Obesity has traditionally been defined as a body mass index (BMI) of 30 kg/m² or more. However, BMI has limitations, and obesity is now defined by a number of factors, including waist circumference. The growing prevalence of obesity is a global health concern. In 2008, 10% of men and 14% of women aged 20+ were obese compared with 5% in men and 8% in women in 1980. Obesity rates in the US are among the highest in the world: in 2009–10, more than 37% of US adults and almost 17% of youth were obese. These trends have affected all ethnic groups, all regions of the country, and all socioeconomic groups, with the largest increases in obesity occurring among children. In recognition of its underlying vasculopathic physiology, and its association with significant morbidity and mortality, the nation’s largest physician group has recently categorized obesity as a disease itself rather than simply a risk factor for other metabolic diseases. The prevailing thought among many is that metabolic diseases are pathologic consequences of adiposity. This article will discuss the health and economic burdens of obesity as well as strategies for treating the condition, with a focus on a recently approved pharmacologic agent: phentermine/topiramate extended-release (PHEN/TPM ER).
Obesity and Weight Management

Figure 1: Historic and Recent Trends in Adult Obesity Prevalence in Adults in the US

A = US men; B = US women. Black dots (bars = 95% confidence interval [CI]) show recorded prevalence from national surveys. Each dot = one data point. Historic trend used all data points; recent trend used data points after 2000. Source: Wang, 2011.30

Obesity and Weight Management

In addition to life-threatening adverse health consequences, obesity also increases the likelihood of disabling conditions such as osteoarthritis,16,17 benign prostate hypertrophy,18 infertility,19 asthma,20,21 and obstructive sleep apnea; approximately 70% of patients with the latter condition are obese.22 Obesity has also been implicated in anatomical changes that predispose patients to upper airway obstruction and reduced neuromuscular control of the air passages during sleep.22,23 Obesity accelerates the initial onset and progression of physical disability in older adults.24 Maternal obesity is associated with an increased risk for congenital anomalies.25 The early onset of obesity compounds the health burden. Since obesity is prevalent at a much younger age than in previous generations, recent projections suggest a growth in the proportion of the population living with chronic disabilities and a potential threat to the continued increase in life expectancy achieved by medical and public health advances during the past century.26

The chronic and acute health consequences of obesity present a considerable burden to society, not only by impairing health-related quality of life,24 but also because of the economic impact, a result of increased healthcare costs, and lost productivity.29

Compared with normal-weight individuals, obese patients incur 46% increased inpatient costs, 27% more physician visits and outpatient costs, and 80% more spending on prescription drugs.29

Projections suggest that there will be 65 million more obese adults in the US by 2030 (see Figure 1), resulting in an additional 6–8.5 million cases of diabetes, 5.7–7.3 million cases of heart disease and stroke, 492,000–669,000 additional cases of cancer, and 26–55 million lost quality-adjusted life years for the US and UK combined. This is associated with an increased medical expenditure of $48–66 billion/year in the US.26 Another model suggests that by 2030, 42% of the population will be obese, with the prevalence of severe obesity predicted to be 11%. This report states that, if obesity were to remain at 2010 levels, the combined savings in medical expenditure over the next 2 decades would be $549.5 billion.27

There is clearly a need for clinical intervention to tackle the obesity epidemic. Modest weight loss (2.6–4.9 kg) is associated with improvements in weight-related comorbidities29,30 and greater benefits are seen with increased weight loss.29 A recent report suggested that healthcare systems could make substantial cost savings through anti-obesity medications that promote weight loss, and consequently reduce the progression to type 2 diabetes, and improve blood pressure (BP). According to this study, a permanent weight loss of 10 to 15% among overweight or obese adults aged 65 years or older would yield $9,445 to $18,905 in gross per capita savings throughout their lifetime, and $8,070 to $13,474 over 10 years.30

Treatment of Obesity

The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) recommends that the initial goal of weight-loss therapy in overweight and obese individuals should be to reduce bodyweight (BW) by 10% from baseline.31 The mainstay of obesity treatment is lifestyle modification, which consists of reductions in caloric intake (by 500–1,000 calories per day), increases in physical activity, and changes in health behaviors. However, only 15–20% of patients successfully achieve and maintain a 5% weight loss at 1 year.32,33 Given the frustrations doctors and patients face in achieving results by use of diet and exercise, pharmacologic therapies, or bariatric surgery are also viable options for patients meeting eligibility criteria.34 The indication for bariatric surgery is restricted to those with severe obesity (BMI ≥35 kg/m²) owing to the risks associated with invasive procedures,34,35 although laparoscopic gastric banding may be considered for patients with BMI ≥30 kg/m² with one or more adverse health consequences due to excessive body fat.36

Recommendations by the American College of Physicians and the American Society of Bariatric Physicians suggest that pharmacotherapy should form part of an overall strategy for managing overweight and obesity, which should include appropriate recommendations for diet, physical activity, and behavior therapy.3,37 Despite these recommendations, until recently, few pharmacologic therapeutic options existed. In recent years, many drugs that have been effective weight loss medications have had to be withdrawn from the market as a result of unacceptable side effects.38–40 Prior to 2012, orlistat (Alli®, GlaxoSmithKline; Xenical® , Roche) was the only weight loss drug approved by the US Food and Drug Administration (FDA) for long-term use, following the 2010 market withdrawal of sibutramine.41,42 Orlistat is associated with moderate weight loss43 but gastrointestinal side effects in 15–30% of patients including intestinal cramps, flatus, fecal incontinence, oily spotting, and flatus with discharge limit its use.40

In 2012, the FDA approved two new drugs for chronic weight management in adults with a BMI ≥30 kg/m² (obese) or ≥27 kg/m² (overweight) who have one or more weight-related comorbidities, to be used in conjunction with a reduced-calorie diet and increased physical activity.43–45 Lorcaserin (Belviq®, Arena Pharmaceuticals) is a selective agonist of the serotonin (5-hydroxytryptamine) 2C (5-HT2c) receptor.46,47 PHEN/TPM ER (Qsymia®, Vivus) is a fixed-dose combination of phentermine (an anorectic agent), and the antiepileptic drug topiramate.48,49

Both phentermine and topiramate are approved by the FDA as monotherapy, with different indications. Phentermine is a sympathomimetic amine and was approved (at a dose of up to 37.5 mg/day) as a short-term obesity treatment by the FDA in 1959.49 Although its exact mechanism of action is unknown, its effect on weight management is likely mediated by the release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption; other metabolic effects may also be involved.49 Topiramate, a fructose monosaccharide with sulfamate...
The Role of Phentermine/Topiramate Extended-release in the Treatment of Obesity

**Table 1: Summary of Clinical Trial Data Investigating the Efficacy and Safety of Phentermine/Topiramate Extended-release**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial Design</th>
<th>Effect on Weight Loss</th>
<th>Effect on Comorbidities</th>
<th>Adverse Events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQUIP</td>
<td>Phase III, 56 weeks, n=1,167, BMI 27–45 kg/m², with ≥2 WRC</td>
<td>At 56 weeks, patients in the placebo, PHEN/TPM ER 3.75/23, and 15/92 groups lost 1.6 %, 5.1 %, and 10.9 % of baseline BW, respectively (p&lt;0.0001), 10 % weight loss achieved by 7.4 % of placebo, 18.8 % of 3.75/23, and 47.2 % of 15/92 group (p&lt;0.0001)</td>
<td>The PHEN/TPM ER 15/92 group had significantly greater changes, relative to placebo, in systolic BP, diastolic BP, glucose, triglycerides, total cholesterol/HDL ratio, total cholesterol, LDL, and HDL. The 3.75/23 group had numerically, but not always statistically significant changes compared with placebo, in all variables</td>
<td>Drug-related SAEs occurred in 0.4 % with placebo, 0.4 % with 3.75/23, and 0.2 % with 15/92</td>
<td>64</td>
</tr>
<tr>
<td>CONQUER</td>
<td>Phase III, 56 weeks, n=2,487, BMI ≥35 kg/m²</td>
<td>At 56 weeks, change in BW was −12.2 %, p&lt;0.0001, and −9.8 % in the placebo, 7.5/46 and 15/92 groups, respectively (p&lt;0.0001). 10 % weight loss was achieved by 7.4 %, 37.3 %, and 47.6 % of the placebo, 7.5/46, and 15/92 groups, respectively; p&lt;0.0001</td>
<td>Change in systolic BP −9.1 mm Hg, −6.9 mm Hg, and −4.9 mm Hg in 15/92, 7.5/46, and placebo groups, respectively, in population with hypertension. RR of progression to type 2 diabetes among patients without type 2 diabetes at baseline was reduced by 50 % in the 15/92 patient group (RR versus placebo, 0.47, 95 % CI 0.25–0.88)</td>
<td>Rates of SAEs were similar across treatment groups: 4 % with placebo, 3 % with 7.5/46, and 6 % with 15/92</td>
<td>66</td>
</tr>
<tr>
<td>SEQUEL</td>
<td>Phase III, 52 weeks, n=678, extension of CONQUER</td>
<td>Mean % changes in BW from baseline were −1.8 %, −9.3 %, and −10.5 % for placebo, 7.5/46, and 15/92, respectively (p&lt;0.001); 10 % BW loss was achieved by &lt;50 % of PHEN/TPM ER, and &lt;12 % of the placebo group</td>
<td>Systolic and diastolic BP decreased by 3–5 mm Hg; reductions in triglycerides and increases in HDL; reduction in fasting glucose and insulin concentration, decreased progression to diabetes (annualized incidence rates 3.7 %, 1.7 %, and 0.9 % in placebo, 7.5/46, and 15/92 groups, respectively)</td>
<td>AEs lower in second year than first; SAEs in weeks 0–108: 6.2 % with placebo, 5.9 % with 7.5/46, and 8.1 % with 15/92. During weeks 56–108: 4.0 % with placebo, 2.6 % with 7.5/46, and 4.1 % with 15/92</td>
<td>67</td>
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</table>

**Clinical Studies Evaluating the Safety and Efficacy of Phentermine/Topiramate Extended-release**

Available evidence supports PHEN/TPM ER as an efficacious, well-tolerated anti-obesity agent with significant impact on associated weight-related comorbidities. To date, clinical studies investigating the efficacy and safety of PHEN/TPM ER are summarized in Table 1. All were performed in conjunction with a lifestyle intervention based on caloric reduction, lifestyle counseling, and encouragement of physical activity, and all comorbidities were actively managed, including modification in medications if clinically indicated.

PHEN/TPM ER is available in four dosage strengths. The top dose contains phentermine 15 mg and topiramate ER 92 mg, both lower than the approved maximum doses for previously approved indications (40 % of the maximum approved dose of phentermine and 23 % of the maximum approved dose of topiramate). The other dosage strengths are 3.75 mg/23 mg, 7.5 mg/46 mg, and 11.25 mg/69 mg, but the latter dose was not studied in clinical trials. The ER formulation was developed to allow once daily dosing, a lower peak concentration (Cmax) and a protracted peak time (Tmax). The combination has demonstrated greater efficacy in weight loss than the maximal response achieved with either individual agent alone at equivalent doses, a result of each component targeting multiple mechanisms that influence energy balance.

PHEN/TPM ER is contraindicated in pregnant women; in patients with glaucoma; in patients with hyperthyroidism; in those receiving treatment or within 14 days after treatment with monoamine oxidase inhibitors; and in patients with hypersensitivity to sympathomimetic amines, topiramate, or any of the inactive ingredients in PHEN/TPM ER.

Patients with severe obesity (BMI ≥35 kg/m²) were randomized into three arms: placebo (n=514), PHEN/TPM ER 3.75/23 mg (n=241), and PHEN/TPM ER 15/92 mg (n=512) in the 56-week randomized placebo-controlled EQUIP trial (Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial). (NB PHEN/TPM ER was originally termed controlled-release rather than extended-release.) Primary end points of the study were percentage weight lost and proportions of patients achieving 5 % weight loss. Secondary end points included systolic and diastolic BP fasting glucose, and blood lipid parameters. Of the patients who completed the study (59.9 %), those in the 15/92 mg group lost significantly more weight than patients in the 3.75/23 mg group (p<0.0001), and patients in both PHEN/TPM ER groups lost significantly more weight than patients receiving placebo (p<0.0001 for all comparisons). In the prespecified intention-to-treat (ITT) with last observation carried forward (LOCF) analysis, according to FDA standards, patients receiving 15/92 mg PHEN/TPM ER, 3.75/23 mg, and placebo lost 10.9 %, 5.1 %, and 1.6 % of BW, respectively. Patients who completed the course of PHEN/TPM ER lost 14.4 %, 6.7 % and 2.1 % of BW in the 15/92 mg, 3.75/23 mg, and placebo groups. In the ITT-
Figure 2: SEQUEL Clinical Trial – Percentages (and 95 % CIs) of Subjects Achieving ≥5 %, ≥10 %, ≥15 %, or ≥20 % Weight Loss with Phentermine/Topiramate from Baseline to Week 108 (Intention-to-treat Population)

<table>
<thead>
<tr>
<th>Weight Loss (%)</th>
<th>Placebo (n=227)</th>
<th>PHEN/TPM ER 7.5/46 (n=153)</th>
<th>PHEN/TPM ER 15/92 (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5</td>
<td>11.5</td>
<td>31.0</td>
<td>75.2*</td>
</tr>
<tr>
<td>≥10</td>
<td>22.2</td>
<td>24.2*</td>
<td>79.3*</td>
</tr>
<tr>
<td>≥15</td>
<td>6.6</td>
<td>31.9*</td>
<td>53.9*</td>
</tr>
<tr>
<td>≥20</td>
<td>7.2</td>
<td>15.3*</td>
<td>31.9*</td>
</tr>
</tbody>
</table>

Standardized lifestyle intervention was used across all treatment groups. *p<0.0001 compared with placebo; †p=0.0072 compared with placebo. Phentermine/topiramate extended-release (PHEN/TPM ER) 7.5/46, 7.5 mg PHEN/46 mg TPM ER, PHEN/TPM ER 15/92, 15 mg PHEN/92 mg TPM ER. CI = confidence interval.

LOCF analysis, percentages of patients losing ≥5 %, ≥10 %, and ≥15 % of BW were, respectively, 66.7 %, 47.2 %, and 32.3 % on 15/92 mg; 44.9 %, 18.8 %, and 7.3 % on 3.75/23 mg; and 17.3 %, 7.4 %, and 3.4 % on placebo (all comparisons p<0.05 versus placebo). Among completers, at 15/92 mg, 48.1 % lost ≥15 % of BW, 67.7 % lost ≥10 %, and 83.5 % lost ≥5 %. Therapeutic efficacy was demonstrated in both doses across a wide range of initial BMI, with evidence suggesting that the 15/92 mg dose is more efficacious than the 7.5/46 mg dose in patients with severe obesity (BMI ≥35 kg/m²).

The 56-week CONQUER study (Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults) assessed the efficacy and safety of PHEN/TPM ER for weight reduction in adults who were overweight or obese (BMI 27–45 kg/m²) and had two or more weight-related comorbidities. The study included patients with a history of depression or those taking antidepressants, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin re-uptake-norepinephrine inhibitors (SNRIs), or bupropion. Depression is a common comorbid condition with obesity, but prior to the CONQUER trial, most weight loss studies had excluded patients with depression or a history of the condition. Patients (n=2487) were randomized into three treatment arms: placebo (n=994), PHEN/TPM ER 7.5/46 mg (n=498), and PHEN/TPM ER 15/92 mg (n=995).

Among patients who completed the study: at 56 weeks, the change in BW was –1.4 kg (least-squares mean –1.2 %, 95 % confidence interval [CI] –1.8 to –0.7), –8.1 kg (–7.8 %, –8.5 to –7.1; p<0.0001), and –10.2 kg (–9.8 %, –10.4 to –9.3; p<0.0001). The NIH recommended target of ≥10 % BW loss was achieved in 7 %, 37 % and 48 % of the placebo, PHEN/TPM ER 7.5/46 mg, and 15/92 mg groups, respectively (p<0.0001, ITT-LOCF).

The SEQUEL (Two-year Sustained Weight Loss and Metabolic Benefits with Controlled-release Phentermine/topiramate in Obese and Overweight Adults) study was a placebo-controlled, double-blind, 52-week extension study in patients completing the CONQUER study, evaluating the efficacy and safety of PHEN/TPM ER for a total of 108 weeks. Of 866 eligible patients, 676 (78 %) chose to continue in the study. PHEN/TPM ER was well tolerated over the study period. At week 108, PHEN/TPM ER was associated with significant, sustained weight loss across all treatment arms (ITT-LOCF, p<0.0001 compared with placebo). The mean percentage changes in BW from baseline were –1.8 %, –9.3 %, and –10.5 % for placebo, 7.5/46 mg, and 15/92 mg, respectively, and 10 % BW loss was achieved by >50 % of those taking PHEN/TPM ER, whereas <12 % of the placebo group achieved this target (see Figure 2).

Obese patients treated with PHEN/TPM ER also showed a significant reduction in obesity-related adverse health consequences. In the EQUIP and SEQUEL studies, the PHEN/TPM ER 15/92 mg group had significantly greater improvements in systolic and diastolic BP, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) compared with placebo (see Figure 3).64,67 In the CONQUER study, significant improvements were reported in BP, waist circumference, and concentrations of lipid, fasting insulin, glycemic, and inflammatory biomarkers in the PHEN/TPM ER groups compared with placebo. Cardiometabolic risk factors improved significantly in the PHEN/TPM ER groups, with significant reductions in BP; particularly in patients with hypertension at baseline, and in triglycerides, high-sensitivity C-reactive protein, and total cholesterol, in patients with dyslipidemia at baseline.64

In the CONQUER study, in patients with hypertension, changes in systolic BP were –9.1 mm Hg, –6.9 mm Hg, and –4.9 mm Hg, respectively, in the PHEN/TPM ER 15/92 mg, 7.5/46 mg, and placebo groups from a baseline of approximately 134/84 mm Hg.64 Furthermore, more patients on PHEN/TPM ER were able to decrease the number of antihypertensive medications than those on lifestyle alone/placebo.64 In an analysis of pooled data from the CONQUER and EQUIP trials to analyze the effect of treatment on prehypertensive patients only, 18.5 % of the prehypertensive patients treated with placebo progressed to hypertension compared with 9.7 % of patients treated with 3.75/23 mg (n=134), 11.3 % of patients treated with 7.5/46 mg (n=80), and 9.7 % treated with 15/92 mg (n=454; p<0.05 for all doses versus placebo). Approximately 35 % to 38 % of patients with prehypertension achieved normal BP levels (p<0.05 for all doses versus placebo).65

A recent phase II study (n=45) evaluated the safety and efficacy of PHEN/TPM ER for the treatment of sleep apnea in obese patients through weight loss.67
The Role of Phentermine/Topiramate Extended-release in the Treatment of Obesity

At week 28, there was a 10.2 % mean decrease in weight in the PHEN/TPM ER 15/92 mg group compared with 4.3 % in the placebo group (p=0.0006) and a positive, significant (p=0.0003) correlation between percent change in weight and change in apnea–hypopnea index. Significant improvements in overnight oxygen saturation and reduction in BP compared with placebo were also reported.

**Safety Data for Phentermine/Topiramate Extended-release**

Common AEs were consistent across the wide range of patient populations studied in the EQUIP, CONQUER, and SEQUEL studies. Paresthesia, dry mouth, and constipation (up to 21 % in the 15/92 mg groups) were reported most frequently, with insomnia, dizziness, and dysuria in less than 13 % of participants. In the CONQUER study, dose-related trends were noted for rates of dry mouth, constipation, dysgeusia, paresthesia, insomnia, dizziness, irritability, and disturbance in attention. Depression-related symptoms were also reported in 7 % and anxiety-related symptoms in 8 % of the highest-dose subjects, respectively. A small increase in heart rate was seen in the CONQUER trial: 0.1 beats per minute in the 7.5/46 mg group and 1.7 beats per minute with 15/92 mg.

Potentially serious safety concerns regarding PHEN/TPM ER include teratogenicity. Data from the North American AED and Pregnancy Registry (NAAPR) showed a 10 times higher-than-expected incidence in women treated with topiramate during pregnancy. Data from the Sone Epidemiology Center Birth Defects Study (BDS) and the Center for Disease Control’s National Birth Defects Prevention Study (NBDBS) suggest that first trimester topiramate exposure may confer an increased risk for oral clefts with a combined odds ratio of 5.4 (95 % CI 1.5–20.1). However, a more recent population-based cohort study of 837,795 liveborn infants in Denmark did not find an increased incidence of birth defects—the adjusted prevalence odds ratio (OR) for major malformations in infants exposed to topiramate during pregnancy compared with infants not exposed to any antiepileptic drug was 1.44 (95 % CI 0.58–3.58). There are no restrictions on the use of PHEN/TPM ER in women of childbearing age; however, it is recommended that patients be counseled on pregnancy avoidance, effective contraception is utilized, and testing is encouraged to detect early pregnancy. The FDA has required a Risk Evaluation and Mitigation Strategy (REMS) in order to inform clinicians and females of reproductive potential about these safety concerns.

There has been concern about the association of obesity drugs with cardiac valvulopathy, which led to the withdrawal of the weight-loss drugs fenfluramine and dexfenfluramine. This effect was driven by off-target effects of these two serotonergic drugs on the 5-hydroxytryptamine receptor 2B receptor (5-HT2B) on the heart. Neither phentermine nor topiramate has any serotonergic activity. Echocardiographic studies in humans support the assertion that phentermine is not causally related to valvulopathy. Additionally, a population-based study evaluating the risk for newly diagnosed idiopathic valvarular disease in patients using dexfenfluramine, fenfluramine, or phentermine as an appetite suppressant found no cases of cardiac-valvar abnormalities among those who took phentermine alone. In a phase II trial, echocardiographic changes were evaluated in 100 patients who received phentermine alone or phentermine in combination with topiramate, and found no treatment-emergent valvar heart disease.

In summary, the weight loss associated with PHEN/TPM ER, together with improvement in obesity-related adverse health consequences, indicates a positive benefit: risk ratio. Patient and healthcare provider education has been made available to ensure that PHEN/TPM ER treatment is targeted to appropriate patients who are most likely to benefit.

As a result of these data, a treatment algorithm for PHEN/TPM ER has been proposed as part of the labeling. This begins with initiation at 3.75 mg /23 mg once daily for 2 weeks followed by a dose increase to the recommended dose of 7.5 mg/46 mg once daily for 12 weeks. This slower titration than used in the clinical program is intended to improve tolerability further. Patients are evaluated after 12 weeks for weight loss, and ‘responders’ (patients with weight loss of 3 % or more of BW) are maintained on that dose. ‘Nonresponders’ (those with weight loss less
that 3 % of BW) are either discontinued or undergo a parallel two-step titration to the 15/92 mg dose.64 Such an algorithm should ensure that only patients who truly benefit remain on therapy, and can be maintained at a dose level that maximizes individual patient benefit/risk.

Summary and Concluding Remarks

The declaration of obesity as a disease may help to direct more serious attention to this condition by patients and providers. It must be stressed that the most effective tool to tackle the obesity epidemic is prevention: treatment alone will fail in the setting of this epidemic. The coverage of obesity medication by health insurance companies has limited their use. However, the well-documented and substantial health and healthcare implications of obesity give great urgency to the need for safe and effective long-term pharmacologic treatment to complement lifestyle modifications. Prior to the approval of PHEN/TPM ER, available anti-obesity therapies generally offered efficacy of 5 to 6% BW loss.65 Chronic treatment options were limited, and patients often had no intermediate treatment options between lifestyle interventions of varying intensity and bariatric surgical treatment options.

Clinical trial data show that PHEN/TPM ER, together with a modest lifestyle intervention, was generally well-tolerated and resulted in robust, dose-related weight loss that was maintained for more than 2 years. PHEN/TPM ER was also associated with improvement in adverse health consequences of obesity, including the most common weight-related comorbidities of hyperglycemia, dyslipidemia, and hypertension, in conjunction with reduced use of concurrent medications. In conclusion, PHEN/TPM ER, with lifestyle modification, represents a valuable new agent in the treatment armamentarium to counteract increasing rates of obesity and obesity-related adverse health consequences.
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