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Weight Loss Incretins

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Bottom line at the top: The hype over GIP and GLP-1 agonists for weight loss and diabetes control is largely justified. Claims made for patches which mostly contain herbs having similar biologic effects, are not. A prescription from a practicing medical provider for an FDA-approved drug, plus moderate exercise and a dietary effort to not sabotage weight loss or sugar control, are likely to combine to achieve success.

The Why: In answer to overweight Americans' desire for a quick fix to lose weight because their efforts to control their food/activity balance have not been successful, scientists developed medications in the past that were similar to amphetamines, anti-depressants or other drugs that alter brain activity, like phentermine, bupropion, naltrexone, Lamictal (for binge eating disorder) and Contrave, all of which had side effects and/or did not induce much weight loss. A patient of mine asked me to write ahout the new weight loss drugs after she used multiple skin patches marketed on-line to act like popular GIP agonist drugs, but had unexpected and unpleasant side effects.

Recently the weight loss medication pipeline shifted to analogues of natural peptide hormones made by the gut in response to food ingestion, called incretins, from the Latin increscere, meaning increase, in this case increasing pancreatic insulin output. When we eat, intestinal cells release these peptides to stimulate insulin secretion by the pancreas, slow digestion, decrease appetite for more food and control glucose production. The most well-known incretins are glucagon-like-peptide-1 and glucose-dependent insulinotropic peptide, commonly known as GLP-1 and GIP. Though they both stimulate pancreatic insulin release and normalize gut, bone and fat metabolism, GLP1 more profoundly reduces appetite and slows stomach emptying, leading to weight loss. They are both rapidly degraded by an enzyme, DPP4, also made by intestinal cells and which itself is rapidly degraded. Medications affecting these hormones were developed to treat diabetes, the first being the gliptins, synthetic molecules which slow DPP4 degradation, therefore prolonging the body's natural GLP-1 and GIP activity, enabling natural, longer-lasting glucose and appetite control. The gliptins fell out of favor due to high cost compared to metformin, which is the primary medication for obesity-related diabetes, concerns about an increased risk of pancreatitis and the advent of injectable GLP-1 receptor agonists (an agonist is something that acts similarly).

The Discoveries: Scientists have suspected and known about incretins for decades. After identifying insulin in 1906, scientists suspected insulin-"adjacent" hormones. which Jean La Barre first called incretins in 1932 and were finally identified in 1970 (GIP) and the 1980s (GLPs1&2). Pancreas and gut cells have receptors which bind and are activated by incretins. The drugs we now commonly call GLP-1 drugs are actually GLP1R (R for receptor) agonists. The synthetic drups differ from naturally occurring GLP-1 by structural changes conferring resistance to DPP4 degradation, like a functionally combined GLP1-gliptin.

The current medications: In this class, there are now seven active FDA-approved synthesized GIP-like peptides for diabetes and weight control, comprising fifteen different drug options and as many as thirteen different brand-name medications. By blocking the GLP1 receptor, they slow our body's natural GLP1 degradation. One drug, orforglipron (Foundayo), functions similarly, but is structurally very different. Two have an approved oral formulation and another two oral brands are being reviewed. No patches or stickers are FDA-

approved, as natural GLP1 and GIP peptides do not cross the skin barrier. The only brand that combines both GLP1 and GIP agonists, for synergistic brain-level appetite suppression, is tirzepatide (Eli Lilly company's Mounjaro and Zepbound.

Cost and Coverage: These medications cost between $700 and $1,400 per month. No brand is available over the counter. Four, semaglutide, liraglutide, dulaglutide and tirzepatide are approved to reduce at least some cardiovascular events, like death, heart attack and stroke, in high-risk patients. Medicare Part D, via its GLP-1 Bridge program will pay for eligible patients to receive Foundayo tablet, Wegovy tablet or injection, or Zepbound (tirzepatide) Kwikpen, with a $50/month copay. Other insurance coverage varies too much for me to generalize.

While none of these drugs are available without a prescription, people can engage online providers to order and supply these drugs, ostensibly without clinical monitoring. Many online providers supply patches or stickers. Using approved formulations, people lose an average of 5-25% of their body weight in two years (which varies by drug and lifestyle modifications), though most studies are shorter. People predictably regain much of the lost weight after drug cessation in a pattern of initial rapid weight gain, gradually declining over time. The amount regained varies with the medication taken and the person's lifestyle.

Side Effects: GLP1 drugs typically cause gastrointestinal adverse effects like nausea, vomiting, diarrhea and constipation, (all typically worse with larger meals, and may have headache, fatigue and injection site reactions. Pancreatitis and a type of thyroid cancer are rare but require monitoring.

Herbal "alternatives": Multiple herbs, like fenugreek, bitter melon, curcumin, ginseng, berberine and ginger can induce GLP1-type physiologic effects, some by boosting our natural GLP1 output, but none would produce an effect of the magnitude of any of the approved drugs. Patches often contain vitamins, tea extract and garcinia cambogia. Since the latter and all the above-mentioned herbs have potential side effects, they may be what caused my patient's unpleasant side effects.

Lifestyle: The FDA requires all trials submitted for incretin-based drug approval to include healthy diet and exercise advice for all trial participants. The recommended lifestyle must emphasize a diet of nutrient-dense food and adequate protein (1.2-1.5 grams/Kg of ideal weight/day) providing at least 500 fewer calories than normally consumed, by restricting sugar, other carbs and fat, and at least 150 minutes per week of moderate aerobic exercise. Someone who can successfully follow this prescription might not need medication, but the principle behind the medication is to make it easier to do so.