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Review Article

Emerging Pharmacology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Current Advances and Future Therapeutic Perspectives

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major global health problem and represents the hepatic manifestation of metabolic dysfunction. It is characterized by accumulation of hepatic fat in individuals with one or more cardiometabolic risk factors and encompasses a broad clinical spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis and hepatocellular carcinoma. The disease was previously known as non-alcoholic fatty liver disease (NAFLD), while NASH has been renamed MASH under the updated nomenclature. Increasing prevalence of obesity, type 2 diabetes mellitus, dyslipidaemia and metabolic syndrome has contributed to the rapidly expanding burden of MASLD. Although lifestyle modification remains the cornerstone of management, pharmacological treatment has undergone major transformation during the last few years. Resmetirom, a selective thyroid hormone receptor-β agonist, was the first drug specifically approved for non-cirrhotic MASH with moderate-to-advanced fibrosis. Semaglutide, a glucagon-like peptide-1 receptor agonist, subsequently became another major advance after demonstrating significant improvement in MASH resolution and fibrosis in the phase 3 ESSENCE trial. Other promising therapeutic approaches include dual incretin agonists such as tirzepatide, glucagon/GLP-1 receptor agonists such as survodutide, pan-peroxisome proliferator-activated receptor agonists such as lanifibranor, fibroblast growth factor-21 analogues such as pegozafermin and efruxifermin, liver-directed thyroid hormone receptor-β agonists such as VK2809, and antifibrotic approaches including galectin-3 inhibition. These therapies act on diverse mechanisms including hepatic lipid oxidation, insulin resistance, appetite regulation, mitochondrial function, inflammation and fibrosis. The future of MASLD pharmacotherapy is likely to involve precision medicine, combination therapy and

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simultaneous targeting of metabolic and fibrogenic pathways. This review discusses the pathogenesis of MASLD, major pharmacological targets, currently available therapies, emerging drugs, clinical evidence, safety considerations, limitations and future directions.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common chronic liver disorders worldwide. It is closely associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension and other components of metabolic syndrome [1,2]. The disease is increasingly recognized not simply as an isolated liver disorder but as a systemic metabolic condition involving complex interactions between adipose tissue, liver, skeletal muscle, intestine and cardiovascular system.

The terminology of fatty liver disease has undergone an important change. In 2023, an international multidisciplinary consensus replaced the term non-alcoholic fatty liver disease (NAFLD) with metabolic dysfunction-associated steatotic liver disease (MASLD). The inflammatory form of the disease, previously called non-alcoholic steatohepatitis (NASH), is now termed metabolic dysfunction-associated steatohepatitis (MASH) [1]. This terminology emphasizes positive metabolic risk factors rather than defining the condition primarily by exclusion of alcohol consumption.

MASLD includes a wide spectrum of disease. Some patients have relatively stable hepatic steatosis, whereas others develop hepatocellular injury, inflammation and progressive fibrosis. MASH is the progressive phenotype in which hepatocyte injury and inflammation occur together with variable degrees of fibrosis. Advanced fibrosis is particularly important because it is strongly associated with liver-related complications, cirrhosis and hepatocellular carcinoma [2,3].

The increasing prevalence of obesity and T2DM has resulted in a substantial increase in MASLD worldwide. Importantly, cardiovascular disease remains a major cause of morbidity and mortality in patients with MASLD, making management of metabolic and cardiovascular risk factors an essential part of treatment [4].

For many years, pharmacological treatment for MASLD was largely limited to drugs used to treat associated metabolic disorders. Vitamin E and pioglitazone were used in selected patients, while statins were employed primarily for cardiovascular risk reduction. No drug was specifically approved for MASH. This situation changed dramatically with the development of agents directed against hepatic lipid metabolism, insulin resistance, inflammation and fibrosis [5,6].

Resmetirom became the first specifically approved MASH-targeted therapy for patients with non-cirrhotic disease and moderate-to-advanced fibrosis. Semaglutide has subsequently expanded the therapeutic landscape, with the 2025 ESSENCE trial providing phase 3 evidence for histological improvement in MASH [7,8]. Current AASLD guidance now incorporates semaglutide and resmetirom into treatment considerations for appropriately selected patients with F2–F3 fibrosis.

These developments have transformed MASLD from an area of limited pharmacological options into one of the most rapidly evolving fields of hepatology. This review focuses on the emerging pharmacology of MASLD and MASH, with particular emphasis on mechanisms of action, clinical evidence, safety, limitations and future therapeutic strategies.

2. EPIDEMIOLOGY AND DISEASE BURDEN

MASLD is highly prevalent across both developed and developing countries. Its occurrence parallels the prevalence of obesity, T2DM and metabolic syndrome [2,9]. The burden is expected to increase further because of continuing changes in dietary patterns, sedentary lifestyles and increasing prevalence of obesity.

MASLD can occur in individuals with obesity as well as in individuals with normal body weight. The latter group is sometimes described as having lean MASLD. Although metabolic risk may be less obvious in lean individuals, insulin resistance, visceral adiposity, genetic factors and altered lipid metabolism may still contribute to disease development [4].

T2DM is one of the strongest predictors of advanced fibrosis and disease progression. Patients with both MASLD and diabetes require particular attention because diabetes accelerates hepatic and cardiovascular complications [4,10].

- Cardiovascular disease
- T2DM
- Chronic kidney disease
- Hypertension
- Dyslipidaemia
- Obesity-related complications
- Cirrhosis
- Hepatocellular carcinoma

3. PATHOGENESIS OF MASLD

MASLD is a complex multifactorial disease. The earlier two-hit hypothesis has largely been replaced by a multiple-hit model in which several metabolic and cellular abnormalities act simultaneously [3,11].

3.1 Insulin resistance

Insulin resistance is a central feature of MASLD. Impaired insulin action in adipose tissue increases lipolysis and the release of free fatty acids into the circulation. The liver consequently receives an excessive supply of fatty acids. At the same time, hepatic insulin resistance may coexist with increased de novo lipogenesis. The resulting imbalance between fatty-acid uptake, synthesis, oxidation and export promotes triglyceride accumulation in hepatocytes [3,11].

Insulin resistance → increased lipolysis → increased free fatty acids → hepatic lipid accumulation → steatosis

3.2 Hepatic lipotoxicity

Simple accumulation of triglycerides may not itself be the major cause of hepatocellular injury. Toxic lipid intermediates such as ceramides, diacylglycerols and free fatty acids can induce cellular stress. Lipotoxicity contributes to mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, hepatocyte apoptosis and inflammatory signalling [3,11].

3.3 Mitochondrial dysfunction

Mitochondria are central to fatty-acid oxidation and energy metabolism. Excessive lipid delivery can overload mitochondrial pathways, producing reactive oxygen species and impairing ATP production. Mitochondrial dysfunction therefore represents an important pharmacological target. Agents that improve hepatic fatty-acid oxidation,

such as THR-β agonists and FGF21 analogues, may improve the metabolic environment of the liver [7,12].

3.4 Oxidative stress

Excessive production of reactive oxygen species results in oxidative damage to proteins, lipids and DNA. Oxidative stress can activate inflammatory and fibrogenic pathways. Antioxidant strategies have therefore been investigated, although the clinical effectiveness of antioxidant therapy remains limited compared with newer mechanism-based approaches [13].

3.5 Inflammation

Damaged hepatocytes release intracellular molecules that activate innate immune pathways. Kupffer cells and recruited immune cells produce inflammatory mediators such as tumour necrosis factor-α, interleukin-6 and other cytokines. Persistent inflammation contributes to hepatocyte injury and activation of hepatic stellate cells [11,14].

3.6 Fibrogenesis

Progressive fibrosis is the most important pathological determinant of long-term liver-related outcomes. Chronic hepatocellular injury activates hepatic stellate cells. Activated stellate cells transform into myofibroblast-like cells and produce extracellular matrix proteins, particularly collagen. Chronic injury → Kupffer-cell activation → stellate-cell activation → extracellular matrix deposition → fibrosis. Because fibrosis progression determines the risk of cirrhosis, direct antifibrotic therapy represents an important area of drug development [14].

3.7 Gut–liver axis

The intestine contributes to MASLD through alterations in intestinal microbiota, intestinal permeability, bacterial metabolites and bile-acid signalling. Changes in the gut microbiome can influence energy extraction, inflammation, bile-acid metabolism, insulin resistance and intestinal permeability. Consequently, microbiome-directed therapies and bile-acid pathway modulators are being investigated as future treatments [15].

4. PHARMACOLOGICAL TARGETS IN MASLD

The major pharmacological targets currently under investigation include: hepatic lipid metabolism; thyroid hormone receptor-β; GLP-1 signalling; GIP signalling; glucagon signalling; PPAR signalling; FGF21 pathways; FXR/bile-acid signalling; inflammatory pathways; fibrogenic pathways; oxidative stress; and the gut–liver axis. This diversification of therapeutic targets reflects the complex pathophysiology of MASLD.

5. CURRENT MANAGEMENT OF MASLD

5.1 Lifestyle modification

Lifestyle modification remains the foundation of treatment. Calorie restriction, increased physical activity and sustained weight reduction can decrease hepatic steatosis and improve metabolic health [5,16]. Weight loss is particularly important because greater degrees of sustained weight reduction are associated with greater improvement in MASH and fibrosis. However, long-term maintenance of substantial weight loss is difficult for many patients. This limitation has encouraged development of pharmacological approaches that can support sustained metabolic improvement.

6. RESMETIROM: A MAJOR ADVANCE IN MASH PHARMACOTHERAPY

Resmetirom is a selective thyroid hormone receptor-β (THR-β) agonist and represents one of the most important advances in MASH pharmacology.

6.1 Pharmacological rationale

Thyroid hormones regulate hepatic lipid metabolism. THR-β is highly expressed in the liver and participates in regulation of fatty-acid oxidation, mitochondrial function and cholesterol metabolism [12]. Resmetirom selectively activates THR-β and therefore attempts to reproduce beneficial hepatic effects of thyroid hormone while minimizing unwanted systemic thyroid hormone effects.

6.2 Mechanism of action

Resmetirom → THR-β activation → increased mitochondrial fatty-acid oxidation → reduced hepatic lipid accumulation. It also enhances pathways involved in cholesterol metabolism and hepatic lipid clearance.

6.3 Clinical evidence

The MAESTRO-NASH phase 3 trial evaluated resmetirom in patients with MASH and fibrosis. Resmetirom significantly improved histological endpoints compared with placebo [7]. The trial demonstrated improvements in MASH resolution and fibrosis-related endpoints, providing important evidence for the clinical efficacy of THR-β agonism. Resmetirom subsequently became the first drug specifically approved by the U.S. FDA for adults with non-cirrhotic MASH and moderate-to-advanced fibrosis [7].

6.4 Pharmacological effects

Resmetirom reduces hepatic fat, increases fatty-acid oxidation, improves hepatic lipid metabolism, reduces atherogenic lipid parameters, improves MASH activity and has potential antifibrotic effects.

6.5 Adverse effects

Common adverse effects include diarrhoea, nausea, pruritus, vomiting and abdominal symptoms. Thyroid status and clinically relevant drug interactions should be considered during treatment. Current guidance emphasizes appropriate selection of patients with significant fibrosis and monitoring of treatment response and safety [5,17].

7. SEMAGLUTIDE AND THE INCRETIN-BASED APPROACH

Semaglutide is a long-acting GLP-1 receptor agonist widely used for diabetes and obesity. Its effects are particularly relevant to MASLD because obesity and insulin resistance are major drivers of the disease.

7.1 Mechanism of action

GLP-1 receptor activation produces increased glucose-dependent insulin secretion, reduced glucagon secretion, delayed gastric emptying, reduced appetite, reduced caloric intake, weight loss and improved insulin sensitivity. The hepatic benefits are therefore partly mediated indirectly through substantial metabolic improvement.

7.2 Effects on MASLD

GLP-1 activation → reduced appetite → weight loss → improved insulin sensitivity → reduced hepatic fat → reduced MASH activity. Semaglutide may also exert direct or indirect effects on hepatic inflammation and lipid metabolism.

7.3 ESSENCE trial

The phase 3 ESSENCE trial enrolled patients with biopsy-defined MASH and F2–F3 fibrosis. Once-weekly semaglutide 2.4 mg was evaluated against placebo [8]. The trial showed significant improvement in MASH resolution and fibrosis-related endpoints. The results represented a major advance in incretin-based therapy for MASH. The updated AASLD guidance published in 2025 incorporated semaglutide into the management of appropriately selected patients with MASH and moderate-to-advanced fibrosis.

7.4 Adverse effects

The most frequent adverse effects are gastrointestinal: nausea, vomiting, diarrhoea, constipation and abdominal discomfort. Dose escalation can improve tolerability. Clinicians should also consider gallbladder disease, pancreatitis risk, dehydration-related kidney injury and loss of lean mass in appropriate patients [17].

8. TIRZEPATIDE: DUAL GIP/GLP-1 RECEPTOR AGONISM

Tirzepatide activates both the glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor. This dual mechanism provides substantial effects on appetite, body weight, insulin sensitivity, glycaemic control and hepatic steatosis.

8.1 Mechanism

GIP + GLP-1 receptor activation → improved insulin action + reduced food intake → weight reduction → reduced hepatic fat and inflammation.

8.2 SYNERGY-NASH trial

In the phase 2 SYNERGY-NASH study, tirzepatide demonstrated significant MASH resolution compared with placebo and produced substantial metabolic benefits [18]. The findings are important because tirzepatide may address several major drivers of MASLD simultaneously.

8.3 Advantages

Significant weight reduction; improved glycaemic control; reduced liver fat; improvement in MASH activity; cardiometabolic benefits.

8.4 Limitations

Long-term fibrosis and clinical-outcome data remain necessary before its precise position as a MASH-directed therapy can be established.

9. SURVODUTIDE: GLUCAGON/GLP-1 DUAL AGONISM

Survodutide is a dual agonist of the glucagon receptor and GLP-1 receptor. The combination is pharmacologically attractive because GLP-1 reduces appetite and improves glucose metabolism, whereas glucagon may increase energy expenditure and lipid mobilisation.

9.1 Mechanism

GLP-1 activation → reduced appetite + improved glycaemic control. Glucagon activation → increased energy expenditure + lipid mobilisation. Together: dual receptor activation → weight loss + reduced hepatic steatosis + metabolic improvement.

9.2 Clinical evidence

A phase 2 trial involving patients with MASH and fibrosis demonstrated significantly greater MASH improvement with survodutide than placebo [19]. Improvement in liver fat was also observed. However, gastrointestinal adverse effects such as nausea, diarrhoea and vomiting were relatively

common. The results support further development of survodutide as a potential MASH therapy.

10. PPAR AGONISTS

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that regulate glucose metabolism, fatty-acid oxidation, inflammation and fibrogenesis. The three principal PPAR isoforms are PPAR-α, PPAR-γ and PPAR-δ. Because these receptors influence several components of MASLD pathogenesis, PPAR agonists are attractive multi-target therapies.

10.1 Lanifibranor

Lanifibranor is a pan-PPAR agonist that activates PPAR-α, PPAR-δ and PPAR-γ. PPAR activation may improve insulin sensitivity, increase fatty-acid oxidation, reduce lipotoxicity, decrease inflammation, modulate stellate-cell activity and reduce fibrogenic signalling. The NATIVE phase 2b trial demonstrated improvement in disease activity and fibrosis-related outcomes [20]. Potential adverse effects include weight gain, peripheral oedema and gastrointestinal symptoms. Therefore, the benefit-risk profile must be carefully assessed.

11. FGF21 ANALOGUES

Fibroblast growth factor 21 (FGF21) is an endocrine metabolic hormone involved in glucose and lipid homeostasis. FGF21 signalling influences fatty-acid oxidation, glucose metabolism, lipid metabolism, energy expenditure and inflammation. Long-acting FGF21 analogues are being developed to reproduce these metabolic effects therapeutically.

12. PEGOZAFERMIN

Pegozafermin is a long-acting FGF21 analogue. FGF21 receptor signalling enhances lipid oxidation, improves insulin sensitivity and reduces hepatic fat. In addition to improving liver-related parameters, FGF21 analogues can improve circulating triglyceride levels and other metabolic abnormalities. In a randomized phase 2b trial, pegozafermin produced improvements in fibrosis and MASH resolution compared with placebo [21]. These findings support continued development of FGF21 analogues. Long-term efficacy, durability of fibrosis improvement and clinical outcomes require further evaluation.

13. EFRUXIFERMIN

Efruxifermin is another long-acting FGF21 analogue. It has demonstrated improvements in liver fat, liver enzymes, lipid metabolism, fibrosis-related endpoints and MASH activity. Longer-term phase 2b data in patients with F2–F3 fibrosis have shown encouraging fibrosis improvement, supporting continued development. However, results in compensated MASH cirrhosis highlight the difficulty of reversing advanced fibrosis. In a phase 2b study, the primary fibrosis endpoint at 36 weeks was not significantly different from placebo [22]. This illustrates an important principle: the effectiveness of metabolic therapies may depend strongly on the stage of fibrosis.

14. LIVER-DIRECTED THYROID HORMONE RECEPTOR-β AGONISTS

Resmetirom has validated THR-β as an important therapeutic target. Other liver-directed THR-β agonists, including VK2809, are being developed to enhance hepatic lipid metabolism.

Potential advantages include increased hepatic fatty-acid oxidation, reduction of liver fat, improved cholesterol metabolism, liver-selective pharmacological action and potential reduction of systemic thyroid hormone effects. The development of multiple THR-β agonists

demonstrates the importance of hepatic lipid metabolism as a pharmacological target [12,23].

15. FXR AND BILE-ACID SIGNALLING

The farnesoid X receptor (FXR) is a nuclear receptor activated by bile acids. FXR regulates bile-acid synthesis, lipid metabolism, glucose metabolism, inflammation and fibrogenic signalling. FXR activation can suppress hepatic lipogenesis and influence bile-acid homeostasis.

Obeticholic acid was one of the most extensively studied FXR agonists in MASH. Although it demonstrated antifibrotic activity, development highlighted important challenges related to adverse effects, particularly pruritus and lipid abnormalities [24]. The experience with obeticholic acid demonstrates that a biologically effective drug must also demonstrate an acceptable long-term benefit-risk profile.

16. ANTIFIBROTIC THERAPIES

Fibrosis is the strongest histological predictor of liver-related outcomes. Consequently, direct antifibrotic therapies are an important area of drug development. Potential targets include hepatic stellate cells, transforming growth factor-β signalling, integrins, galectin-3, collagen formation, extracellular matrix turnover and inflammatory pathways. Future therapies may combine metabolic correction with direct inhibition of fibrogenesis.

17. GALECTIN-3 INHIBITION

Galectin-3 is involved in macrophage activation, inflammation and fibrogenesis. Belapectin is a galectin-3 inhibitor under investigation for MASH-related fibrosis and portal hypertension. The rationale is: Galectin-3 inhibition → reduced macrophage/stellate-cell activation → reduced fibrogenesis. Clinical studies have produced mixed results, but recent data have renewed interest in galectin-3 as a potential antifibrotic target. Importantly, antifibrotic therapy may be particularly valuable in patients in whom metabolic improvement alone is insufficient.

18. SGLT2 INHIBITORS

Sodium-glucose cotransporter-2 inhibitors are primarily used for T2DM, heart failure and chronic kidney disease. Examples include empagliflozin, dapagliflozin and canagliflozin. Potential hepatic benefits include weight reduction, improved insulin sensitivity, reduced visceral adiposity, improvement in liver enzymes and reduction in liver fat. Although SGLT2 inhibitors are promising in MASLD, evidence is currently stronger for metabolic, cardiovascular and renal benefits than for histological reversal of fibrosis [25].

19. PIOGLITAZONE

Pioglitazone is a PPAR-γ agonist used in T2DM. It improves insulin sensitivity and has demonstrated beneficial effects on MASH activity in selected patients.

Mechanism: PPAR-γ activation → improved adipose insulin sensitivity → reduced free fatty-acid delivery to liver → reduced hepatic lipotoxicity.

Advantages: improves insulin sensitivity, improves glycaemic control, can improve MASH activity, and is particularly relevant in patients with T2DM.

Limitations: weight gain, oedema, risk of heart failure exacerbation, fracture risk and delayed onset of hepatic benefit. Therefore, pioglitazone is generally selected according to individual metabolic and clinical characteristics rather than used universally for MASLD.

20. VITAMIN E

Vitamin E is an antioxidant that has been studied in MASH because oxidative stress contributes to hepatocyte injury. Its proposed mechanism is: Vitamin E → reduced lipid peroxidation → reduced oxidative injury → improvement in hepatic inflammation. Clinical trials have demonstrated improvement in selected histological features in certain patients [13]. However, limitations include inconsistent fibrosis benefit, uncertainty regarding long-term use and need for patient selection. Therefore, vitamin E does not occupy the same therapeutic position as newer MASH-targeted agents.

21. STATINS AND DYSLIPIDAEMIA MANAGEMENT

Cardiovascular disease is a major contributor to mortality in MASLD. Therefore, treatment of dyslipidaemia is essential. Statins reduce LDL cholesterol and cardiovascular risk and treat a major metabolic comorbidity. MASLD itself should not be considered a reason to withhold statin therapy when clinically indicated. However, statins are primarily cardiovascular risk-reducing therapies rather than direct MASH antifibrotic agents.

22. COMPARISON OF MAJOR EMERGING THERAPIES

23. ROLE OF COMBINATION THERAPY

MASLD is a multifactorial disease; therefore, a single drug may not adequately address all pathogenic mechanisms. Combination pharmacotherapy is an important future concept.

23.1 Metabolic + liver-directed therapy GLP-1/GIP therapy + THR-β agonist: weight reduction and improved insulin sensitivity + increased hepatic lipid oxidation → potentially greater reduction in liver fat and MASH activity.

23.2 Incretin + FGF21 therapy Incretin agonist + FGF21 analogue: reduced appetite and weight + enhanced lipid oxidation → potential complementary effects.

23.3 Metabolic + antifibrotic therapy Weight/metabolic therapy + direct antifibrotic agent: correction of metabolic drivers + inhibition of stellate-cell activity → potential reduction in fibrosis progression.

However, combination therapy should not be routinely adopted without evidence from controlled clinical trials. The 2025 AASLD semaglutide guidance specifically notes that combination use of resmetirom and semaglutide has not yet been adequately studied, illustrating the current evidence gap.

24. NON-PHARMACOLOGICAL THERAPY AND ITS RELATION TO PHARMACOTHERAPY

Pharmacotherapy should complement rather than replace lifestyle intervention.

24.1 Diet: A calorie-controlled diet can reduce hepatic fat and improve insulin sensitivity.

24.2 Exercise: Both aerobic and resistance exercise may reduce hepatic steatosis even when substantial weight loss does not occur.

24.3 Weight reduction: The magnitude and durability of weight loss are important determinants of hepatic improvement.

24.4 Bariatric/metabolic surgery: In selected patients with severe obesity, metabolic surgery can produce substantial and sustained weight reduction and may improve MASH and fibrosis.

Therefore, the modern approach is: Lifestyle modification + metabolic risk management + appropriate pharmacotherapy rather than pharmacotherapy alone.

25. PATIENT SELECTION FOR PHARMACOTHERAPY

Not every patient with MASLD requires MASH-directed pharmacotherapy. Patients should first undergo assessment of metabolic risk factors, liver enzymes, fibrosis risk, diabetes status, body weight, cardiovascular risk, kidney function and potential drug interactions.

Non-invasive tests such as FIB-4, vibration-controlled transient elastography, magnetic resonance elastography and the ELF test can help identify patients at increased risk of significant fibrosis.

Current guidance focuses treatment of MASH-directed agents on appropriately selected patients with significant fibrosis, particularly F2–F3 disease [5,17].

26. MONITORING OF PHARMACOLOGICAL THERAPY

Monitoring should be individualized according to the drug used.

Baseline assessment: liver function tests, renal function, lipid profile, glycaemic parameters, body weight, fibrosis assessment and relevant drug interactions.

During therapy monitor treatment adherence, body weight, liver enzymes when clinically appropriate, metabolic parameters, adverse effects and non-invasive fibrosis measures where appropriate.

Response assessment may include reduction in ALT, reduction in liver fat, improvement in metabolic parameters, weight reduction and improvement in non-invasive fibrosis markers. However, non-invasive markers should not automatically be interpreted as equivalent to histological response.

27. SAFETY CONSIDERATIONS

Emerging MASLD therapies have different safety profiles.

Resmetirom: important considerations include gastrointestinal adverse effects, thyroid-related issues and drug interactions.

Semaglutide: common adverse effects are gastrointestinal. Clinicians should remain alert to gallbladder disease, pancreatitis risk, dehydration-related renal injury and other class-specific risks.

Tirzepatide: gastrointestinal adverse effects are common, particularly during dose escalation.

Survodutide: nausea, vomiting and diarrhoea may limit tolerability.

PPAR agonists: weight gain and oedema are important considerations.

FGF21 analogues: injection-site reactions and gastrointestinal effects may occur, while long-term safety continues to be evaluated.

Therefore, efficacy must always be balanced against tolerability and long-term safety.

28. CHALLENGES IN MASLD DRUG DEVELOPMENT

28.1 Disease heterogeneity: MASLD is not a single uniform disease. Patients differ in obesity, diabetes, lipid abnormalities, genetic background, inflammation and fibrosis stage.

28.2 Fibrosis develops slowly: meaningful fibrosis improvement may require prolonged treatment.

28.3 Histological assessment: liver biopsy remains an important research endpoint but is invasive, expensive and subject to sampling variability.

28.4 Surrogate endpoints: improvement in liver enzymes or liver fat does not necessarily guarantee improvement in long-term clinical outcomes.

28.5 Advanced fibrosis and cirrhosis: many drugs perform differently in F2–F3 disease compared with established cirrhosis.

28.6 Cost and accessibility: novel therapies may be expensive, creating challenges for widespread implementation.

28.7 Long-term adherence: many therapies require prolonged treatment. Treatment discontinuation may lead to loss of metabolic or hepatic benefits.

29. PRECISION MEDICINE IN MASLD

Future MASLD treatment is likely to become increasingly personalized. Patients may eventually be classified according to degree of fibrosis, presence of T2DM, obesity phenotype, lipid abnormalities, inflammatory activity, genetic risk, gut microbiome profile and cardiovascular risk.

For example: obesity-dominant phenotype → incretin-based therapy; lipid-dominant phenotype → THR-β-directed therapy; insulin-resistant phenotype → PPAR/incretin approaches; fibrosis-dominant phenotype → antifibrotic therapy. Such an approach could improve treatment response while reducing unnecessary exposure to ineffective therapies.

30. EMERGING RESEARCH AREAS

30.1 Gut microbiome-directed therapies: probiotics, prebiotics, microbiota-derived metabolites, bile-acid modulation and microbiome-targeted drugs.

30.2 Mitochondrial therapies: improving mitochondrial function and reducing oxidative stress may prevent hepatocyte injury.

30.3 Anti-inflammatory therapy: selective inhibition of inflammatory pathways may reduce progression from steatosis to MASH.

30.4 Direct antifibrotic therapy: targeting stellate cells and extracellular matrix turnover could provide benefits independent of weight loss.

30.5 Multi-receptor agonists: drugs targeting GLP-1, GIP and glucagon pathways represent an important direction in metabolic pharmacology.

30.6 Combination therapy: the most effective future strategy may involve two or more complementary mechanisms.

31. FUTURE THERAPEUTIC LANDSCAPE

The emerging pharmacological landscape can be broadly divided into five categories:

A. Hepatic lipid-targeting drugs — Example: resmetirom

B. Weight-loss and incretin therapies — Examples: semaglutide, tirzepatide

C. Multi-receptor metabolic therapies — Examples: survodutide and other multi-agonists

D. Metabolic/fibrosis-modifying therapies — Examples: lanifibranor and FGF21 analogues

E. Direct antifibrotic therapies — Examples: galectin-3 and other fibrogenic pathway inhibitors

The future is therefore likely to move from single-target treatment to pathway-based combination treatment.

32. PROPOSED PHARMACOLOGICAL ALGORITHM

MASLD diagnosis → Assessment of metabolic risk factors → Non-invasive fibrosis assessment → Low fibrosis risk: lifestyle intervention, weight management, diabetes management, lipid management and cardiovascular risk reduction → Significant fibrosis/MASH: lifestyle intervention plus appropriate MASH-directed pharmacotherapy → F2–F3 fibrosis: consider approved MASH-directed therapy according to eligibility → monitor efficacy and safety → assess treatment response → long-term follow-up → consider emerging/combination therapy when supported by evidence.

33. DISCUSSION

The pharmacological treatment of MASLD has entered a new era. Earlier approaches mainly addressed metabolic comorbidities, while current therapies increasingly target the molecular mechanisms responsible for hepatic steatosis, inflammation and fibrosis.

Resmetirom has provided proof that direct modulation of hepatic lipid metabolism can improve clinically relevant histological endpoints. The drug has also demonstrated the therapeutic value of selective THR-β activation [7].

Semaglutide represents a complementary approach. Rather than acting primarily through a liver-specific receptor, it produces substantial systemic metabolic effects through GLP-1 receptor activation. Weight reduction, improved insulin sensitivity and decreased hepatic fat collectively contribute to improvement in MASH [8].

Tirzepatide takes this concept further by activating both GIP and GLP-1 receptors. Survodutide adds glucagon receptor activation to GLP-1 signalling and may increase energy expenditure while reducing appetite [18,19].

FGF21 analogues represent another important class because they directly influence lipid and energy metabolism. Pegozafermin and efruxifermin have generated encouraging fibrosis-related results, although further phase 3 evidence is required [21,22].

PPAR agonists provide another multi-pathway approach. Lanifibranor simultaneously influences metabolism, inflammation and fibrogenesis, making it mechanistically attractive [20].

An important lesson from previous drug-development failures is that improvement in one disease component does not necessarily translate into meaningful long-term clinical benefit. Obeticholic acid demonstrated antifibrotic efficacy but encountered important safety and regulatory challenges [24]. This highlights the importance of evaluating not only histological efficacy but also cardiovascular safety, tolerability, quality of life and long-term liver outcomes.

The increasing number of active pharmacological pathways also raises the possibility of combination therapy. MASLD is driven by multiple simultaneous abnormalities; therefore, targeting hepatic lipid metabolism, obesity, insulin resistance and fibrosis together may ultimately produce greater benefit than targeting one pathway alone.

Nevertheless, combination therapy must be supported by clinical trials because theoretical synergy does not guarantee clinical benefit. Current guidance specifically acknowledges the limited evidence regarding combinations of newly approved MASH-directed treatments.

34. CONCLUSION

MASLD has evolved from a condition with limited pharmacological treatment options into a rapidly expanding therapeutic field. The understanding of its pathogenesis has identified numerous potential targets, including hepatic lipid metabolism, insulin resistance, incretin signalling, glucagon signalling, PPAR pathways, FGF21 signalling, bile-acid pathways, inflammation and fibrosis.

Resmetirom represents a major milestone as the first specifically approved therapy targeting MASH in patients with significant non-cirrhotic fibrosis. Semaglutide has further expanded treatment options by demonstrating significant histological benefits while simultaneously addressing obesity and metabolic dysfunction. Tirzepatide, survodutide, lanifibranor, pegozafermin, efruxifermin, VK2809 and antifibrotic agents represent important emerging approaches.

The future of MASLD pharmacotherapy is unlikely to depend on a single magic bullet. Instead, successful treatment will probably involve individualized therapy based on disease stage, metabolic phenotype, fibrosis risk and comorbidities. Combination therapy involving metabolic, liver-directed and antifibrotic mechanisms may eventually provide the most comprehensive approach.

Continued development of non-invasive biomarkers will improve patient selection and treatment monitoring, while long-term clinical-outcome trials will determine which emerging agents translate into reductions in cirrhosis, hepatic decompensation, hepatocellular carcinoma and mortality.

Thus, the emerging pharmacology of MASLD represents a transition from nonspecific metabolic management toward mechanism-based, personalized and potentially combination pharmacotherapy.

35. KEY POINTS

1. MASLD is a metabolic liver disease strongly associated with obesity, T2DM and dyslipidaemia.

2. MASH with significant fibrosis represents a high-risk phenotype.

3. Insulin resistance, lipotoxicity, oxidative stress, inflammation and fibrogenesis are major therapeutic targets.

4. Resmetirom is a selective THR-β agonist targeting hepatic lipid metabolism.

5. Semaglutide provides an important incretin-based approach.

6. Tirzepatide targets both GIP and GLP-1 receptors.

7. Survodutide combines glucagon and GLP-1 receptor activation.

8. Lanifibranor targets PPAR-α, PPAR-δ and PPAR-γ.

9. Pegozafermin and efruxifermin target FGF21 pathways.

10. FXR and galectin-3 remain important investigational targets.

11. SGLT2 inhibitors and pioglitazone may be useful for selected metabolic phenotypes.

12. Lifestyle modification remains fundamental.

13. Cardiovascular risk reduction is essential because cardiovascular disease is a major cause of mortality in MASLD.

14. Combination therapy may become important in the future.

15. Precision medicine may ultimately determine which therapy is best for each patient.

CURRENT EVIDENCE AND REGULATORY STATUS

Resmetirom is currently a key MASH-directed therapy for adults with non-cirrhotic disease and moderate-to-advanced fibrosis (F2–F3). It received U.S. FDA approval in March 2024 and is used together with diet and exercise. Its approval established thyroid hormone receptor-β (THR-β) activation as a clinically validated liver-directed strategy. [7,26]

Semaglutide has subsequently expanded the therapeutic landscape. In the phase 3 ESSENCE trial, once-weekly semaglutide 2.4 mg improved histologic outcomes in patients with MASH and F2–F3 fibrosis. The 2025 AASLD update provides practical recommendations for patient selection, monitoring and safety, while emphasizing continued lifestyle intervention. [8,27]

These advances should be interpreted within the broader MASLD framework: treatment selection depends on fibrosis stage, metabolic phenotype, comorbidities, contraindications, tolerability, cost and local regulatory availability. [5,27]

Table 1. Major pharmacological approaches in MASLD/MASH

Agent/ class	Target	Principal pharmacological effect	Clinical role/ evidence	Important limitations
Resmetirom	THR-β	↑ hepatic fatty-acid oxidation and lipid clearance	Approved for non-cirrhotic MASH with F2–F3 fibrosis	GI effects; thyroid/drug-interaction monitoring
Semaglutide	GLP-1 receptor	Weight loss, improved insulin sensitivity and metabolic control	Phase 3 ESSENCE; FDA-approved MASH indication in 2025	GI effects; long-term outcome data evolving
Tirzepatide	GIP/GLP-1 receptors	Potent weight and glycaemic effects; ↓ liver fat	Promising phase 2 MASH data	Histologic/long-term outcome evidence still evolving
Survodutide	Glucagon/GLP-1 receptors	Weight loss, energy expenditure and metabolic improvement	Promising phase 2 MASH/fibrosis data	GI tolerability; phase 3 evidence awaited
Lanifibranor	PPAR-α/δ/γ	Metabolic, anti-inflammatory and antifibrotic effects	Promising phase 2b data	Oedema/weight gain; investigational
Pegozafermin / efruxifermin	FGF21 pathway	Improves lipid oxidation and metabolic homeostasis	Promising MASH/fibrosis studies	Investigational; durability and outcomes under study
Pioglitazone	PPAR-γ	Improves insulin sensitivity	Selected patients, especially T2DM	Weight gain, oedema, fracture risk
SGLT2 inhibitors	SGLT2	Glycosuria, weight and cardiometabolic benefits	Useful for metabolic/renal/CV	Not primarily approved as MASH therapy

			indications; liver evidence emerging	

Evidence interpretation: Histological improvement is an important surrogate endpoint, but the ultimate value of a MASLD therapy depends on durable reduction in hepatic decompensation, hepatocellular carcinoma, cardiovascular events and mortality. Long-term outcome studies therefore remain essential.

ABBREVIATIONS

MASLD – metabolic dysfunction-associated steatotic liver disease; MASH – metabolic dysfunction-associated steatohepatitis; THR-β – thyroid hormone receptor-beta; GLP-1 – glucagon-like peptide-1; GIP – glucose-dependent insulinotropic polypeptide; PPAR – peroxisome proliferator-activated receptor; FGF21 – fibroblast growth factor 21; FXR – farnesoid X receptor; SGLT2 – sodium-glucose cotransporter-2; T2DM – type 2 diabetes mellitus; ALT – alanine aminotransferase; AST – aspartate aminotransferase; FIB-4 – fibrosis-4 index; VCTE – vibration-controlled transient elastography; MRE – magnetic resonance elastography; HCC – hepatocellular carcinoma.

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