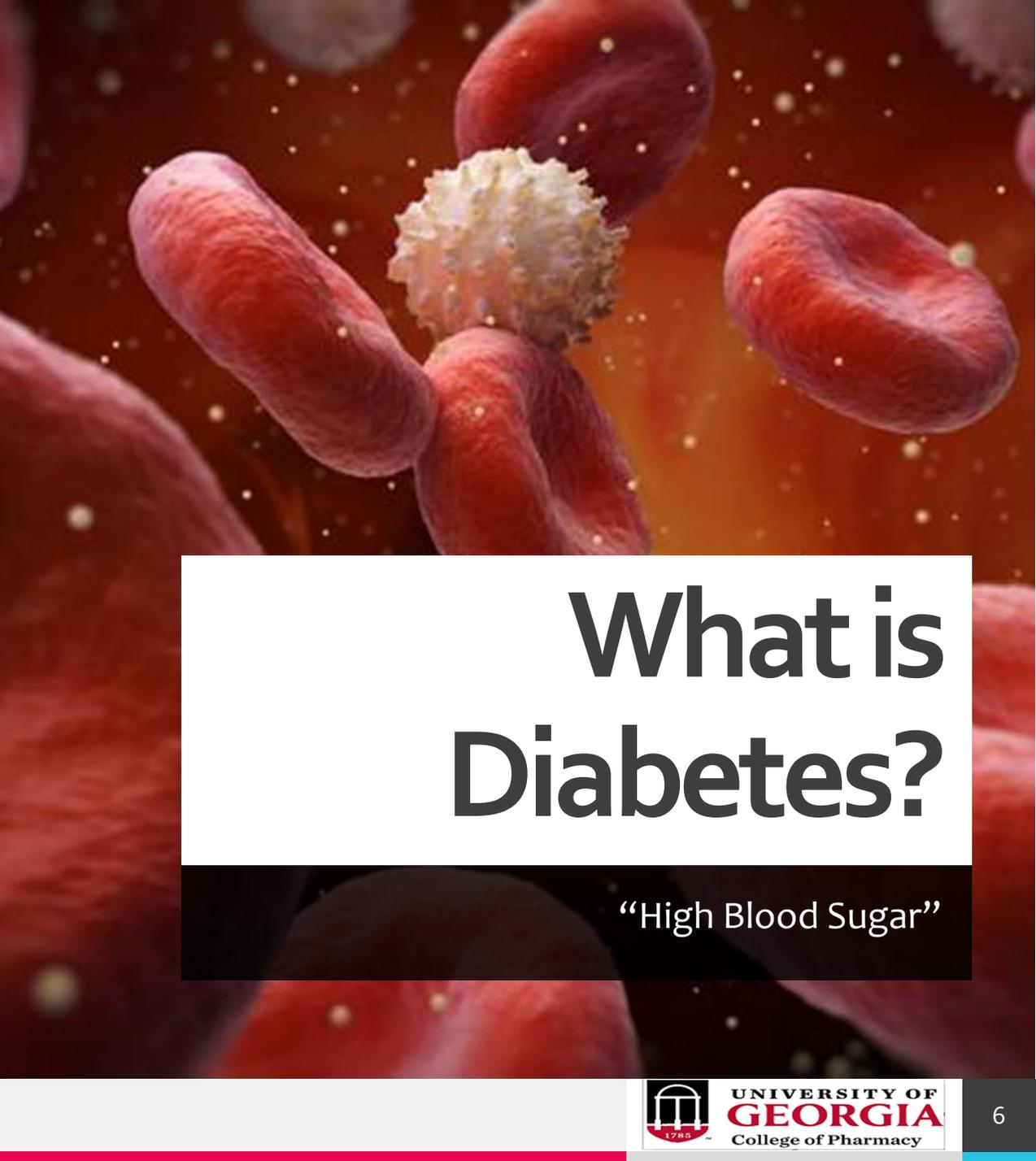
What is Not Diabetes?



What is diabetes?



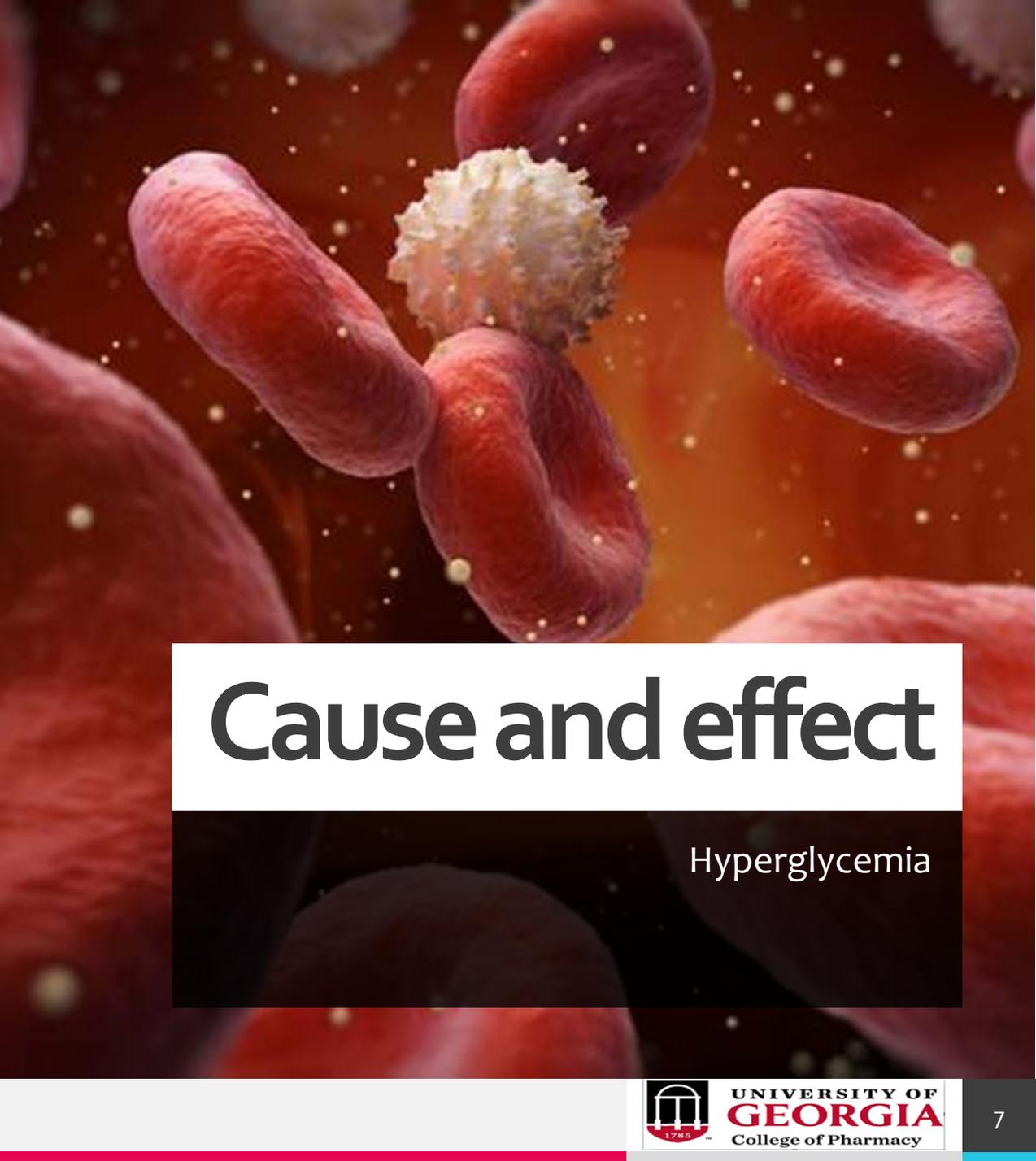
- Fasting Plasma Glucose
 - Prediabetes: 100-125 mg/dL
 - Diabetes: 126 and above on a repeat test
- Oral Glucose Tolerance Test (OGTT)
 - 2 hr Plasma Glucose result
 - Prediabetes: 140-199 mg/dL
 - Diabetes: 200 and above on repeat test
 - Gestational: 180 or higher at 1 hr; 155 or higher at 2 hr; 140 or higher at 3 hr
- Random Plasma Glucose Test
 - Random blood glucose of 200 mg/dL, plus presence of:
 - Increased urination
 - Increased thirst
 - Unexplained weight loss
 - FPG or OGTT will be checked on a different day to confirm
- Hemoglobin A1c
 - Prediabetes: 5.7-6.4%
 - Diabetes: 6.5%



What is Diabetes?

“High Blood Sugar”

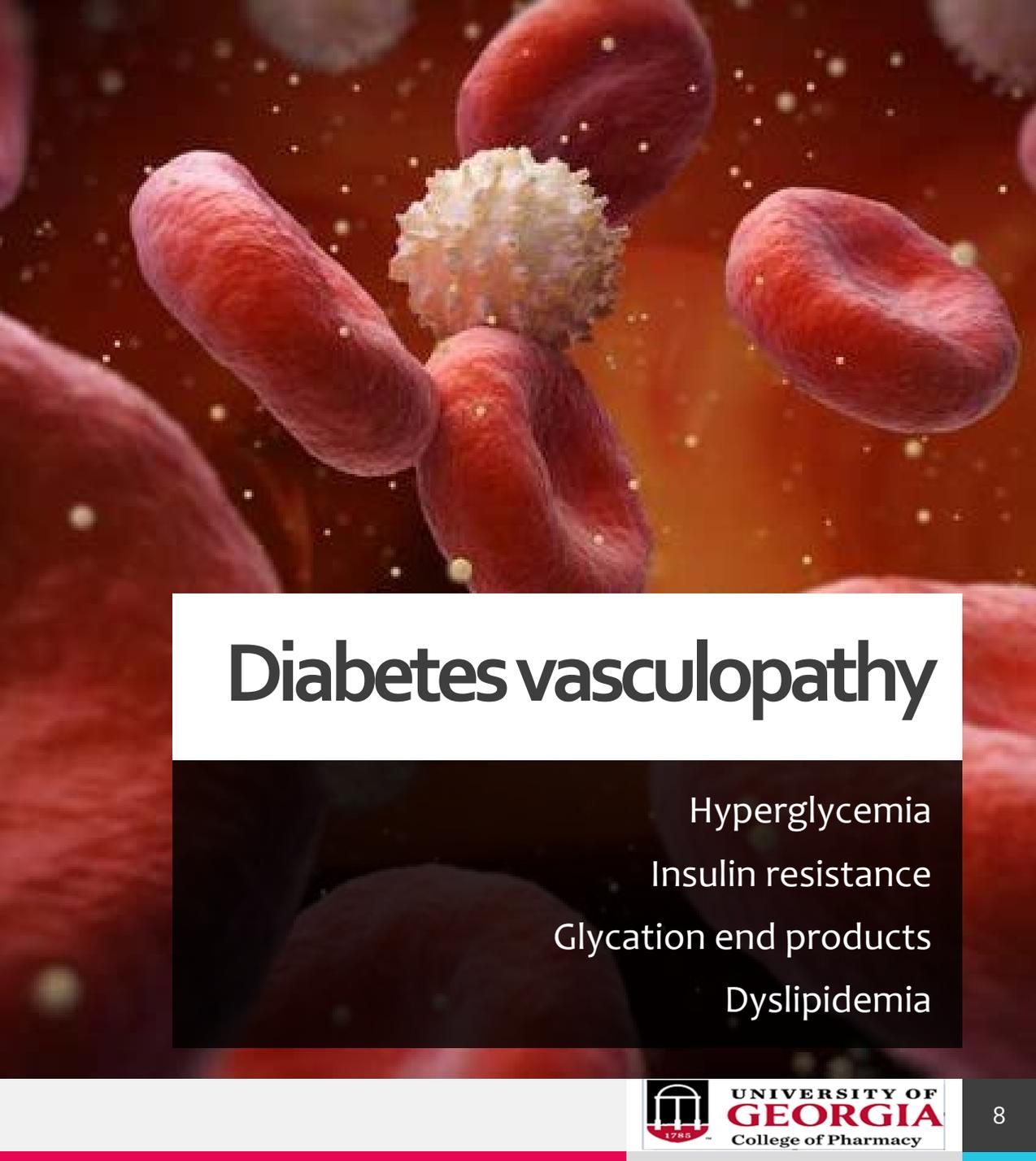
- Hyperosmotic diuresis
 - Frequent thirst, urination
- Fatigue
- Excess hunger
- Infection
- Non-healing wounds

A microscopic view of blood cells. Several red blood cells (erythrocytes) are visible, characterized by their biconcave disc shape and reddish color. A single white blood cell (leukocyte) is also present, appearing as a larger, more irregularly shaped cell with a prominent, multi-lobed nucleus. The background is a dark, reddish-brown color with small, bright yellowish-green particles scattered throughout, suggesting a fluid environment.

Cause and effect

Hyperglycemia

- Hyperglycemia pathophysiology
 - Glycated proteins=altered function
 - Decreased nitric oxide=oxidative effects
 - Protein Kinase C/cytokine effects
 - Osmotic effects
- Endothelial damage
 - Macrovascular complications
 - Microvascular complications

A microscopic view of blood cells, including several red blood cells and one white blood cell, set against a dark red background with small white specks.

Diabetes vasculopathy

Hyperglycemia

Insulin resistance

Glycation end products

Dyslipidemia

- Accelerated atherosclerotic changes
 - Coronary Artery Disease
 - Cerebral vascular accidents
 - Peripheral vascular disease

Macrovascular

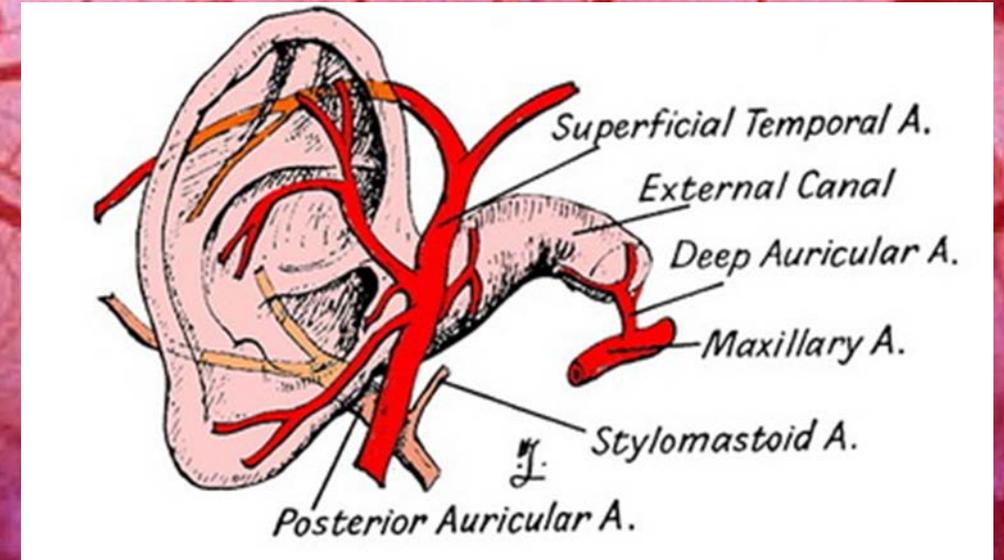
2-4 increase in cardiovascular mortality and stroke

Leading cause of diabetes related deaths

- Retinopathy 49%
 - Leading cause of blindness ages 20-74
- Neuropathy 42%
- Nephropathy 35%
 - Diabetes Kidney Disease
 - Leading cause of chronic kidney disease in the U.S.

Microvascular

- Proposed mechanisms:
 - Microvascular damage
 - Changes to the sensory neurons or fibers of the auditory nerve
 - Otitis externa, infection
 - Ototoxic medications



Hearing loss

Persons with diabetes: twice as common

Pre-diabetes: 30% more common

A photograph of medical supplies on a dark green surface. In the foreground, several white, oblong pills are scattered. Behind them, an orange pill bottle is tipped over, spilling more pills. To the right, a clear insulin syringe with black markings is visible. In the background, a black glucose meter with a small screen and buttons is partially visible.

Diabetes Treatment

ABC's of Diabetes Treatment

A1C

Blood Pressure

Cholesterol



Insulin sensitizers

Biguanides (Metformin)

- Suppresses hepatic glucose output
- Enhances insulin sensitivity of muscle and fat.
 - Weight loss, GI upset
 - Caution/contraindicated in renal failure

Thiazolidinediones

- Rosiglitazone (Avandia), Pioglitazone (Actos)
- Agonists of peroxisome proliferator-activated receptor gamma
- Enhance sensitivity of muscle and fat, and mildly, the liver, to exogenous and endogenous insulin.
 - Weight gain, fluid retention, bone fractures in women
 - Pioglitazone did not increase CV risks, and lowers TG, increases HDL, and increases LDL particle size



Insulin secretogues

Stimulate insulin from the pancreas, enhancing glucose uptake by muscles and fat, and decreasing hepatic glucose production. Oral medications.

Sulfonylureas

- Chlorpropamide (Diabinese)
- Glyburide (Glynase, DiaBeta, Glycron, Glynase PresTab, Micronase)
- Glimepiride (Amaryl)
- Glipizide (Glucotrol, Glipizide XL)
- Tolazamide (Tolinase)
- Tolbutamide (Orinase, Tol-Tab)
 - Weight gain, hypoglycemia
 - **25% reduction in microvascular complications with or without insulin***

Glinides

- Nateglinide (Starlix), Repaglinide (Prandin)
- More rapid onset of action and shorter duration, less risk of hypoglycemia
 - Weight gain, fluid retention, bone fractures in women
 - Pioglitazone did not increase CV risks, and lowers TG, increases HDL, and increases LDL particle size

*United Kingdom Prospective Diabetes Study

Alpha-Glucosidase Inhibitors

Competitively block the enzyme alpha glucosidase in the brush borders of the small intestine, decreasing absorption of carbohydrates.

Acarbose (Precose)

- Oral
- GI upset
- No hypoglycaemia
- Avoid use in patients with severe hepatic or renal impairment
- Dose before carbohydrate-containing meals

Miglitol (Glyset)

- Oral
- GI upset
- No hypoglycemia

Incretins

GLP-1 receptor agonists: Glucagon-like peptide-1 is produced in the small intestine; GLP-1 stimulates insulin secretion and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner. Also delays gastric emptying and suppresses appetite through central pathways.

Dipeptidyl peptidase-4 is a cell membrane protein that degrades GLP-1. Suppression of DPP-4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner

GLP-1 Receptor Agonists

- Injection
- Weight loss, GI upset
- Short acting: Exenatide (Byetta), 2x daily dosing
- Intermediate acting: Liraglutide (Victoza), daily dosing
- Long Acting: Exenatide ER (Bydureon), Dulaglutide (Trulicity); weekly dosing
- Liraglutide shown to decrease CV risk

DPP-4 Inhibitors

- Oral
- Weight neutral, headache, nasopharyngitis, hypoglycemia with SU or insulin
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)

Pramlintide

Synthetic form of amylin, hormone that is secreted by the beta cells to suppress glucagon secretion, slow gastric emptying, and suppress appetite through central pathways. Efficacy data from well conducted studies is lacking. Dosage varies in different patients.

Pramlintide (Symlin)

- FDA approved for adjunctive therapy with insulin, but used off label with metformin and SU in either Type 1 or 2 DM
- SubQ
- Can reduce insulin requirements by 50%
- Weight loss

- Nausea, GI complaints
- Hypoglycemia



Bromocriptine

Mechanism is unknown. Fast release bromocriptine improves glycemic control in patients with Type 2 DM when taken within 2 hrs of waking up.

- Oral
- Therapeutic dose varies

- Nausea, GI complaints



Sodium glucose cotransporter-2 (SGLT-2) Inhibitors

SGLT-2 is a protein acting as sodium-glucose cotransporter in the kidney's proximal tubules whose main function is reabsorption of the filtered glucose from the urine back into the circulation, responsible for about 90% of total glucose reabsorption. Inhibition leads to the excretion of glucose in the urine.

Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)

- Oral
- Weight loss
- Lower blood pressure
- Empagliflozin, Canagliflozin shown to decrease CV risk
- UTIs, polyuria
 - Volume depletion
- vaginal yeast infections
- Renal dose adjustment
- Canagliflozine associated with increased amputations
 - Caution in patients with previous amputation, hx of ulceration, peripheral sensory neuropathy and PVD



Insulin

Discovered in 1921, and remains the most effective method of reducing hyperglycemia. Hypoglycemia is a concern, but actual risk of insulin-induced episodes requiring therapy occur in 1-3 per 100,000 patient years. Weight gain can occur and is typically about 2-4 kg.

Rapid-acting

- Aspart (Novolog)
- Lispro (Humalog)
- Glulisine (Apidra)

Short acting

- Regular insulin (Humulin R, Novolin R)

Intermediate, basal

- Insulin NPH

Long-acting, basal

- Insulin glargine (Lantus, Toujeo, Basaglar)
- Insulin detemir (Levemir)
- Insulin degludec (Tresiba)

Premixed

- 75% Insulin lispro protamine/25%insulin lispro (Humalog mix 75/25)
- 50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)
- 70% NPH insulin/30% regular



Blood Pressure

140/90; 130/80 “may be appropriate for individuals at high risk of cardiovascular disease, if can be achieved Without undue treatment burden.”

ACEI

- Lisinopril, **Ramipril**, Enalapril, fosinopril, captopril, quinapril, perindopril, **trandolapril**, moexipril

Angiotensin Receptor Blockers (ARBs)

- Valsartan, losartan, **irbesartan**, candesartan, olmesartan, telmisartan

Thiazide-like diuretics

- Indapamide, chlorthalidone

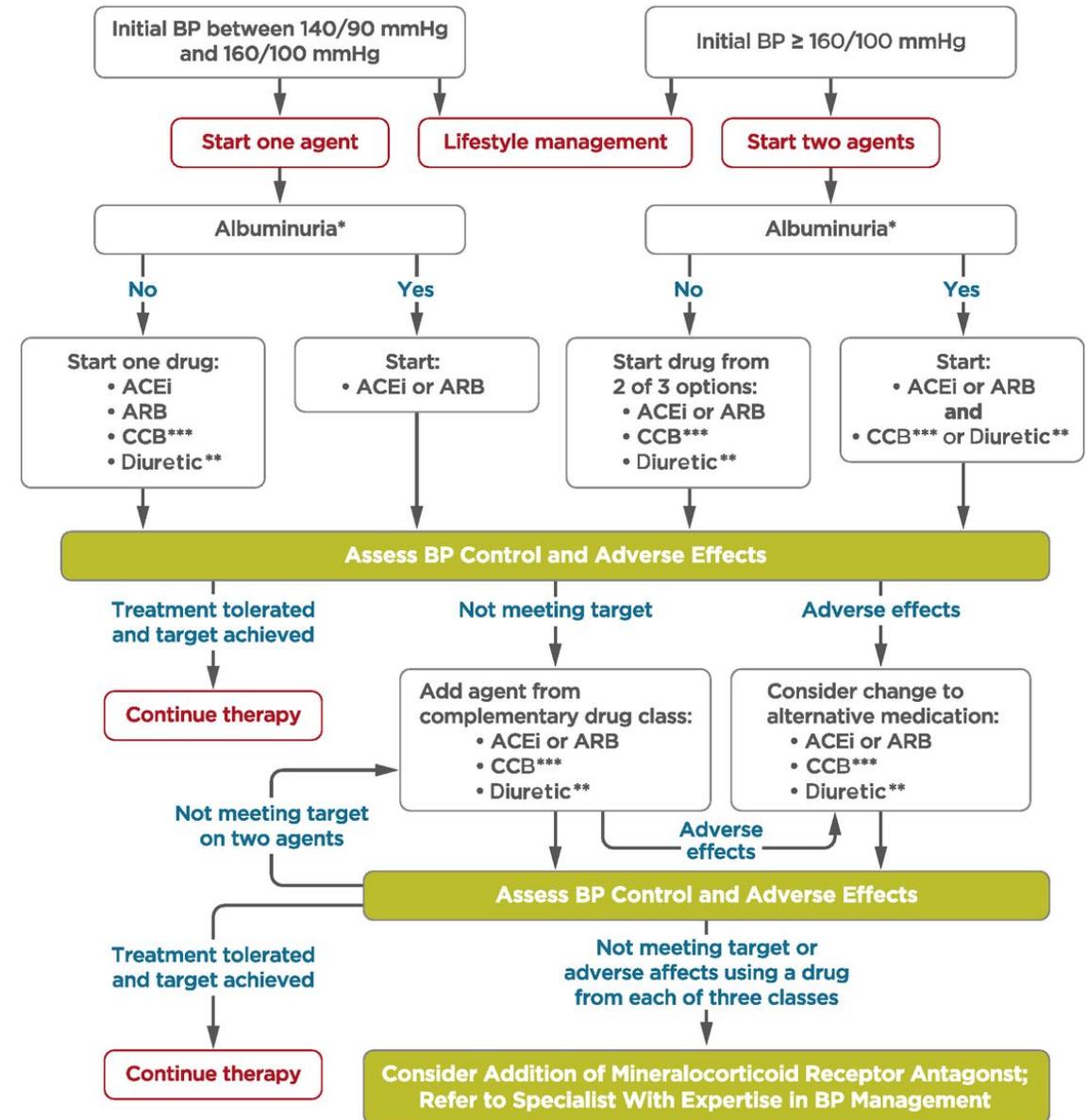
Dihydropyridine Calcium channel blockers

- *Amlodipine*, felodipine, **nicardipine**, *nifedipine*, nimodipine, lacidipine, lercanidipine

Beta blockers

- Prior MI, active angina or heart failure
- **Metoprolol**, *sotalol*, *practolol*, *bisoprolol*
- Can mask hypoglycemic symptoms
- ACCORD post-hoc analysis: CV event risk higher

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



Cholesterol-lowering

Statins

High-intensity (lowers LDL \geq 50%)	Moderate-intensity (lowers LDL by 30-50%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
	<i>Simvastatin</i> 20-40 mg
	Pravastatin 40-80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2-4 mg

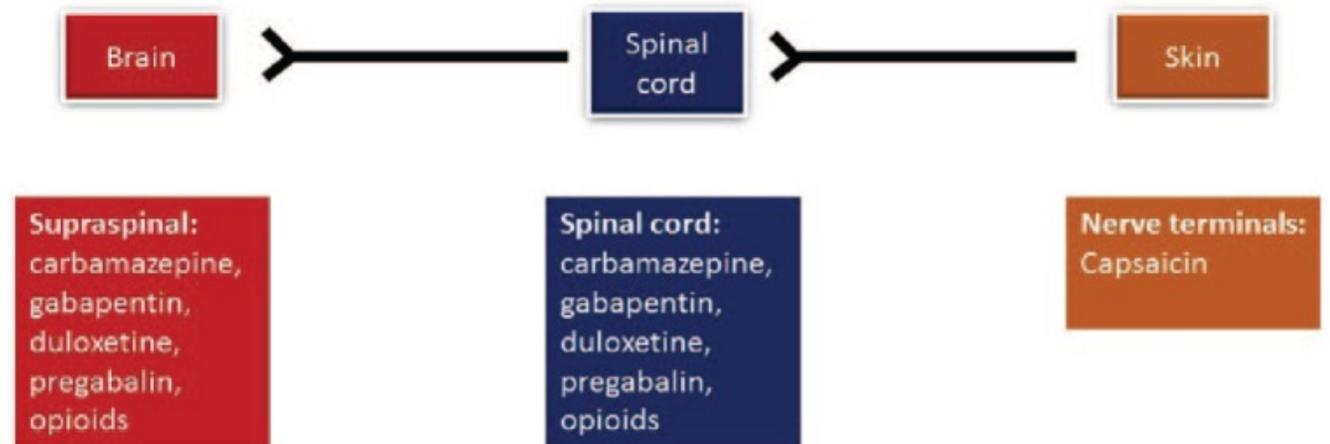
Non-statin

- Ezetimibe (Zetia)
 - Inhibits intestinal absorption of cholesterol
 - Liver, muscle side effects, especially with renal impairment
 - Diarrhea, URT infections, cough
 - Can elevate hepatic transaminases with concomitant use of statins
- PCSK9 inhibitors
 - Monoclonal antibodies: evolocumab (Repatha), alirocumab (Praluent)
 - Proprotein convertase subtilisin kexin 9 stops LDL from being removed from the blood: inhibition dramatically reduces LDL cholesterol
 - Injection every 2-4 weeks
 - Neurocognitive problems

Neuropathy

- **Tricyclic agents (TCAs)**
 - Amitriptyline
 - Desipramine
 - imipramine
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs)**
 - Duloxetine
 - Venlafaxine
- **Gamma-aminobutyric acid (GABA) analogues**
 - Gabapentin, pregabalin
- **Carboxamides**
 - Carbamazepine

- NSAIDs
- Opioids
- Tramadol
- **Topical treatments**
 - Capsaicin



Depression and Diabetes

Bi-directional link:

- Women with depression were 17% more likely to develop diabetes even after researchers adjust for other risk factors.
- Women taking antidepressants were 25% more likely to develop diabetes
- Women with diabetes were 29% more likely to develop depression after taking into account other depression risk factors
- Women who took insulin were 53% more likely to develop depression during the 10 year study.





Drug-Induced Ototoxicity

Risks and Mechanisms



Risk Factors for Drug- Induced Ototoxicity

- Impaired renal function
- Genetic
- Intrinsic ototoxic potential of the drug
- Combination of ototoxic drugs
- Dose, duration
- Prior exposure to aminoglycosides
- Prolonged exposure of inner ear tissues to aminoglycosides



More than
200
medications
are known to be
**OTOTOXIC
OR POISONOUS
TO THE EARS**

Mechanisms of Ototoxicity

Aminoglycosides- up to 33%

- Irreversible destruction of outer hair cells in the Organ of Corti
 - Disruption of mitochondrial protein synthesis
 - Free oxygen radicals
 - Activation of kinases
 - Interaction with transition metals to form free radicals
- Cleared slowly from inner ear fluids, 30 day half life
 - Continued monitoring up to 6 months after cessation
- Toxicity less common in neonates and children

- Streptomycin
 - Preferentially affects the vestibular system
- Gentamicin
 - Affects both cochlear and vestibular, but primarily vestibular
- Neomycin
 - One of most cochleotoxic AG orally and in high doses
- Kanamycin
- Amikacin
 - Very little vestibular toxicity, less ototoxic than gentamicin
- Tobramycin
 - Frequently used in otic and topical preparations
 - Primarily vestibulotoxic

Mechanisms of Ototoxicity

Macrolides- sporadic reports

- Erythromycin
 - Generally reversible
 - Patients tend to have other risk factors
 - Renal, hepatic failure, doses of >4gm/d, and IV admin.
- Azithromycin, Clarithromycin
 - Reports are sporadic and further investigation needed
- Possible mechanism: disruption of ion transport in the stria vascularis

Vancomycin- direct causation inconclusive

- Usually tinnitus
- Patients with elevated serum concentrations attributed to renal failure or concurrently receiving aminoglycosides
- Data unclear but suggests reversible ototoxicity

Mechanisms of Ototoxicity

Loop diuretics: 6-7%

- Furosemide, bumetanide, ethacrynic acid most common; particularly Furosemide doses >240mg/hr
- Experimentally shown: torsemide, azosemide, ozolinone, indacrinone and piretanide
- Changes in ionic gradients between the perilymph and endolymph of the stria vascularis cause edema of the epithelium
- Overall, ototoxicity is self-limited and reversible; some reports of irreversible in neonates

Antineoplastic agents- 35.3-100%

- Cisplatin, and to a lesser degree carboplatin
- Free-radical production leading to mitochondria-mediated and caspase-mediated apoptotic cell death
- Permanent hearing loss

Mechanisms of Ototoxicity

Salicylates- 1%

- Enters cochlea quickly, and perilymph levels parallel serum levels
- Increasing levels produce tinnitus and a reversible flat sensorineural hearing loss
- Most commonly observed in the elderly
- High dose, elderly, dehydration
- Therapeutic levels:
 - 25-50 mcg/ml for analgesic and antipyretic effects
 - 150-300 mcg/ml for acute rheumatic fever
- Tinnitus: can occur at serum levels as low as 200 mcg/ml

Quinine

- Quinine toxicity can produce hearing loss, vertigo, headache, nausea and vision loss.
- Hearing loss usually sensorineural and reversible



Medication Management

Barriers to Adherence

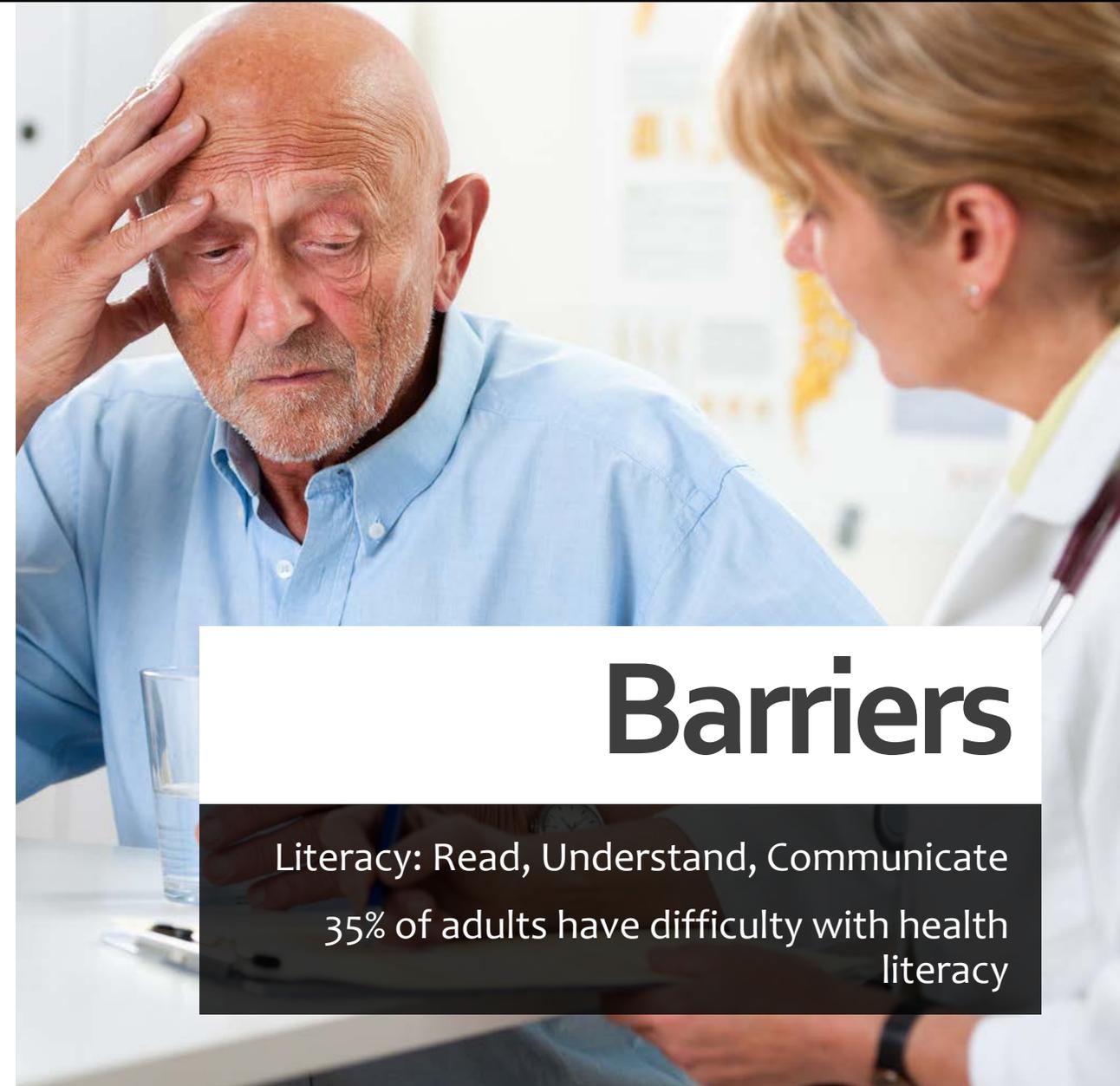


- Financial barriers
- Literacy barriers
- Language barriers
- Cultural attitudes towards medications
- Depression
- Differential access to pharmacies



Barriers

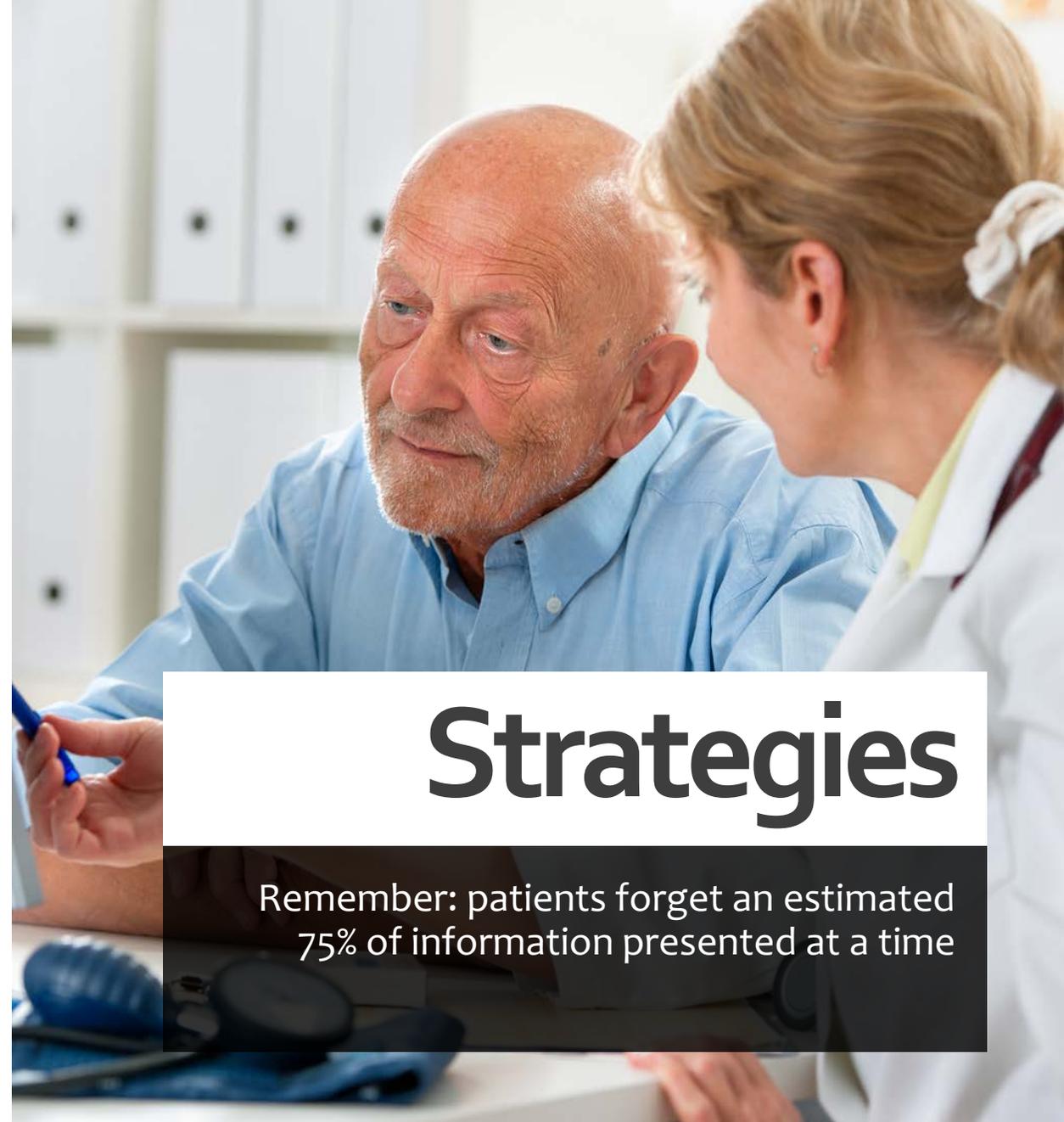
- On average, low health literacy equates with reading at a 5th grade level, while medical information tends to be presented at a 10th grade level.
- People with low health literacy are twice as likely to have poor glycemic control.
- Four domains of health literacy adapted from the Institute of Medicine expert panel on medication information:
 - Cultural and conceptual knowledge: ability to understand medication information
 - Oral literacy: **ability to listen to** and communicate medication information
 - Print literacy: **ability to read** and understand written medication information
 - Numeracy: ability to understand numbers associated with the dose, directions, quantity of medications and refills



Barriers

Literacy: Read, Understand, Communicate
35% of adults have difficulty with health literacy

- Additional aids to enforce written information
 - Graphics, pictograms, icons, animations
 - Verbal counseling in combination with written info
- Personalized information
 - Medication reviews
- Ease of navigation
 - Bullets, subheadings, icons, bolding, underlining, larger font size and shorter words
- Accessibility
 - Having access to information at home
 - Automated telephone reminder systems



Strategies

Remember: patients forget an estimated 75% of information presented at a time



Thank You

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