Obesity is claimed to be a disease – the 'ambiguous' hype for a treatment

Medication for obesity, diabetes, and eventually for drug addiction based on 'omic' technology is problematic.

At the end of the last decade of the twentieth century, obesity was declared to be a disease (1, 2). Because of the severe health consequences, overnutrition and obesity are pressing problems not only for curative medicine but also for public health. Will a medication that might combat a very complex disease be a wide-ranging solution?

Weight reduction through rainbow pills and other remedies

The first attempt to use a combination of different pharmaceutical products to decrease weight goes back over 80 years. After it was detected that the drug amphetamine helps to reduce weight, it was combined with other drugs, directly or indirectly lower weight, such as diuretics, laxatives, thyroid hormones, digitalis, benzodiazepines, potassium, corticosteroids, and antidepressants. The various combinations of capsules and tablets were brightly colored and known as 'rainbow diet pills.' The numerous side effects of each of the remedies were hazardous and caused many deaths. They were finally banned by the US Food and Drug Administration (FDA) (3).

Another failure in the attempt to get a medication against obesity is the 'fen-pen' episode. The medicine was a combination of fenfluramine and phentermine. Fenfluramine initially acted against a rare neurological disease in children, while phentermine was claimed to reduce appetite and, by this, people's weight. Together with lifestyle modification, a satisfactory reduction in weight was achieved. However, the significant side effects were severe vavular heart diseases. In one study, out of 20 patients, six developed the disease. The manufacturer finally withdrew the remedy rather suddenly, which created a massive problem for about four million Americans, who no longer had the means to put their hope on reducing weight by taking the drug (4).

A variation of Shakespeare: To have it or not to have (the medicine) it is the question

Since August 2023, several editorials in the journal 'Science' have mentioned the treatment with a hormone agonist, previously used in the treatment of diabetes mellitus but also showing promising weight reduction effects, as mentioned previously in this blog (5). The promising therapy is the glucagon-like peptide 1 receptor (GLP-1) antagonist. The optimistic exclamation in Science titled 'Turning the tide on obesity' got a question mark (6). Despite the call for caution in Science in August, the journal selected the development of the GLP-1 antagonist as the breakthrough of the year 2023 (7). The title of the Editorial reading then, 'More questions than answers' (8), somehow contradicted the selection of the GLP-1 development as an exceptional development. An accompanying one-page overview about the 'outstanding' scientific achievement was written under the title 'Obesity meets its match. Blockbuster weight loss drugs show promise for a wider range of health benefits' (7).

Why is this clocking? Excitement with the warning not to be too euphemistic. The short overview concluded with the sibylline hint that obesity…' as a chronic illness with roots in

biology'…is not…'a simple failure of willpower. And that may have as much impact as any drug' (7). One wonders whether interfering with the expression of genes within the central nervous system (CNS) is just a political statement in the discussion of how to perceive obesity, one of the keystones of non-communicable diseases. Or finally, is Science willing, which up to now doesn't really question the harmful consequences of genetically engineered vaccines during the COVID-19 campaigns, to be more careful this time (9)?

Vaccination cannot be compared to medication. The first involves a healthy population, while the medicinal invention is given to the diseased. Some compare the proportion of obesity in the population with an epidemic. Millions of individuals might be given medical treatment, and side effects must be minimal to avoid a disaster.

The function of the GLP-1 agonist in the energy balance

The control of the energy balance depends on factors ruling eating behavior. Environmental factors include food attraction, social and circumstantial influences, mental stress, and the expression of genes (10). What has now been considered a future weapon against a major public health problem started with detecting a complex hormonal function in controlling the energy balance through the central nervous system.

After food ingestion, glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) are secreted predominantly from cells in the small intestine and the colon. Through 'proglucagon,' GLP-1 and GLP-2 act complementarily and divergently with glucagon. They increase glucose-induced insulin secretion and have a glucose-lowering effect. GLP-1 is involved in the control of gastrointestinal motility and protects cardio- and neurological organs. GLP-2 effects are less well known but seem to influence chronic intestinal disorders positively (11).

Pleiotropic effects in genetics

Genes possess so-called 'pleiotropic' effects in that some alleles of the gene work in one way but other alleles in the opposite way. This also applies to GLP-1 and its analogs on cell signaling (12). It was proved by injecting GLP-1 receptor agonists into rats to control diabetes and reduce weight. Also, the neurons responsible for the effects could be identified (13). The therapeutic impact on the brain areas responsible for responding to hunger and satiety is the feeling of being full, which also decreases the wish to eat more. This phenomenon is called 'food noise.' The purpose of using GLP-1 analogs in treating diabetes mellitus type (T2DM) is to reduce energy intake.

GLP-1 agonist drugs

At the beginning of the decennium, 'exenatide' was the first drug using GPL-1 agonist, not from humans but from a lizard (7). It was not a first-line therapy but combined with the recommendation to be on a diet, exercise, and take metformin (14). The human version of the GLP-1 medication for T2DM is 'liraglutide' (Victoza) on the market since 2010 and needs to be subcutaneously injected (15). In 2014, the FDA also recommended the drug for weight loss with the name Saxenda (7). A drug marketed more recently by the Lilly company combined GLP-1

with GIP (glucose-dependent insulinotropic) tirzepatide as Zepbound, recommended for obesity and overweight reduction (16).

The Danish drug company Novo Nordisk with ‘semaglutide’ developed an LPG-1 version with the improvement of only one injection per week instead of once or twice daily, such as for liraglutide. The treatment is being marketed for T2DM as ‘Ozempic.’ The response of the pharmaceutical market increased the value of the company's shares tremendously to more than the gross domestic product of Denmark when it was allowed to market semaglutide as ‘Wegovy’ for reducing obesity (7). Results of two publications in the New England Journal of Medicine in 2021 and 2023, supported by Novo Nordisk, enhanced the use of 2.4 mg semaglutide applied once per week by subcutaneous injection for weight reduction and paved the way for the inroad into the treatment of obesity and overweight.

Two randomized, double-blind studies published in the years 2021 and 2023

The study published in 2021 included 1.961 adults with a BMI of 30 or greater, randomly assigned 2:1 for treatment with either the drug or a placebo for 68 weeks. Lifestyle intervention was provided for both groups. In the mean, the experimental group lost 14.9% weight against 2.4% for the placebo group. Of those receiving the drug, 86.4% lost 5% of their weight, compared to 31.5% in the placebo group. A weight loss of 15% or more was achieved by 612 persons under treatment versus 28 individuals with a placebo (17).

The second study, in 2023, tested obese participants with preexisting cardiovascular disease and a BMI of 27 and higher within the age of 45 years or higher. Of the about seventeen thousand patients enrolled, none had diabetes. In the multicenter, double-blind, randomized trial, with an assignment ratio of 1:1, 8.803 participants received the drug, and 8.801 the placebo. The drug was given for 34.2 (±13.7) months with a follow-up of 39.8 (±9.4) months. Of the patients under the drug, 569 (6.4%) either died from cardiovascular causes or survived a myocardial infarction or stroke. From the placebo group, 701 patients met the unfortunate endpoint of the trial. The difference between the two groups tested by the hazard ratio was highly significant (18).

Study dropouts, side effects, and other shortcomings

The most frequent side effects for the semaglutide group of the overweight study were mild to moderate nausea and diarrhea. However, more participants in the group receiving the drug dropped out of the study because of gastrointestinal events compared to the placebo group (59 (4.5%) vs. 5(0.8%) (17). Similarly, the dropouts because of ‘adverse events’ in the cardiovascular study were with 1461 (16.6%) patients, significantly higher than for the placebo group with 718 (8.2%) patients (18).

The rather high proportion of participants who dropped out of the two studies and the side effects of treatment with GLP-1 agonists were not why Science cautioned to be too optimistic for the ready success of GLP-1 agonist medications. Of major concern for the Editorials were the necessity of injections and the fact that treatment has to be continued lifelong because the patients' weight will be regained after ceasing the therapy. Still, the continuous subcutaneous application is highly expensive. The question will be who and how long a patient can pay for the

injections and whether and how long health insurance will cover the costs (6, 8). Individuals under treatment might be concerned not only with the price of the treatment but also with the possible side effects they could experience.

As mentioned above, nausea, vomiting, diarrhea, and constipation are less severe, but serious diseases may hit the unlucky ones. In investigating adverse gastrointestinal events, a database in the USA covering 16 million patients between 2006 and 2020 was used. Information was obtained from 4144 liraglutide and 613 semaglutide users. For comparison reasons, 654 clients under Contrave (bupropion-naltrexone), not a GPL-1 drug but approved for weight management, were included in the study (19). Increased risks for the two GLP-1 agonists were observed for pancreatitis (adjusted Hazard Ratio (HR) 9.09), bowel obstruction (ileus) (HR 4.22), and gastroparesis (similar to constipation) (HR 3.67). The 95% confidence interval for all three side effects observed for the two GPL-1 agonist treatments compared to Contrave was highly significant. The 'absolute' risk, however, is rather low. Pancreatitis per 1000 person-years for semaglutide and liraglutide, with 4.6 and 7.6, was low, as well with liraglutide with 8.1 for ileus, and for the two GLP-1 drugs with 9.1 and 7.3 for gastroparesis. There were no significant differences in the side effects for biliary disease between GPL-1 agonist treatments and Contrave. Still, all three weight reduction schemes had relatively high events per 1000 person-years, with 11.7, 18.6, and 12.6. Liraglutide, with 162, had the highest total number of cases throughout the observation, compared to 5 cases for semaglutide and 16 for Contrave (20).

Reduce weight, but you might wish to kill yourself

The comparison of the GPL-1 agonists with Contrave allowed the authors to assess side-effect risks against another drug with a different composition and application. Still, all three were used for weight reduction. Contrave is a combination of naltrexone and bupropion. The first one is an opioid antagonist, and the second one is an antidepressant. The combination of both aims to help lose weight (19). An impressive number of temporary and severe side effects are recorded (21). The drug also has a Box Warning because of the risk of suicidal thoughts and behavior. The formerly known Black Box Warning for the FAD is the highest safety-related notice (22). In 2020, the FDA focused on liraglutide in warning about suicidal thoughts in adolescents, and recently, the European Medicines Agency (EMA) was 'probing a possible link' …of the two GLP-1 agonist medications and …' suicidal ideas' (23).

GLP-1 agonists also might work against drug addiction

The wide range of more or less severe adverse treatment effects, including the danger of committing suicide, should not come as a surprise. The GLP-1 agonists are involved in the genetic regulation of food intake, metabolism, and energy balance, influence the parasympathetic nervous system, and are active in the gastrointestinal tract as well as the brain, interfering with the 'normal' biological function (24). Presently, GLP-1 agonists are even tested for treating Alzheimer's and Parkinson's diseases (25). Investigation with GLP-1 agonists also explored the reduction of the so-called 'rewarding' system among others for cocaine and heroin (26, 27). Not unexpectedly, the result of a small clinical trial with Saxenda (liraglutide) reducing craving in opiate addiction in humans was widely spread in the media recently (28).

It doesn't need an expert in psychology to assume that suicide is thought to be a way out of a deep depression under treatment with GLP-1 agonists, which block the 'rewarding' system for a reliving alcoholic drink or some opiates. However, the FDA sees no connection and advises patients not to stop taking GLP-1 Ras, arguing that 'preliminary evaluation does not suggest a causal link' (29). One wonders what might happen in the future when the GPL-1 agonist injection starts to become a widespread medication for mentally unstable groups, such as those with opiate drug addiction. The risk for suicidal thoughts in opiate drug users might increase considerably compared with the mentally much more stable groups of patients from T2DM or obesity. Before drug-addicted adolescents are exposed to GPL-1 agonist treatment, a much more in-depth investigation into suicide danger should be required.

Conclusion

To dispute discrimination against those overnourished and obese, as pointed out by the Editorials of the Science journal, is very much required since it is utterly harmful and contra-productive. However, whenever the pharmaceutic industry comes up with a product based on the 'omic' technologies (30), the danger of 'opening a can of worms' is imminent. The mRNA vaccines during COVID-19 are a telling example of a worldwide calamity (9, 31).

Economic perspectives will encourage the industry to make medications against obesity for many countries as feasible as soon as possible. To elevate the GLP-1 agonist to be an outstanding achievement of science in the year 2023 (2566) is questionable. Obesity, as well as drug addiction, are pressing public health problems, which might increase the pressure to use the medication on a large scale once it is feasible. Unforeseen disturbing interactions with other CNS areas linked to motivation, eating habits, and emotional reactions cannot be excluded (32). Obesity treatment in primary care still has to rely on lifestyle intervention, and in case obesity is seriously threatening the health and life of patients, surgical intervention might be necessary. Proved to be safe, feasible, and available, adjunctive therapies for lifestyle intervention should be considered with all precautions (33).

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