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DIABETES MEDICATIONS: SIDE EFFECTS: REAL OR NOT
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• No conflicts of interest
• I won’t mention allergic reactions/anaphylaxis, which can be caused by any medication.

• I won’t include pregnancy/lactation issues.

• More esoteric drugs are not mentioned here (ex: colesevelam[Welchol], pramlintide [Symlin], bromocriptine [Cycloset]).

• I won’t mention the side effects to the pocketbook of the meds, since sulfonylureas are the only inexpensive medications; and Human R and Human N vials are also fairly inexpensive.
METFORMIN

• GI upset: less with lower doses and with long-acting formulations and if taken with food.

• B12 deficiency: especially with higher doses. Especially important to check B12 level if patient has neuropathy despite being well controlled on metformin or if symptoms of B12 deficiency.
METFORMIN

• Dementia: some recent studies indicate metformin might be linked to increased dementia risk (possibly related to B12 deficiency). Other recent studies indicate metformin might lower the dementia risk. Other studies show no effect on dementia.

• Renal insufficiency. No consistent evidence that metformin causes renal insufficiency directly. One study from Taiwan suggested metformin might worsen kidney function in patients with moderate CKD in 2018 (Wei-Hao, et al), but generally most studies do not show worsening renal function from metformin.) Data on stopping metformin when renal function worsens has been misinterpreted as metformin caused the renal worsening.
METFORMIN

• Renal function: shouldn’t start if Cr is $\geq 1.4$ in females and $\geq 1.5$ in men. In a patient on metformin, stop it if GFR is $<30\%$.

• Lactic acidosis: very rare risk, mostly in patients with renal or hepatic insufficiency. Exceedingly rare. Often a patient presents ill to the hospital and has a high lactic acid level but no acidosis (lactic acidemia), due to illness and not metformin.
METFORMIN

• Is contra-indicated in CHF.

• ?does it have to be held for 2 days after contrast is given?
METFORMIN

• Does it lower the risk of certain cancers?
• Plenty of data suggest yes.
• However, DM increases the risk of cancer.
METFORMIN

• Is metformin contaminated with worms?

• Some patients have stopped taking metformin due to this misinformation. The closest I can come to figuring out why they think this, is that there are studies using metformin in roundworms, and the studies show that roundworms live longer when exposed to metformin.
SULFONYLUREA (INSULIN SECRETAGOGUES)

• Hypoglycemia. More pronounced in elderly and patients with reduced renal or hepatic function.

• All sulfonylureas have a black box warning about increasing the risk of CV morbidity/mortality. This is based on data from glyburide, and might not be a class effect.

• Some are renally excreted and some hepatically excreted.

• Sulfa allergy: likely doesn’t cross over to sulfonylureas in most patients.
SULFONYLUREA

- Cause pancreatic burnout: there are no data to definitively support this. If the BG improves with a sulfonylurea, the theoretic benefit might be just the opposite.
MEGLITINIDES (INSULIN SECRETAGOGUES)

• Repaglinide (Pranidin)
• Nateglinide (Starlix)
• Hypoglycemia.
DPP-4 INHIBITORS

• Sitagliptin (Januvia)
• Saxagliptin (Onglyza)
• Alogliptin (Nesina)
• Linagliptin (Tradjenta)
DPP-4 INHIBITORS

- GI symptoms: (diarrhea or constipation): less common.
- Nausea/vomiting: not overly common.
- Headache.
DPP-4 INHIBITORS

• Possible increases hospitalizations for heart failure with alogliptin and saxagliptin.

• Saxagliptin: 27% increase risk of hospitalizations for heart failure in the SAVOR-TIMI trial

• All DPP-4 inhibitors carry this heart failure warning, though.

• Sitagliptin in TECOS study did not affect heart failure.

• DPP-4 inhibitors seem to be neutral as far as coronary artery disease risk.
DPP-4 INHIBITORS

- Dosage reduction in kidney insufficiency needed except for linagliptin.
- Effective in reducing microalbuminuria.
SGLT-2 INHIBITORS

- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Canagliflozin (Invokana)
- Ertugliflozin (Steglatro)
SGLT-2 INHIBITORS

• Volume depletion/dehydration: especially first few days to weeks. Might have to reduce any pre-existing diuretics when SGLT-2 inhibitor started.

• Worsen renal function: early effect only (pre-renal cause).

• Renal function: some have data indicating reduction in albuminuria and decreased progression to albuminuria.

• Reduction in efficacy in patients with CKD.
SGLT-2 INHIBITORS

• Yeast infections: fairly common, vaginal or penile yeast infections. Usually respond well to fluconazole 150 mg. Women can have improvement with antifungal creams.

• Worsening bone density: data with canagliflozin indicates possible increase in fracture risk, but data are questionable. Uncertain if would be a class effect or the mechanism behind this.
• Lower extremity amputations (toes, feet, BKA, AKA): canagliflozin has data suggested this risk is increased. Most of the patients had significant pre-existing lower extremity atherosclerosis and/or significant peripheral neuropathy. Recent data questions whether this is true. If true, possibly due to volume contraction. Uncertain if it is a class effect.
SGLT-2 INHIBITORS

• Bladder cancer: data from dapagliflozin initially suggested the risk might be increased. However, no evidence to suggest this since then.

• Hyperkalemia: data from canagliflozin suggested this. Not sure if a class effect but has only shown for canagliflozin. Might have to reduce any potassium sparing diuretics or potassium raising meds when canagliflozin is started.
SGLT-2 INHIBITORS

• CV risk reduction (empa: data that it reduces risk in secondary prevention; cana: data on reduction of risk in primary prevention).

• DKA: low risk. Occurs at lower BG levels than expected (200s mg/dl range). Most cases occurred in cana, but it has been approved and used longest. Many of the patients with DKA turned out to actually have had type 1 DM. Not sure as to a mechanism and if this is a class effect. Must be watched. For now, don’t use in patients with type 1 DM.
GLP-1 RECEPTOR AGONISTS (GLP-1 RA)

• Exenatide (Byetta, Bydureon).
• Dulaglutide (Trulicity).
• Semaglutide (Ozempic).
• Liraglutide (Victoza)
• These hyperstimulate and tonically stimulate the GLP-1 receptor.
GLP-1 RA

• Nausea/vomiting: common side effect.
• Constipation or diarrhea: common.
• Earlier satiety and reduced appetite: this is what contributes to the weight loss with these agents.
• Pancreatitis: low risk, not certain about this as a side effect.
• Pancreatic cancer: recent data suggest no increased association with GLP-1 agonists; but the incidence in the studies is so low, might never know.
GLP-1 RA

• Nasopharyngitis: common side effect in drug trials of many drugs.
• Headache: sometimes.
• Injection site reactions: not overly common.
• Gall bladder disease: recent studies.
GLP-1 RA

- Bydureon: large lasting lump at the injection site. Less with new formulation.
GLP-1 RA

• Thyroid cancer: medullary thyroid cancer/C-cell hyperplasia: only documented in animals. No reports to my knowledge in humans from GLP-1 agonists. Not associated with other forms of thyroid cancer.

• Shouldn’t use in patients with a history of MEN, medullary thyroid cancer, family history of MEN or medullary thyroid cancer.
THIAZOLIDINEDIONES

• Pioglitazone (Actos).
• Rosiglitazone (Avandia).
THIAZOLIDINEDIONES

• Fluid retention: can be very problematic.

• Weight gain. Interestingly, there are data indicating that patients who gain more weight, might be patients who respond to these agents the best.

• Don’t use in CHF patients.

• CV morbidity and mortality. Might be neutral. Might be beneficial. There are data indicating that pioglitazone has a beneficial effect on carotid intima thickness.
• Rosiglitazone and CV morbidity/mortality. The meta analysis that condemned rosiglitazone was found through later data to be not correct.
THIAZOLIDINEDIONES

- Increased fracture risk: unknown mechanism.
ALPHA-GLUCOSIDASE INHIBITORS

• Acarbose (Precose)
• Miglitol (Glyset)

• GAS AND BLOATING!!!
INSULIN

• Anabolic hormone.

• HYPOGLYCEMIA: insulin is one of the top drugs that cause ER/hospital visits.

• Weight gain: muscle and/or fat.

• Cancer: recent data suggest insulin is likely not causative. However, patients with DM have an increased risk of cancer. Insulin is a growth factor.

• Sodium/fluid retention.
INSULIN

• Injection site reactions.

• Lipodystrophy: lipohypertrophy and lipoatrophy. Rotate shots and AVOID injecting in these areas.

• Formation of insulin antibodies: can cause unpredictable function of insulin.
INSULIN

• Increase in CV morbidity and mortality: no data consistently show that insulin itself increases morbidity or mortality.

• Some studies show that intensive insulin might increase CV morbidity/mortality in the hospital, but in some of these studies, it turned out the people on intensive insulin therapy who were not well controlled on it, were the group with increased risk. (ACCORD)
INSULIN

CONCERNS

- Not using effectively, not titrating to achieve efficacy.
- Not using rapid-acting insulin for carb meals if the BG rises after eating.
• Over-basalization of patients. Many patients are on too much basal insulin, since it is easy to increase if BG control is sub-optimal. BUT, many times if BG control is sub-optimal, what the patient really needs is to have prandial rapid-acting insulin with one or more meals rather than raising the basal insulin dose.

• DON’T adjust the basal insulin dose just based on the fasting BG or the A1c. Instead the basal insulin dose should be adjusted based on whether the BG is consistently rising or falling in a fasting state (for instance: overnight, assuming no snack at bedtime and no rapid-acting insulin given at bedtime).
INSULIN PUMPS

• Malfunctions that lead to hyperglycemia/DKA:
  • Bad infusion site (kinked or pulled out of the skin).
  • Bad insulin in the pump’s reservoir or in the insulin vial used to fill the reservoir.
• When patient BG > 250mg/dL and have bolused for that BG with an insulin pump and it doesn’t come down, THINK…what’s under there?