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Glucagon-like peptide-1 receptor agonist

Glucagon-like peptide-1 receptor agonists, also known as **GLP-1 receptor agonists (GLP-1-RA)** or **incretin mimetics**, are agonists of the GLP-1 receptor. This class of medications is used for the treatment of type 2 diabetes[1][2] Some drugs are also approved for obesity. One of their advantages over older insulin secretagogues, such as sulfonylureas or meglitinides, is that they have a lower risk of causing hypoglycemia.[3] GLP-1 has a short duration of action, so to overcome this limitation several modifications in either the drugs or the formulations are being developed.[4]

The 2022 ADA standards of medical care in diabetes include GLP-1-RA as a first line pharmacological therapy for type 2 diabetes, specifically in patients with atherosclerotic cardiovascular disease or obesity.[5]

Contents

Health effects

A 2021 meta-analysis found a 12% reduction in all-cause mortality when GLP-1 analogs are used in the treatment of type 2 diabetes, as well as significant improvements in cardiovascular and renal outcomes.[6] A *JAMA* article meta-analysis in 2018 (covering studies concerning GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors) showed GLP-1 agonists were associated with lower stroke risk than controls.[7]

Preclinical research has suggested the possibility that the drugs may increase the risk of pancreatitis and pancreatic cancer.[8] Analyses of human trials have not found an increased risk of pancreatitis but are insufficiently powered to rule out an effect on pancreatic cancer.[9][10][11]

Studies in rodents have shown GLP1 mediated thyroid c-cell hyperplasia.[12]

A 2020 Cochrane systematic review did not find enough evidence of reduction of all-cause mortality, serious adverse events, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, end-stage renal disease nor health-related quality of life when comparing metformin monotherapy to Glucagon-like peptide 1 analogues in the treatment of type 2 diabetes.[13]

Approved

- exenatide (brand names Byetta and Bydureon, manufactured by AstraZeneca), approved in 2005/2012
- liraglutide (Victoza for diabetes, Saxenda for obesity, manufactured by Novo Nordisk), approved in 2010[14]
- lixisenatide (Lyxumia in Europe, Adlyxin in the United States, manufactured by Sanofi), approved in 2016[15]
- albiglutide (Tanzeum, manufactured by GSK), approved in 2014[16]
- dulaglutide (Trulicity, manufactured by Eli Lilly), approved in 2014[17]
- semaglutide (Ozempic and Rybelsus for diabetes, Wegovy for obesity, manufactured by Novo Nordisk), approved in 2017[18]
- tirzepatide (Mounjaro, manufactured by Eli Lilly), approved in 2022[19]

Under investigation

- taspoglutide, phase III halted Sept 2010[1]
- efpeglenatide[20]

Mechanism

These agents work by activating the GLP-1R, rather than inhibiting the breakdown of GLP-1 as do DPP-4 inhibitors, and are generally considered more potent.[21]

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