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Weight Loss Medication of the Future – Will We Soon Live in a Society Without Obesity?

The promise of a new weight loss medication sounds tempting: inject it via a ready-made pen once a week and watch the pounds fall off. Can it really be that simple? Will excess mortality and morbidity due to obesity be a problem of the past?

Obesity – A widespread disease and a serious problem

According to the World Health Organization (WHO), in 2022 around 2.5 billion adults worldwide – 43% of the adult population – were overweight, with 890 million of these being obese. Since 1990 adult obesity has doubled and adolescent obesity has even quadrupled.[1,2] For the first time obesity can be considered a bigger global health threat than malnutrition.[3] This trend is still on the rise, with the World Obesity Federation predicting that by 2035 over 51% of the global population – more than four billion people – could be overweight.[4]

In the WHO Europe region, 13% of deaths are attributable to a high body mass index (BMI). Overweight and obesity are the main cause of years of healthy life lost due to disease (YLDs), as obesity is associated with numerous comorbidities such as hypertension, type 2 diabetes, metabolic syndrome, cardiovascular disease, sleep apnoea and many more. The The U.S. National Health and Nutrition Examination Survey (NHANES) 2017–2020 found a higher prevalence (57.7%) of hypertension in obese people compared to 31.1% in the normal weight population; for diabetes 23.3% were reported compared to 6.6%.[5] People with obesity have an average life expectancy that is five years shorter, and with a BMI > 40 kg/m^2 this increases to eight to 10 fewer years.[6] As a formula, mortality increases by 29% for every 5 kg/m^2 of BMI.[7]

This reveals a large, steadily growing target group that is affected by increased excess mortality and morbidity and would benefit considerably from a permanent weight reduction.

How does the weight loss injection work?

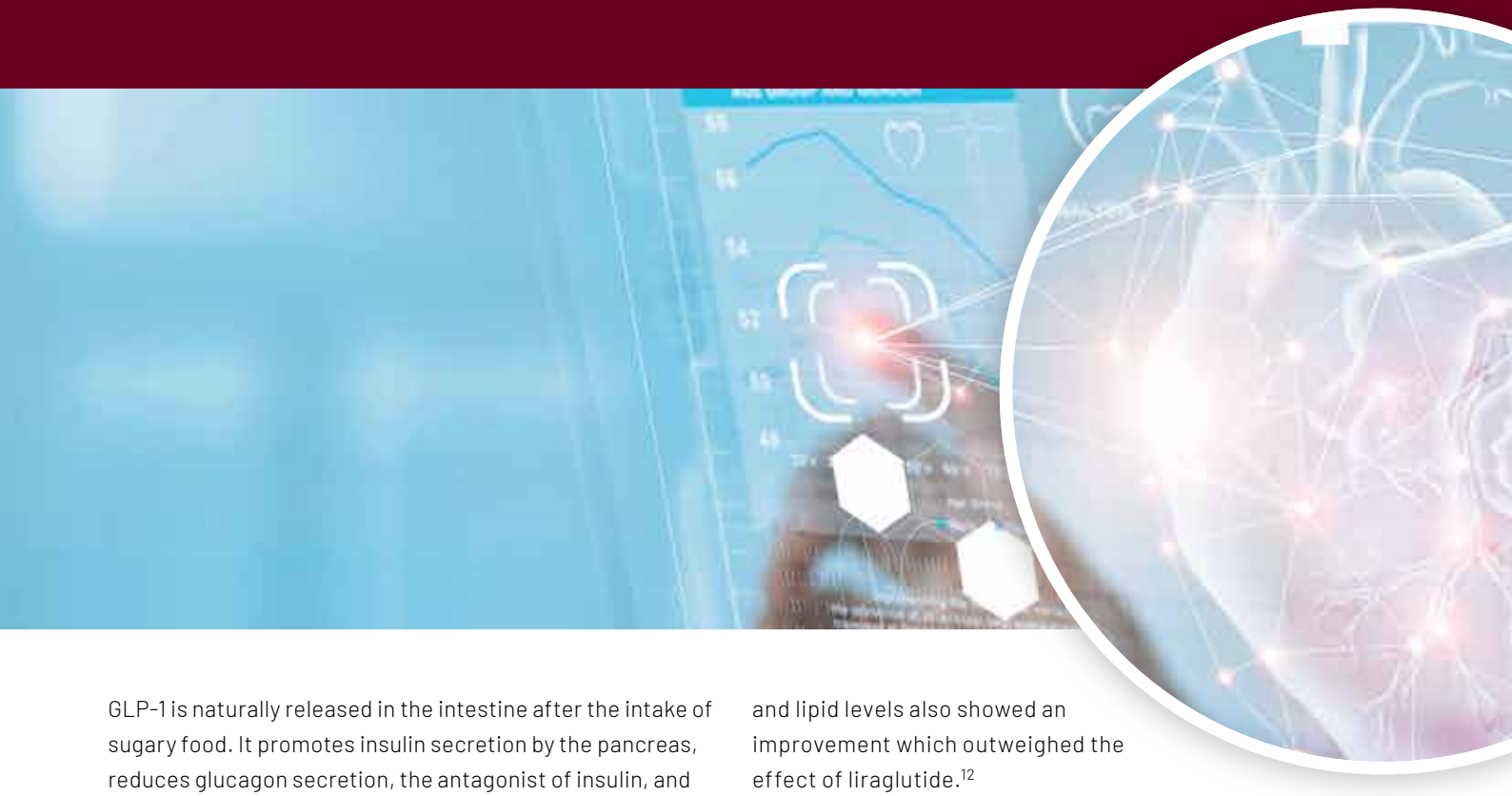
Even if the current hype surrounding weight loss injections might suggest otherwise, glucagon-like peptide-1 (GLP-1) analogues, also known as incretin mimetics, are not new. The first GLP-1 analogue, exenatide, was approved as an anti-diabetic drug back in 2005, and liraglutide has been available for prescription as a weight loss medication since 2014.[8] As the name GLP-1 analogues implies, these medications mimic the body's own GLP-1, but have a significantly longer half-life.

Underwriting Focus

2024, Nr. 1

Dr. Katharina Dorn, Gen Re, Cologne, Germany

Content



GLP-1 is naturally released in the intestine after the intake of sugary food. It promotes insulin secretion by the pancreas, reduces glucagon secretion, the antagonist of insulin, and thus improves blood glucose levels.[9] It also slows gastric emptying and has an appetite-suppressing effect in the brain.[10] These properties have now been utilised by extending the half-life of the natural hormone. Liraglutide has to be administered daily in the belly, leg or arm with a pre-filled pen, whereas a more advanced version, semaglutide, has to be administered only once a week.

Semaglutide has been approved as an antidiabetic agent in the U. S. under the name Ozempic since 2017. Its weight-lowering effect was already known from approval studies and therefore the drug was being used in obese patients. Initially, semaglutide was prescribed off-label as a dietary supplement, with no authorisation for weight loss use. Subsequent studies have led to authorisation under the brand name Wegovy – since June 2021 in the U. S. and since January 2022 in the EU. The recommended indication for prescription is a BMI of 30 kg/m^2 or higher or a BMI of 27 kg/m^2 or higher with at least one comorbidity.

Semaglutide – A game-changer?

So far, research results are promising. Important study programmes are the weight loss STEP 1-6 trials and the cardiovascular outcome study SELECT. Here are some of the findings. The STEP-5 trial tested semaglutide as an adjunct to lifestyle interventions (individual counselling, 500 kcal deficit/day, 150 minutes of exercise per week) in adults who are overweight or obese. An average weight loss of 15.2% in the semaglutide group compared to 2.6% in the placebo group was reported.[11]

In addition to weight loss, unhealthy visceral body fat was significantly reduced, which also led to decreased inflammatory activity as measured by C-reactive protein. Blood pressure, fasting blood glucose, HbA1c and lipid levels also showed an improvement which outweighed the effect of liraglutide.[12]

It can be assumed that, in addition to weight loss, the risk of weight-associated comorbidities is reduced. Several studies currently are researching the effects of GLP-1 analogues on obstructive sleep apnoea, fatty liver, kidney disease, osteoarthritis, and other chronic diseases.

The SELECT study focused on the question of whether semaglutide can prevent serious cardiovascular events in obese people without diabetes but with a history of cardiovascular disease. The results indicate a 20% reduction in serious cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) with semaglutide over a three-year observation period.[13]

Therefore, in March 2024 the U. S. Food and Drug Administration (FDA) approved the new indication for the use of Wegovy for adults with cardiovascular disease and either obesity or excess weight.[14] Another study showed that semaglutide significantly reduced symptoms and physical limitations in obese patients with heart failure.[15]

A significant decrease in non-fatal heart attacks and non-fatal strokes was also achieved in patients with type 2 diabetes, but the number of fatal cardiovascular events did not differ between the semaglutide and placebo groups.[16] Additionally, semaglutide was demonstrated to have a kidney-protective effect in diabetes patients,[17] delaying the progression of chronic renal insufficiency[18] and reducing the risk of respiratory diseases.[19]

This shows a promising health benefit beyond pure weight loss, but the extent to which the results can be generalised to patients with just obesity and without a history of cardiovascular disease must be investigated in follow-up studies.

Risks and side-effects

Every drug that works also has side-effects. What do these look like with semaglutide?

Most common side-effects (more than one in 10 people):

- Gastrointestinal complaints: nausea, diarrhoea, vomiting, constipation, stomach/abdominal pain, bloating, flatulence, heartburn, gastritis – usually mild to moderate in severity
- Headaches, nasopharyngitis, fatigue/exhaustion, dizziness, gallstones, hair loss

Occasional side-effects (one in 100 people):

- Low blood pressure, dizziness, palpitations
- Delayed gastric emptying

Serious side-effects:

- Acute pancreatitis (one in 1,000 up to one in 100 people). Semaglutide is contraindicated in case of a history of pancreatitis
- Severe allergic reactions (one in 1,000 people)
- Worsening possible for existing retinopathy (up to one in 10). Semaglutide is contraindicated in case of retinopathy

It is important to always consider the side-effects in relation to the therapeutic effect. For example, a regularly used drug such as ibuprofen has mild to moderate gastrointestinal complaints as a frequent side-effect (>10%). This is considered as an acceptable downside to the pain-relieving effect.

At the commencement of treatment, semaglutide is administered in low doses and the dose is increased slowly so that the patient is gradually acclimated to the drug. The initial symptoms of side-effects usually subside in the first few weeks, but it can take up to 20 weeks. As a result, long-term use can be seen as a positive factor, as discontinuation due to side-effects is less likely.[20]

For semaglutide, the risk of acute pancreatitis stands out as a serious side-effect; the associated mortality rate can vary from 1% (mild acute form) to 10 to 30% (severe acute pancreatitis).[21] However, in the STEP 1-6 studies and the SELECT study, this diagnosis was made in only 0 to 0.2% of users.

Particularly for Disability products, the risk of gastroparesis (stomach paralysis) should be considered. Slowed gastric emptying is a known and desired effect of the treatment, but complete gastric paralysis/gastroparesis is not currently listed as a side-effect. The symptoms are similar (nausea, more frequent vomiting, feeling of fullness, belching) and can complicate the differential diagnosis, especially in a GP setting.[22]

An analysis of health insurance data from 613 non-diabetic semaglutide patients in the U. S. reported that 1.4% of users were either diagnosed with gastroparesis or classified as having gastroparesis for the study because medication was prescribed to promote gastrointestinal motility.[23] However, if these data are compared with the average prevalence of gastroparesis in the general population using the same recording method, i. e. from health records and excluding diabetics, the prevalence of 0.9 to 2.7% shows that the frequency is not above average, even with semaglutide.[24,25]

No cases of gastroparesis were recorded during the authorisation trials and, according to previous medical reports, it can be assumed that even in the case of drug-induced gastroparesis, discontinuation of the drug leads to a full recovery.

Overall, semaglutide use for patients with existing severe gastrointestinal problems or inflammatory bowel disease should be considered with caution. The package insert refers to the limited experience for this potentially more vulnerable user population. As gastrointestinal symptoms usually occur at the start of use and when the dose is increased, a short duration of use (<6 months) and possible side-effects should be looked at carefully, especially for Disability products.

Other risks that have been under observation since approval include depressive mood, self-harming behaviour, and even suicidal thoughts. The European Medicines Agency (EMA) is currently investigating around 150 reported cases of such side-effects with GLP-1 agonists, while the FDA has documented 265 cases since 2010. Clarifying the cause is still a problem here: did a vulnerability or illness exist previously, or were GLP-1 analogues the trigger? Taking into consideration the total number of users (> 20 million semaglutide users worldwide, 5.6 million in the U. S. alone), the correlation is low and they have not yet been listed as side-effects.

In animal studies, higher doses of semaglutide have shown an increased risk of medullary thyroid cancer. According to the EMA, the current data do not show a causal relationship in humans.[26] Prescription should be done with caution if patients present with a family history of thyroid cancer or if they have already had the disease.

When used as a dietary supplement, the semaglutide doses administered can get more than twice as high as for the original indication for diabetes (2.4 mg vs. 1 mg once a week). Long-term studies are still pending, even if the symptoms observed to date are in line with the side-effects reported for GLP-1 analogues, which have been approved since 2005.

Finally, reduced appetite and decreased food intake are a risk for nutrient deficiency if paired with an unbalanced diet.

How long does the treatment take?

Semaglutide as a weight loss treatment requires lifelong use. Studies show that discontinuation of the drug for one year leads to a gain of approximately two-thirds of the previously lost weight.[27] After losing weight everyone is at risk of regaining weight, but the risk of rapid and high weight gain is increased if (1) the weight can be maintained only with medication; (2) the person was previously significantly obese; and (3) discontinuation of medication is likely. In underwriting, a small loading could be administered depending on the applicant's initial weight before starting medication and the duration of semaglutide use.

Data on the long-term discontinuation rate are not yet available, but analyses for GLP-1 analogues in diabetics outside of controlled clinical trials show high discontinuation rates of 45 to 47% under 12 months and 65 to 70% under 24 months for the UK and the U. S.[28,29] In Spain, around 50% of users discontinued treatment after two years,[30] a Danish evaluation reported 45% after five years.[31]

One reason cited for the discontinuation of medication is the high cost of treatment, but bothersome side-effects, dissatisfaction with the daily self-injection and unsatisfactory weight loss and blood glucose control can also play a role.[32] The extent to which these findings can be transferred to the more effective semaglutide, which can also be taken orally, remains to be seen. Nevertheless, based on other weight loss studies, it can be assumed that even a period of healthy lifestyle intervention reduces the risk of comorbidities or delays their development.[33]

Why not simply exercise and diet?

The placebo group from the authorisation studies showed that moderate lifestyle interventions for obesity tend to have a low average success rate. In the STEP 5 study, a 500 kcal deficit per day and 150 minutes of exercise per week led to an average weight loss of only 2.4%. The reasons for this are complex.

First, numerous studies show that people process food differently in terms of efficiency. For example, in one test people were given a diet with an additional 1,000 kcal over eight weeks under strict observation, including their exercise behaviour. Some of the people gained 1.4 kg, while others gained 7.2 kg.[34] Twins show a similar weight gain in such studies.[35] This indicates a genetic component for factors such as how much of the food energy is converted into body heat (thermogenesis) and how efficiently nutrients

are metabolised. This also depends on the microbiome: the composition of microorganisms in the stomach. The proportion of muscle is another factor that is influenced by genetics and affects metabolism rates.

In addition, changes in the brain have been detected. Functional magnetic resonance imaging (MRI) scans indicated that when seeing food the brain of obese test people showed greater activity in various areas that are also involved in addictive behaviour.[36] The administration of GLP-1 analogues was able to reduce this overactivity in the reward centres, which subsequently led to a reduction in food intake.[37]

Another study showed that losing 1 kg subsequently led to an average increase in being hungry of around 100 kcal.[38] If losing more weight, the urge to eat to counteract the weight loss is correspondingly bigger. The body is evolutionarily designed to maintain weight and not to lose it, hence it compensates for weight loss. In addition, stricter diets and the associated loss of muscle mass can also result in a lower calorie requirement after losing weight, which makes the endeavour even more difficult. In addition, obese people carry a higher average psychosocial burden and are more likely to be affected by mental illness.[39]

Contrary to a widely held opinion, for extremely obese people it is unfortunately not that easy to lose weight and to maintain long-term weight loss through lifestyle interventions alone, as they have to cope with more difficult physical and psychological variables than a person of normal weight.

Who bears the costs?

Obesity is considered a chronic disease. Nevertheless, many private and public health insurances are still hesitant to cover the costs of treatment. This can be partially explained by the high expenditures, the large target group, and the necessary life-long use. In Germany, the current out-of-pocket cost is € 300 per month/€ 3,600 per year, which many of those affected cannot afford in the long term. In the U. S., the annual costs are as high as $12,000. Prices can be expected to fall in the medium term when the patent expires and generics become available. Wegovy is patent-protected in Europe and Japan until 2031, in the U. S. until 2032 and in China until 2026.

If all the obese people in Germany (19% of the population) were to be supplied with Wegovy injections at the current price, this would amount to over € 50 billion. This is more than the total expenditure for all prescription drugs covered by public health insurance in 2022 (totalling € 48.8 billion). For the U. S., it was projected that even with a 65% discount on the current price, the prevention of one heart attack, stroke or cardiovascular death would cost $1.3 million.[40]

It is therefore unlikely that in the future the treatment costs for patients with a BMI of ≥30 kg/m2 will be covered, even with cheaper generics; instead, it is expected that only the most high-risk groups with a significantly higher BMI and corresponding comorbidities will receive paid treatment.

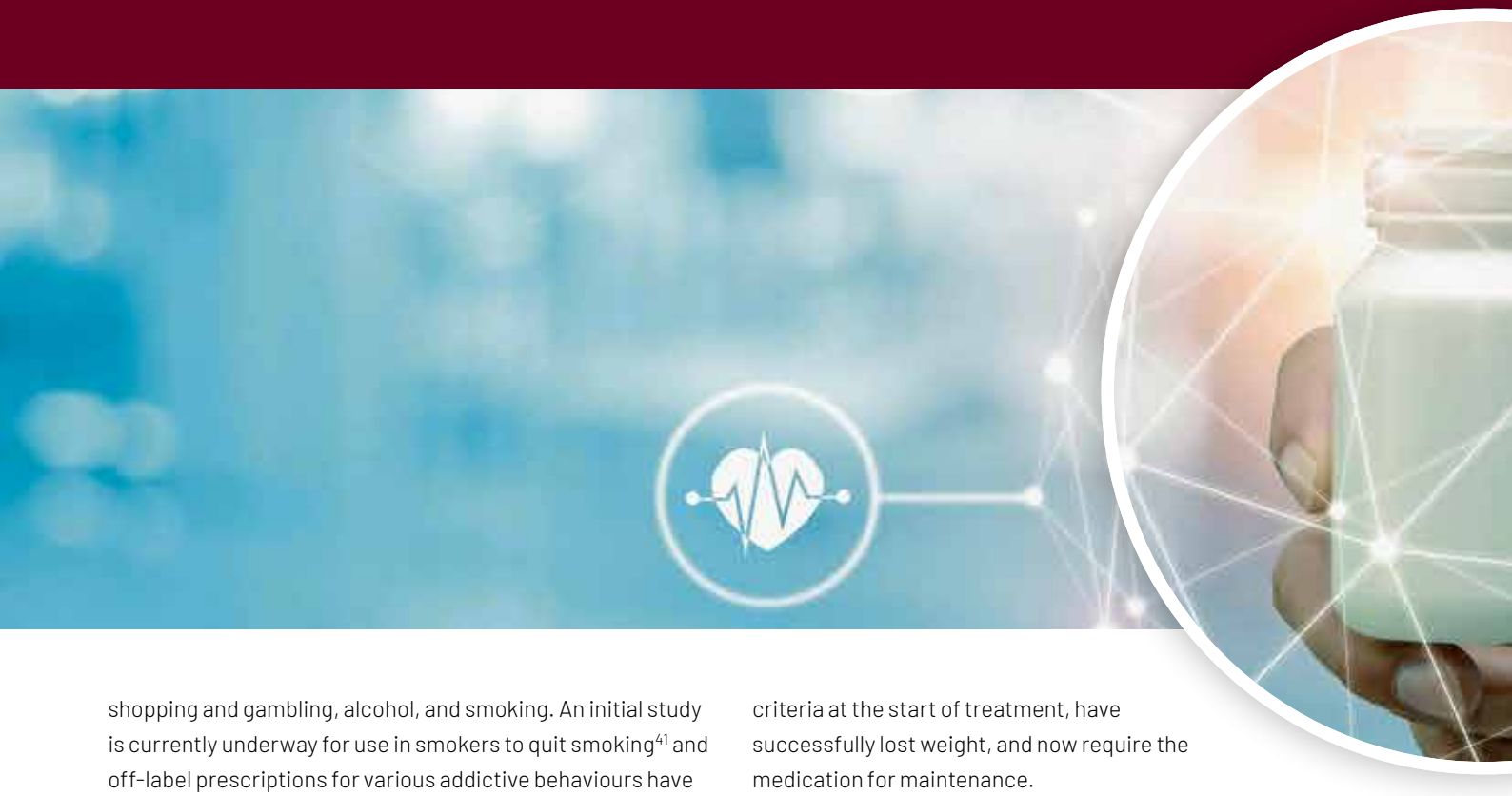
In some countries, semaglutide is already reimbursed by private health insurance companies as a slimming product. As a pilot test in the UK, the Department of Health has started covering two years of treatment for patients with at least one weight-related condition and a BMI of ≥30 kg/m2. Japan's public insurance also covers the costs for patients with a BMI ≥35 kg/m2, or a BMI ≥27 kg/m2 and two or more comorbidities, since November 2023.

It remains to be seen how cost coverage will change globally once sufficient study data on the additional benefits beyond weight loss are available.

Further potential of semaglutide and GLP-1 analogues

The Evoke and Evoke+ studies are investigating the use of GLP-1 analogues in early Alzheimer's disease, as epidemiological studies have indicated a reduced risk of dementia. The results are expected in 2025.

Increasingly seen are anecdotal reports about the drugs leading to a reduction in cravings for other addictions, such as



shopping and gambling, alcohol, and smoking. An initial study is currently underway for use in smokers to quit smoking[41] and off-label prescriptions for various addictive behaviours have already been made. In animal studies, reduced alcohol and cocaine consumption was demonstrated for semaglutide;[42] for alcohol this was also confirmed for GLP-1 analogues in clinical studies with humans.[43,44]

What must be taken into account in risk assessment?

In risk assessment, positive factors are a longer duration of treatment (>6 months), a stable weight after a long use, few subjective side-effects (if known), physical activity, and a well-planned diet. Previous treatment interruptions, on the other hand, should be viewed negatively.

It is important to determine whether the prescription is appropriate for the indication (type 2 diabetes or obesity BMI ≥30 kg/m2, or a BMI > 27 kg/m2 with comorbidity), or whether the drugs were used off-label for people who are only slightly overweight or even have normal weight. For the latter, no study data are available, particularly on safety and benefit/risk assessment. Psychological problems may also need to be clarified.

Over-the-counter sales are available in some markets, such as the United Arab Emirates or Mexico, and in many countries the black market takes advantage of the high demand. Therefore, it can be quite difficult to determine whether someone is taking semaglutide, or even misusing it, as lifestyle drug. These cases are currently considered critical until study results are available – similar to semaglutide off-label prescriptions as anti-addiction medication for e. g. alcohol misuse and smoking.

In the case of normal to slightly overweight applicants, it must therefore be clarified whether they fulfilled the indication criteria at the start of treatment, have successfully lost weight, and now require the medication for maintenance.

As no long-term data are available on the drop-out rate, a loading may currently be applied to take into account the increased risk of weight regain. It should reflect the person's initial weight, the duration of treatment and any known interruptions in treatment.

Semaglutide is just the beginning

Novo Nordisk, the manufacturer of semaglutide, has become Europe's most valuable company, worth $567 billon.[45] Of course, other companies want to join this promising business, and more GLP-1 analogues are flooding the market.

Further developments such as tirzepatide (Zepbound), a di-agonist, mimic not only GLP-1, but gastric inhibitory polypeptide (GIP), an additional incretin, too. With an average weight loss of 24.5% for people with a BMI > 35 kg/m2 (SURMOUNT-1 study)[46] it achieves a similar weight loss success to bariatric surgery, which ideally results in 20 to 30% total weight loss. Zepbound was approved in the U. S. in November 2023 and the process is currently underway for Europe.

The triple agonist retatrudide, also known as "triple G", goes one step further and activates GLP-1, GIP and glucagon receptors. The phase 2 study shows a promising average weight reduction of 24.2% compared to 2.1% in the placebo group.[47]

As alternative to injections, semaglutide can be administered orally. Semaglutide is already approved as an oral antidiabetic agent under the name Rybelsus, but not yet for weight loss. However, the OASIS 1 approval study showed a comparable average weight reduction to Wegovy, with 15% (or 17.4% if discontinuations are not taken into account) compared to 2.4% in the placebo group.[48] An approval extension for this indication

can be expected. For oral administration, however, the active ingredient must be dosed significantly higher (up to 50 mg daily compared to 2.4 mg per week for Wegovy).

Overall, GLP-1 analogues represent a promising alternative to bariatric surgery, and we will encounter them more and more frequently in everyday risk assessment.

About the author

Dr. Katharina Dorn *is a biologist in the field of genetics and neurobiology. Since 2019, she has been working as an Underwriter in the Gen Re L/H department ELM Claims Underwriting Biometrical Evaluation Services, Cologne. She is responsible for underwriting support for the German and International markets.*

Tel. +49 221 9738 185
katharina.dorn@genre.com

Endnotes

1 World Health Organization. (2024). Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 22 March 2024)

2 World Obesity Federation. (n. d.). Prevalence of obesity. https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity (accessed 22 March 2024)

3 NCD Risk Factor Collaboration, Phelps, N. H., Singleton, R. K., Zhou, B., et al. (2024). Worldwide trends in underweight and obesity from 1990 to 2022: A pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *The Lancet*, 403, 10431. https://www.thelancet.com/journals/lancet/article/PIIS0 140-6736(23)02750-2/fulltext (accessed 22 March 2024)

4 World Obesity Federation. (2023). World Obesity Atlas 2023. https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2023 (accessed 22 March 2024)

5 Stierman, B., Atful, J., Carroll, M. D., et al. (2021) National Health and Nutrition Examination Survey 2017 –March 2020 Prepandemic Data Files—Development of Files and Prevalence Estimates for Selected Health Outcomes. National Health Statistics Reports Number 158. https://www.cdc.gov/nchs/data/nhsr/nhsr158-508.pdf (accessed 22 March 2024)

6 Prospective Studies Collaboration, Whitlock, G., Lewington, S., et al. (2009). Body-mass index and cause-specific mortality in 900,000 adults: Collaborative analyses of 57 prospective studies. *The Lancet*, 373 (9669), 1083-1096

7 Ibid at Note 5

8 U. S. Food & Drug Administration. (2020). FDA approves weight management drug for patients aged 12 and older. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-weight-management-drug-patients-aged-12-and-older (accessed 22 March 2024)

9 Hinnen D. (2017). Glucagon-like peptide 1 receptor agonists for type 2 diabetes. *Diabetes Spectrum: A Publication of the American Diabetes Association*, 30 (3), 202-210

10 Blundell, J., Finlayson, G., Axelsen, M., et al. (2017). Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. *Diabetes, Obesity & Metabolism*, 19 (9), 1242-1251

11 Garvey, W. T., Batterham, R. L., Bhatta, M., et al. (2022). Two-year effects of semaglutide in adults with overweight or obesity: The STEP 5 trial. *Nature Medicine*, 28 (10), 2083-2091

12 Rubino D. M., Greenway F. L., Khalid U. et al. (2022). STEP 8 Investigators. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*, Jan 11 ;327 (2):138-150

13 Lincoff, A. M., Brown-Frandsen, K., Colhoun, H. M., et al. (2023). Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med.*, 389 (24), 2221-2232

14 U. S. Food & Drug Administration. (2024). FDA approves first treatment to reduce risk of serious heart problems specifically in adults with obesity or overweight. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or (accessed 22 March 2024)

15 Kosiborod, M. N., Abildstrøm, S. Z., Borlaug, B. A., et al. (2023). Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 389 (12), 1069-1084

16 Marso S. P., Bain S. C., Consoli, A., et al. (2016). SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.*, 375 (19):1834-1844

17 Popoviciu, M. S., Păduraru, L., Yahya, G., et al. (2023). Emerging role of GLP-1 agonists in obesity: A comprehensive review of randomised controlled trials. *International Journal of Molecular Sciences*, 24 (13), 10449

18 Gragnano, F., De Sio, V., & Calabrò, P. (2024). FLOW trial stopped early due to evidence of renal protection with semaglutide. *European Heart Journal Cardiovascular Pharmacotherapy*, 10 (1), 7-9

19 Yu, M., Wang, R., Pei, L., et al. (2023). The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: A meta-analysis of randomized controlled trials. *Diabetology & Metabolic Syndrome*, 15 (1), 164

20 Shu, Y., He, X., Wu, P., et al. (2022). Gastrointestinal adverse events associated with semaglutide: A pharmacovigilance study based on FDA adverse event reporting system. *Frontiers in Public Health*, 10, 996179

21 Carroll, J. K., Herrick, B., Gipson, T., et al. (2007). Acute pancreatitis: Diagnosis, prognosis, and treatment. *American Family Physician*, 75 (10), 1513-1520

22 Bravo, F., Lenglinger, J., Borbely, Y., et al. (2023). Wenn der Magen "nicht mehr richtig schafft". *Schweiz. Gastroenterol*. 4, 64-77

23 Sodhi, M., Rezaeianzadeh, R., Kezouh, A., et al. (2023). Risk of gastrointestinal adverse events associated with glucagon-like peptide-1 receptor agonists for weight loss. *JAMA*, 330 (18), 1795-1797

24 Jung, H. K., Choung, R. S., Locke, G. R., 3 rd, et al. (2009). The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*, 136 (4), 1225-1233

25 Ye, Y., Yin, Y., Huh, S. Y., et al. (2022). Epidemiology, etiology, and treatment of gastroparesis: Real-world evidence from a large US national claims database. *Gastroenterology*, 162 (1), 109-121.e5

26 European Medicines Agency. (2023). Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 23-26 October 2023. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-23-26-october-2023 (accessed 22 March 2024)

27 Wilding, J. P. H., Batterham, R. L., Davies, M., et al. (2022). Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes, Obesity & Metabolism*, 24 (8), 1553-1564

28 Weiss, T., Yang, L., Carr, R. D., et al. (2022) Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. *BMJ Open Diabetes Research and Care*, 10 :e0025177

29 Ibid at Note 28

30 Palanca, A., Ampudia-Blasco, F. J., Calderón, J. M., et al. (2023). Real-world evaluation of GLP-1 receptor agonist therapy persistence, adherence and therapeutic inertia among obese adults with type 2 diabetes. *Diabetes Therapy: Research, Treatment and Education of Diabetes and Related Disorders*, 14 (4), 723-736

31 Malik, M. E., Falkentoft, A. C., Jensen, J., et al. (2023). Discontinuation and reinitiation of SGLT-2 inhibitors and GLP-1 R agonists in patients with type 2 diabetes: A nationwide study from 2013 to 2021. *The Lancet Regional Health Europe*, 29, 100617

32 Sikirica, M. V., Martin, A. A., Wood, R., et al. (2017). Reasons for discontinuation of GLP1 receptor agonists: data from a real-world cross-sectional survey of physicians and their patients with type 2 diabetes. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 10, 403-412

33 Gong, Q., Zhang, P., Wang, J., et al. (2019). Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *The Lancet Diabetes & Endocrinology*, 7 (6), 452-461

34 Levine, J. A., Eberhardt, N. L., & Jensen, M. D. (1999). Role of nonexercise activity thermogenesis in resistance to fat gain in humans. *Science*, 283 (5399), 212-214

35 Bouchard, C., Tremblay, A., Després, J. P., et al. (1990). The response to long-term overfeeding in identical twins. *N Engl J Med.*, 322 (21), 1477-1482

36 Volkow, N. D., Wang, G. J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: Implications for obesity. *Trends in Cognitive Sciences*, 15 (1), 37-46

37 van Bloemendaal, L., IJzerman, R. G., Ten Kulve, J. S., et al. (2014). GLP-1 receptor activation modulates appetite- and reward-related brain areas in humans. *Diabetes*, 63 (12), 4186-4196

38 Polidori, D., Sanghvi, A., Seeley, R. J., et al. (2016). How strongly does appetite counter weight loss? Quantification of the feedback control of human energy intake. *Obesity (Silver Spring, Md.)*, 24 (11), 2289-2295

39 Sarwer, D. B. & Polonsky, H. M. (2016). The psychosocial burden of obesity. *Endocrinology and Metabolism Clinics of North America*, 45 (3), 677-688

40 Airfinity. (2023). Wegovy costs $1.3 m to prevent one heart attack, stroke, or cardiovascular death. https://www.airfinity.com/articles/wegovy-costs-usd1-1 m-to-prevent-one-heart-attack-stroke-or-cardiovascular (accessed 22 March 2024)

41 ClinicalTrials.gov. (n. d.). Effects of semaglutide on nicotine intake. https://classic.clinicaltrials.gov/ct2/show/NCT05530577 (accessed 22 March 2024)

42 Aranäs, C., Edvardsson, C. E., Shevchouk, O. T., et al. (2023). Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. *EBioMedicine*, 93, 104642

43 Quddos, F., Hubshman, Z., Tegge, A., et al. (2023). Semaglutide and tirzepatide reduce alcohol consumption in individuals with obesity. *Scientific Reports*, 13 (1), 20998

44 Klausen, M. K., Thomsen, M., Wortwein, G., et al. (2022). The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. *British Journal of Pharmacology*, 179 (4), 625-641

45 Companies ranked by Market Cap - CompaniesMarketCap.com (accessed 10 May 2024)

46 Jastreboff, A M., Aronne, L. J., Ahmad, N. N., et al. (2022). Tirzepatide once weekly for the treatment of obesity. *N Engl J Med.*, 387 (3), 205-216

47 Jastreboff, A. M., Kaplan, L. M., Frías, J. P., et al. (2023). Triple-hormone-receptor agonist retatrutide for obesity: a phase 2 trial. *N Engl J Med.*, 389 (6), 514-526

48 Knop, F. K., Aroda, V. R., do Vale, R. D., et al. (2023). Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): A randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, 402 (10403), 705-719

Publisher
General Reinsurance AG
Theodor-Heuss-Ring 11
50668 Cologne
Germany
Tel. +49 221 9738 0

Edited by
Mirko von Haxthausen (Managing Editor),
Andres Webersinke, Anke Siebers, Annika Schilling,
Carina Betz, Dr. Celia (Ying) Zhang, Dave Nicholas,
Donna Michele, Holger Schmarowski
Tel. +49 221 9738 156
mirko.vonhaxthausen@genre.com

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