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Pharmacological Approaches to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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ABSTRACT

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a growing metabolic condition defined by a progressive buildup of fat in the liver and linked to obesity, insulin resistance, type 2 diabetes and dyslipidaemia. This review focuses on the understanding of the pathophysiology and molecular mechanisms of MASLD, the widely used and currently available therapies, and future therapeutic strategies. Secondary information from published research articles, clinical trials, systematic reviews, meta-analyses and relevant biomedical literature was obtained and a narrative review approach was used. The disease progression mechanisms such as insulin resistance, hepatic lipid accumulation, oxidative stress, inflammation, mitochondrial dysfunction and fibrosis are discussed. Also reviewed are the pharmacological interventions, pioglitazone, GLP-1 receptor agonists, SGLT2 inhibitors, PPAR agonists and thyroid hormone receptor-β agonists. New agents, such as resmetirom, FGF21 analogues and tirzepatide, show encouraging results with regard to liver fat, liver steatohepatitis, and fibrosis-related parameters. Pharmacological treatment may offer further benefits than lifestyle changes in some cases, according to clinical evidence. It is difficult to make treatment decisions, however, due to differences in response, side effects, drug interactions and lack of certainty about long-term outcomes. The study emphasizes the need for personalized treatment, ongoing assessment and incorporation of pharmacologic treatment along with lifestyle modifications. It states that the development of targeted drugs presents opportunities for developing new treatments for MASLD and more long-term clinical studies are needed to confirm the effectiveness and safety of treatments.

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INTRODUCTION

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) refers to a metabolic liver condition characterized by accumulation of excessive fat in the liver cells, (hepatocytes) associated with the presence of ≥ 1 cardiometabolic risk factor. MASLD has been introduced to replace non-alcoholic fatty liver disease (NAFLD) to more accurately classify the disease and highlight the metabolic dysfunction that is driving the disease. MASLD is a serious public health problem due to its growing prevalence and close links to obesity, type 2 diabetes mellitus, insulin resistance, dyslipidaemia and cardiovascular complications. The clinical spectrum of the disease can range from uncomplicated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive fibrosis, cirrhosis and hepatocellular carcinoma (HCC) **(Girish & John, 2025).**

Excessive accumulation of lipids in the liver, defective insulin signalling, oxidative stress, mitochondrial dysfunction and chronic inflammation are all interconnected processes that contribute to the development and progression of MASLD. Treatment of the disease prioritizes lifestyle modification, but there are many patients who find it challenging to maintain their weight loss and diet. In addition, people with advanced fibrosis or metabolic abnormalities may benefit from further treatment to slow the progression of the disease and complications. Thus, drug development and therapeutic research in this field have become an important field.

In recent years, several new pharmacological therapies have been developed that can target various metabolic and inflammatory mechanisms associated with MASLD. This includes insulin-sensitizing agents, Glucagon-like peptide-1 (GLP-1) receptor agonists, thyroid hormone receptor-beta agonists, peroxisome proliferator-activated receptor agonists and sodium-glucose cotransporter-2 inhibitors. Resmetirom is also a promising new drug in the treatment of certain patients with non-cirrhotic MASH and moderate-to-severe fibrosis. In addition, investigational treatments for targeting the fibroblast growth factors, the metabolism of lipids, and inflammation of liver cells are under investigation in clinical trials **(Drygalski, 2025).**

This study examines the pathophysiology and molecular mechanisms of MASLD, conventional therapeutic approaches and current pharmacological interventions. It also highlights novel drug candidates, their mode of action, clinical evidence, and safety considerations and limitations to propose novel directions for more effective, and personalized, treatment approaches.

Objectives of the Study

- To examine the pathophysiology and molecular mechanisms involved in the development and progression of MASLD.
- To review the conventional therapeutic approaches and their limitations in MASLD management.
- To evaluate the pharmacological agents used in MASLD, including their mechanisms of action and therapeutic benefits.
- To explore emerging and investigational drug therapies and their clinical effectiveness.
- To assess the safety profiles, adverse effects and limitations of pharmacological interventions in MASLD.

RESEARCH METHODOLOGY

This research employs a secondary research method with a narrative literature review design. Published research articles, systematic reviews, meta-analysis and clinical practice guidelines were used to obtain relevant information from scientific databases including PubMed, Google Scholar and other biomedical literature sources to address the selected clinical trials. The study was focused on the pathophysiology, molecular mechanisms, conventional management, pharmacological interventions, emerging drug candidates, mechanisms of action and clinical outcomes and safety profile related to MASLD.

Overview and Pathophysiology of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Metabolic Dysfunction-Associated Steatotic Liver Disease is a metabolic condition that occurs when there is an accumulation of triglycerides inside of the liver

cells in people with one or more cardiometabolic risk factors. Increased body weight, abdominal obesity, impaired glucose regulation, type 2 diabetes mellitus, and hypertension and abnormal lipid profiles are some of the factors. Due to its close association with cardiovascular disease, chronic kidney disease and other metabolic complications, MASLD is now known to be a multisystem condition and not just limited to the liver. The disease course can markedly differ among people, depending on their genetic susceptibility, metabolism, environmental exposure and lifestyle **(Mejía-Guzmán et al., 2025).**

Pathophysiology of MASLD is the imbalance of hepatic lipid acquisition, synthesis, oxidation and export. Triglyceride accumulation can be due to increased delivery of free fatty acids (FFA) from adipose tissue, excessive dietary fat intake, and enhanced de novo lipogenesis. The liver under physiological condition regulates lipid balance by oxidizing fatty acids and synthesizing very-low-density lipoproteins. Insulin resistance, however, disrupts these regulatory mechanisms that lead to an increased production of hepatic lipids and their storage.

Early, MASLD may manifest as 'simple' hepatic steatosis (the presence of fat but no significant hepatocellular inflammation or injury). In some individuals, it evolves into MASH, which is defined as a combination of the two features, i.e. steatosis with inflammation and hepatocellular ballooning. Inflammatory activity can lead to activation of hepatic stellate cells, leading to the deposition of excessive extracellular matrix and fibrosis. The advanced fibrosis can then evolve into cirrhosis and progress to develop portal hypertension, liver failure and hepatocellular carcinoma (HCC) **(Phoolchund & Khakoo, 2024).**

Diseases develop in a number of ways, such as oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory cytokines, and changes in gut microbiota. There may be other genetic differences that make some people more susceptible, such as in genes that regulate lipid metabolism. It is important to note that not all patients with steatosis, in fact, go on to develop progressive liver disease. The knowledge of these pathological processes is crucial to identify therapeutic targets and to find pharmaceutical drugs that could help restore metabolic function and decrease hepatic inflammation and progression of fibrosis.

Molecular and Metabolic Mechanisms Involved in MASLD Progression

Molecular and metabolic changes, which are complex, to the liver underpin the progression of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), including the metabolic regulation of lipid metabolism, insulin signalling, mitochondrial activity and inflammatory responses in the liver. The principle mechanism is insulin resistance that leads to enhanced release of free fatty acids (FFA) from fat tissue and uptake of FFA by hepatocytes. At the same time, hyperglycaemia and hyperinsulinaemia promote hepatic de novo lipogenesis by transcriptional regulators like sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP). These processes lead to fat buildup in liver cells (hepatocytes) called hyperlipidaemia **(Ren et al., 2026).**

Another significant mechanism of the progression of MASLD is mitochondrial dysfunction. High fatty acid oxidation leads to overproduction of reactive oxygen species (ROS) that can cause damage to cell membranes, proteins and mitochondrial DNA. Several intracellular signalling pathways are activated by oxidative stress, which are responsible for hepatocyte damage and inflammatory responses. ER stress also contributes significantly by disrupting protein processing, calcium homeostasis and cellular homeostasis leading to hepatocyte apoptosis and metabolic dysfunction.

The mechanisms of inflammation are especially crucial during the progression from simple steatosis to MASH. Activation of lipotoxic metabolites and damaged hepatocytes, as well as the presence of oxidative stress, trigger the release of inflammatory mediators such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β). These mediators stimulate Kupffer cells and other immune cells leading to chronic liver inflammation. In addition, activation of HSCs can promote collagen production and deposition of extracellular matrix that leads to progressive liver fibrosis **(Solleiro-Villavicencio et al., 2025).**

The gut-liver axis also contributes to the development of MASLD by changes in the gut microbiota, increased gut permeability and uptake of bacterial products into the portal circulation. There may be additional genetic risk factors, such as polymorphisms of PNPLA3, TM6SF2 and MBOAT7 that would further influence susceptibility to hepatic fat accumulation and fibrosis. These molecular mechanisms, taken together, offer significant therapeutic targets for the development of therapeutic interventions that enhance insulin sensitivity, control lipid metabolism, minimize oxidative stress and hepatic inflammation and fibrogenesis.

Current Therapeutic Approaches and Limitations of Conventional Management

Treatment for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is aimed at enhancing metabolic health and minimizing liver fat levels and preventing progression to steatohepatitis, fibrosis, and cirrhosis. The traditional therapies focus on lifestyle changes, dietary measures, and regular exercise and management of associated metabolic disorders. This is because there is a strong association between excess adiposity, insulin resistance and accumulation of lipids in the liver, which is a widely accepted therapeutic goal. Calorie restriction, healthy eating and exercise can lead to sustained weight loss that can help reduce liver enzymes, liver fat content and in some patients, MASH and fibrosis **(Adinolfi et al., 2026).**

In general, dietary intervention guidelines suggest that consumption of saturated fats, refined carbohydrates, added sugars and sugar-sweetened drinks should be decreased and that vegetables and fruits, whole grains, dietary fibre and unsaturated fats should be increased. The Mediterranean dietary pattern has drawn a great deal of attention due to its many beneficial effects on insulin sensitivity and cardiometabolic risk. Regular aerobic and resistance exercise work also help to better regulate glucose, improve body composition and lipid metabolism, even without significant caloric deficit.

Conventional treatment also requires the management of associated conditions such as type 2 diabetes mellitus, hypertension, dyslipidaemia and obesity. Medications to control glucose, lipids and hypertension may be prescribed as needed for the patient. For some patients with severe obesity, bariatric surgery can achieve significant metabolic benefits and decrease hepatic steatosis **(Meyvis et al., 2013).**

However, traditional methods have a number of drawbacks. Adopting a lifestyle change on a long-term basis is challenging due to socioeconomic factors, lack of patient awareness, eating habits and limited participation in exercise programmes. In addition, lifestyle interventions may not be adequate to improve patients with advanced fibrosis and/or severe metabolic dysfunction. Conventional management also does not specifically target all molecular mechanisms of hepatic inflammation and fibrogenesis. As a result, there is growing interest in pharmacological approaches with the ability to target specific metabolic, inflammatory and fibrotic pathways. Lifestyle modifications, combined with drug therapy if appropriate, may be a more holistic strategy to manage MASLD.

Pharmacological Management of MASLD

Pharmacological management of Metabolic Dysfunction-Associated Steatotic Liver Disease is based on the pharmacological targeting of metabolic, inflammatory and fibrotic mechanisms associated with the development and progression of the disease. While lifestyle modification is the mainstay of therapy, a growing role of pharmacological therapy is emerging in individuals with significant metabolic dysfunction, obesity, type 2 diabetes mellitus and progressive liver disease. Drug selection is based on the extent of the disease, fibrosis stage, any metabolic conditions involved, clinical evidence and regulatory approval.

Insulin-sensitising agents have been studied for their role in improving insulin resistance and hepatic steatohepatitis, especially pioglitazone. Metformin is a commonly used drug to control glycaemia in people with diabetes, but it is not a specific treatment for histological changes associated with MASH. GLP-1 receptor agonists, such as semaglutide and liraglutide, help to reduce weight, improve control of blood sugar levels, and lower the amount of fat in the liver. Semaglutide has also been approved by the FDA for certain adults with MASH and moderate to advanced fibrosis, adding a new area of interest to the pharmacological treatment arena **(Chavez-Tapia et al., 2006).**

Another category of drugs important for the thyroid is thyroid hormone receptor-beta agonists. Resmetirom primarily targets the receptor beta in the liver and promotes the use of fat in the body, while blocking fat accumulation in the liver. It's okay in the U.S. for certain adults with MASH (non-cirrhotic) and moderate to advanced fibrosis.

Other agents that have been probed include peroxisome proliferator-activated receptor (PPAR) agonists like saroglitazar and lanifibranor, which affect lipid metabolism, insulin sensitivity, and inflammatory pathways.

Empagliflozin and dapagliflozin are SGLT2 inhibitors that could offer extra metabolic advantages due to enhanced glycaemic management, weight loss and favourable impact on hepatic steatosis. Also, new therapies based on the use of analogues of the fibroblast growth factor, modulation of the farnesoid X receptor and other molecular targets are being tested for hepatoprotective and anti-fibrotic properties **(Androutsakos et al., 2022).**

Although these have occurred, the use of pharmaceuticals still needs to be carefully evaluated for efficacy, side effects, contraindications and long term safety. Importantly, some of the drugs used in patients with MASLD are not liver-directed drugs. Thus, the treatment needs to be tailored to the stage of the disease and associated metabolic derangements, in addition to lifestyle modification.

Table 1: Classification of Pharmacological Agents Used in MASLD

Drug category	Examples	Primary therapeutic target
Insulin sensitizers	Pioglitazone, Metformin	Insulin resistance
GLP-1 receptor agonists	Semaglutide, Liraglutide	Glucose regulation and weight reduction
Dual incretin agonists	Tirzepatide	GLP-1 and GIP receptors
Thyroid hormone receptor agonists	Resmetirom	Hepatic lipid metabolism
PPAR agonists	Saroglitazar, Lanifibranor	Lipid metabolism and inflammation
SGLT2 inhibitors	Empagliflozin, Dapagliflozin	Glucose regulation
FGF21 analogues	Efruxifermin, Pegozafermin	Metabolic regulation and fibrosis
FXR-related agents	Obeticholic acid	Bile acid metabolism

Emerging and Investigational Pharmacological Therapies

The emergence of investigational and new drug treatments is a significant step toward the management of MASLD, especially for those patients who develop progressive steatohepatitis and hepatic fibrosis. While weight loss and metabolic risk control are the primary focus of conventional therapies, newer drug candidates are targeted to specific molecular pathways related to lipid accumulation, inflammation, oxidative stress & fibrogenesis. These days, researchers are focusing on agents that can not only enhance hepatic metabolism but also inhibit the liver damage.

One of the most promising investigational therapeutic approaches is the use of analogues of fibroblast growth factor 21 (FGF21). The FGF21 is a metabolic hormone that plays a role in glucose metabolism, fatty acid oxidation, energy expenditure and lipid metabolism. Analogues are being developed to enhance insulin sensitivity, lower the number of circulating triglycerides, and lower the amount of fat in the liver. FGF21-based drugs such as efruxifermin and pegozafermin have shown promising results in clinical trials on patients with MASH and fibrosis. They are therefore good candidates for clinical development due to their possible antifibrotic effects **(Rama et al., 2026)**.

Another emerging class are analogues of fibroblast growth factor 19 (FGF19). These agents affect bile acid biosynthesis, lipid metabolism and metabolic signalling, through the farnesoid X receptor (FXR) and related pathways. Engineered analogue of FGF19 named Aldafermin has been researched for its potential to decrease liver fat and liver injury markers. But more data is needed to prove long-term clinical effects and safety.

There is also a great deal of interest in dual and multi-agonist therapies as MASLD comprises multiple communicating metabolic pathways. Tirzepatide is a drug that activates both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, and has been shown to help patients lose weight and improve outcomes related to MASH. There are also other multi-receptor agonists in development that will bring about more metabolic benefits by having multiple hormonal signals work together **(Ahmed et al., 2026).**

Another strategy is to use acetyl-CoA carboxylase (ACC) inhibitors since de novo lipogenesis is a critical pathway of ACC. These drugs inhibit this enzyme to help prevent the liver from making fat and triglycerides. In the same way, diacylglycerol acyltransferase (DGAT) inhibitors act on the last step of triglyceride formation and have the potential to modulate the storage of hepatic lipids. But changes in lipid metabolism could have compensatory effects that must be carefully evaluated for their effectiveness and safety **(Hasanat-uludhhiyah et al., 2025).**

The investigational strategies to consider are anti-inflammatory drugs, anti-fibrotic drugs, and agents that inhibit hepatic stellate cell activation. Research is also exploring therapies directed towards mitochondrial function, oxidative stress, gut microbiota and immune signalling. A few candidates have shown promising results; however, their effectiveness, dosage, and long-term safety and approval have yet to be determined. Combination therapy, involving metabolic and liver-directed drugs, may be used in the future to gain more control of the disease.

Table 2: Emerging and Investigational Pharmacological Therapies for MASLD

Drug/agent	Pharmacological class	Therapeutic target	Research focus
Efruxifermin	FGF21 analogue	FGF21 signalling	MASH and fibrosis
Pegozafermin	FGF21 analogue	FGF21 signalling	Hepatic inflammation and fibrosis
Aldafermin	FGF19 analogue	FGFR4-related signalling	Lipid and bile acid metabolism
Lanifibranor	Pan-PPAR agonist	PPAR-α, PPAR-δ, PPAR-γ	Steatohepatitis and fibrosis
Firsocostat	ACC inhibitor	Acetyl-CoA carboxylase	Hepatic lipogenesis
Tirzepatide	Dual incretin agonist	GLP-1 and GIP receptors	MASH resolution and metabolic improvement

Mechanisms of Action of Pharmacological Agents in MASLD

The pharmacological treatments available for the treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease work via different molecular and biochemical mechanisms that impact on liver lipid metabolism, insulin signalling, inflammation and fibrosis. The mechanisms of this are important to consider when assessing therapeutic effectiveness and to determine the best treatment options. As a disease with the multifactorial metabolic component, it is clear that there is no single pharmacological target that can solve all the pathological processes. Hence, the present drug discovery efforts are aimed at targeting drugs that control hepatic fat accumulation, enhance insulin sensitivity, alleviate oxidative stress and prevent progressive hepatic damage **(Zhang et al., 2025).**

The insulin-sensitizing drugs, especially pioglitazone, work by activating peroxisome proliferator-activated receptor-gamma (PPAR-γ). Nuclear receptor that controls genes related to lipid and glucose metabolism. This activation makes the tissue more sensitive to insulin, enhances glucose uptake and decreases the amount of free fatty acids circulating to the liver. These effects could reduce the toxic effects of fat on the liver and bowel inflammation. Pioglitazone does cause some weight gain and fluid retention, though, which makes it unsuitable for some patients. The mechanism of action of metformin is mainly on hepatic gluconeogenesis and enhancement of insulin sensitivity, which includes partial activation of AMP-activated protein kinase (AMPK) signalling. While it can be used to treat MASH, its primary use in MASLD is to treat diabetes, which is typically associated with the condition **(Smith, 2001).**

The GLP-1 receptor agonists such as semaglutide and liraglutide increase the insulin response to glucose, decrease inappropriate glucagon secretion, slow down the emptying of the stomach, and increase satiety. These processes help to create better glycaemic control and significant weight loss. Lessened amounts of body fat and increased insulin sensitivity later lower the supply of fatty acids to the liver. Tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor activator that offers enhanced metabolic actions via dual incretin signalling.

Resmetirom is selective for thyroid hormone receptor beta, which is mainly expressed in the liver. Activated, it boosts fatty acid oxidation in the liver, regulates cholesterol metabolism, and diminishes the accumulation of lipids in the liver. Likewise, PPARs affect multiple metabolic pathways. The activation of PPAR-alpha stimulates fatty acid oxidation, PPAR-gamma affects insulin sensitivity and adipocyte function, and PPAR-delta affects energy expenditure and lipid metabolism. This is the rationale for the therapeutic value of selective and pan-PPAR agonists **(Liu et al., 2026).**

SGLT2 inhibitors lower the reabsorption of glucose from the kidneys, leading to a greater loss of glucose in the urine, better glycaemic control and slight weight loss. They seem to have beneficial effects on liver function, which are linked to better systemic metabolism and decreased insulin resistance. FGF21 analogues function through the fibroblast growth factor receptors and beta-Klotho co-receptors, which modulate lipid oxidation, glucose control and energy metabolism. They could also have an impact on inflammatory and fibrotic pathways **(Padda et al., 2025).**

Other investigational agents target hepatic lipogenesis and bile acid regulation. ACC inhibitors inhibit the production of fatty acids, while DGAT inhibitors prevent the production of triglycerides. FXR related therapies have an impact on bile acid synthesis, lipid metabolism and inflammatory signalling. Together, these pharmacological mechanisms offer several avenues for targeting MASLD and pave the way for liver-targeted and combination therapies.

Table 3: Mechanisms of Action of Pharmacological Agents in MASLD

Pharmacological agent	Mechanism of action	Expected therapeutic effect
Pioglitazone	PPAR-γ activation	Improved insulin sensitivity
Metformin	Inhibition of hepatic gluconeogenesis; AMPK-related signalling	Improved glucose regulation
Semaglutide	GLP-1 receptor activation	Weight reduction and metabolic improvement
Tirzepatide	GLP-1 and GIP receptor activation	Improved glucose and lipid metabolism
Resmetirom	Thyroid hormone receptor-β activation	Increased hepatic lipid metabolism
Saroglitazar	PPAR-α and PPAR-γ activation	Improved lipid and glucose metabolism
Empagliflozin	SGLT2 inhibition	Increased urinary glucose excretion
Efruxifermin	FGF21 receptor signalling	Improved metabolic regulation and potential antifibrotic effects
Obeticholic acid	FXR activation	Regulation of bile acid synthesis

Clinical Evidence and Outcomes of Pharmacological Interventions

The number of clinical studies powered by pharmacological interventions for MASLD has grown significantly, including randomized controlled trials, multicentre clinical trials and systematic reviews. The studies have assessed the efficacy of various drug classes to improve hepatic steatosis and the resolution of steatohepatitis, fibrosis and metabolic abnormalities. Histological improvements, especially MASH resolution, with no worsening of fibrosis and improvement in fibrosis without worsening of MASH, are important outcomes in current therapeutic trials. Other measures include liver enzyme changes, body weight, insulin resistance, lipid profiles and non-invasive liver disease measures **(Pages et al., 2026).**

Several clinical trials have shown Pioglitazone to be beneficial for steatohepatitis, especially in type 2

diabetes mellitus. Reports of improvements in hepatic inflammation, in hepatocellular ballooning, and in insulin sensitivity. The results of significant fibrosis improvement are, however, less consistent. There are some beneficial effects on glycaemic control and some metabolic parameters with metformin, but clinical trials have not proven enough histological efficacy for its recommendation as a specific MASH treatment.

GLP-1 receptor agonists have shown promising clinical results. In the phase III ESSENCE trial, semaglutide showed 62.9% of treated participants achieved MASH resolution, a rate that was not associated with an increase in fibrosis, compared to 34.3% receiving placebo. Liver fibrosis was improved without worsening MASH in 36.8% and 22.4%, respectively. These results led to its speedy FDA approval in August 2025 in certain adults with MASH and moderate to severe fibrosis **(Sanyal et al., 2025).**

Resmetirom shows also significant histological benefits. Among non-cirrhotic patients with MASH and moderate to advanced fibrosis, treatment in the phase III MAESTRO-NASH trial resulted in better MASH resolution and fibrosis-related outcomes than placebo. The approval in March 2024 marked a significant milestone in liver-directed pharmacotherapy.

There are also some promising investigational treatments. In clinical studies, tirzepatide has demonstrated efficacy in resolving MASH and improving fibrosis-related outcomes. There are promising results with FGF21 analogues (efruxifermin and pegozafermin) in MASH and fibrosis patients. Lanifibranor is another critical investigational compound since it has the potential to modulate metabolic, inflammatory and fibrotic pathways, being a pan-PPAR agonist. But these investigational agents should not be treated as approved drugs until there is sufficient clinical and regulatory evidence to support this **(Loomba et al., 2024).**

Although the results have been encouraging, one should be aware that clinical trial differences exist in patients, treatment duration, dosage, disease severity and methods of evaluation of the disease by histology when comparing the various pharmacological agents. Moreover, enhanced surrogate and histological endpoints do not necessarily translate into fewer liver related deaths, fewer transplants or other long-term complications. Therefore, additional follow-up and real-world data are required to prove long-term efficacy of these treatments.

Table 4: Clinical Evidence and Outcomes of Pharmacological Interventions

Drug	Clinical trial	Major findings	Therapeutic significance
Pioglitazone	PIVENS and related studies	Improvement in steatohepatitis in selected patients	Insulin sensitization
Semaglutide	ESSENCE Phase III	MASH resolution: 62.9% vs 34.3% with placebo	Histological improvement
Resmetirom	MAESTRO-NASH Phase III	Improved MASH resolution and fibrosis endpoints	Liver-directed treatment
Tirzepatide	SYNERGY-NASH Phase II	MASH resolution: 44–62% vs 10% with placebo	Dual incretin therapy
Efruxifermin	HARMONY Phase IIb	Positive fibrosis-related outcomes	Investigational antifibrotic therapy
Pegozafermin	ENLIVEN Phase IIb	Improvement in fibrosis and MASH endpoints	FGF21-based therapy
Lanifibranor	NATIVE Phase IIb	Improvement in steatohepatitis activity	Pan-PPAR therapy

Safety Profile, Adverse Effects and Drug Interactions

Safety of pharmacologic agents is a key factor in treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease, given that patients often have multiple metabolic conditions that necessitate long-term medication use. Polypharmacy and drug interactions are more likely with these people who can be obese, have type 2 diabetes mellitus, hypertension, dyslipidaemia and cardiovascular disease. Thus, the choice of drug treatment should take into account therapeutic effectiveness, tolerability, contraindications, potential side effects and overall metabolic and hepatic status of the patient. Monitoring is essential to recognise the side effects of treatment and to ensure correct use of treatment **(Armes et al., 2025).**

Pioglitazone has been linked to a number of side effects such as weight gain, peripheral oedema, fluid retention and an increased risk of heart failure in susceptible patients. It can also cause bone fractures, especially if it is used over a long period of time. Therefore caution should be taken when using it in patients with cardiovascular complications. Metformin is well tolerated, although gastrointestinal upset including abdominal discomfort, diarrhoea and nausea are common. Chronic use can lead to a B12 deficiency and toxicity in severe renal impairment patients can lead to an increased risk of lactic acidosis **(Shah & Mudaliar, 2010).**

Typical side effects of GLP-1 receptor agonists (like semaglutide and liraglutide) usually include digestive issues like stomach discomfort, constipation, diarrhoea, and vomiting. This type of reactions tends to be more noticeable when initiating treatment and increasing the dose. Other important risks encountered in clinic are gallbladder problems and pancreatitis and dehydration-induced acute kidney injury. The drug also has warnings for thyroid C-cell tumors in the U.S. and has not been studied in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. Some oral medications may not be absorbed if the stomach empties slowly **(Filippatos et al., 2014).**

Gastrointestinal disturbances such as diarrhoea, nausea and abdominal discomfort may occur in the gastrointestinal system as a side effect of Resmetirom. Other safety factors involve hepatotoxicity and gall-bladder related negative effects. May interact with some statins: may increase the blood levels and risk of muscle effects. Further, the exposure to resmetirom may be impacted by inhibitors or inducers of the pathways in which it is metabolized or transported. So, proper medication review and monitoring is required during treatment.

SGLT2 inhibitors such as empagliflozin and dapagliflozin can lead to genital mycotic infections, urinary tract infection, volume depletion and hypotension. The rare severe complications are euglycaemic diabetic ketoacidosis, especially in prolonged fasting, acute illness or perioperatively. Medicines should be used with special caution in people with poor kidney function or in patients with dehydration. Depending on the type of PPAR agonist and its pharmacological properties, unwanted side effects may include oedema, weight gain, gastrointestinal disturbance and changes in lipid parameters **(Gorgojo-Martínez et al., 2024).**

New therapies like FGF21 analogues, FXR agonists and other experimental drugs have yet to be tested for safety in bigger clinical trials and in longer-term follow-up studies. Adverse reactions that may occur are gastrointestinal intolerance, changes in lipid metabolism, changes in laboratory parameters of the liver and metabolism at the site of injection. Investigational agents may also interact with other drugs, if they are used together.

Table 5: Safety Profile, Adverse Effects and Limitations of Pharmacological Agents

Drug/class	Common adverse effects	Major limitations
Pioglitazone	Weight gain, oedema	Heart failure risk
Metformin	Nausea, diarrhoea	Limited histological efficacy in MASH
Semaglutide	Nausea, vomiting, diarrhoea	Gallbladder complications
Tirzepatide	Gastrointestinal disturbances	Long-term liver outcomes require further evaluation

Drug/class	Common adverse effects	Major limitations
Resmetirom	Diarrhoea, nausea, pruritus	Drug interactions and hepatic monitoring
SGLT2 inhibitors	Genital infections, increased urination	Not established as specific MASH treatment
PPAR agonists	Oedema, weight changes	Agent-specific safety concerns
FGF21 analogues	Gastrointestinal and injection-site reactions	Long-term safety not fully established

CONCLUSION

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a complex metabolic disorder associated with insulin resistance, obesity, dyslipidaemia and other cardiometabolic risk factors. The transition from a simple hepatic steatosis to the metabolic dysfunction-associated steatohepatitis (MASH), fibrosis and cirrhosis makes it imperative to have effective and comprehensive therapeutic strategies. This review highlights that while lifestyle modification is the cornerstone of managing MASLD, more and more, pharmacological therapies are playing a crucial role, especially in patients with progressive disease and metabolic complications. There are several drug classes that have demonstrated beneficial effects on hepatic fat accumulation, inflammation, metabolic regulation and fibrosis, including the GLP-1 receptor agonists, PPAR agonists, thyroid hormone receptor-β (TPOX) agonists, SGLT2 inhibitors, and analogues of FGF21. The recent clinical trials of new drugs such as semaglutide, resmetirom, and tirzepatide have shown remarkable advancements in the field of targeted therapies. But population differences, duration of treatment and the different outcome measures and long-term follow-up make direct comparisons difficult. In addition, there is uncertainty about the long-term clinical benefits and costs of treatment and risk of adverse effects or drug interactions. The treatment of MASLD therefore needs to be tailored by the severity of the disease, metabolic profile, comorbidities, and their tolerance to treatment. Long term clinical outcomes, combination treatment, personalized treatment and the discovery of reliable markers for patient response to therapy should be studied in the future. Overall, the progress in pharmacology research is promising, and appropriate medication combined with lifestyle modification and comprehensive metabolic risk management, will remain crucial to the effective treatment of MASLD.

Suggestions

- Healthcare professionals should identify individuals who have an obesity, type 2 diabetes, dyslipidaemia and other metabolic risk factors, and seek to assess the presence of MASLD and disease progression at an early stage.
- Pharmacological treatment should be complemented with regular exercise, proper nutrition, weight management and behavioural changes to enhance metabolic health.
- The choice of drugs should take into account disease severity, fibrosis stage, metabolic conditions, contraindications, adverse effects and individual patient needs.
- Long-term effectiveness, safety, cost-effectiveness and clinical outcomes of emerging therapies should be assessed in randomized controlled trials in patients with advanced fibrosis.
- Future research should focus on combination therapies with complementary mechanisms and use of biomarkers to determine the predictors of treatment response and to direct precision medicine.

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