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Northern California Chapter ACP Update In Medicine I

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Goals: At the end of this presentation you will

- Learn about the use of D-Mannose to prevent recurrent UTIs, and how this treatment compares to current recurrent UTI treatments in efficacy and cost
- Review the basics of Diabetes Medications, mechanisms of action and side effects
- Be aware of a rare sodium-glucose cotransporter-2 (SGLT2) inhibitor side-effect that could be deadly, and that you should alert every diabetes patient about before starting this therapy

Question 1:

A healthy 53-year old woman with a history of recurrent urinary tract infections (UTIs), asks about the benefit of using 2gm of daily D-mannose powder diluted in water instead of daily nitrofurantoin 50mg to prevent future UTIs. She should be advised:

1. D-mannose has not been shown to be useful in preventing recurrent UTIs
2. D-mannose is significantly more effective than nitrofurantoin in preventing recurrent UTIs
3. D-mannose and nitrofurantoin are equally effective in preventing recurrent UTIs, with D-mannose treatment having fewer reported side effects.
4. Neither daily D-mannose nor nitrofurantoin have been shown to be effective in preventing recurrent UTIs

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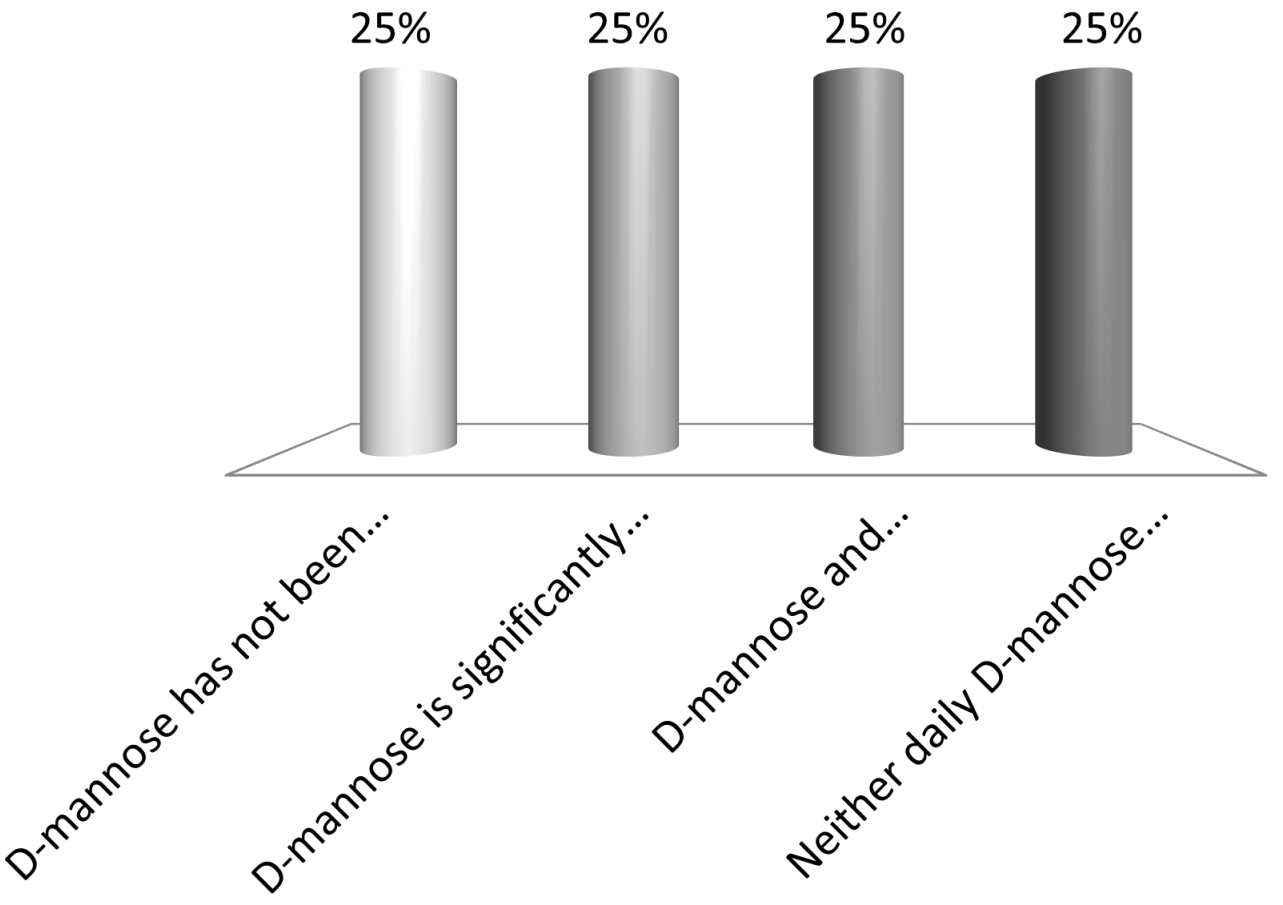

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Question 1 Explanation:

- **D-mannose and nitrofurantoin are equally effective in preventing recurrent UTIs, with D-mannose treatment having fewer reported side effects.**
- A 2014 randomized clinical trial of 308 female patients aged 20-79 (median age 49) with a history of recurrent UTI who were followed for 6 months after UTI treatment with either no therapy (control group), 2gm of daily D-mannose powder diluted in water, or daily nitrofurantoin 50mg.
- Both treatments were more effective than no therapy in preventing recurrent UTIs (% UTI recurrence: D-mannose=14.6%, nitrofurantoin=20.4%, no therapy=60.8%) but the effectiveness of the two treatment groups were not statistically significant from each other.
- The D-mannose group reported significantly fewer side effects than the nitrofurantoin group
- 8% of the D-mannose group reported SEs (diarrhea) vs 27.2% of the nitrofurantoin group (diarrhea, vaginal burning, nausea, headache, skin rash).

Citation: Kranjčec, B., Papeš, D. & Altarac, S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol 2014;32:79–84.*doi:10.1007/s00345-013-1091-6OpenUrl

Question 1 Key Points:

- **D-mannose and nitrofurantoin are equally effective in preventing recurrent UTIs, with D-mannose treatment having fewer reported side effects.**
- Up to a 75% reduction in recurrent UTIs vs No Therapy

- **But what about a cost comparison? (cash price)**

Question 1 Key Points:

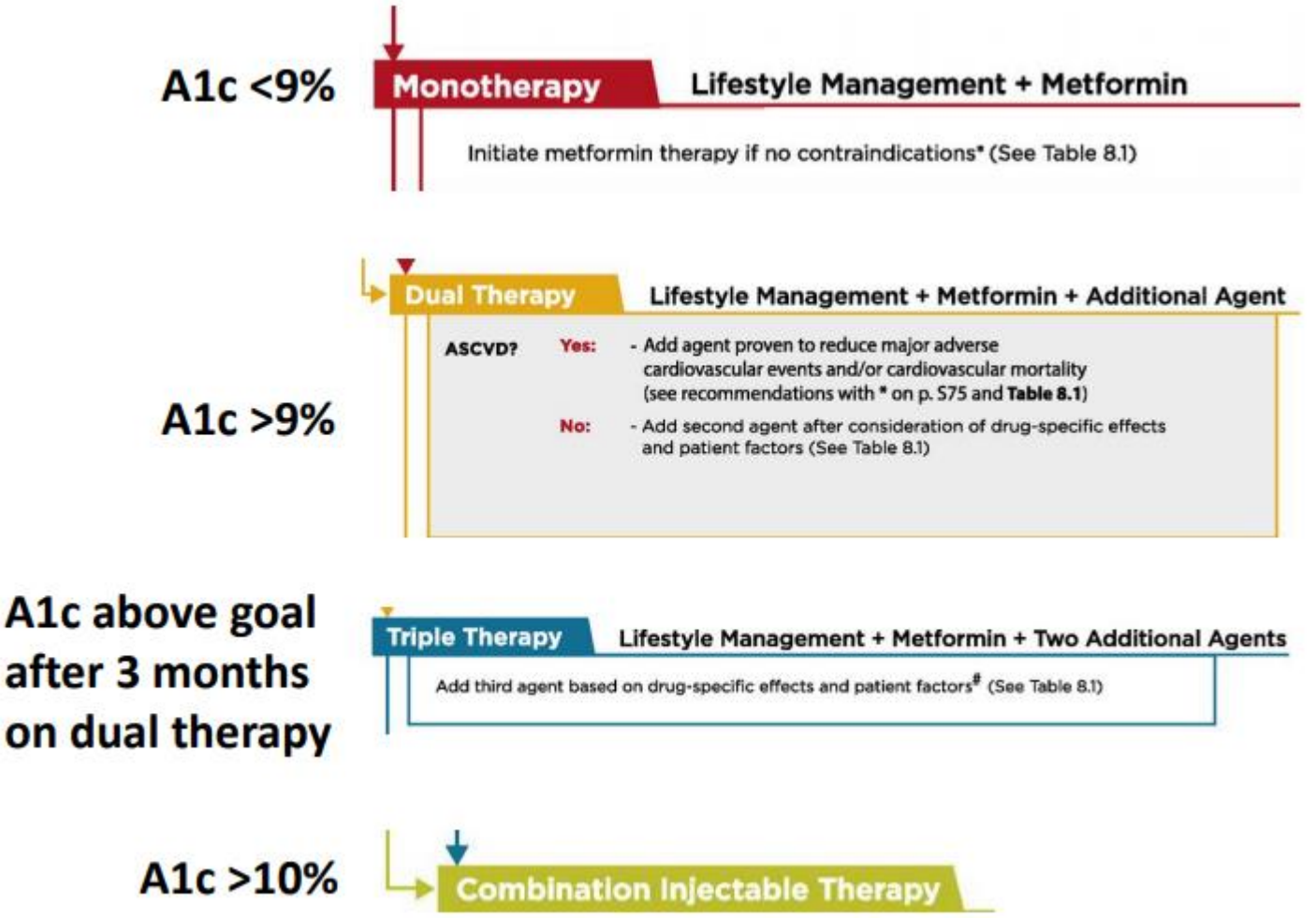
- **D-mannose and nitrofurantoin are equally effective in preventing recurrent UTIs, with D-mannose treatment having fewer reported side effects.**
- Up to a 75% reduction in recurrent UTIs vs No Therapy

- **But what about a cost comparison? (cash price)**
- **D-Mannose is less expensive**

- A 30d supply of Nitrofurantoin is $25-30/month w/ coupon ($45-75/month without coupon)
- A 30d supply of 2gm D-Mannose OTC supplements is $7-13/month

Source:
GoodRx.com cash price with coupon https://www.goodrx.com/nitrofurantoin?dosage=50mg&form=capsule&label_override=nitrofurantoin&quantity=30
Amazon.com search for D-Mannose 1gm capsules

ADA 2018 Recommendations:



https://med.virginia.edu/cme/wp-content/uploads/sites/262/2018/09/Medical-Grand-Rounds-2018-Update-on-Diabetes.pdf (Heather Ferris, MD, PhD)
American Diabetes Association Clin Diabetes 2018;36:14-37

ADA 2018 Recommendations:

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TABLE 7. Drug-Specific and Patient Factors to Consider When Selecting Antihyperglycemic Treatment in Adults With Type 2 Diabetes

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Canagliflozin: not recommended with eGFR <45 ▪ Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 ▪ Empagliflozin: contraindicated with eGFR <30	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	▪ Exenatide: not indicated with eGFR <30 ▪ Lixisenatide: caution with eGFR <30 ▪ Increased risk of side effects in patients with renal impairment	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required; can be used in renal impairment	▪ Potential risk of acute pancreatitis ▪ Joint pain
Thiazolidinediones	High	No	Gain	Potential Benefit: pioglitazone	Increased Risk	Low	Oral	Neutral	▪ No dose adjustment required ▪ Generally not recommended in renal impairment due to potential for fluid retention	▪ **FDA Black Box:** Congestive heart failure [**pioglitazone, rosiglitazone**] ▪ Fluid retention (edema; heart failure) ▪ Benefit in NASH ▪ Risk of bone fractures ▪ Bladder cancer (pioglitazone) ▪ ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	▪ Glyburide: not recommended ▪ Glipizide & glimepiride: initiate conservatively to avoid hypoglycemia	▪ FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin **Human Insulin**	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	▪ Lower insulin doses required with a decrease in eGFR; titrate per clinical response	▪ Injection site reactions ▪ Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Analogs						High	SQ			

**See Inzucchi et al.* Diabetes Care *2015;38:140–149 for description of efficacy. †U.S. Food and Drug Administration–approved for CVD benefit. NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.*

American Diabetes Association

American Diabetes Association Clin Diabetes 2018;36:14-37

Diabetes Medication Review:

- **SGLT2 Inhibitors (canagliflozin):** ↓ proximal tubule reabsorption of glucose from urine (+glucose on urine dipstick). Mild weight loss, clear benefit in CHF, CAD, CKD, Fatty Liver patients (EMPA-REG, CANVAS,E-LIFT trials). **SEs** include Normoglycemic DKA, orthostasis, polyuria, UTI & yeast infections, bone fractures, ↑LDL, groin infections & 2x amputation risk.
- **GLP1 Agonists (liraglutide):** ↑ satiety signal to brain, ↓ gastric emptying, ↓glucagon, ↑insulin release when ↑glucose, injectable, expensive, no hypoglycemia, mild weight loss. **SEs:** Headache, nausea, diarrhea, infection/URI (Abs), rare thyroid cancers. Benefit in CAD, CHF, ↓CKD progression (LEADER, Sustain-6, Rewind trials, pending Phase 3 **oral** Pioneer-6 trial, avail by 2020?)
- **DDP4 Inhibitors (sitagliptin):** ↑ incretin, ↑insulin, ↓ glucagon, ↓hepatic glucose production. Modest effect, **few** side effects (no hypoglycemia), can be renally adjusted, good for elderly and dialysis patients.
- **Metformin:** ↓ hepatic glucose production, ↓ intestinal absorption of glucose, increases insulin sensitivity (increases peripheral glucose uptake and utilization). Inexpensive, effective, + weight loss, **SEs** diarrhea, cannot use in mod/severe renal disease.
- **Skipping:** Thiazolidinediones, Sufonylureas, Alpha-glucosidase Inhibitors, Insulins (Lispro, Regular, NPH, Glargine)

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Question 2:

A 66-year old man with a history of HTN, elevated Lipids and Type 2 Diabetes has been taking Metformin 1000mg BID but his PCP recently added a sodium-glucose cotransporter-2 (SGLT2) inhibitor to improve his glycemic control. He should be advised:

1. The SGLT2 may cause weight gain
2. To be alert for and seek immediate care for any genital redness, pain or signs of genital infection
3. He no longer needs to limit his carbohydrate intake
4. The SGLT2 may increase his risk of heart failure

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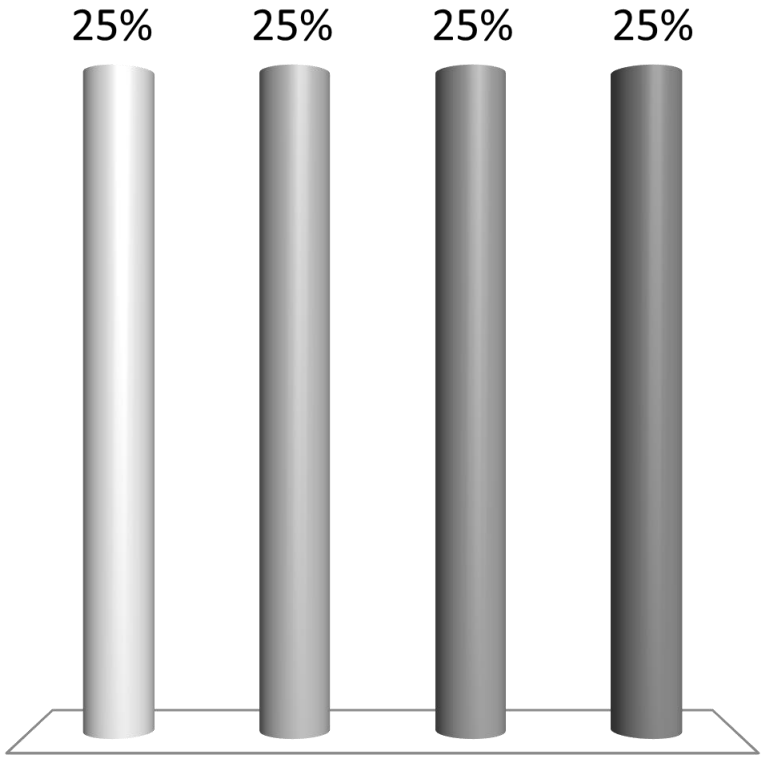

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Question 2 Explanation:

- **To be alert for and seek immediate care for any genital redness, pain or signs of genital infection**
- First approved in 2013, the SGLT2 inhibitor class includes canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. They lower blood sugar by blocking the SGLT2 protein which involves glucose reabsorption from proximal renal tubule resulting in increased glucose excretion into the urine and lower blood glucose levels. In 2017, an estimated 1.7 million US patients filled an SGLT2 prescription.

Citation: https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm

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- By comparison, only 6 cases of Fournier's Gangrene (all men) were found in a review of the past 30 years of other anti-diabetic drug class literature.

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Key Points:

- **Metformin is still our first line diabetic medication**

- **Newer Diabetic Agents (GLP1 Agonists, SGLT2i, DDP4i)** are more expensive, with recent trials showing benefit in decreasing CAD & CHF mortality & CKD progression, but we must be aware of unusual side effect profiles and black box warnings.

- **SGLT2 Inhibitors: Patients should seek medical attention immediately** if they experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly, so it is important they seek treatment right away.

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