more likely to provoke these adverse symptoms, indicating a dose-dependent relationship [40].

Less common side effects included dyspepsia, fatigue, headache, eructation (belching), hair loss, gastroesophageal reflux, dizziness, and gastritis (Table 2). Hypoglycemia can occur in individuals with type 2 diabetes, especially when they are consuming insulin or insulin secretagogues such as sulfonylureas [12, 41]. Rare side effects include gallbladder disease, pancreatitis, acute kidney injury (typically related to hypovolemia), hypersensitivity reactions, and gastroparesis [12, 41]. Ophthalmic complications have been rarely reported, which could relate to direct toxicity or rapid GLP-1-correction of hyperglycemia [52]. Rare cases of suicidality have been reported, although preliminary evaluation using the FDA Adverse Reporting System, post hoc analysis of the STEP clinical trials, and 1 large cohort study have not confirmed any definitive link; the FDA and European Agencies are monitoring potential risk [53–55].

Nutritional deficiencies

Individuals using GLP-1s to treat obesity experience significant reductions in appetite and energy intake, with observed caloric reductions of 16%–39% [56]. This large, rapid reduction can lead to insufficient intakes of essential vitamins and minerals, especially at energy intakes <1200 kcal/d for females and < 1800 kcal/d for males [57]. Some examples of nutrients of concern include iron, calcium, magnesium, zinc, and vitamins A, D, E, K, B1, B12, and C [58]. Signs of frank nutrient deficiency include fatigue beyond expected levels, excessive hair loss, skin flakiness or itching, muscle weakness, poor wound healing, and unusual bruising [59]. GI side effects may further compromise nutrient absorption and exacerbate preceding or new risk of nutrient insufficiency.

Individuals with obesity are also more likely to have suboptimal dietary patterns at baseline that predispose them to nutrient deficiencies prior to starting therapy, for example, due to high ultraprocessed food consumption or highly restrictive diets [60]. Obesity itself can also increase risk of nutrient deficiencies at baseline due to alterations in nutrient absorption, distribution, metabolism, or excretion [61]. All these issues highlight the importance of proactively managing dietary composition and quality to maximize nutrient intake within a lower calorie intake [58].

Muscle and bone loss

Rapid weight reduction from (but not limited to) GLP-1 use frequently leads to loss of both fat and muscle mass [62, 63]. In the STEP 1 trial, of the average 13.6-kg–weight reduction, 8.3 kg (62%) was fat mass and 5.3 kg (38%) was lean body mass (including muscle and other non-fat tissues) [14]. Because muscle mass is about half of lean body mass, this corresponds to ~20% of total weight reduction being muscle loss. In the SURMOUNT 1 trial (pooling doses), total lean mass was reduced by 8.5 absolute percentage points [15]. Modeling data suggest that loss of muscle mass varies by sex, representing 10%–15% of total weight reduction in females and 20%–25% of total weight reduction in males, in the absence of structured strength training [64].

These reductions in fat mass, lean body mass, and muscle mass correlate with the degree of body weight reduction and are similar to those documented with other obesity therapies that achieve large weight reductions, such as bariatric surgery and very low-calorie restricted diets [65]. However, lean mass reduction is also affected by the degree of calorie restriction, overall rapidity of weight reduction, and presence or absence of strength training exercises [66]. Low protein consumption due to reduced appetite may also contribute to muscle loss and increased risk for sarcopenia, particularly among those with older age, perimenopausal or menopausal status, lower testosterone, sedentary behavior, or lack of resistance/strength training [67–70].

Rapid weight reduction with GLP-1s or other therapies can also affect bone density. Weight reduction that is substantial (≥14%) and rapid (over 3–4 months) is associated with significant bone loss [71], whereas more moderate and slower weight reduction may better preserve bone mass [72]. Bone loss is influenced by initial body weight, age, sex, physical activity, extent of energy restriction and protein intake, and rate of weight reduction, with older individuals and females experiencing greater bone loss [71]. In the absence of structured nutrition and exercise efforts, loss of muscle and bone may be exacerbated by intermittent use of GLP-1s and weight regain or "weight cycling," increasing risk of sarcopenic obesity.

Adherence and costs

In manufacturer-sponsored trials of GLP-1s for obesity, reported adherence (sustained use) has ranged from 83% to 88% at 66–68 weeks [15, 73]. Adherence is much lower in practice: about 33%–50% at 1 years and 15% at 2 years [5–8]. Discontinuation is associated with older age (≥65 years), poor weight response, and moderate or severe GI side effects [74]. The relative influences of other factors on discontinuation are unclear, including changes in insurance coverage, high out-of-pocket costs, medication shortages [75], or "false cessation" due to switching to compounded (pharmacy prepared) GLP-1s. Low adherence may also relate to lower public and clinician awareness of the need for long-term use after a weight goal, health goal, or plateau is reached.

The current US list price for GLP-1s for obesity ranges from ~$12,000 to $16,000 per year [2]. Full costs may be incurred by those who self-pay, due to either off-label use or no payer coverage. With manufacturer coupons and discounts, costs can be lowered to ~$7000 to $8000 per year [76–78]. Coverage and costs for Medicaid programs vary by state, as each state determines coverage decisions and negotiates prices with the drug manufacturers. Some states have dropped coverage for GLP-1s due to high costs and unsuccessful pricing negotiations [79]. Medicare does not currently cover GLP-1s for obesity, but recently announced that they will be among the drug classes which the federal government will aim to negotiate in 2025; average price reductions in prior negotiations for other drug classes have ranged from 38% to 79% from the original list price [80]. Coverage by private insurers is highly variable, with some providing coverage, others providing coverage but with clinical restrictions or lifetime caps, and others not providing coverage. Local and regional