

Concurrent use of DPP-4 inhibitors and GLP-1 agonists in patients with type 2 diabetes

Managing diabetes may require combination therapy to achieve treatment goals; however, clinical guidelines do not recommend the concurrent use of GLP-1 receptor agonists and DPP-4 inhibitors in patients with type 2 diabetes. The American Association of Clinical Endocrinology (AACE) 2023 consensus statement recommends against using a combination of incretin-based therapies (e.g., DPP-4 inhibitors with GLP-1 agonists or dual GIP/GLP-1 agonists).¹ Similarly, the 2025 American Diabetes Association (ADA) Standards of Care guidelines do not recommend using both classes concomitantly, explicitly stating that the combination of a GLP-1 agonist with a DPP-4 inhibitor lacks additional glucose-lowering beyond that of a GLP-1 agonist alone for diabetes management.²

Both classes act on the incretin pathway in slightly different ways. DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin and alogliptin) inhibit the DPP-4 enzyme, blocking the enzymatic degradation of GLP-1 and GIP hormones, thereby increasing insulin secretion and decreasing glucagon secretion to lower blood glucose.³ GLP-1 receptor agonists (semaglutide, dulaglutide, liraglutide and exenatide) directly stimulate GLP-1 receptors to increase insulin secretion and suppress glucagon release.⁴

Tirzepatide, one of the newest agents, is a dual GIP and GLP-1 receptor agonist. In addition to having GLP-1 agonistic effects, its dual agonism stimulates the pancreas to suppress glucagon secretion during hyperglycemia and promotes fatty acid and glucose uptake in fat tissue.

Due to overlapping mechanisms of action, potentially increased risk of adverse effects (e.g., gastrointestinal disturbances or pancreatitis) and the lack of additional glucose-lowering when used together, concurrent use of DPP-4 inhibitors with GLP-1 agonists or dual GIP/GLP-1 agonists is not recommended.

If a patient is on both classes concurrently and will discontinue the DPP-4 inhibitor (continue GLP-1 or GIP/GLP-1), tapering off the DPP-4 is not necessary. Although there are no standardized recommendations for discontinuing a GLP-1 or GIP/GLP-1, tapering off these agents is recommended to mitigate side effects and reduce the risk of regaining weight. This can be accomplished by gradually reducing the dose (e.g., 1 mg to 0.5 mg) or decreasing frequency (e.g., every 7 days to every 10-14 days) over about 2-8 weeks, depending on the dose and patient tolerability. Individual patient factors should be considered to determine the most appropriate regimen. Some factors are shown in the table below.

Comparing GLP-1 agonists and DPP-4 inhibitors

	GLP-1 receptor agonists	DPP-4 inhibitors
Generic (Brand name)	Semaglutide (<i>Ozempic, Rybelsus, Wegovy</i>) Liraglutide (<i>Victoza</i>) Dulaglutide (<i>Trulicity</i>) Exenatide (<i>Byetta</i>)	Sitagliptin (<i>Januvia</i>) Linagliptin (<i>Tradjenta</i>) Saxagliptin (<i>Onglyza</i>) Alogliptin (<i>Nesina</i>)
Glucose-lowering efficacy	High to very high	Intermediate
Hypoglycemia risk	No	No
Weight loss	Intermediate to very high	Neutral
Cardiovascular effects	Benefit in MACE Neutral in HF	Neutral in MACE Neutral in HF
Renal effects	Benefit	Neutral
Renal dose adjustments	No	Yes
GI adverse symptoms	Moderate	Neutral
Other considerations	Medullary thyroid carcinoma/MEN2	Rare arthralgias/myalgias
Cost	\$\$\$	\$-\$

MACE: major adverse cardiovascular events; HF: heart failure; MEN2: multiple endocrine neoplasia, type 2

References:

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3. Deacon CF. Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2020;16(11):642-653. doi:10.1038/s41574-020-0399-8
4. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* 2018;27(4):740-756. doi:10.1016/j.cmet.2018.03.001