VIEWPOINT

Obesity and Glucagon-Like Peptide-1 Receptor Agonists

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A new, yet familiar, debate in translational science has erupted. After many years of remarkable advances in basic science, novel therapeutic interventions have emerged, offering the promise of an effective treatment for obesity. Should the world embrace this novel pharmacological solution as the answer to the obesity pandemic? Or should the world be concerned that the medicalization of obesity will dull incentives for healthier lifestyles and allow market forces to perpetuate a profitable cycle of cause and cure?

The World Health Organization (WHO) believes this is a false dichotomy. Obesity (defined by the WHO as a chronic and relapsing disease) has now reached pandemic proportions with more than 1 billion people affected, and there are increasing cases in almost every country in the world.[1] The approval of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the treatment of obesity creates potential for a transformation of the whole health system that could halt and reverse the global obesity pandemic through prevention and effective integrated management.

The global burden of obesity constitutes a major public health challenge that also undermines social and economic development throughout the world, and has the effect of increasing inequalities between countries and within populations. Global costs associated with obesity are predicted to be US $3 trillion per year by 2030, and these costs for obesity could absorb up to 18% of national health expenditure in countries with prevalence rates of 30% for obesity. There were 5 million obesity-related deaths from noncommunicable diseases in 2019, representing 12% of all deaths from noncommunicable diseases worldwide.[2]

The seriousness of the crisis is now widely recognized. Yet there are many challenges that continue to hinder a successful national and global response. Perceptions and attitudes toward obesity, including the debate about whether obesity represents a risk factor or a disease, are widely divergent. Efforts to address the stigma associated with obesity have, in some cases, evolved into a narrative that obscures the importance of obesity-related morbidity and mortality. Compared with other noncommunicable diseases, there remains a lack of knowledge on the associated biological and genetic factors, and there are inconsistencies in the appreciation of the effect of obesity on other noncommunicable diseases and the overall burden of disease. There is limited evidence on long-term management interventions and their effectiveness among populations most at risk and in low-income settings in relation to issues such as access and adherence.

The knowledge gaps are compounded by wider system challenges of fragmentation of care, insufficient collaboration between sectors and settings, shortage of clinical guidelines and protocols, and level of competency and skill to manage obesity as a chronic and relapsing disease. These system challenges result in a lack of sustained investment in an approach that integrates obesity prevention and treatment health services that are affordable, accessible, and sustainable.

In addition to the system constraints, there is a lack of demand for obesity prevention and management health services from the people with the disease because of stigma, complex social and commercial determinants, and the lack of practical and accessible treatments. Efforts to slow the obesity pandemic have focused almost exclusively on policies that help embed healthy diets and regular physical activity as the most accessible, available, and affordable behaviors of daily life. Although there is good evidence on the effectiveness of such policies to prevent obesity, it is time to recognize that multisectoral efforts to influence behaviors around healthy diet and exercise have so far failed to treat obesity or turn the tide on the obesity pandemic.

In this context, the new class of GLP-1 RAs have the potential to be transformative. Randomized clinical trials have suggested that this new drug class may lead to reductions in body weight (ranging from 10%-25% compared with placebo) along with beneficial effects on a range of other conditions, including cardiovascular disease, hyperglycemia, kidney dysfunction, and others.[3,4] The US Food and Drug Administration granted regulatory approval[5] for semaglutide in 2021 for the treatment of obesity and for tirzepatide in 2023 based on the effects of these drugs on body weight and associated cardiometabolic risk factors assessed in a wide range of studies.

Health systems across the globe now may be able to offer a treatment response integrated with lifestyle changes that opens the possibility of an end to the obesity pandemic. However, medication in isolation will not be enough to address the obesity crisis. It is imperative to deliver a corresponding health system response that ensures universally available services to prevent, treat, and manage the disease in a way that is accessible, affordable, and sustainable. Current service delivery models that intervene only for individuals with severe obesity or when obesity-related comorbidities appear must be replaced with models that recognize obesity as a chronic disease that demands a social, public health, and clinical response.

A whole of society approach for the prevention and management of obesity, including multisectoral health promotion and disease prevention measures and amplified by food and urban environmental policies and actions, will be essential if the global disease burden is to be stemmed and reversed.

The WHO has concerns that without adequate health system preparedness, a siloed tertiary care medicalized approach dominated by GLP-1 RAs will herald a distorted response to obesity that is neither sufficiently comprehensive nor equitable. In the short-term, for example, even the basic conditions for an effective pharmacological response (properly indicated, equitably available at scale, affordable, and accessible) have not been met. Other concerns must also be addressed, including the rise of a counterfeit products market, the high cost of the current products, the production

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and supply challenges, and a range of issues that commonly face efforts to scale-up new pharmaceuticals.

The availability of GLP-1 RAs is already unlocking new demand for services among people with obesity. In turn, this demand is generating new interest in obesity from clinicians, governments, policymakers, program managers, and the pharmaceutical industry. These elements were previously lacking and hindered an effective global public health and clinical response to the obesity pandemic. With some of the conditions for success now in place, there is a new opportunity to welcome pharmacological treatment advances as an entry point for a sustainable transformation of health systems, unlocking capacity to turn the tide on the obesity pandemic by preventing, treating, and managing obesity as a chronic disease.

At the World Health Assembly in 2022, member states adopted the WHO Acceleration Plan to Stop Obesity,[6] which aimed to transform the prospects of success by adopting a systematic approach for policy implementation, including transformation of health systems. Thirty-three countries committed to be part of the plan and curb their national obesity prevalence by 5% by 2030 through accelerated implementation of a selection of proven interventions. The WHO is supporting these countries to integrate obesity management health services within existing health service delivery platforms and with a primary health care and life course approach. The aim is to enroll people living with obesity into a chronic care program that is characterized by a multimodal clinical algorithm with structured lifestyle interventions and medical and surgical therapy when needed.

To this end, the WHO is currently working to develop guidelines on the use of GLP-1 RAs in adults with obesity to provide clarity on the clinical indications, application, and programmatic considerations globally, including their use in low- and middle-income countries. The guidelines are being developed with an independent, expert, and diversified group that will maintain rigorous adherence to the systematic use of evidence as the basis for all policies (publication of the guidelines is anticipated in July 2025). The guidelines will include evidence-based recommendations for the use of GLP-1 RAs in the treatment of obesity in adults. The guidelines will outline when and how this class of antiobesity medications may be integrated as one component of a multimodal chronic care model that includes clinical and structured lifestyle interventions.

The WHO believes that the advent of GLP-1 RAs, and their efficacy in the treatment of obesity and comorbidities, constitutes a positive shift for the conditions and architecture needed to mount a global health systems response to obesity—a response that has previously proved impossible. However, in heralding the treatment breakthrough offered by GLP-1 RAs, the global community must be mindful that pharmacological intervention alone will be insufficient.

The critical question is not whether these pharmacological interventions are welcome or unwelcome, but whether GLP-1 RAs offer an opportunity for global health systems to embrace and deliver the transformation needed to offer access to treatment of obesity as a chronic disease in a way that promotes health equity by removing barriers to care across countries and for the populations within the countries.[7] We believe society is at a pivotal juncture and now has the tools to transform and reduce the health effects of obesity globally. We must seize the moment.

ARTICLE INFORMATION

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