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CARDI·OH
Ohio Cardiovascular and Diabetes Health Collaborative

Talking With Your Patients About Diabetes Pharmacotherapy:
Side Effects and Adverse Events

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In the United States, over 40 medications belonging to 12 different classes share a common indication: "an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."[1] Despite this large pharmaceutical armamentarium, optimal glycemic control is often not achieved.[2]

Adherence to medication regimens is crucial for achieving glycemic control, yet patient concerns over side effects (SE) and adverse events (AE) remain one of the largest barriers to patients taking medications appropriately.[3] An effective communication style combined with clear explanations of medication benefits, SE, and potential AE can improve adherence.[4,5]

The terms *side effect* and *adverse event* are often mistakenly used interchangeably. Virtually every medication has potential SE that may be more common, dose-related, secondary effects of drug action. AE are typically more infrequent, unintended consequences that may not be dose-dependent. AE tend to be more severe than SE, requiring timely identification to mitigate more serious medical consequences. Drug package inserts typically avoid the terms *side effect* and *adverse event* and rather lump both under the term *adverse reaction*, listing some as mild and some as severe. For the sake of clarity in this narrative, we refer to SE and AE as defined above.[6]

It is important to discuss SE and AE with patients, especially when initiating new medications. Likewise, patients who understand what to expect are less likely to discontinue medications prematurely. An effective strategy for this communication is to educate patients using a guiding conversation style and to engage patients with a plan should SE or AE occur.

Common Side Effects and How They Can Be Minimized

Table 1 reviews the SE of pharmacotherapy used in patients with type 2 diabetes and provides clinical pearls on how to prevent or minimize common SE.[7,8] Potential AE are also listed with their associated frequency to help clinicians guide conversations with patients.

Table 1. Common Pharmacotherapy Side Effects and Important Adverse Events

Metformin

Side Effects
- GI upset (diarrhea, nausea, vomiting)

Methods to Minimize Side Effects
- Take on a full stomach
- Start at low dose and titrate to tolerated dose
- Use extended-release formulation

Adverse Events
- Vitamin B12 deficiency (7-17%)[9]
- Lactic acidosis* (<1%)[10] (This black box warning is primarily from metformin's predecessor, phenformin. In a series of over 300 case studies of lactic acidosis comparing metformin with other medications as well as other observational studies of cohorts the incidence of lactic acidosis does not appear to be higher for metformin than other diabetes medications.)[11]

Contraindications
- eGFR <30, acute or chronic metabolic acidosis (including diabetic ketoacidosis)

Sodium-Glucose Cotransporter-2-Inhibitor (SGLT2i)

Side Effects
- Increased frequency of urination
- Reduction in blood pressure
- Urinary tract infection
- Genital mycotic infections

Methods to Minimize Side Effects
- Take in the morning
- Maintain proper genital hygiene
- Increase water intake
- Check blood pressure
- Consider reduction in dose of loop diuretics if taking them

Adverse Events
- Diabetic ketoacidosis (0.3-0.9%)[12]
- Increased risk of amputations
- Necrotizing fasciitis of perineum* (0.001-0.003%)[13] (Necrotizing fasciitis is based upon FDA adverse event reporting system and has not been confirmed in randomized controlled trials or large epidemiologic studies.)

Contraindications
- Patients on dialysis

Glucagon-like Peptide-1 Recetor Agonist (GLP-1 RA) and Dual GLP-1 RA and Gastric Inhibitory Polypeptide (GIP)

Side Effects
- Abdominal pain
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Reduction in appetite

Methods to Minimize Side Effects
- Eat smaller meals throughout the day instead of one or two large meals
- Decrease meal size by 50% when starting or titrating dose
- Stop eating as soon as patient feels full
- Minimize greasy and high fat content foods
- Extend time period on lower dose until patient tolerates prior to increasing dose

Adverse Events
- Pancreatitis (0.2-0.5%)[14]
- Retinopathy due to diabetes* (1.9%)[15] (Semaglutide was associated with worsening retinopathy in SUSTAIN-6; this does not appear to be related to the GLP-1 RA itself, but due to rapid correction in glucose which was also observed in the Diabetes Control and Complications Trial.)[16]
- Aspiration risk during surgical procedures

Contraindications
- Caution with use in advanced chronic kidney disease. Should not be used in personal or family history of medullary thyroid carcinoma, patients with multiple endocrine neoplasia type 2 (medullary thyroid cancer [presenting with a thyroid mass or nodule], pheochromocytoma [presenting with sweating, tachycardia, refractory hypertension], hyperparathyroidism due to adenoma or hyperplasia [presenting with symptoms of hypercalcemia]).

Dipeptidyl Peptidase-4 Inhibitor (DPP-4i)

Side Effects
- Headache
- Nasopharyngitis

Methods to Minimize Side Effects
N/A

Adverse Events
- Pancreatitis (0.13%)[17]
- Peripheral edema (4%)
- Arthralgia[18]
- Exacerbation of heart failure symptoms[19]† (only observed with saxagliptin and possibly alogliptin, mechanism unknown)
- Severe arthralgias (mechanism unknown)

Contraindications
- Caution in advanced chronic kidney disease

Sulfonylurea (SFU)

Side Effects
- Weight gain, hypoglycemia
- Combined use with insulin increases the risk of hypoglycemia

Methods to Minimize Side Effects
- Avoid skipping meals
- Advise on appropriate glucose monitoring
- Choose later generation and extended-relase formulation
- Maintain consistent diet and exercise routine and diet
- Monitor for hypoglycemia and provide patient with instructions on how to treat if it occurs

Adverse Events
- Cardiovascular mortality[20] (controversial: not observed in CAROLINA-CV outcomes trial comparing glimepiride to linagliptin‡)

Contraindications
- Caution in advanced chronic kidney disease

Insulin

Side Effects
- Weight gain
- Hypoglycemia

Methods to Minimize Side Effects
- Take at the same time each day
- Eat consistent meals
- Maintain consistent physical activity
- Monitor home blood glucose (CGM preferred)
- Maintain a consistent exercise routine and diet
- Monitor for hypoglycemia and provide patient with instructions on how to treat if it occurs

Adverse Events
- Edema
- Hypokalemia (due to glucose shifts and is a transient issue)[21]
- Prolonged hypoglycemia for long-acting insulin

Contraindications
- N/A

Thiazolidinedione (TZD)

Side Effects
- Weight gain
- Edema

Methods to Minimize Side Effects
- Do not use in patients with heart failure
- Use lowest effective dose
- Can consider reducing dose or discontinuing medication if side effects occur

Adverse Events
- Increased fractures (5.1%)
- Myalgia
- Bladder cancer (0.23 - 0.54%) (controversial)
- Elevated liver enzymes* (0.3%)[22] (observed with troglitazone as idiosyncratic reaction, but not seen with pioglitazone)

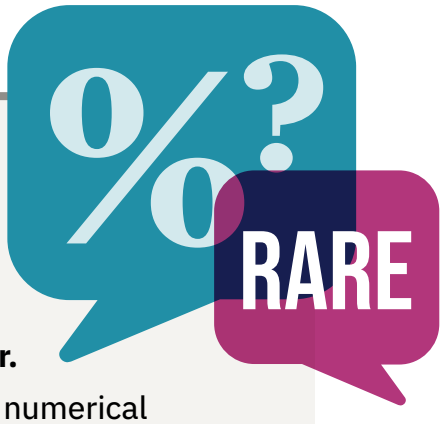
Contraindications
- Patients with NYHA Class III/IV heart failure (initiation of therapy)

*Appears in FDA-approved labeling, but evidence is inconclusive.
†SAVOR-TIMI 53 trial demonstrated increased HF hospitalizations vs. Placebo (3.5% vs 2.8%; p=0.007)
‡Relative risk 1.16-1.55. CAROLINA did not demonstrate increased CV risk with glimepiride vs. linagliptin [23]

Patient Communication

It can be challenging to engage patients in their own care while simultaneously preventing therapeutic inertia and promoting adherence. All life-threatening AE should be presented—either through discussion and/or as written information. The main challenges to effective communication with patients are time constraints and not wanting to unduly worry or dissuade patients from considering treatments where the potential benefits may outweigh the risks. Physicians and pharmacists may have complementary roles in discussions about the benefits of medications and how to take them, common SE and how to deal with them, and any uncommon yet concerning AE and how to monitor for and treat them. One study demonstrated that physicians discuss SE and AE only one-third of the time, an obvious opportunity for improvement.[4] While pharmacists are often thorough, too much information can lead to information overload and overwhelm patients. Shared decision making is advocated, yet patients may be reluctant to initiate new medications, and clinicians may feel obliged to persuade.[4] (See Cardi-OH's expanded resource on Shared Decision Making.)

Framing of information can influence patients' perceptions. See Table 2 for examples of potential biases and their potential effects.[23,24] Prescribers should be aware of potential biases when communicating about new medications.



It can be challenging for patients to interpret the frequency of how often SE or AE occur.

Patients may prefer numerical frequency descriptors (i.e., 1%, 0.1%) over verbal descriptors (i.e., infrequent, rare, very rare). An overreliance on verbal frequency descriptors may result in an overestimation of SE frequency and negatively impact patient intentions to comply with prescribed treatment. Percentages are useful as numerical descriptors except for frequencies less than 1%, in which case a natural frequency such as "1 in 1,000" or "1 in 10,000" is suggested.

The European Medicines Agency and the Council for International Organizations of Medical Sciences define events as:

common: up to 1 in 10 people

uncommon: up to 1 in 100 people

rare: up to 1 in 1,000 people

very rare: 1 in 10,000 people [25,26]

Table 2. Cognitive Biases and Potential Effects

Cognitive Bias	Patients are expected to....	Example
Risky choice framing	Be more risk-averse when facing the prospect of a gain and more risk-seeking when facing a loss	Healthy patient declines a statin while patient with pancreatic cancer chooses risky chemotherapy
Attribute framing	Be more likely to choose a treatment when it is framed positively than framed negatively	Patient chooses 90% chance of survival vs. 10% chance of dying
Absolute vs. relative risk framing	Be more likely to choose a treatment when risk reductions are presented in relative terms vs. absolute terms	Patient chooses a treatment framed as "50% reduction in mortality risk" but may be less inclined to choose that treatment framed as "a reduction in mortality rate from 2% to 1%"
Default bias	Be more likely to pursue a treatment when it is presented as the default option	Patient chooses insulin if presented as the default next option for treatment
Optimism bias	Perceive their odds of a positive outcome as higher than that of other similar patients	Patient willing to pursue high cost treatment with limited effectiveness
Projection bias	Assume their preferences will remain the same over time	Patient unwilling to use injectable medication now and anticipate the same attitude in the future
Present bias	Place disproportinate weight on their current perspective rather than future perspective	Minor side effects may lead to nonadherence

During office conversations, it is important for providers to consider who is doing the work[29]

Clinician work includes diagnosing and presenting various treatment options.

Patient work includes implementing diet and exercise and other healthy lifestyle behaviors as well as adhering to medications and monitoring.

Shared work involves discussions about treatment options, treatment benefits, SE, and AE with guided, shared decision making.[23]

A guiding style of communication is helpful for discussions about medications (see Cardi-OH's expanded resource on Motivational Interviewing [MI]):

- Guiding style (guiding vs. directive or following)
- Spirit of MI (collaboration, evoking the patient's ideas about change, and emphasizing patient autonomy)
- Open-ended questions
- Reflective listening
- Educate with permission ("chunk and check" by providing education in small portions and checking for understanding)

See Table 3 for an example dialogue about initiating a new medication.

Table 3. Example Dialogue of How a Prescriber Can Guide a Patient on Starting a New Diabetes Medication

Situation	Example Provider-Guided Conversation
Discuss lab results with the patient	▪ I see from your labs that the trend we discussed last time of your A1C being elevated has continued. Unfortunately, this increases the risk of complications from your diabetes.
Ask the patient how they feel about starting a new medication Recognize that many patients are reluctant to initiate additional medications for various reasons. If patients are not in agreement to initiate a new medication and the prescriber is not aware, the result may be a prescription that is never filled (i.e., primary nonadherence).	▪ Your glucoses have been running high. What are your thoughts about adding another medication?
Address patient reluctance about additional medication, cost, or SE and explore the "no change" option Explore the "no-change" option. It is best to candidly inquire rather than to assume a newly prescribed medication will be taken and later learn about nonadherence.	▪ It seems you are concerned about SE. There are ways to address those concerns, and one of the potential benefits is weight loss. ▪ Where do you see your diabetes going if you decide not to make any changes?
Educate patient about initiating a new medication Assess knowledge, get permission to educate, and use open-ended questions.	▪ What is your understanding about a medication called Ozempic (semaglutide)? If it's ok with you I could explain a bit about how it works, some possible SE, some rare AE, and why I think it might be a good choice to help improve your diabetes. ▪ Many times, people are concerned about possible SE. Semaglutide can often cause nausea or diarrhea. However, there are ways to help deal with that. What concerns do you have about SE? Every medication, including those you get over the counter, have some potential side effects. If you like, I could explain some ways to help minimize those SE.
Discuss possible AE Encourage informed, shared decision making.	▪ We should also discuss some possible AE. Most of them are rare, but we must keep them in mind as they could possibly cause more serious health concerns. There are two main things to discuss. You should not take this medication if you have a personal or family history of medullary thyroid carcinoma. Also, this medication should not be taken by patients with multiple endocrine neoplasia type 2, a rare, genetic syndrome that causes multiple tumors of endocrine glands. Here's how we can together watch out for these and deal with any problems.
Acknowledge patient autonomy and invite shared decision making	▪ If you agree, we could discuss some other options and together decide which makes the most sense for you.
Promote medication understanding and informed consent	▪ If you would like more time or information before deciding, I can provide some written information, and you may have further discussions with our clinical pharmacist.
Promote adherence and decrease therapeutic inertia	▪ How would you feel about having a follow-up visit soon so we can address any concerns you might have and assess how well the medication is working?

For more information, access Cardi-OH's expanded resource on SE and AE.

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