Addressing Tamoxifen-Associated Weight Gain: Lifestyle and Pharmacotherapy Options

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Abstract

Tamoxifen, a selective estrogen receptor modulator (SERM), is commonly prescribed in hormone receptor-positive breast cancer. While effective in reducing recurrence and mortality, tamoxifen is associated with weight gain in a significant proportion of patients. This weight gain complicates survivorship care, particularly given obesity's association with recurrence risk and all-cause mortality. Although lifestyle modification remains the standard of care for weight management, many breast cancer survivors struggle to achieve sufficient results with behavioral interventions alone. Current guidelines from oncology and obesity societies provide limited, nonspecific direction regarding pharmacologic weight management for tamoxifen-treated patients. Medication classes including GLP-1 receptor agonists, tirzepatide, phentermine-topiramate, bupropion-naltrexone, and orlistat are reviewed with attention to efficacy, safety, potential interactions, and tamoxifen-specific considerations. Practical monitoring strategies and prescribing considerations are provided to support oncology practitioners. This narrative review summarizes available evidence on tamoxifen-associated weight gain and outlines considerations for the use of anti-obesity medications in this population.

Breast cancer is the most frequently diagnosed cancer among women in the United States and continues to be one of the leading causes of cancer-related mortality (ACS, 2026). In 2026, about 321,910 new cases of invasive breast cancer are expected, with more than 42,000 deaths (ACS, 2026). Hormone receptor-positive (HR+) breast cancer accounts for approximately 70% to 80% of all breast cancer cases (ACS, 2026). Tamoxifen, a selective estrogen receptor modulator, is commonly prescribed as standard adjuvant endocrine therapy for premenopausal women with hormone receptor–

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positive breast cancer (Burstein et al., 2019). Five years of tamoxifen therapy has been shown to reduce the 15-year risk of breast cancer recurrence by approximately 40% and the risk of death by about 30% compared with no endocrine therapy (Bekes & Huober, 2023).

While tamoxifen's effectiveness in reducing breast cancer recurrence and mortality is well established, its long-term use has been linked to weight gain. Recent studies show that weight gain during tamoxifen therapy is common, affecting approximately 39% to 61% of women, depending on menopausal status and duration of therapy. A retrospective study of 1,282 breast cancer survivors revealed 33.7% had at least a 5% weight gain at 5 years (Raghavendra et al., 2018). In a study of postmenopausal women receiving endocrine therapy, 56% of patients gained weight, with an average increase of approximately 1.5 kg over the treatment period (Ginzac et al., 2018). Weight gain was more pronounced in women with lower initial fat mass and in those who had received prior chemotherapy, suggesting that baseline body composition and treatment history may influence risk of weight gain during endocrine therapy. In a prospective cohort of 309 women initiating adjuvant endocrine therapy, 67% of premenopausal and 43% of postmenopausal participants experienced clinically significant weight gain (≥ 5%) during treatment (Uhelski et al., 2024).

Several mechanisms have been proposed to explain tamoxifen-associated weight gain. Tamoxifen exerts mixed agonist and antagonist effects depending on the tissue. Estrogen is known to suppress appetite via hypothalamic pathways; by disrupting this signaling, tamoxifen may promote increased food intake or changes in satiety perception (Zhu et al., 2023). Tamoxifen may also influence lipid metabolism and glucose homeostasis, contributing to insulin resistance and increased fat storage (Klöting et al., 2020). These effects may be partially mediated by hepatic estrogen receptor activity, leading to alterations in triglyceride levels and fat distribution (Klöting et al., 2020). Lastly, tamoxifen has been associated with reduced resting energy expenditure and loss of lean body mass, especially among postmenopausal women, which can lead to slower metabolism and increased fat mass, even without significant changes in diet or physical activity (Klöting et al., 2020).

In breast cancer survivors, excess adiposity is associated with higher risk of recurrence, second primary cancers, and all-cause mortality. Obesity is also linked to other malignancies and cardiometabolic disease, highlighting the importance of intentional weight management in survivorship. A body mass index (BMI) of 30 kg/m^2 or higher is associated with recurrence and all-cause mortality (Ligibel et al., 2022). However, BMI alone does not fully capture an individual's risk profile. In postmenopausal women, changes in hormone levels lead to redistribution of body fat toward the abdomen, increasing visceral adiposity, an important driver of cardiometabolic risk, even when BMI remains within the normal range. Therefore, a more comprehensive assessment is appropriate. This may include measuring waist circumference to estimate central fat accumulation, using body composition analysis to distinguish between lean and fat mass, and evaluating for sarcopenia, which may be accelerated by menopause and cancer treatment.

In addition to metabolic and endocrine mechanisms, tamoxifen is also associated with several gastrointestinal symptoms that may influence treatment tolerance. Nausea is among the most frequently reported effects and often occurs during the early phase of therapy (Drugs.com, 2025). Patients may also describe dyspepsia, bloating, or general abdominal discomfort, and some experience changes in bowel habits such as constipation or diarrhea (Drugs.com, 2025). Less commonly, tamoxifen has been associated with elevated liver enzymes or hepatic steatosis, which may be identified through routine monitoring and may present with subtle or nonspecific symptoms (Drugs.com, 2025). Rare cases of hypertriglyceridemia-induced pancreatitis have been reported (Drugs.com, 2025).

CURRENT GUIDELINES

Professional organizations offer guidance on weight management in cancer survivors, outlining when to initiate lifestyle interventions and consider pharmacologic treatment. The American Cancer Society's 2024 Nutrition and Physical Activity Guidelines recommend lifestyle-based strategies as the primary approach to weight management in cancer survivors, with an emphasis on

nutrition, physical activity, and behavioral support. The American Society of Clinical Oncology (ASCO) recommends considering pharmacologic treatment for individuals with a BMI of 30 kg/m^2 or higher, or 27 kg/m^2 or higher when accompanied by obesity-related comorbidities (Ligibel et al., 2022). Similarly, the Obesity Medicine Association supports the early use of FDA-approved anti-obesity medications for patients meeting these BMI thresholds, in combination with lifestyle modifications (Tondt et al., 2023). Both the ASCO and OMA emphasize that BMI should be used as a screening tool as metabolic, behavioral, and social determinants modify risk at any BMI value. Treatment goals typically include a clinically meaningful weight loss of at least 5% of total body weight, with the OMA recommending reassessment of pharmacologic treatment at 3 months and continuation, if at least 5% weight loss is achieved.

PHARMACOLOGIC OPTIONS

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide 2.4 mg (Wegovy) and liraglutide 3.0 mg (Saxenda), enhance insulin secretion, delay gastric emptying, and promote satiety, leading to reduced appetite (Table 1). In clinical trials, semaglutide has been associated with average weight reductions of approximately 15% of baseline body weight over 68 weeks, while liraglutide has produced reductions of approximately 5% to 8% over 56 weeks (Rubino et al., 2022). Common side effects include nausea (reported in approximately 30% to 50% of patients), vomiting (5% to 15%), diarrhea (10% to 20%), and constipation (around 10%; Rubino et al., 2022). These gastrointestinal symptoms may exacerbate tamoxifen-related discomfort in some patients. Fatigue and dehydration can occur as secondary effects of persistent gastrointestinal side effects. Although gastrointestinal adverse effects are common, they are typically mild, dose-dependent, and tend to improve after the dose escalation period. Less common but serious adverse events include pancreatitis (less than 1%) and gallbladder disease (approximately 1% to 2%; Rubino et al., 2022).

The long-term safety of GLP-1 receptor agonists in individuals with active or prior cancer remains unclear. In the Satiety and Clinical Adiposity Liraglutide Evidence (SCALE) trial, a higher incidence of breast cancer was observed in the liraglutide group compared with placebo, although this difference was not statistically significant (Pi-Sunyer et al., 2015). A systematic review and meta-analysis by Nagendra et al. (2023), which examined 37 randomized controlled trials, found no statistically significant increase in overall cancer risk among GLP-1 users, including no specific association with breast cancer. However, most included trials were of limited duration and not powered to detect malignancies. More recently, Wang et al. (2024) conducted a large retrospective, multi-center cohort study involving over 1.6 million adults with type 2 diabetes and no prior history of obesity-related cancers. This study found no significant difference in breast cancer risk between those treated with GLP-1 receptor agonists and those treated with insulin (Wang et al., 2024). Data remain insufficient to fully assess long-term cancer risk.

Tirzepatide (Zepbound), a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, was FDA-approved in November 2023 for chronic weight management (U.S. Food and Drug Administration, 2023). GIP is an incretin hormone that stimulates insulin secretion in a glucose-dependent manner and may enhance the metabolic effects of GLP-1 when combined in dual agonist therapies. In the SURMOUNT trials, tirzepatide produced a 15% to 22% total body weight reduction over 72 weeks (Jastreboff et al., 2022). Like GLP-1 receptor agonists, tirzepatide's side effects are predominantly gastrointestinal, with nausea, vomiting, diarrhea, constipation, and abdominal discomfort commonly reported, affecting up to 70% of patients, especially during dose escalation (Jastreboff et al., 2022). Tirzepatide has demonstrated greater weight-loss efficacy and a more favorable gastrointestinal side-effect profile compared with earlier GLP-1 receptor agonists in clinical trials. It has no known interaction with tamoxifen. Its long-term safety in hormone-sensitive cancers remains unknown.

Phentermine-topiramate (Qsymia) is a combination drug used for chronic weight management. Phentermine, a sympathomimetic amine, suppresses appetite by increasing the release of norepinephrine in the hypothalamus, while topiramate, an anticonvulsant, promotes weight loss

Table 1. Comparison of Anti-Obesity Medications in the Context of Breast Cancer Survivorship and Tamoxifen Use

Medication	Mechanism of action	Efficacy	Cancer safety considerations	Dosing	Common side effects
Semaglutide (Wegovy)	GLP-1 receptor agonist; increases insulin, delays gastric emptying, promotes satiety	High (~15% weight loss in STEP trials)	No increased cancer risk reported; long-term safety in survivors remains understudied	Weekly injection	Nausea, vomiting, diarrhea, headache
Liraglutide (Saxenda)	GLP-1 receptor agonist; similar to semaglutide, with daily administration	Moderate (~5–8% weight loss)	Higher (non-significant) incidence of breast cancer in SCALE trial; warrants caution	Daily injection	GI upset, nausea, injection site reactions
Tirzepatide (Zepbound)	Dual GIP/GLP-1 receptor agonist; enhances insulin secretion, promotes satiety, delays gastric emptying	Very high (~20% weight loss in SURMOUNT trials)	No direct cancer risk observed; lacks long-term safety data in hormone-sensitive populations	Weekly injection	Nausea, diarrhea, vomiting, fatigue
Phentermine-Topiramate (Qsymia)	Appetite suppressant + anticonvulsant; reduces appetite and increases energy expenditure	Moderate to high (~10% weight loss)	May increase BP and mood disturbance; caution with cardiovascular or psychiatric comorbidities	Oral, daily	Dry mouth, insomnia, paresthesia, mood changes
Bupropion-Naltrexone (Contrave)	Antidepressant + opioid antagonist; reduces cravings via reward pathway modulation	Moderate (~5–9% weight loss)	Seizure risk and GI upset; consider mental health status and seizure threshold	Oral, daily	Nausea, constipation, headache, insomnia
Orlistat (Alli, Xenical)	Lipase inhibitor; blocks dietary fat absorption in the gastrointestinal tract	Modest (~5% weight loss)	Minimal systemic risk; monitor for fat-soluble vitamin deficiencies and GI intolerance	Oral, with meals	Oily stools, flatulence, vitamin A/D/E/K deficiency

Note. GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; GI = gastrointestinal; BP = blood pressure.

by enhancing satiety and increasing energy expenditure (Gadde et al., 2011). In clinical trials, this combination has resulted in average weight loss of 8% to 10% of total body weight over 56 weeks (Gadde et al., 2011). Phentermine is metabolized through the CYP3A4 pathway, similar to tamoxifen. While there is no known interaction between the two medications, this shared pathway may warrant caution. Reported side effects include dry mouth, constipation, insomnia, paresthesia, and dysgeusia (Gadde et al., 2011). Potential serious adverse effects include increased heart rate, elevated blood pressure, cognitive impairment, and kidney stones (Gadde et al., 2011). Topiramate has been associated with neuropsychiatric side effects, including mood disturbances, anxiety, and cognitive slowing (Gadde et al., 2011).

Bupropion, an antidepressant, and naltrexone, an opioid receptor antagonist, are combined in a single medication, Contrave, to reduce appetite and food cravings by modulating the brain's reward and stress pathways (Apovian et al., 2015). This combination is believed to promote weight loss by decreasing hedonic eating and improving emotional regulation, which may be particularly helpful in managing the psychological aspects of weight gain such as depression and emotional eating (Apovian et al., 2015). Clinical trials report average weight loss of 5% to 7% of baseline body weight over 56 weeks (Apovian et al., 2015). Side

effects include nausea, constipation, headache, dizziness, dry mouth, and insomnia. Naltrexone side effects include nausea or constipation (Apovian et al., 2015). Because this medication can affect mood and sleep, it should be used cautiously in patients with depression, fatigue, or sleep problems, including those related to tamoxifen.

Orlistat, a gastrointestinal lipase inhibitor, reduces dietary fat absorption (Apovian et al., 2015). In clinical trials, average weight loss with orlistat has been reported as approximately 3% to 5% of baseline body weight over 52 weeks (Apovian et al., 2015). Orlistat's most common side effects are gastrointestinal, including diarrhea and oily stools (Apovian et al., 2015). Orlistat can reduce the absorption of fat-soluble vitamins (A, D, E, K), and caution should be used for those at risk for bone loss (Apovian et al., 2015).

CLINICAL PRACTICE IMPLICATIONS

For women struggling to manage tamoxifen-associated weight gain despite lifestyle interventions, adjunctive pharmacotherapy may warrant consideration as part of a patient-centered care plan. Weight management advice should acknowledge the physiological challenges of tamoxifen-related weight gain to avoid reinforcing blame or shame in survivorship care. In a focus group, findings emphasize the importance of transparent, person-centered communication about weight and weight management, as women expressed a desire to be seen as individuals rather than being offered generalized advice (Nyrop et al., 2021). This reinforces the need for tailored, respectful discussions in survivorship care, particularly when addressing tamoxifen-associated weight gain.

Lifestyle interventions remain the cornerstone of survivorship care for women receiving tamoxifen. The 2024 American Cancer Society Nutrition and Physical Activity Guidelines for Cancer Survivors recommend a diet rich in vegetables, fruits, whole grains, legumes (particularly soy), and fiber, while limiting saturated fats. Additionally, the ACS recommends engaging in 150 to 300 minutes of moderate-intensity aerobic activity per week, such as brisk walking, swimming, or cycling, or 75 to 150 minutes of vigorous-intensity activity (Rock et al., 2022). In addition, strength training is recommended at least twice weekly to engage major muscle groups (Rock et al., 2022). Resistance-based exercise helps mitigate tamoxifen-associated muscle loss, preserve bone density, and reduce the risk of sarcopenia (Rock et al., 2022). These activities improve insulin sensitivity, which may help counteract tamoxifen-related metabolic changes (Jones & Parker, 2022). Although lifestyle interventions remain foundational, real-world adherence can be limited by tamoxifen-induced fatigue, emotional distress, and metabolic changes that complicate weight loss efforts. For women unable to achieve meaningful weight control through lifestyle intervention alone, adjunctive pharmacotherapy may warrant consideration as part of individualized, patient-centered survivorship care.

Advanced practitioners (APs) play a crucial role in mitigating tamoxifen-associated weight gain and supporting survivorship care. Routine screening for weight change should be integrated into follow-up visits, allowing clinicians to identify early trends and intervene proactively. Additionally, APs are well-positioned to normalize conversations about weight gain, reducing stigma and helping survivors understand the metabolic effects of endocrine therapy. When clinically appropriate, APs should evaluate and initiate anti-obesity medications using current guidelines to tailor treatment to individual risk profiles. Because coverage for anti-obesity GLP-1 therapies is inconsistent across payers and out-of-pocket costs can exceed $1,000 per month, particularly for those insured by Medicaid or high-deductible plans, APs can also serve as advocates, navigating prior authorizations and appealing denials when necessary (Williams et al., 2024). Finally, effective management requires collaboration across oncology, primary care, endocrine/obesity specialists, and nutrition, creating a coordinated, supportive framework that strengthens survivorship outcomes and enhances quality of life.

CONCLUSION

Tamoxifen-associated weight gain is a multifactorial issue that affects metabolic health and quality of life. Lifestyle modification remains central to care. Anti-obesity medications may offer an additional tool for patients who meet guideline-based criteria. While the

ACS emphasizes lifestyle modification and the ASCO and OMA outline BMI-based criteria for pharmacotherapy, the variation in guideline specificity around pharmacotherapy for weight management in cancer survivors reveals a gap in survivorship care. Advanced practitioners play an important role in supporting weight management for breast cancer survivors receiving tamoxifen. Careful consideration must be given to potential interactions, side effects, and individual patient needs. Including cancer survivors in future pharmacotherapy studies will be critical to building evidence-based recommendations. Clinical decisions regarding anti-obesity medications may involve collaboration with primary care providers, obesity specialists, or endocrinologists.

Disclosure

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