Obesity Treatment – Is Pharmacotherapy the Answer?

More than 2 billion adults worldwide (39%) are overweight; of these adults, more than 650 million (13%) are obese, according to the World Health Organization. In the United States alone, recent studies suggest that more than 40% of adults are obese. Exercise, diet, and behavior modification remain the cornerstone of treatment. However, many affected patients cannot lose weight or maintain weight loss with that approach. Hence, medical and surgical options (e.g., bariatric surgery) have been developed to reduce and maintain weight loss. Among the patients who are considering their options, the long-term safety of any weight-loss regimen is critical to its widespread acceptance and adherence.

Clinical experience with the first generation of anti-obesity drugs was not encouraging, despite successful weight loss, because of side effects. In particular, agents such as dexfenfluramine and fenfluramine stimulated 5-hydroxytryptamine 2B (5-HT2B) serotonin receptors, which led to pulmonary hypertension and heart valve problems. Other medications such as orlistat, liraglutide, naltrexone-sustained release with bupropion-sustained release, and lorcaserin have provided additional options, but questions persist about their long-term safety.

In obesity, a weight loss of 5%–10% can significantly improve risk factors for obesity-related diseases and delay or prevent type 2 diabetes in persons at high risk. Behavioral treatments can result in a weight loss sufficient to improve health for many patients, but often, the weight is regained over time. For many people, reduction in weight is difficult to achieve; however, maintaining the weight loss is even harder. Hence, there is a need for adjunctive treatments that can assist patients with carrying out the changes in lifestyle needed to produce and sustain weight loss. Weight-loss medications are available and many medications are approved by the Food and Drug Administration for weight loss.

The history of weight-loss medications is checkered. When amphetamines were approved for the treatment of obesity in the 1960s, obesity drugs were labeled only for short-term use. In 1992, a series of seminal articles by Weintraub showed the feasibility of treating obesity with long-term forms of core therapy similar to treatments for other diseases. The usefulness of such an approach was apparent to those who had long noted that weight loss was rarely sustained after weight-loss drugs were withdrawn. The two drugs, used in combination were fenfluramine and phentermine, effectively known as Fen/Phen, had been on the market for years and were believed to be safe and effective. Not long afterward, dexfenfluramine, which had been in use in Europe for more than a decade, became the first drug approved for long-term treatment of obesity in the United States. The use of Fen/Phen and dexfenfluramine exploded despite nagging concerns about the adverse effect of pulmonary hypertension with approximately 14 million prescriptions written for either fenfluramine or dexfenfluramine from 1995 until the withdrawal of these drugs from the market in 1997.

Drugs used to treat obesity differ from medications for other chronic diseases in how they are used. Obesity is a visible and stigmatizing condition. Few people want to be obese, and obese persons often have tried numerous times and with a variety of methods to lose weight. Because of the social emphasis on thinness, weight loss is also frequently attempted by people whose weight is normal or only slightly above normal. Therefore, a drug that appears to be efficacious in reducing body weight will undoubtedly be used not only to reduce medical risk among those who are obese but also to improve appearance among those less likely to have a medical benefit from weight loss. Thus, as Bray has suggested, a careful assessment of safety of anti-obesity medications may be even more important than for drugs used to treat other conditions, in which the drugs are less liable to be misused. In addition, although weight loss in the obese persons is known to improve risk factors and might be anticipated to reduce cardiovascular morbidity and mortality, no study has yet demonstrated conclusively that any weight-loss medication treatment has such an effect. Research on this critical issue is ongoing. Whether those who lose weight with anti-obesity medications have health outcomes similar to those who lose weight through lifestyle changes alone also remains uncertain.

How health-care professionals are going to make decisions with regard to use of anti-obesity medications in clinical practice? Overweight and obese patients should be carefully evaluated to assess their medical risk as well as their readiness to attempt weight loss. Although nondrug treatments should be the primary intervention, for many patients, attempts to lose weight or maintain weight loss through diet and exercise alone will not be sufficient. For patients whose weight and risk factors put them at high risk for obesity-related disease, physicians and patients may choose to initiate adjunctive treatment with anti-obesity medications. Weight-independent effects on such risk factors may be considered when choosing the appropriate medication as well as adverse effects, patient’s preferences, and response to treatment. As Wadden made it clear, the efficacy of drug therapy is markedly improved with the concomitant use of behavioral treatment. This finding is consistent with the National Institute of Health guidelines, which recommend that weight-loss...
medications be used as a part of a comprehensive program that includes diet therapy and physical activity.

Improved therapeutic approaches are needed to promote and sustain weight loss safely and effectively in obese patients to treat and prevent many obesity-related conditions. Advances in our understanding of the complex systems regulating energy balance, the genetic determinants of obesity, and environmental factors that promote obesity should lead to not only the development of more effective and tolerated treatment options but also for primary prevention of obesity.

Aditya Kumar Rangbulla
Obesity Medicine Specialist, Ascension Medical Group, Appleton, WI, USA

Address for correspondence:
Dr. Aditya Kumar Rangbulla, Ascension Medical Group, 1501 S Madison Street, Appleton 54915, WI, USA.
E-mail: adityarangbulla@gmail.com

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