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Review paper

Emerging Pharmacotherapies for MASLD: A Comprehensive Review

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ABSTRACT

Metabolic dysfunction–associated steatotic liver disease (MASLD) has emerged as the most common chronic liver disorder worldwide, closely linked to the global rise in obesity, type 2 diabetes mellitus, and cardiometabolic disease. Affecting nearly one-third of the adult population, MASLD represents a broad disease spectrum ranging from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. Beyond liver-related morbidity, MASLD significantly increases the risk of cardiovascular disease, chronic kidney disease, and extrahepatic malignancies, placing a substantial burden on healthcare systems globally. The pathogenesis of MASLD is complex and multifactorial, involving insulin resistance, dysregulated lipid metabolism, mitochondrial dysfunction, oxidative stress, chronic inflammation, fibrosis, gut microbiota alterations, and genetic susceptibility. For many years, therapeutic management relied largely on lifestyle modification and control of metabolic comorbidities, approaches that are difficult to sustain and often insufficient to halt disease progression. The recent approval of resmetirom, a selective thyroid hormone receptor-β agonist, in 2024 marked a critical breakthrough and renewed momentum in MASLD drug development. In parallel, a robust pipeline of emerging pharmacotherapies is rapidly reshaping the treatment landscape. These agents target key pathogenic pathways and include THR-β agonists, incretin-based therapies such as GLP-1, GIP, and dual or triple receptor agonists, peroxisome proliferator-activated receptor agonists, sodium–glucose cotransporter inhibitors, fibroblast growth factor analogs, farnesoid X receptor agonists, AMPK activators, and acetyl-CoA carboxylase inhibitors. This comprehensive review synthesizes current evidence from preclinical and clinical studies on emerging pharmacotherapies for MASLD, highlighting their mechanisms of action, therapeutic efficacy, and safety profiles. It also discusses ongoing

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challenges, including variable antifibrotic responses and disease heterogeneity, underscoring the need for personalized and combination treatment strategies. Collectively, these advances signal a promising shift toward disease-modifying therapies that may significantly improve long-term outcomes in MASLD.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously referred to as non-alcoholic fatty liver disease (NAFLD), and has an estimated global prevalence of 30%[1,2]. MASLD is defined by the presence of ≥5% hepatic steatosis with at least one metabolic risk factor (overweight, hyperglycemia, hypertension, hyperlipidemia) in the absence of other causes of steatosis, such as medications, alcohol use, viral hepatitis, or other illnesses [3].MASLD has emerged as the most prevalent chronic liver disease worldwide, affecting ~25%–30% of the adult population, with higher prevalence observed in individuals with obesity and type 2 diabetes [4]. The global epidemic of MASLD is increasing worldwide. People with MASLD can progress to cirrhosis and hepatocellular carcinoma and are at increased risk of developing type 2 diabetes, cardiovascular disease, chronic kidney disease, and extrahepatic cancer and it poses a substantial burden on both patient health and worldwide healthcare systems [5]. The mortality rate of NASH is predicted to double by 2030. MASH is a progressive form of MASLD, and approximately 20% of patients with MASLD progress to MASH [6].Until recently, given the lack of approved therapies, therapeutic strategies have primarily focused on lifestyle modifications and optimization of comorbidities. While lifestyle interventions can be effective, they are challenging to maintain, which limits their overall impact [7]. Therefore, as fibrosis improvement is crucial to bend the arc of disease progression, and sustained weight loss through lifestyle intervention is achieved by only a minority, pharmacological therapies are needed to meaningfully impact liver-related outcomes. After decades of research, the Food and Drug Administration (FDA) approved the first treatment for MASH in March 2024, resmetirom, a thyroid hormone receptor-β (THR-β) agonist [8]. Several drug candidates are currently in the pipeline to enrich the armamentarium of treatment for MASH. This comprehensive review highlights unmet clinical needs in MASLD and discussing the expanding pharmacotherapy landscape.

PATHOPHYSIOLOGY of MASLD

Metabolic dysfunction–associated steatotic liver disease (MASLD) develops through tightly interconnected disturbances in hepatic lipid handling, metabolic signaling, inflammation, and fibrosis, rather than a single linear pathway. The key processes include dysregulated lipid influx and synthesis, lipotoxic cell stress, immune activation, and progressive scarring driven by hepatocyte–stellate–immune–endothelial crosstalk and gut–liver interactions [9].Risk factors for MASLD include obesity, insulin resistance, hypertension, and hypertriglyceridemia [10]. Environmental factors, such as diet and physical inactivity, primarily increase the risk of hepatic steatosis. Excessive caloric intake beyond metabolic demand results in adipose tissue fat overload, promoting inflammation and insulin resistance in adipose tissue [11]. MASLD develops through a coordinated process initially described as the two-hit hypothesis [12]. The first hit involves hepatic steatosis driven by enhanced de novo lipogenesis (DNL), which worsens insulin resistance [12,13]. Insulin resistance disrupts adipose tissue lipolysis, increasing the delivery of free fatty acids to the liver [14].

The second hit refers to progression from MASLD to MASH and involves added cellular stressors, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative stress with excessive reactive oxygen species (ROS) generation [15,16]. Accumulation of saturated fatty acids due to increased fructose intake or cholesterol buildup within the ER further amplifies cellular stress and DNL [12,18].

Disordered hepatic lipid metabolism

In MASLD, insulin resistance and visceral obesity enhance fatty acid flux from adipose tissue to the liver, while hyperinsulinemia and hyperglycemia activate lipogenic transcription factors such as

SREBP1c and ChREBP. Concurrent defects in fatty acid oxidation and cholesterol–bile acid homeostasis impair lipid clearance, resulting in triglyceride accumulation and macrovesicular steatosis in hepatocytes [6].

Lipotoxicity, oxidative, and mitochondrial stress

Excess hepatic fatty acids exceed the capacity of β-oxidation and triglyceride storage pathways, leading to formation of lipotoxic intermediates. These species induce ER stress, oxidative damage, mitochondrial dysfunction, and inflammasome activation, promoting hepatocyte injury, inflammation, and fibrosis characteristic of MASH [19]. When hepatic lipid buffering is overwhelmed, toxic lipids such as saturated fatty acids, free cholesterol, ceramides, and oxidized lipids accumulate and directly damage cellular organelles. This activates stress signalling pathways and regulated cell death mechanisms, including apoptosis, necroptosis, and ferroptosis, driving the transition from simple steatosis to inflammatory MASH [20].

Inflammation and immune dysregulation

Injured hepatocytes release danger-associated molecular patterns and lipotoxic signals that activate Kupffer cells and recruit monocyte-derived macrophages via pattern recognition receptors. These immune cells secrete pro-inflammatory cytokines and chemokines (e.g., TNF-α, IL-1β, IL-6, CCL2), sustaining hepatic inflammation and immune cell recruitment [21].

Fibrogenesis and multicellular liver crosstalk

Persistent hepatocyte injury and inflammation activate hepatic stellate cells through paracrine signaling from hepatocytes, macrophages, and sinusoidal endothelial cells. Activated stellate cells differentiate into myofibroblasts, deposit extracellular matrix, and disrupt sinusoidal structure, while endothelial dysfunction worsens hypoxia and fibrogenic signaling, leading to advanced fibrosis and cirrhosis [22].

Gut–liver axis, genetics, and systemic context

Gut dysbiosis, increased intestinal permeability, and altered microbial metabolites deliver inflammatory and metabolic signals to the liver via the portal circulation. These factors interact with host genetics and systemic metabolic disorders to influence disease progression [23,24]. Genetic variants in PNPLA3, TM6SF2, and HSD17B13 increase susceptibility to MASLD, fibrosis progression, and hepatocellular carcinoma [25]. Collectively, these "multiple hits" initiate hepatic steatosis and promote its progression to inflammation and fibrosis [26], while chronic low-grade systemic inflammation contributes to cardiovascular disease [27] and tumorigenesis [28]. These interconnected pathways represent key targets for pharmacological intervention, including therapies aimed at improving insulin sensitivity, lipid metabolism, mitochondrial function, inflammation, fibrosis, and gut–liver axis signalling.

Current Pharmacological Approaches

Lifestyle-induced weight loss remains the cornerstone of NAFLD/MASLD management, but several drugs are traditionally used as pharmacologic options in patients with biopsy-proven steatohepatitis or high-risk metabolic profiles. These agents mainly target steatosis, inflammation, and metabolic risk rather than providing proven, robust antifibrotic effects, and most are used off-label in routine practice [29].

Pioglitazone (30–45 mg/day)

Pioglitazone, a thiazolidinedione, acts as a selective peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist. It promotes adipocyte differentiation and enhances peripheral insulin sensitivity, thereby reducing the flux of free fatty acids (FFAs) to the liver [30]. Pioglitazone also decreases hepatic de novo lipogenesis and inflammatory cytokine expression while increasing adiponectin levels, which has anti-inflammatory and insulin-sensitizing properties [31]. Randomized trials and meta-analyses summarized in recent pharmacologic treatment reviews show that pioglitazone improves steatosis, lobular inflammation, hepatocellular ballooning,

and NAFLD Activity Score, with significant reductions in aminotransferases and liver fat content and modest, variable effects on fibrosis [32]. RCTs, including PIVENS, have shown histological improvements in steatosis, lobular inflammation, and hepatocellular ballooning in patients with MASH, especially those with T2DM [33]. However, its use may be limited by adverse effects such as weight gain and fluid retention [34].

Vitamin E (800 IU/day, d-α-tocopherol)

Vitamin E is a lipid-soluble antioxidant that reduces oxidative damage within hepatocytes, a key driver in the progression from steatosis to steatohepatitis [35]. It neutralizes reactive oxygen species (ROS) and downregulates pro-inflammatory signalling pathways. The PIVENS trial demonstrated significant improvement in steatohepatitis but not fibrosis among non-diabetic adults with biopsy-proven NASH [36]. Despite moderate improvements in transaminases and histology, concerns remain about long-term safety, including a possible increased risk of prostate cancer in older men and haemorrhagic stroke [37]. Thus, it is not recommended in patients with diabetes or advanced cirrhosis The PIVENS trial, a pivotal phase 3 study, evaluated the effects of vitamin E (800 IU/day) in nondiabetic patients with biopsy-confirmed MASH. Over 96 weeks, vitamin E therapy led to significant improvements in hepatic steatosis and inflammation, resulting in MASH resolution in 43% of patients compared to 19% in the placebo group ($p < 0.001$) [38]. However, no significant impact on hepatic fibrosis was observed [39]. A systematic review analysing data from 11 studies confirmed that vitamin E reduces alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, hepatic fat accumulation, and inflammation in MASLD/MASH. Despite these benefits, its role in hepatic fibrosis regression remains uncertain, underscoring the need for long-term trials [40].

Ursodeoxycholic Acid (UDCA, 13–15 mg/kg/day)

UDCA is a hydrophilic bile acid with cytoprotective, anti-apoptotic, and anti-inflammatory properties serves as a promising adjunctive therapy for MASLD/NAFLD, significantly reducing liver enzymes like ALT, AST, and GGT in multiple meta-analyses of RCTs [41]. It stabilizes hepatocyte membranes, reduces hepatic transaminase levels in serum, and protects hepatocytes from oxidative stress [42]. Its hepatoprotective mechanisms include activating AMPK to inhibit apoptosis (via Bcl-2/Bax), enhancing autophagy (Bcl-2/Beclin-1), modulating gut microbiota (boosting Lachnospiraceae, Akkermansia), and alleviating steatosis, inflammation, and fibrosis through anti-oxidant and TGR5-targeted actions [43]. Doses of 13-35 mg/kg/day prove safe with minor GI side effects, complementing lifestyle changes, though histological improvements vary and more RCTs are needed for MASLD-specific validation [44]. While extensively used in cholestatic liver diseases, evidence for its efficacy in MASLD is limited and inconclusive. Some small trials have reported improvements in liver enzymes and steatosis, but histological benefits are uncertain [45].

Emerging Therapeutic Strategies and Novel Targets for MASLD/MASH

THR-β Agonists

Thyroid hormone receptor-β (THR-β) agonists are liver-directed thyromimetics that selectively stimulate THR-β in hepatocytes, enhancing fatty acid β-oxidation, reducing de novo lipogenesis, and improving atherogenic dyslipidaemia while avoiding the cardiac and skeletal adverse effects linked to THR-α activation [46,47]. Resmetirom (MGL-3196) is the first-in-class oral THR-β agonist to reach phase 3, showing significant reductions in liver fat by MRI-PDFF and improvements in LDL-cholesterol, triglycerides, and apolipoprotein B in NAFLD/MASH populations [47,48]. In histology-based trials (MAESTRO-NASH), once-daily 80–100 mg resmetirom achieved both regulatory-relevant endpoints of NASH resolution and ≥1-stage fibrosis improvement versus placebo. These data led to regulatory approval in 2024 for MASH with fibrosis in some regions, positioning resmetirom

as a benchmark for this drug class [48,49]. Second-generation THR-β agonists such as VK2809, ASC41, CS27109 and TG68 are designed for enhanced hepatoselectivity through prodrug or liver-targeting chemistry, with preclinical models showing robust reductions in hepatic steatosis and improvements in systemic metabolic parameters[46,50,51]. Early-phase clinical data for VK2809 and ASC41 demonstrate meaningful relative decreases in liver fat content and aminotransferases, with preservation of cardiovascular safety markers [50,52] These agents are being explored as monotherapy or in combination with GLP-1 receptor agonists, FGF-21 analogues or FXR agonists for advanced MASLD [53]. Across trials, THR-β agonists generally show an acceptable safety profile, with predominantly mild gastrointestinal symptoms and transient, modest changes in thyroid-axis parameters, and no consistent signal for arrhythmia or bone toxicity at therapeutic doses.[46,47,48] However, current reviews emphasise that heterogeneity of MASLD phenotypes, limited long-term outcome data, and the need for careful patient selection by fibrosis stage and cardiometabolic risk remain key challenges before broad adoption [46,53]. Future research should prioritise head-to-head comparisons with other mechanism-based agents and evaluation of hard outcomes such as decompensation, cardiovascular events and mortality [53].

GLP-1 and GIP Receptor Agonists

GLP-1 receptor agonists and dual GLP-1/GIP agonists promote weight loss through appetite suppression, enhanced insulin secretion, and reduced gastric emptying, indirectly decreasing hepatic steatosis and lipogenesis in MASLD [54,55]. Semaglutide stands out as the first to hit phase 3, cutting liver fat on MRI scans and clearing NASH histology in nearly 60% of patients versus under 20% on placebo, though fibrosis gains were smaller [56,57]. Tirzepatide takes it further as a dual-action powerhouse, delivering even bigger weight drops and MASH resolution rates up to 62% with fibrosis steps forward in SYNERGY-NASH trials. That success earned both approvals for obesity/diabetes and spotlights them as MASLD frontrunners [57,58]. Newer players like liraglutide, dulaglutide, plus triple agonists (GLP-1/glucagon/GIP) show solid drops in liver fat and enzymes across early studies and animal work [59,60]. Phase 2 data for VK2809-style combos and multi-agonists hint at stronger fibrosis benefits, paving way for pairing with THR-β or FXR drugs in tough cases [59,61]. Gastrointestinal intolerance affects 20-40% initially (nausea predominant); gallbladder events increased 1.5-2-fold but hepatotoxicity absent across 50,000+ patients. Histological gains correlate with ≥15% weight loss; long-term decompensation/HCC prevention and cost-effectiveness data remain pending phase 3 completion [62].

PPAR Agonists

PPARs are nuclear hormone receptors regulating lipid metabolism and glucose homeostasis; α/δ/γ agonists modulate hepatocyte/adipocyte pathways to suppress steatosis, inflammation, and fibrosis, while pan-PPAR agents like lanifibranor achieve multi-isoform synergy in MASLD pathogenesis [63]. Pioglitazone (30-45 mg daily, PPAR-γ dominant) achieves MASH resolution in 51% and primary histological endpoint in 58% of biopsy-proven patients versus placebo [64]. Lanifibranor (800-1200 mg daily), a pan-PPAR agonist, reduces liver fat ≥50% by MRI-PDFF with SAF-A improvement in 49% vs 19% placebo (NASH-FITTER phase 2b) [65]. Lanifibranor histology demonstrates MASH resolution without fibrosis worsening in 45% (1200 mg dose) plus ≥1-stage fibrosis regression in 34% [66] Pioglitazone shows phase 3 histological benefits while lanifibranor advances to NATiV3 phase 3 [67]. Saroglitazar (PPAR-α/γ, India-approved) improves MASH histology and fibrosis regression in Asian NAFLD cohorts per EVIDENCES IV study [68]. Elafibranor (PPAR-α/δ) and selective PPAR-δ denifanstat reduce steatosis 40-60% with ALT normalization in phase 2 MASLD trials [69]. VK2809 (dual THR-β/PPAR-δ) demonstrates significant liver fat reduction; early signals support monotherapy and GLP-1/THR-β combinations [70]. Pioglitazone risks include weight gain (2-4 kg), bone fractures (OR 1.45), and heart failure exacerbation; lanifibranor causes mild anemia (Hb -1.2 g/dL),

transient CK elevation, and GI intolerance without hepatotoxicity [71]. Pan-PPARs provide superior antifibrotic activity versus selective agonists but require long-term cardiovascular event and decompensation outcome confirmation against resmetirom/incretins [72].

SGLT1 and SGLT2 Inhibitors

Sodium-glucose co-transporter 1 and 2 (SGLT1/2) are key glucose transporters in the intestine and kidneys, and molecular targets of antidiabetic drugs, flozins. SGLT1 inhibition in the intestine reduces postprandial glucose absorption, while SGLT2 inhibition in the kidneys promotes urinary glucose excretion. Together, these effects reduce glucose and insulin levels, enhance fatty acid β-oxidation, lower insulin resistance, and promote caloric deficit, all relevant to MASLD pathophysiology [73].SGLT2 and dual SGLT1/2 inhibitors lower plasma glucose by promoting urinary glucose excretion and blunting intestinal glucose absorption, which reduces insulin levels, body weight, and hepatic de novo lipogenesis in MASLD.73 In addition, these agents activate hepatorenal protective pathways (AMPK, Nrf2, FGF-21, HIF-1α), attenuating oxidative stress, inflammation, and fibrogenic signaling in steatotic liver disease [74]. Empagliflozin (10–25 mg/day) significantly reduces liver fat on MRI-PDFF and lowers ALT and γ-GT levels in patients with type 2 diabetes and NAFLD, as shown in the E-LIFT trial. Sustained reductions in hepatic fat and improvements in non-invasive fibrosis markers were confirmed over 52 weeks in MASLD. Dapagliflozin (10 mg/day) in recent phase 3 MASH studies increased rates of MASH resolution and fibrosis improvement, with accompanying reductions in liver stiffness and aminotransferases [77]. Across phase 2–3 trials, canagliflozin, ipragliflozin, and other SGLT2 inhibitors consistently reduce CAP-measured steatosis and liver enzymes, with modest improvements in liver stiffness and fibrosis indices [73,78]. Dual SGLT1/2 inhibitors show similar hepatic benefits with stronger postprandial glucose control, and combination strategies with GLP-1 receptor agonists or finer none are under investigation [73,79]. SGLT2/SGLT1/2 inhibitors are well tolerated, with mainly genitourinary infections, volume depletion, and rare ketoacidosis, and no signal of liver toxicity. They improve steatosis and liver enzymes, but confirmation of fibrosis regression and long-term liver outcomes requires phase 3 MASLD trials [73,77,79].

FGF Inhibitors and Acetyl-CoA Carboxylase (ACC) Inhibitors

FGF21 is an endocrine hormone predominantly produced by the liver, playing a crucial role in regulating glucose and lipid metabolism. FGF21, primarily synthesized in hepatocytes, activates FGFR1c/β-Klotho receptor complexes to potentiate peripheral insulin action, accelerate β-oxidation, curtail triglyceride biosynthesis, and mitigate macrophage infiltration in adipose and liver tissue [80]. FGF19 variants primarily suppress bile acid synthesis via FGFR4/FGFR1c while ACC1/ACC2 drive malonyl-CoA formation for lipogenesis and CPT1 inhibition, making both pathways attractive for steatosis-fibrosis dual targeting [81]. Efruxifermin, an Fc-FGF21 fusion, reduces liver fat by 50–75% on MRI-PDFF and achieves MASH resolution without fibrosis worsening in 40–60% across phase 2b doses versus 15% placebo, with sustained fibrosis regression signals at 96 weeks [82,83].Pegozafermin (glycol PEGylated FGF21) demonstrates ≥1-stage fibrosis improvement in 22–27% and MASH resolution in 23–37% of F2–F3 patients during 24-week phase 2b ENLIVEN, maintaining benefits through 48-week extension [84]. Aldafermin (engineered FGF19) yields rapid 30–50% liver fat reductions and fibrosis trends over 24 weeks in phase 2 [85].MK-4074 (liver-targeted ACC1/ACC2 inhibitor) produces 36% intrahepatic fat reduction after 4 weeks at 200 mg BID (NCT01431521), outperforming pioglitazone [86]. PF-05221304 monotherapy achieves 50–65% liver fat decreases with ALT reductions, but elevates triglycerides 8–200%; DGAT2 inhibitor PF-06865571 co-administration (NCT03776175) does not fully counteract this hyperlipidaemia [87,88]. FGF21/FGF19 therapies exhibit primarily mild GI effects and injection reactions; long-term antifibrotic durability and FGF19 oncogenicity

risks require phase 3 clarification [82,84]. ACC inhibitors excel at steatosis but provoke hypertriglyceridemia necessitating lipid co-management; cardiovascular and fibrosis endpoint confirmation pending [86,87].

AMPK Activators

AMP-activated protein kinase (AMPK) serves as a central regulator of cellular energy homeostasis, influencing pathways related to lipid metabolism, glucose uptake, and inflammation [88]. Out of many downstream effects of AMPK activation, the most important in MASLD are inhibition of ACC, which promotes ß-oxidation; inhibition of sterol regulatory element-binding protein 1 (SREBP-1c), which downregulates fatty acid synthase (FAS) and de novo lipogenesis; and inhibition of β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, which reduces cholesterol synthesis and promotion of glucose transporter 1 and 4 translocation towards cell membranes. Thus, AMPK activation has been proposed as a therapeutic strategy to mitigate hepatic steatosis and improve insulin sensitivity [89]. PXL770, a novel direct allosteric AMPK activator, reduces liver fat by 10–15% on MRI-PDFF and lowers ALT by 15–20 U/L in presumed NASH patients with/without T2DM during 12-week phase 2a DESTINY-1, with greater responses in high-risk T2DM-NASH subgroups[89]. Metformin, an indirect AMPK activator via LKB1/AMPK signalling, improves steatosis and ALT in 30% of NASH patients and decreases NAFLD progression risk by 40% in meta-analyses of T2DM cohorts. PXL770 advances to phase 2b while metformin provides established metabolic support in MASLD [90]. ATX-304, a direct pan-AMPK activator, reduces hepatic steatosis, oxidative stress, and lipid synthesis while improving cholesterol handling in preclinical MASH models, warranting clinical translation [91]. KN21, a 4-chloro-benzenesulfonamide derivative, ameliorates steatosis and fibrosis via direct AMPK activation in diet-induced MASH mice by suppressing stellate cell activation [92]. AICAR, a pharmacologic AMPK agonist, alleviates ferroptosis and endoplasmic reticulum stress in experimental NAFLD through activation of the Nrf2/HO-1 pathways [93]. PXL770 demonstrates favourable tolerability with only mild gastrointestinal effects and no hepatotoxicity, whereas metformin carries a risk primarily of lactic acidosis in patients with renal impairment [94]. While AMPK activators excel at metabolic reprogramming, they currently lack phase 3 clinical trial data demonstrating histological endpoints. Direct AMPK activators such as PXL770 and ATX-304 may supersede metformin in fibrosis regression [92]. However, head-to-head trials comparing these agents versus resmetirom, incretin-based therapies, and long-term outcome data are still needed [95].

CONCLUSION

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has rapidly become a major global health concern, with its progression to MASH, fibrosis, cirrhosis, and hepatocellular carcinoma posing significant clinical challenges. Despite the growing understanding of its multifactorial pathogenesis, there remains no single approved pharmacotherapy that addresses the full spectrum of disease mechanisms. Emerging therapeutic agents targeting metabolic pathways, inflammation, lipid homeostasis, and fibrogenesis have shown encouraging results in both preclinical and clinical studies. Drugs such as FXR agonists, PPAR agonists, GLP-1 receptor agonists, FGF21 analogs, THR-β agonists, and multi-agonists represent a new era of targeted treatment strategies with potential to modify disease outcomes. However, variations in patient phenotype, disease heterogeneity, and long-term safety concerns highlight the need for personalized therapeutic approaches and combination regimens. As the therapeutic pipeline continues to expand, large-scale, long-duration clinical trials are essential to validate the efficacy, safety, and real-world applicability of these agents. Overall, the future of MASLD therapy appears promising, with emerging pharmacotherapies offering hope for effective disease modification and improved patient outcomes. The therapeutic landscape for MASLD is rapidly evolving with several promising agents that reduce liver fat and, in some cases, achieve histologic NASH resolution.

Fibrosis regression remains the critical determinant for long-term clinical benefit. Combination strategies, validated non-invasive endpoints, and long-term safety/outcomes data will shape future standards of care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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