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MINIREVIEWS

Anti-obesity medications, the new frontiers in metabolic dysfunction-associated fatty liver disease: Efficacy, limitations, and future directions

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Abstract

The convergence of the global obesity and metabolic dysfunction-associated fatty liver disease (MAFLD) pandemics necessitates innovative therapeutic strategies. Anti-obesity medications, especially incretin-based treatments such as glucagon-like peptide-1 receptor agonists and multi-agonists (*e.g.*, tirzepatide, retatrutide), have shown a strong ability to reduce body weight and to significantly improve inflammation, hepatic steatosis, and MAFLD biomarkers. The mechanistic transition from satiety induction to synergized energy expenditure is highlighted in this review, which critically evaluates the evidence supporting these agents. Notwithstanding its apparent effectiveness, obstacles such as a dearth of reliable fibrosis regression data, the possibility of sarcopenia, notable side effects, financial and insurance-related obstacles, and the widespread problem of weight gain after stopping all therapeutics reduces enthusiasm. The full potential of anti-obesity medications in MAFLD will ultimately necessitate a multimodal strategy that tackles these constraints through systemic change, multidisciplinary care, and future research.

Key Words: Weight regain; Fibrosis; Sarcopenia; Glucagon-like peptide-1; Obesity; Metabolic associated steatohepatitis; Metabolic dysfunction-associated fatty liver disease

Core Tip: Novel anti-obesity drugs, especially incretin-based treatments, successfully lower body weight and enhance metabolic dysfunction-associated fatty liver disease indicators like inflammation and steatosis. However, there are major obstacles that limit their long-term potential. These include the frequent recurrence of weight gain following discontinuation, significant side effects, high costs, risks of muscle loss, and inadequate data on fibrosis reversal. In addition to additional research and systemic healthcare reforms to address these limitations, a comprehensive, multidisciplinary approach is necessary to fully realize the potential of these medications for metabolic dysfunction-associated fatty liver disease.

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INTRODUCTION

The rising global prevalence of obesity has directly fueled an increase in its hepatic complication, metabolic dysfunction-associated Fatty liver disease (MAFLD). The advent of highly effective anti-obesity medications (AOMs) has thus opened a new frontier for management[1]. This review aims to synthesize the current evidence on the efficacy of AOMs, particularly the newer incretin-based therapies, for treating MAFLD, while providing a critical appraisal of their limitations, safety concerns, and the practical challenges surrounding their use. The potential for weight loss has greatly increased with the development of long-acting glucagon-like peptide-1 (GLP-1) receptor mono-agonists, GLP-1 receptor/glucose-dependent insulinotropic polypeptide (GIP) receptor dual-agonists, and GLP-1 receptor/GIP receptor/glucagon receptor tri-agonists. They work through three different mechanisms: (1) Satiety; (2) Satiety plus anti-emesis; and (3) Satiety plus anti-emesis plus increased energy expenditure. Despite the efficacy of these treatments, more drug research iterations within these frameworks have started to produce diminishing returns in terms of efficacy increases. These early successes in attaining significant weight loss could be compared to the invention of the wheel, a major innovation that paves the way for subsequent innovations[1].

LITERATURE REVIEW

Major databases (PubMed, Scopus, Web of Science, and EMBASE) were used to conduct a thorough literature search that included all publications published up until November 30, 2025. The following Boolean operators were used in the search strategy to combine free-text keywords and Medical Subject Headings terms: “anti-obesity medications” AND “MAFLD” OR “NAFLD (non-alcoholic fatty liver disease)”, or MASLD (metabolic dysfunction associated steatotic liver disease) “efficacy” AND “safety”, “GLP-1 receptor agonists”, “tirzepatide”, “orlistat”, or “semaglutide”. The term non-alcoholic fatty liver disease NAFLD is used here to reflect the wider clinical spectrum now reclassified as MAFLD or metabolic associated steatotic liver disease (MASLD) in accordance with updated nomenclature guidelines, even though it was included in the search to guarantee thorough retrieval of pertinent literature. Peer-reviewed publications in English that covered randomized controlled trials, cohort studies, meta-analyses, empirical data, and systematic reviews were all considered eligible studies.

This review’s focus was on AOMs with primary or secondary approval for managing weight, especially those with new data in MAFLD. Agents like metformin and orlistat were taken into consideration during screening but were eventually disqualified because of insufficient long-term weight loss efficacy in recent comparative trials (orlistat) or limited MAFLD-specific evidence (metformin). We excluded conference abstracts, non-peer-reviewed publications, and research involving only animals. To capture both recent and foundational evidence, there were no publication date restrictions.

EFFICACY OF AOMS ON MAFLD: CLINICAL AND MECHANISTIC INSIGHTS

The anti-obesity medications used in MAFLD/ MASLD are summarized in Figure 1. We only discuss the most recently used AOMs.

GLP-1 receptor agonists (GLP-1 RAs) are a mainstay in the treatment of MAFLD and type 2 diabetes mellitus (T2DM) because of their combined effects on weight loss and glycemic control. Exenatide, a GLP-1-like molecule found in Gila monster saliva, was one of the first GLP-1 RAs to be created. Its precise mode of action is still unknown, but it has demonstrated efficacy in improving lipid metabolism by reducing postprandial triglycerides and ceramides independently of weight loss, as well as in reducing the incidence of MAFLD when compared to dipeptidyl-peptidase-4 (DPP-4) inhibitors [2,3].

Liraglutide, a long-acting lipidated GLP-1 RA, is now widely used to treat diabetes and obesity. The primary therapeutic benefit of liraglutide is weight loss, but it has also been shown to reduce inflammation and liver fibrosis, though steatosis is not significantly impacted[4].

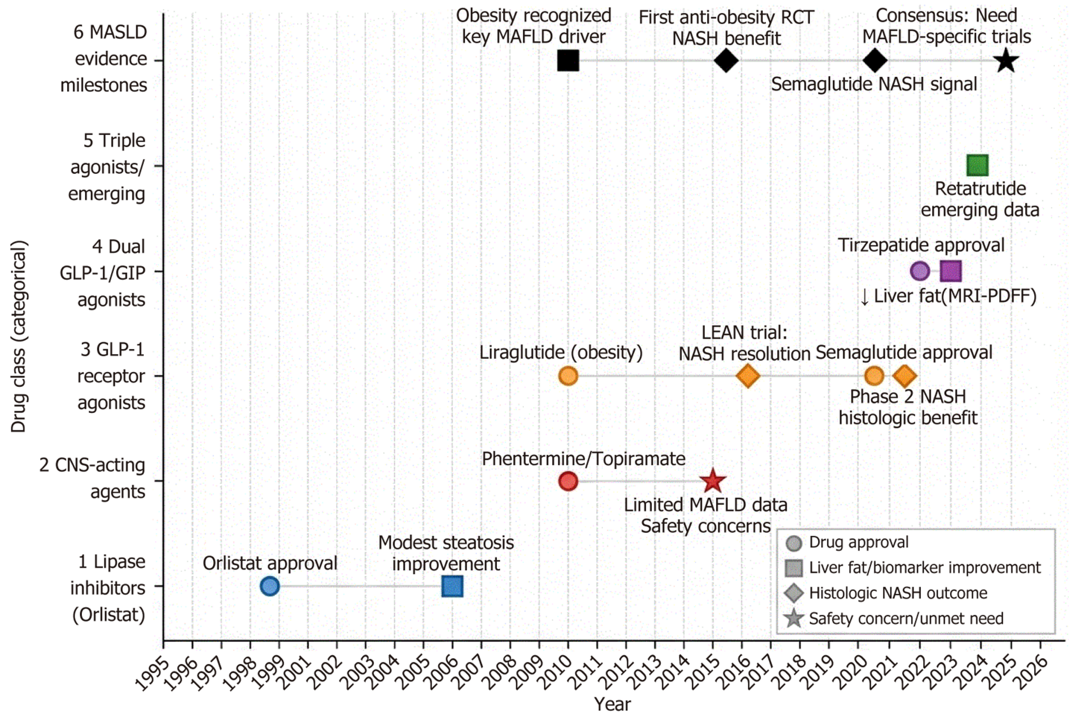

Figure 1 Historical evolution of anti-obesity pharmacotherapy and its application in metabolic associated steatotic liver disease and metabolic dysfunction-associated fatty liver disease. Early agents such as orlistat and centrally acting drugs showed limited hepatic benefit. The introduction of incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists, marked a paradigm shift with demonstrated improvements in liver fat and histologic resolution of steatohepatitis. Dual and triple incretin agonists show promising metabolic effects, although metabolic associated steatotic liver disease-specific histologic outcomes remain under investigation. MASLD: Metabolic associated steatotic liver disease; GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; CNS: Central nervous system; MAFLD: Metabolic dysfunction-associated fatty liver disease; RCT: Randomized controlled trial; NASH: Non-alcoholic steatohepatitis; MRI: Magnetic resonance imaging; PDFF: Proton density fat fraction.

Semaglutide was recently approved as a GLP-1 RA and is mainly used to treat obesity and T2DM. Because of its pleiotropic mode of action, it has sparked interest for possible therapeutic benefits in a range of illnesses. This medication shares 94% of the same amino acid sequence as human GLP-1. By lessening the drug's vulnerability to dipeptidyl-peptidase-4 enzyme degradation, these modifications improve the drug's stability. Semaglutide's molecular mechanisms affect many metabolic pathways, including lipid metabolism, insulin synthesis, glucose homeostasis, energy expenditure, and appetite regulation[5].

Semaglutide has shown promising results for liver health, including a greater likelihood of non-alcoholic steatohepatitis (NASH) resolution and significant decreases in lobular inflammation, steatosis, and hepatocellular ballooning. Notably, semaglutide decreased liver stiffness and steatosis, as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), when compared to a placebo. A meta-analysis involving 2413 patients found that semaglutide significantly improved liver fat content and liver stiffness while also significantly lowering blood ALT and AST levels. However, semaglutide treatment was associated with a higher incidence of major adverse events (P = 0.04) than a placebo [6,7].

Semaglutide may reduce the cardiovascular risk in individuals with T2DM and obesity because it is linked to a decrease in inflammation. A meta-analysis of 13 clinical studies with 26131 participants looked at the effects of semaglutide on C-reactive protein levels in relation to placebo or other medications that lower blood sugar. Lower C-reactive protein index readings were associated with the semaglutide medication when compared to the control and placebo groups[8].

The gut microbiota is crucial in the development of MAFLD because it regulates energy balance, lipid metabolism, and inflammation through mechanisms like bile acid metabolism and endotoxin production. Semaglutide improves inflammation and cognitive function in mice by reducing harmful bacteria and restoring beneficial gut flora, which may be advantageous for MAFLD and related disorders[9,10]. *In vitro* study of the drug's effects on MAFLD found that while semaglutide treatment significantly reduced hepatocyte steatosis, it also increased autophagy and decreased hepatocyte death[11].

Additionally, semaglutide can reduce fat buildup and liver inflammation in T2DM with MAFLD through controlling the expression of specific genes, such as miR-5120 and alpha/beta-hydrolase domain-containing 6 (ABHD6). A recently identified integral membrane protein known as ABHD6 breaks down monoacylglycerol and may be linked to a number of metabolic diseases, including T2DM, obesity, insulin resistance, and metabolic syndrome. 1-monoacylglycerol accumulates when ABHD6 expression is suppressed by miR-5120, which in turn activates peroxisome proliferator-activated receptor-alpha and peroxisome proliferator-activated receptor-gamma. This activation affects insulin secretion, insulin sensitivity, and lipid metabolism. It especially promotes the process of lipid browning. By binding to GLP-1 receptor, semaglutide appears to increase the expression of miR-5120 and decreases that of ABHD6. Additionally, semaglutide regulates N6-methyladenosine alterations and gut flora, which enhances pancreatic beta cell activity[12,13].

A new study that included 48 patients with concomitant T2DM and MAFLD, ages 42 to 71, who received semaglutide treatment for 52 weeks, found that patients responding to subcutaneous semaglutide medication showed a decrease of at least 1 grade of MAFLD on ultrasound. Additionally, exosomes isolated from patients responding to treatment produced less alpha smooth muscle actin, an activator of stellate cells that causes liver fibrosis[14]. These findings shed light on semaglutide's potential efficacy in lowering liver fibrosis in MAFLD.

Subcutaneous semaglutide treatment was administered to 320 NASH patients, including 230 with stage F2 or F3 fibrosis, in a recent phase 2 trial. Compared to placebo, a significantly higher percentage of patients achieved NASH resolution. It's interesting to note that 43% of patients in the semaglutide group showed improvement in their fibrosis stage, compared to 33% in the placebo group (P = 0.48)[15].

Dual and triple agonists

Cotadutide is a dual agonist of the glucagon and GLP-1 receptors that is another intriguing drug in development. According to clinical trials, cotadutide is a promising therapy option for NASH since it dramatically improves glycemic management, lowers body weight, and improves liver markers when compared to a placebo[16].

Tirzepatide: A leading dual agonist

The 39-amino acid synthetic peptide tirzepatide has a lot of promise for treating liver and metabolic disorders because it acts as a dual agonist at GIP and GLP-1 receptors. In addition to its proven ability to lower body weight, tirzepatide has shown compelling evidence of improving liver function. A recent phase 2 trial that included patients with metabolic associated steatohepatitis (MASH) and moderate to severe fibrosis found that 52 weeks of tirzepatide medication was more effective than a placebo in treating MASH without aggravating fibrosis. Significant reductions in liver fat and improvements in MASH-related biomarkers, and adiponectin, were observed in *post hoc* studies following four weeks of high-dose treatment[17].

Additionally, a study using animal models found that tirzepatide significantly reduced hepatic and serum cholesterol levels, mitigated liver injury, and outperformed semaglutide in reducing hepatic lipid accumulation[18]. Notably, while AST levels drop similarly with both treatments, ALT levels drop more with high dosages of tirzepatide than with dulaglutide[19]. The SURPASS-3 imaging study provided additional evidence of tirzepatide's efficacy in reducing liver fat content, showing that all doses significantly decreased liver fat (40%-47%) when compared to basal insulin degludec (11%, P < 0.001)[20]. Additionally, a preclinical study confirmed that MAFLD improved in every treatment group, with surgery enjoying the greatest benefit from tirzepatide at 100 nM/kg[21].

Tirzepatide showed a remarkable ability to reduce liver fat by about 47% in individuals with T2DM. Additionally, it significantly reduced the levels of subcutaneous and visceral abdominal fat. Tirzepatide treatment for 52 weeks was more successful than a placebo in treating MASH without exacerbating fibrosis[22]. Notably, tirzepatide outperformed semaglutide at all doses in lowering glycated hemoglobin levels in the open-label, phase 3 trial SURPASS-2[23].

Retatrutide: A potent triple agonist

The triple agonist retirutide, which acts on the glucagon, GIP, and GLP-1 receptors, is currently being researched for its effects on obesity and related metabolic disorders. Its potential as a treatment for obesity and MAFLD is demonstrated by its notable weight loss and potential benefits for liver function[20,24]. Retatrutide, a triple agonist that targets the GIP, GLP-1, and glucagon receptors, demonstrated exceptional efficacy in a phase 2 clinical trial for MAFLD. After taking dosages of 8 mg and 12 mg over a 48-week period, over 85% of subjects experienced the abolition of hepatic steatosis, and retirutide significantly reduced liver fat when compared to a placebo[25].

Head-to-head and combination studies

There aren't many studies that compare the results of different treatment regimens, as far as we know. Semaglutide was compared to dapagliflozin in 187 obese patients with T2DM and MAFLD. Those treated with oral semaglutide over a 6-month period showed greater reductions in glycated hemoglobin A1c levels and liver stiffness than those taking dapagliflozin plus metformin. Semaglutide showed improved benefits for liver function by significantly reducing liver stiffness from 8.07 kPa to 6.51 kPa[26].

In a preclinical study, tirzepatide, semaglutide, and bariatric surgery were compared in rats fed a high-fat diet. At high dosages, tirzepatide reduced body weight by 17.7% more than semaglutide (10.7%) and bariatric surgery (15.5%). Tirzepatide may be more helpful than bariatric surgery in treating obesity and, by extension, MAFLD because these two conditions co-occur[27]. Additionally, in a study including 261 patients with T2DM and MAFLD, the effects of semaglutide plus metformin were compared to the effects of metformin alone. The dual therapy group had significantly lower levels of gamma-glutamyltransferase, liver fibrosis index, ALT, and AST. These results demonstrate semaglutide's ability to enhance liver function and slow the advancement of fibrosis in comparison to metformin alone[28]. In a 26-week phase 2 trial, tirzepatide significantly reduced body weight and glycated hemoglobin A1c; 37.7% of patients lost at least 10% of their body weight, while dulaglutide only achieved this in 9.3% of cases[19].

THE OTHER SIDE OF THE COIN: CHALLENGES AND LIMITATIONS OF AOMS

The challenges and limitations of the use of ant-obesity medications in patients with MAFLD are summarized in Figure 2.

Clinical and safety concerns sarcopenia

It has been discovered that the loss of lean muscle mass brought on by AOM-induced weight loss exacerbates sarcopenia and reduces functional ability, particularly in patients with cirrhosis or even those in the early stages of MAFLD. Patients with MAFLD may gain weight again after stopping AOMs alone. The only likely explanation for weight gain after stopping AOMs is an increase in fat mass, which may replicate metabolic dysfunction at levels greater than those seen before starting AOMs. Finally, since the long-term safety of AOMs in cirrhosis has not yet been evaluated, it is crucial to take into account the potential for worsening sarcopenia with weight loss of more than 10% to 20%[29]. Maintaining adequate protein and other nutrient intake and integrating physical activity, particularly resistance training, into a comprehensive obesity treatment plan are two essential strategies for maintaining muscle mass. Oral nutritional supplements can help patients maintain a balanced diet and counteract or prevent nutrient deficiencies, particularly in those who have decreased appetite or food aversion. These objectives and tenets emphasize how crucial it is for patients to have access to medical professionals who can provide evidence-based recommendations regarding diet and exercise [30].

Lack of robust fibrosis regression

Regression of fibrosis is linked to fewer liver-related complications in NASH patients[31]. A growing stage of fibrosis raises the risk of future liver-related morbidities such as decompensation events and hepatocellular carcinoma as well as liver-related and all-cause mortality, according to numerous studies that highlight the importance of fibrosis in predicting outcomes in NAFLD[31-33]. On the other hand, results from two large negative drug trials involving 1135 patients with compensated NAFLD cirrhosis showed that a decrease in fibrosis is associated with improved clinical outcomes. Specifically, patients whose fibrosis decreased after a median follow-up of 16.6 months had a six-fold decreased risk of liver-related incidents[30]. Several anti-obesity drugs are currently approved for the treatment of obesity. Most of them appear to improve steatosis and reduce transaminase levels in patients with NAFLD. It is unclear whether they affect liver-related outcomes like the development of cirrhosis and hepatocellular carcinoma, and little is known about how they affect fibrosis[34].

Adverse events

The 154 randomized clinical trials (112515 participants) with 31 recent studies carried out in the last three years were included in a recent meta-analysis. The medication with the highest risk was tirzepatide [relative risk = 2.13, 95% confidence interval (CI): 1.57-2.89; $P < 0.0001$; $I^2 = 0.0\%$; $\tau^2 < 0.0001$; high certainty]. Phentermine/topiramate, semaglutide, liraglutide, orlistat, naltrexone/bupropion, and topiramate were linked to higher discontinuation rates because of adverse events. GLP-1 RAs tirzepatide, semaglutide, and liraglutide have been associated with a higher risk of gastrointestinal issues. In particular, tirzepatide was associated with the highest risk of vomiting and gastroenteritis. Semaglutide was linked to the highest risk of stomach pain. Among the side effects, liraglutide was linked to the highest risk of eructation moderate certainty), dyspepsia, and diarrhea[35].

Topiramate and phentermine/topiramate had the most detrimental psychological effects because they can simultaneously increase the risk of anxiety, irritability, and sleep disorders. This could be the reason why the label for the phentermine/topiramate medication expressly alerts users to the higher risk of anxiety and insomnia. Additionally, topiramate has been demonstrated to significantly increase the incidence of depression or depressed symptoms and may exacerbate depression in bipolar disorder patients. Therefore, it is important to monitor the risk of depression when taking topiramate[36].

A recent study examined targeted adverse medication events in 24725 liraglutide users, 21454 semaglutide users, and 11538 tirzepatide users. Tirzepatide had the fewest reports of adverse drug events and the weakest pharmacovigilance association strength when compared to the other two drugs. However, semaglutide was associated with several rare adverse events, including suicidal ideation and behavior, vision loss, and hair loss[37].

A recent study screened 4414 papers, of which 81 (involving over 400000 participants) were included[38]. The most common adverse event was gastrointestinal, with no significant difference across investigational biologic therapy: Placebo-subtracted incidences were 5%-39% for nausea, 7%-39% for diarrhea, 2%-31% for constipation, 0%-26% for vomiting, and 2%-20% for abdominal pain. Most adverse events occurred when the dosage was increased and were mild to moderate in severity. Nineteen studies found that gallstones or gallbladder-related issues occurred in 0%-3.1%, 0.2%-7%, and 0%-2.9% of patients treated with liraglutide, semaglutide, and tirzepatide, respectively. Six studies found that 4.9%-7.0% of patients treated with tirzepatide developed alopecia or hair loss, compared to 0.9%-1.4% of patients treated with a placebo. 7% of patients taking oral semaglutide reported hair loss, compared to 3% of patients receiving a placebo. In the real world, 0%-0.6% of patients treated with semaglutide experienced hair loss. Fatigue was listed as an adverse event in 19 publications. In clinical trials, the placebo-adjusted incidence of fatigue ranged from 0% to 15.6%. Bruising, euthymia, irritation, hemorrhage, and itching were among the injection site reactions reported in 24 out of 29 publications, with a placebo-adjusted incidence range of 0%-12.5%. Other dermatological adverse events included cellulitis (< 1%), urticaria (3%), pruritus (1.7%), rashes (3.6%), and peripheral edema (6.5%)[38].

The percentage of patients with pancreatitis was less than 2% in all trials that reported this adverse event (22 publications). Six of the articles had a difference of less than 1%, while eleven had a net difference of 0% between the treatment and placebo arms. However, in a pharmacovigilance evaluation of the Food and Drug Administration (FDA) adverse

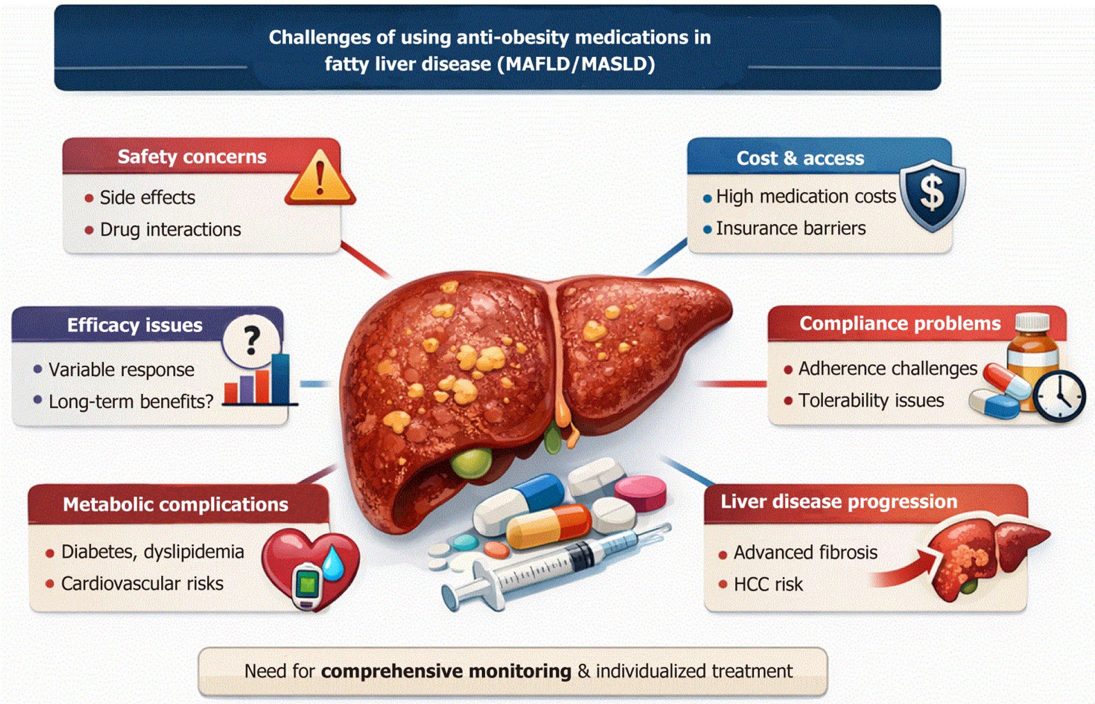

Figure 2 Challenges and obstacles to the use of anti-obesity medications in metabolic dysfunction-associated fatty liver disease and metabolic associated steatotic liver disease. MAFLD: Metabolic dysfunction-associated fatty liver disease; MASLD: Metabolic associated steatotic liver disease; HCC: Hepatocellular carcinoma.

event reporting for semaglutide, pancreatitis was found to be an adverse event signal with high clinical importance. In another study, four (0.2%) people treated with liraglutide experienced pancreatitis as a side effect, whereas none of the placebo group experienced this[39,40].

Shared decision-making and anticipatory counseling at treatment initiation and dose escalation are crucial to better prepare patients for expected adverse events and increase adherence. In addition to pharmacologic intervention and lifestyle counseling, comprehensive obesity management includes proactive management of common gastrointestinal adverse events, appropriate dose adjustments, and symptomatic treatment when side effects continue. Crucially, tolerability and management strategies need to be customized due to variations in the burden of comorbidities, monitoring capacity, and access to care. Combination techniques that address several symptoms may be required to maximize patient comfort and maintain long-term treatment compliance because gastrointestinal symptoms frequently coexist, such as nausea with gastroesophageal reflux disease or constipation[41].

Ocular manifestations: The GLP-1 agonists can cause blurred vision, especially during blood sugar fluctuations, and in rare cases, serious problems like non-arteritic anterior ischemic optic neuropathy, which is linked to rapid glycemic control. However, newer drugs generally show better eye health outcomes than older ones, reducing cataracts and dry eyes, but continued monitoring with your eye doctor is essential. In a recent study, among 25060 matched pairs comparing tirzepatide with semaglutide, no differences emerge across ocular outcomes. Tirzepatide users had lower rates of cataracts and oculomotor dysfunction than those taking naltrexone/bupropion. Semaglutide exhibits comparable trends. Both drugs have good profiles for visual disturbances, but tirzepatide has lower rates than phentermine[42].

Injection-site reactions and immune-mediated reactions like hypersensitivity, urticaria, and bullous pemphigoid are among the dermatological effects linked to GLP-1 RAs. Injection site reactions are treated with topical corticosteroids or antihistamines switching up their injection sites. Drug cessation is frequently necessary for delayed hypersensitivity reactions. Since cross-reactivity is not always present, switching from liraglutide to semaglutide may be considered if hypersensitivity is confirmed[43,44].

The term "Ozempic face", which refers to the loss of facial fat, has garnered media attention because of its cosmetic connotations. Doctors should advise patients about the possible cosmetic effects of Ozempic as well as the various treatment options, such as autologous fat grafting for volume restoration and fillers. Additionally, after treating volume loss, microneedling and lasers may help restore skin elasticity and texture. Additionally, there have been reports of hair loss, especially telogen effluvium, which may be connected to the quick weight loss caused by GLP-1 RA use. In these cases, nutritional deficiencies and physiological stress should be managed. The therapeutic potential of GLP-1 RAs in improving wound healing and treating inflammatory skin conditions like psoriasis is also highlighted by new research [45].

Based on pre-clinical models, long-acting GLP-1 agonists have FDA black box warnings for medullary thyroid C-cell cancer; however, these are ultimately uncommon clinical events. GLP-1 receptor agonist use was not linked to a significantly higher risk of thyroid cancer (1.33 events per 10000 person years) over a mean follow-up of 3.9 years, according to a large retrospective cohort study[46]. In contrast, Bezin *et al*[47] discovered that using GLP-1 RAs was linked to a higher risk of medullary thyroid cancer (adjusted hazard ratio = 1.78, 95%CI: 1.04-3.05) and all thyroid cancer (adjusted hazard ratio = 1.58, 95%CI: 1.27-1.95). Currently, a history of multiple endocrine neoplasia syndromes or thyroid cancer precludes the use of these medications. Adverse events and their management[48] are summarized in Table 1.

Weight regains upon cessation

The effectiveness of AOMs in managing the chronic diseases of obesity and NAFLD is called into question because, in one real-world study conducted in North America, only 16% to 42% of those who began treatment remained on it for more than six months[49].

The duration of therapy and, most importantly, the consequences of stopping it are among the new research questions that are brought up. Is a fresh increase in weight expected? We have a new problem: People who have put on weight after having metabolic surgery, which is thought to be the best treatment for obesity. The current situation is different from the previous one, where participation was routinely denied to those who had surgery or had previously received GLP-1 RA therapy. All of the studies we reviewed demonstrated that weight returned after stopping therapy, even though these drug groups are obviously effective at reducing weight (6%-20% after 52 weeks)[50,51].

According to a recent narrative review, weight rapidly returns when GLP-1 RAs or GIP/GLP-1 RAs are stopped, regardless of whether the treatment is short-term or long-term. This rebound is likely to significantly reduce the metabolic benefits of weight loss. Future research must determine the optimal duration of these treatments or develop strategies or regimens that employ dose reduction to prevent weight gain, given the efficacy of these molecules[52].

The idea that obesity is a chronic illness has highlighted the need for continuous care to sustain long-term treatment results. More invasive surgical procedures and/or continuous therapy (*i.e.*, continuous support for lifestyle interventions through extended-care programs or prolonged use of AOMs) have been the most successful methods for encouraging long-term weight loss maintenance. However, these methods are expensive and might not be suitable for every patient [53]. Following complete dosage cessation, it has been hypothesized that gradual dose reduction of the GLP-1 RA semaglutide will help maintain weight loss for at least 20 weeks[54]. This study is particularly relevant because weight loss often results in a rise in hunger hormones and a fall in satiety hormones, which can persist for up to a year after stopping the diet and increase the risk of weight regain[55]. A more gradual hormonal adjustment to a new body weight set point might be made possible by gradually discontinuing AOMs or diets, especially considering the apparent efficacy of semaglutide dose-tapering. This would reduce the possibility of rapid weight gain, which could be linked to abrupt cessation and hormonal maladaptation. However, this data may indicate that lower doses of AOMs are required to maintain body weight once the desired goal has been achieved. It might be helpful to keep an eye on the potential of dose-tapering as a long-term weight-maintenance strategy. However, since AOMs are typically provided at a set price in most countries, financial incentives are unlikely to encourage dose reduction[1].

Anti-obesity drugs that result in positive changes in body composition may also offer a means of sustaining weight loss once treatment is over. A clinical cohort assessing the effects of supervised exercise in combination with GLP-1 RA treatment showed greater retention of body weight loss one year after treatment termination compared to GLP-1 RA therapy alone. However, the rate at which body weight and fat mass returned after treatment ended was similar for all treatments, suggesting that the relative advantage in weight loss retention was due to a lower body weight prior to treatment termination rather than to exercise-induced changes in body composition. Nevertheless, GLP-1 treatment combined with myostatin or activin type II receptor inhibition may promote favorable body composition changes, which could lead to an anticipated increase in resting energy expenditure and, as a result, a more straightforward path to sustaining weight and fat mass loss[56,57].

Practical and socioeconomic barriers cost and insurance coverage

AOM insurance coverage varies widely in the United States and is not legally required. Twenty-one percent of the 7378 people surveyed in 2015-2016 about their employer-sponsored insurance reported having coverage for AOMs. As of 2017, only 16 out of 50 state Medicaid plans provided coverage for at least one AOM. The use of FDA-approved AOMs is not covered in any way by Medicare Part D[58]. Two GLP-1 RAs, liraglutide and semaglutide, are particularly expensive; their monthly costs, before insurance, range from 324 dollars to 1619 dollars per month. The impact of long-term anti-obesity drug use on medical expenses is a topic of debate.

Provider and patient perceptions

Lack of clinician education and awareness: Primary care doctors lack knowledge about obesity guidelines. The weight and weight loss criteria that are advised by guidelines for starting and continuing anti-obesity medical treatment were only correctly identified by 8% of the 1506 primary care physicians who participated in the survey[59].

Stigma

Because of the widespread perception that poor behavior is the primary cause of obesity, doctors, nurses, students, and nutritionists have both implicit and explicit bias against obese people. When asked about explicit and implicit bias, even obesity specialists who participated in a 2013 medical conference on the topic used terms like “bad” and “lazy” in addition to the word “obese”. The care that patients receive is impacted by these biases. For instance, because they believe that patients with higher body mass indices are less likely to adhere to their recommended dosages, doctors may be hesitant to prescribe anti-obesity drugs to these patients. Patients who are overweight or obese receive less empathy, validation, and reassurance from clinicians during audio-recorded visits[60,61].

Table 1 Management of adverse events of anti-obesity medications

Medication/class	Common adverse events	Management strategies
GLP-1 RAs (semaglutide, liraglutide, tirzepatide)	(1) Nausea, vomiting, diarrhea, constipation, early satiety; rare pancreatitis; (2) Skin lesions; (3) Ozempic face; (4) Ocular adverse events; (5) Blurred vision; and (6) NAION	(1) Slow dose titration; small low-fat meals; short-term antiemetics; dose reduction if persistent symptoms; evaluate severe abdominal pain; (2) Topical corticosteroids and antihistaminic, changing injection sites and switching medications in severe hypersensitivity; (3) Fat volume restoration, fillers, microneedling and laser in addition to nutritional supplements; and (4) Close observation and ophthalmological consultation
Orlistat	Steatorrhea, fecal urgency, bloating, abdominal cramps	Dietary fat restriction (< 30% calories); patient education; vitamin A, vitamin D, vitamin E, vitamin K supplementation
Phentermine/phentermine-topiramate	Insomnia, dry mouth, constipation, tachycardia, hypertension	Morning dosing; hydration and fiber; monitor BP and heart rate
Naltrexone-bupropion	Nausea, headache, anxiety, BP elevation, mood changes	Gradual titration; BP monitoring; mood surveillance

GLP-1 RA: Glucagon-like peptide-1 receptor agonist; NAION: Nonarteritic anterior ischemic optic neuropathy; BP: Blood pressure.

Perception of treatment

To better understand attitudes towards the use of AOMs, a cross-sectional survey of health care professionals and people with obesity in the United States was conducted in 2022. The significance of altering one’s lifestyle and the patient’s responsibility to fight obesity were emphasized by the participants. According to people with obesity, they would be amenable to the long-term use of newly authorized AOMs. Health care professionals believed that their patients would remain with them in the long term if AOMs were successful. People with obesity and health care professionals agreed that a multimodal approach was more advantageous when combining AOMs with a health care professional-guided lifestyle intervention[62].

A cross-sectional online survey was conducted in the United States, United Kingdom, France, and Germany to find out more about preferences for AOM. The survey included 2500 people with obesity and 500 health care professionals. The primary barriers to people with obesity using prescription AOMs were concerns about side effects (33%), a lack of desire to take AOM (34%), and a lack of trust in AOM (26%). Most health care professionals (79%), either prescribed or recommended AOMs. 60% of people with obesity stated efficacy as the main factor in selecting one of the product profiles shown, while 95% of health care professionals stated lowering cardiovascular risk when selecting an AOM to prescribe. When choosing an AOM, effectiveness is a key consideration. Gaining more knowledge could improve people with obesity outcomes and help remove barriers to AOM use[62,63].

In nine Asia-Pacific countries, adult people with obesity and health care professionals who directly care for patients were given a cross-sectional online survey. A total of 10429 people with obesity and 1901 health care professionals completed the survey. A significant portion of people with obesity (63%) and health care professionals (41%) believed that people with obesity was exclusively in charge of weight loss, and only 43% of people with obesity discussed their weight with a health care professional in the preceding five years. Obesity, according to people with obesity (58%) and health care professionals (53%), made it more difficult for people with obesity to form romantic relationships. People with obesity lack of interest (41%) and low motivation (37%) to lose weight were the main excuses offered by health care professionals for not discussing weight. The majority of people with obesity (65%) preferred lifestyle changes over prescription medications for weight loss[64].

To find out how employers and employees perceive AOMs, people with obesity and their employers completed cross-sectional surveys about their opinions on obesity and its management. According to both groups, the most effective method for maintaining long-term weight loss was combining AOMs with lifestyle changes recommended by medical professionals (56.4%; 66.6%). The cost of drug coverage and the affordability of staff medications were identified as barriers, but more than two-thirds (68.6%) of emergency rooms said they would be open to reviewing the current AOM coverage options. Barriers to AOM coverage may be removed, and evidence of the benefits of evidence-based obesity care, direct and indirect cost savings, and the effects of obesity may improve workforce outcomes and obesity care[65].

A recent study claims that a survey provides new insights into the management of obesity by United States health care professionals, such as endocrinologists, primary care physicians, and advanced practice providers. The mentioned treatment barriers, especially cost, affect health care professionals’ capacity to provide patients with the appropriate therapy. Additionally, respondents were much more familiar with GLP-1 RAs than with glucagon receptor agonists or GIP receptor agonists. The new mechanisms of action of glucagon receptor agonists, such as unimolecular glucagon receptor/GLP-1 receptor dual agonists, are anticipated to provide further clinical advantages. These benefits include cardiometabolic effects that go beyond weight loss and the ability to selectively reduce liver fat to improve NAFLD/NASH. Given that the current focus of obesity treatment is on treating issues and comorbidities, this could help with treatment barriers and patient access[66].

CONCLUSION

The therapeutic landscape for MAFLD/MASLD has changed as a result of anti-obesity drugs, which consistently improve liver enzymes, metabolic inflammation, and hepatic steatosis while also achieving significant and sustained weight loss. The strongest efficacy signals, including MASH resolution in certain populations, are shown by incretin-based treatments, especially semaglutide, tirzepatide, and newly developed triple agonists. However, there is still a lack of reliable fibrosis regression and long-term liver-related outcome data. Widespread adoption is hampered by major socioeconomic and healthcare system obstacles, sarcopenia risk, weight gain following discontinuation, and safety concerns. All of these results point to AOMs as effective but insufficient disease-modifying instruments that need to be incorporated into thorough, long-term MAFLD management plans.

Future research should focus on the long-term, outcome-driven studies assessing fibrosis regression, cirrhosis-related events, and hepatocellular carcinoma risk reduction with anti-obesity therapies. Systematic research is needed on strategies to maintain weight loss, such as dose tapering, exercise integration, maintenance dosing, and combination therapies that preserve lean mass. Treatment selection may be optimized by better patient stratification based on metabolic phenotype, sarcopenia risk, and fibrosis stage. Novel combinations may be informed by mechanistic insights that go beyond weight loss, such as hepatic signaling pathways and gut microbiota modulation. Transforming pharmacologic advancements into equitable, practical MAFLD care will require addressing issues of cost, access, clinician education, and stigma associated with obesity.

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