

GLP-1 Agonists, Willpower, and Weight Stigma: A Paradigm Shift for Obesity

Pablo Arrona-Cardoza¹

¹School of Human Nutrition, Faculty of Agricultural and Environmental Sciences, McGill University, Montreal, QC, Canada

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Since 1990, the worldwide prevalence of adult obesity has more than doubled [1]. In Canada, one in three adults has obesity [2]. This high prevalence, its negative health effects [3], and its economic burden [4] have made obesity one of the most challenging public health concerns yet. Populational-level interventions for obesity have been carried out with admirable efforts, such as Chile's food labeling and advertising law [5]. While these efforts should be continued, we must recognize that drastic changes to the food environment could prove too hard, as these must jump over political, economic, and cultural hurdles. In the clinical realm, lifestyle modification, although important, has a record of modest outcomes for weight loss. Of people who lose weight through diet and exercise, more than half regain some weight, and almost 10% gain more than they initially lost [6]. Conversely, bariatric surgery is usually observed to be more effective than lifestyle interventions [7]. However, the invasiveness of the procedure and the risk of complications might deter some from seeking this option. Then, there is pharmacotherapy, which for obesity has had a rocky history [8], until now.

Glucagon-like peptide-1 (GLP-1) is an incretin, a type of gut-derived hormone capable of stimulating pancreatic insulin secretion and acting as an anorexigenic hormone in the brain [9]. GLP-1 receptor agonists (GLP-1RA), while first developed for type 2 diabetes [10], have now demonstrated effectiveness in treating obesity. A weekly injection with 2.4mg of semaglutide (a form of GLP-1RA), resulted in a 14.9% reduction in body weight, compared to just a 2.4% reduction with a placebo [11]. Additional trials have shown improvements in cardiovascular health with semaglutide [12,13]. Now tirzepatide, a combination of GLP-1RA and glucose-dependent insulinotropic polypeptide, has shown similar positive results [14]. Currently, GLP-1RAs are approved in Canada for weight loss [15], with an estimated range of 900,000 to 1.4 million current users [16]. As GLP-

1RAs become widely prescribed, their social relevance will increase. This leads to the question: How does the public perceive these therapies? For example, 357 adults were asked how they perceived a fictional woman who lost weight either by diet and exercise or by using a GLP-1RA. Individuals believed that the woman who lost weight through medications took "the easy way out" and perceived her more negatively compared with the woman who did not use medications [17]. And while not the majority, a sizable portion of the population, has strong, often unfounded, opinions about the controllability of weight. According to a U.S. survey, 34% believe that willpower alone is enough to lose weight [18]. Thus, it can be assumed that these beliefs reinforce increasing issues of weight stigma and bias [19], potentially affecting individuals' pursuit and adherence to treatment for obesity.

This stigma often comes from a misunderstanding of the disease of obesity. Socially, and to an extent in the medical community, we equate obesity with fatness (excess adiposity). But fatness can be better understood as a consequence of obesity, rather than the disease itself [20]. Obesity is a neurobehavioral disease characterized by a "dysregulation" of the hypothalamic control of feeding and a "resetting" of the body weight set-point, which culminates in a chronic, sustained positive energy balance [21]. What are the symptoms of obesity? They mostly appear during attempts to lose weight: hyperphagia, preoccupation/obsession with food, excessive craving, and diminished satiation/satiety [22], challenging the notion that one can lose weight just by willing themselves to "eat less" [23]. Missing this key distinction can create erroneous ideas about anti-obesity medications, such as the idea that they are a "crutch" or a replacement for diet and exercise. In reality, GLP-1RAs are leveling the playing field. For example, GLP-1RAs can reduce "food noise", defined as persistent and intrusive food-related

thoughts [24]. These medications can therefore help create the necessary conditions so that individuals with obesity can readily engage in the lifestyle changes that drive weight loss and reduce the risk of further disease.

Undoubtedly, as with a lot of medications, side effects occur. Nausea, vomiting, and gastrointestinal issues are the most reported [25]. Muscle mass loss has been a side effect portrayed by the media [26]. Nonetheless, closer scrutiny of the data suggests otherwise. In the STEP 1 trial, participants in the semaglutide group lost 10.4 kg of fat and 6.9 kg of lean mass, proportionally less than the placebo group who lost 1.17 kg of fat, and 1.48 kg of lean mass [11]. Still, physicians should prescribe exercise, particularly strength training, due to its benefits, including minimizing muscle loss and maintaining long-term weight loss [27]. However, low exercise participation rates among the population [28] and physicians' reported lack of knowledge about exercise [29] highlight the need for medical school training on this topic. For instance, exercise education has been shown to increase physician and medical student confidence in addressing exercise with patients [30, 31]. Likewise, collaboration with dietitians and mental health experts is crucial, as multidisciplinary approaches to weight loss are preferable [32]. Lastly, the medical community must recognize and address weight stigma. Prejudice against a patient's weight can affect the quality of the patient's overall healthcare, particularly when dealing directly with obesity [33]. If the physician holds unsubstantiated ideas about this new wave of anti-obesity medications, or obesity in general, it can amplify existing bias.

GLP-1RAs indeed show promise in combatting the obesity epidemic. But medications like this must still navigate the same economic, political, and cultural barriers as any other intervention for obesity. Still, research will continue to resolve open questions about these drugs. It is within the healthcare professionals' power to keep educating themselves on how GLP-1RAs work, how to best integrate lifestyle changes, and minimize weight stigma. All this not only to improve the effectiveness of obesity treatment, but also to better the quality of life of individuals suffering from this disease.

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