EDITORIAL

Turning the tide on obesity?

Genetics, ultraprocessed foods, portion distortion, sweetened beverages, screen time, food addiction, intestinal microbiota, diet culture, weight stigma, food insecurity—all have been implicated in the "obesity epidemic." More than a billion people worldwide have obesity, and many more are overweight. With the emergence of new, highly effective weight-loss drugs, might the "fat decades" become a closed chapter in the history of public health?

Historically misattributed to a lack of willpower and the target of quackery, obesity was gradually reconceptualized by medicine as a disease, igniting the search for effective treatments. Until now, medicine has had little to offer and in fact has done harm. From dinitrophenol (cataracts and fatal hyperthermia) to fenfluramine-phentermine (valvular heart disease) to orlistat (fecal leakage), promising weight-loss medications were withdrawn or avoided because of adverse effects. Bariatric surgery became routine but is neither benign nor universally effective. Weight cycling taxed bodies and minds, with emergent eating disorders attributed to repeated episodes of caloric restriction and appetite rebound. Physicians implored patients to lose weight but offered few effective tools.

Meanwhile, the prevalence of obesity steadily advanced—disproportionately affecting marginalized racial, ethnic, and socioeconomic communities. In 2023, the World Obesity Foundation predicted that the global economic impact of overweight and obesity will reach $4.32 trillion by 2035—if current trends continue.

Personal cost is also enormous. Unlike many chronic diseases, obesity is visible. People try everything to lose weight—diets, weight loss and exercise programs, psychotherapy, devices, and surgeries. Repeated failures are the norm and evoke futility and shame. Advocacy and activist organizations abound that help people make peace with their large size in a society that stigmatizes, discriminates, and assigns personal blame.

The medicalization of obesity has inspired extensive research explicating the complex network of biological systems ensuring that we eat to survive. Neuroscientists mapped hunger and satiety brain circuits of genetically defined neurons whose activation can promote or inhibit eating in animals. Unraveling the biology of glucagon-like peptide 1 (GLP-1) enabled the development of GLP-1 receptor agonists, initially to treat type 2 diabetes but now revolutionizing treatment for obesity. By stimulating insulin release to normalize blood glucose concentration, slow gastric emptying, and promote and prolong satiety signals from gut to brain, these drugs bring about impressive weight loss. Patients also report a decrease in "food noise"—the nagging internal dialogue about food that makes many feel powerless to resist the urge to eat. Appetite decreases, satiety increases, and kilos seemingly melt away. Will these blockbuster drugs turn the global obesity tide? And if so, for everyone, or just an advantaged few?

The "GLP1s" are expensive, and off-label use for weight loss will leave some with type 2 diabetes scrambling for their medications. Cost and supply constraints may further amplify health disparities. Those with insurance or resources to pay out of pocket will be the first to benefit. For others, these drugs will be out of reach.

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A boon for pharma but a challenge for patients is that the lost weight is regained when the medications are discontinued, functionally rendering them "forever" drugs. And it is unclear whether weight regain and re-emerging food noise will outweigh the inconvenience of a weekly injectable and unpleasant side effects. Development of alternative delivery options and medications that preserve lean muscle may ensure continued use.

Although standard safety profiles are favorable, what are the risks of taking these drugs for life? Does habituation occur? Will they dissuade people from regular exercise, which carries distinctive health benefits? What are the ramifications of repeated cycles of weight loss and regain due to medication discontinuation by choice, loss of insurance, or availability? And what is the abuse potential for extreme cosmetic purposes, for people with eating disorders, or for gaining advantage in sports where leanness matters?

Tackling these issues is essential to prevent unintended consequences brought on by the meteoric success of these drugs. We are entering an era in which effective obesity treatments exist for the first time. Prevention efforts that address all of the factors that contribute to obesity must be bolstered, not abandoned, to ensure that the next generation will not require lifelong medication to maintain metabolic health.

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