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Dr Sunetra Mondal	**Mondal S**, Gargari P, Nagendra L, Mandal S, Kumar RC, Shah P, Haldar M, Chowdhury S, Mukhopadhyay S. Growth hormone therapy is associated with improved uterine dimensions in girls with Turner syndrome prior to oestrogen replacement. Clinical Endocrinology. 2024 Jan;100(1):66-75.	PubMed
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ORIGINAL ARTICLE

Pharmacotherapy in metabolic-dysfunction-associated steatotic liver disease: an updated review of the past, present and a promising future

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Abstract
Metabolic-dysfunction-associated fatty liver disease (MAFLD) or metabolic-dysfunction-associated steatotic liver disease (MASLD) has been recognised as one of the most important aetiologies of chronic liver disease and also a marker of high risk for atherosclerotic cardiovascular disease (ASCVD) in patients with or without diabetes. The presence of diabetes accelerates the progression of MASLD. The pathogenesis of metabolic dysfunction-associated steatohepatitis (MASH) is complex and the diagnostic procedures to assess histologic endpoints in clinical trials are challenging. This poses significant difficulties in the discovery of newer drugs with meaningful efficacy. A comprehensive literature search using MEDLINE (via PubMed), Scopus and Google Scholar databases was performed to write a narrative evidence-based review on the current status of different pharmacotherapies in MASLD. Despite numerous pharmacotherapies being studied, until recently, there was no approved agent for the treatment of MASH. However, some established and few emerging medications have recently shown promising effects in preventing its progression, as evidenced in preclinical and clinical trials. This narrative review summarises the current status, mechanisms, efficacy and safety of established as well as new and emerging pharmacotherapies for treatment of MASH. It also provides a practical approach to the clinical use of these agents.

Keywords Metabolic-dysfunction-associated steatotic liver disease · Metabolic-dysfunction-associated steatohepatitis · MASH · Fatty liver disease · Vitamin E · Thyroid hormone analogues · Resmetirom

Introduction

Metabolic-dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is one of the most common metabolic diseases worldwide, with reported prevalence rates ranging from 37% of non-diabetic adults to 70% amongst those with type 2 diabetes (T2DM) [1]. Metabolic-dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), is a progressive subtype of MASLD characterised by hepatocellular inflammation, ballooning and Mallory's hyaline deposits observed on liver biopsy. MASH can progress to hepatic fibrosis, cirrhosis and in rare cases, hepatocellular cancer (HCC). It is associated with increased risk of cardiovascular diseases and mortality, and an impaired health-related quality of life.

Optimal care of patients with MASLD and MASH requires a multidisciplinary approach involving endocrinologists, gastroenterologists, hepatologists, cardiologists and nutritionists. MASLD frequently co-exist with diabetes, and some of the anti-diabetic agents have demonstrated significant benefits in improving MASLD and MASH-related outcomes. Concurrently, several MASLD-specific therapeutic agents are being developed to target the multiple pathogenetic pathways in the liver (Fig. 1).

Some of the promising agents recently evaluated for MASH include glucagon-like peptide-1-glucose-dependent insulinotropic polypeptide (GLP-1/GIP) co-agonists, fibroblast growth factor (FGF analogues), thyroid hormone receptor-ß (THR-ß) agonists, peroxisome

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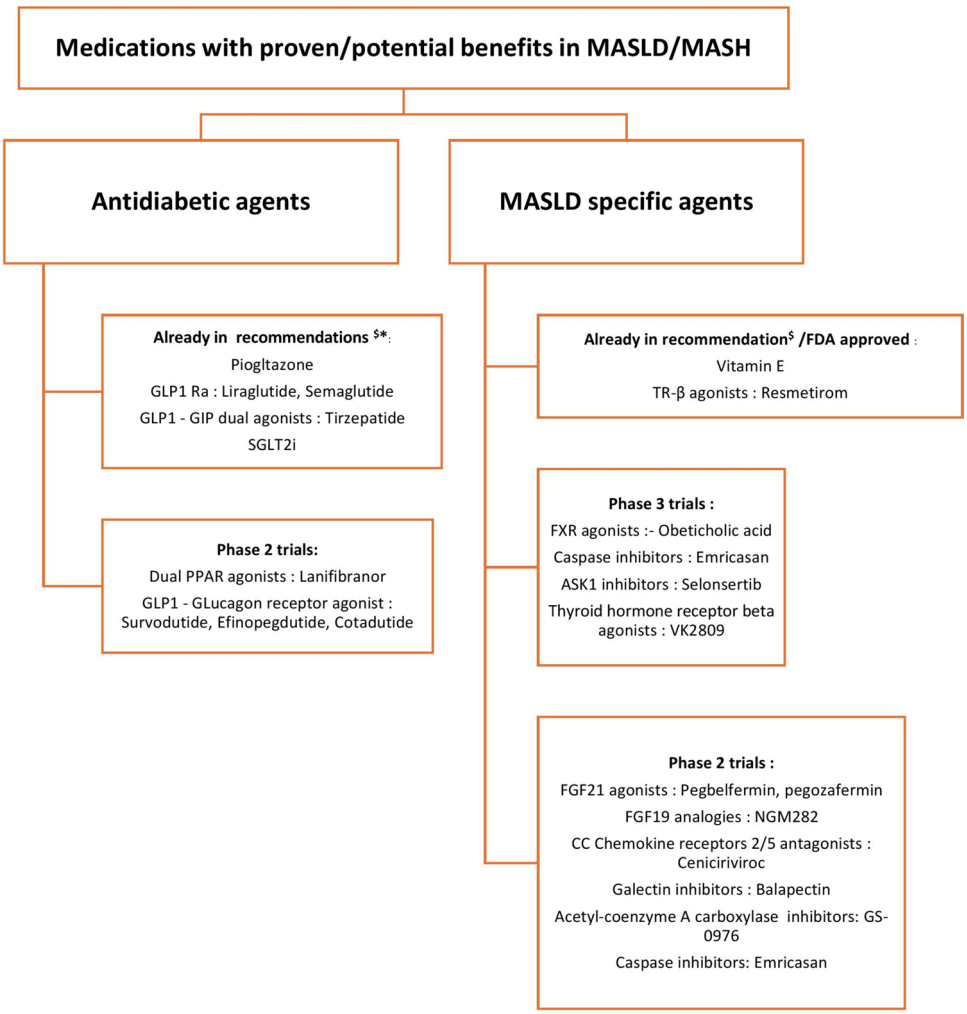

Fig. 1 Current and upcoming pharmacotherapies in non-alcoholic fatty liver disease. $ American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Non-alcoholic Fatty Liver. Disease in Primary Care and Endocrinology Clinical Settings, 2022 and American Association for the Study of Liver Diseases Practice Guidance on the clinical assessment and management of non-alcoholic fatty liver disease, 2023. *Only pioglitazone and vitamin E are mentioned as agents to be considered for their benefit in MASH with and without type 2 diabetes, respectively. The other agents can be preferred as the anti-diabetic agents of choice in MASH if they are otherwise indicated like obesity for GLP1Ra or cardio-protection for SGLT2i. Abbreviations used: MASLD = non-alcoholic fatty liver disease, MASH = non-alcoholic steatohepatitis, SGLT2i = sodium linked glucose cotransporter 2 inhibitor, GLP1 = glucagon-like peptide, GIP = glucose-dependent insulinotropic peptide, FXR = farnesoid X receptor, ASK = apoptosis signal-regulating kinase 1, FGF = fibroblast-like growth factor

proliferator-activated receptor-α/δ (PPAR- α/δ) agonists, Farnesoid x receptor (FXR) agonists and diacylglycerol acyltransferase 2/Acetyl-coenzyme A carboxylase inhibitors (DGAT2i/ACCi). Until the end of last year, none of the agents had been approved by the United States Food and Drug Administration (US-FDA) for the treatment of MASH, although many are being used off-label in many countries. However, this year began with the encouraging results from a phase 3 clinical trial of resmetirom, a liver-directed, THR-ß agonist on liver fibrosis, which showed significant efficacy in reducing liver fibrosis. Resmetirom became the first drug to be approved by the US-FDA for the treatment of patients with MASH and moderate to advanced liver fibrosis.

The current review gives an overview of all pharmacotherapeutic agents developed or repurposed for MASH. It offers a pragmatic approach to selecting appropriate therapies for different stages of MASH guided by clinical and/or biochemical parameters [2].

Methods

We did a comprehensive literature search across MEDLINE (via PubMed), Scopus and Google Scholar databases from inception till December 2024 using the keywords and connecting words in the format:

((“NAFLD” OR “NASH” OR “MASLD” OR “MASH” OR “Non-alcoholic fatty liver disease” OR “Non-alcoholic steatohepatitis” OR “metabolic dysfunction associated fatty liver disease “ OR “Metabolic Dysfunction associated steatotic liver disease” OR “Metabolic Dysfunction Associated Steatohepatitis” OR “Fatty Liver”) AND (“Pharmacotherapy” OR “Treatment” OR “Medications” OR “Drugs” OR “Guidelines” OR “Recommendations”)) as well as did a manual search of references within the articles.

A narrative review based on available evidence, recommendations and practical implications is done.

Anti-diabetic pharmacotherapy with evidence of benefit in MASH

Peroxisome proliferator-activated receptor (PPAR) agonists

Peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor that plays a key role in fatty acid and lipid metabolism and in glucose homeostasis, inflammation and fibrogenesis. Several PPARs have been identified, including PPAR-α, PPAR-β/δ and PPAR-γ. Whilst PPAR-α is a key regulator of fatty acid oxidation in the liver, skeletal muscle and adipose tissues, it also suppresses inflammation mainly by reducing reactive oxygen species production [3]. PPAR-β band δ is important for activating the pathways of hepatic glucose utilisation and de novo lipogenesis whilst promoting hepatic fat oxidation and reducing inflammation [4].

Pioglitazone

Pioglitazone is a PPARγ agonist that improves insulin resistance primarily by targeting adipocyte differentiation. It is one of two anti-diabetic drugs that have been found to be effective in people with obesity, prediabetes or T2DM with MASH, the other being GLP-1 RA. Pioglitazone and GLP-1 RA have been recommended as the preferred drugs for treating hyperglycaemia in adults with T2DM with biopsy-proven MASH or those at high risk of liver fibrosis identified by non-invasive tests [5].

In an early randomised controlled trial (RCT), fifty-five patients with impaired glucose tolerance or T2DM with biopsy-proven MASH were randomly assigned to treatment with either a hypocaloric diet plus pioglitazone 45 mg daily or a hypocaloric diet with placebo. After 6 months of treatment, pioglitazone, as compared to placebo, significantly improved glycemic control, normalised liver enzymes, decreased hepatic fat content and improved hepatic insulin sensitivity in conjunction with diet. The pioglitazone group was associated with improvement in steatosis, ballooning necrosis and inflammation; however, there was no significant reduction in liver fibrosis compared with placebo [6]. The PIVENS trial compared pioglitazone 30 mg per day versus vitamin E 800 IU per day versus placebo in persons with MASH and without diabetes for 96 weeks. Compared to placebo, vitamin E was found to be superior for the treatment of non-diabetic adults with MASH. Even though pioglitazone did not meet the primary endpoint, it was associated with a significant decrease in steatosis, inflammation and hepatocellular ballooning. Pioglitazone also improved insulin resistance and liver aminotransferase levels [7]. A single centre, randomised, placebo-controlled study of 101 patients with either prediabetes or T2DM and MASH followed up for 36 months has shown favourable results with pioglitazone, with 58% of patients who received pioglitazone 45 mg per day achieving the primary outcome (≥ 2-point reduction in NAFLD activity score), whilst 51% had resolution of MASH ($P < 0.001$ vs. placebo for both). Benefits on glucose and lipid metabolism were noted. Pioglitazone therapy was also associated with improvement in mean fibrosis score [8]. A meta-analysis of eight RCTs (five with pioglitazone and three with rosiglitazone) involving 516 patients with biopsy-proven MASH noted a significant improvement in advanced fibrosis in MASH with pioglitazone in people with and without diabetes [9].

The therapeutic use of pioglitazone is offset by its potential side effects, which include weight gain (1–2% with 15 mg/day; 3–5% with 45 mg/day), increased risk of fractures, especially in postmenopausal women, congestive heart failure when used in individuals with pre-existing heart disease and uncertain risk of bladder cancer [5]. Hence, the careful selection of patients is important before initiating this otherwise effective drug in patients with T2DM and MASH.

Lanifibranor

Lanifibranor (IVA337) is a pan-PPAR agonist, and thus can activate all three PPAR isotypes (α, γ, δ) [10]. In a recent phase 2b clinical trial testing the efficacy of lanifibranor (NCT01694849, the NATIVE trial) in obese patients with biopsy-proven MASH, the 1,200-mg dose of lanifibranor significantly decreased histologic Steatosis, Activity and Fibrosis (SAF) score by at least two points in up to 55% patients, along with reduction in liver enzymes, lipids, pro-inflammatory biomarkers and fibrosis test scores [11]. Side effects were mostly mild and included diarrhoea, nausea, peripheral oedema, anaemia and weight gain.

Elafibranor

Elafibranor (GFT505) is a dual PPAR-α/δ agonist, affecting the regulation of many metabolic processes and having anti-inflammatory properties. In a phase 2b trial, on intention-to-treat analysis, there was no significant difference between the elafibranor and placebo groups in the primary outcome of MASH resolution. However, post hoc analysis revealed that a 120-mg elafibranor dose was associated with an improvement in two points in MASLD activity score (48% elafibranor vs. 21% placebo; $P=0.013$) without any worsening of fibrosis [12]. There were also beneficial effects on liver enzymes, lipids, glycemic parameters and pro-inflammatory markers. Elafibranor was mostly well tolerated. A mild, reversible increase in serum creatinine levels was seen. However, recent interim analysis from the phase 3 RESOLVE-IT trial showed that it could not achieve the primary MASH end point nor improve metabolic parameters, following which the development of this drug was halted [13].

Saroglitazar

Saroglitazar (ZYH1) is another dual PPARα/γ agonist with a weaker PPAR-γ effect to reduce the side effects due to PPAR-γ agonism. In an integrated analysis of real-world evidence involving 318 patients with imaging-defined MASLD, treatment with saroglitazar was seen to improve serum aminotransferase levels and liver stiffness assessed by Fibroscan [14]. In a phase 2 placebo-controlled randomised trial involving non-obese patients with MASLD or MASH, only saroglitazar 4 mg daily significantly reduced liver fat content and improved serum liver enzymes [15]. There was a weight gain of around 1.5 kg, but the drug was well tolerated. In a prospective, observational, real-world study in 101 patients with MASLD and T2DM, after 24 weeks of treatment with saroglitazar, there was significant improvement in transaminases, liver stiffness measurement (LSM), and controlled attenuation parameter (CAP) on elastography, along with improvement in HbA1c% and lipid levels [16]. In the phase 3 clinical trials (PRESS V and VI) in patients with diabetic dyslipidaemia, saroglitazar 2 mg and 4 mg significantly reduced triglyceride levels in serum [17, 18]. In the multicentric, EVIDENCES II study, out of 102 patients with biopsy-proven non-cirrhotic MASH, significantly more patients in the saroglitazar group (52.3%) attained the primary end point of decrease in NAS by ≥ 2 points without worsening of fibrosis, as compared to those in the placebo group [23.5%; $P=0.04$] [19]. However, all the studies were from India, conducted on a small group of patients with MASH without cirrhosis and many of these were published only as abstracts. Though no significant adverse effects were seen in the trials, it might be prudent to remember that previously, other dual PPARα/γ agonists like muraglitazar were withdrawn for excess cardiovascular events [20, 21]. Nevertheless, it is the first drug approved by the Drugs Controller General of India (DCGI) for the treatment of MASH with F1–F3 fibrosis and MASLD with co-morbidities, including obesity, diabetes mellitus, dyslipidaemia or metabolic syndrome. Although it is also approved by DCGI for use in patients with or without diabetic dyslipidaemia, the majority of the published literature on this agent comes from patients with diabetic dyslipidaemia.

Pemafibrate

Pemafibrate, a selective peroxisome proliferator-activated receptor α (PPARα) modulator, effectively reduces triglyceride levels and improves other lipid parameters. The efficacy and safety of pemafibrate in patients with high-risk non-alcoholic fatty liver disease (NAFLD) have been increasingly supported by emerging clinical evidence. In a large randomised, placebo-controlled trial involving 10,497 patients with type 2 diabetes and mild-to-moderate hypertriglyceridemia, pemafibrate significantly lowered triglycerides, very-low-density lipoprotein (VLDL) cholesterol, remnant cholesterol, and apolipoprotein C-III levels [22]. Furthermore, a study by Nakajima et al. (2021) [23] demonstrated that pemafibrate treatment improved liver stiffness, as measured by magnetic resonance elastography, and led to reductions in alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), and alkaline phosphatase (ALP) levels in patients with NAFLD.

Incretin-based therapies

The presence of GLP-1 receptor in human hepatocytes is still controversial but GLP-1 has shown indirect protective action on the liver through the gut–pancreas–liver axis. It stimulates hepatic lipogenesis and glucose uptake, reduces hepatic gluconeogenesis and improves insulin sensitivity [24]. GLP-1 RA have demonstrated hepatoprotection by improving hepatic mitochondrial function and insulin sensitivity and by inhibiting the stress response of the injured endoplasmic reticulum. They also promote autophagy to reduce free fatty acid accumulation and lipotoxicity. Reports suggest that patients with MASH have impaired GLP-1 secretion, thus strengthening the proposition of GLP-1 RA as potential therapeutic options for the management of MASH [25]. Various GLP-1 receptor agonists like liraglutide, dulaglutide and semaglutide have been shown to improve the pathogenesis of MASH.

Liraglutide

The Liraglutide Efficacy and Action in NASH (LEAN) study was a multicentre, double-blind, randomised trial of 48 weeks of liraglutide (1.8 mg daily) versus placebo in overweight patients with biopsy-confirmed MASH. The primary endpoint of histological resolution of MASH (disappearance of hepatocyte ballooning) without worsening of fibrosis was achieved in 39% of patients in the liraglutide group versus 9% in the placebo group [26].

Dulaglutide

The trial of Dulaglutide on Liver Fat (D-LIFT) was an open-label, RCT study to examine the effect of dulaglutide (1.5 mg weekly) on liver fat content (LFC). The primary outcome measure was the difference in the change in LFC from baseline to week 24, as quantified by MRI. Dulaglutide-treated participants showed a greater reduction in LFC compared with control participants at week 24 (−32.1% vs. −5.7%, respectively; mean difference −26.4% [95% CI −44.2, −8.6]; $P=0.004$). There was a significant reduction in the end-of-treatment LSM in the dulaglutide group (from 10.8 to 9.3 kPa, $P=0.016$), but the change was non-significant compared to the control group [27]. In the AWARD programme, once weekly, dulaglutide improved liver enzyme levels compared with placebo in a pattern consistent with liver fat reduction [28].

Semaglutide

Semaglutide is a novel GLP-1 RA that has been approved for the treatment of T2DM and obesity. A 72-week phase 2 trial evaluated the effect of semaglutide on the histological resolution of MASH in patients with biopsy-proven MASH and fibrosis. Patients were randomised to receive 0.1 mg, 0.2 mg, or 0.4 mg once daily semaglutide or placebo. The semaglutide 0.4 mg was superior to placebo in MASH resolution without worsening liver fibrosis [29]. On the other hand, a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial amongst 72 subjects having histological evidence of MASH, once weekly subcutaneous semaglutide (2.4 mg for 48 weeks) failed to show any significant improvement in fibrosis or achievement of MASH resolution versus placebo [30]. Another study that aimed to clarify the efficacy and safety of oral semaglutide amongst patients with MASLD with T2DM showed significant improvement in steatosis measured by CAP. Improvement in serum markers of fibrosis (FIB-4 index, ferritin, and type IV collagen) was also found; however, there was no significant improvement in LSM [31].

Very recently, results from part 1 of the ongoing ESSENCE trial, a pivotal phase 3, double-blinded trial in adults with MASH and stage 2 or 3 fibrosis, were announced [32]. Semaglutide (2.4 mg) demonstrated a significantly superior improvement in liver fibrosis without worsening of steatohepatitis (37% vs. 22.5%) and resolution of steatohepatitis without worsening of liver fibrosis (62.9% vs. 34.1%) when added to the current standard of care at the end of 72 weeks.

Tirzepatide

Tirzepatide is a novel, once weekly, dual GIP and glucagon-like peptide-1 receptor agonist (GLP-1 RA) ("twincretin") for the treatment of T2DM. Recently, tirzepatide received the U.S. Food and Drug Administration (US-FDA) approval for weight management in adults with obesity. The SURPASS-3 MRI sub-study investigated changes in LFC, visceral adipose tissue, and abdominal subcutaneous adipose tissue with tirzepatide compared to insulin degludec in a subpopulation of SURPASS-3 participants. The mean baseline LFC was 15.71%. Tirzepatide 10 mg and 15 mg were found to reduce the LFC by more than half (–8.09%), compared with a reduction of 3.38% with insulin degludec [33]. Significant reductions in visceral adipose tissue and abdominal subcutaneous adipose tissue were also observed. Alongside these benefits, there were significant improvements in glycaemic control, lipid profiles, total body weight and liver enzymes (ALT and AST) [34]. Unfortunately, no liver fibrosis assessment was undertaken by biopsy or non-invasive methods such as elastography. In the more recently conducted SYNERGY-MASH trial, tirzepatide was found to be more effective than placebo with respect to resolution of MASH without worsening of fibrosis. A total of 44% in the 5-mg tirzepatide group, 56% in the 10-mg group and 62% in the 15-mg tirzepatide group met the criteria for resolution of MASH, all of which were significantly higher than placebo. Proportion of patients achieving improvement of at least one fibrosis stage without worsening of MASH was 55% in the 5-mg tirzepatide group, 51% in the 10-mg tirzepatide group and 51% in the 15-mg tirzepatide group. As for other incretin-based therapy, side effects were mostly gastrointestinal and mild-moderate in severity [35].

Survodutide

Survodutide, which is a novel glucagon/GLP-1 receptor dual agonist with a receptor ratio of 1:8, has shown statistically significant results in MASLD. In a 48 week phase II trial on 293 participants with biopsy-confirmed MASH stage F1–F3, once weekly subcutaneous survodutide was administered at doses of 2.4, 4.8 or 6 mg along with a placebo arm [36]. Improvement in MASH without worsening of fibrosis was seen in 47% of participants receiving survodutide 2.4 mg, 62% of those receiving 4.8 mg and 43%

of those in the 6.0 mg group, all of which were significantly higher than placebo. Reduction in LFC by at least 30% was seen in 63% of participants in the survodutide 2.4 mg group, 67% of those in the 4.8 mg group, and 57% of those in the 6.0mg group, and 14% of those in the placebo group. An improvement in fibrosis of at least one stage was seen in more than 20% in each group. Overall, the results suggested an improvement in MASH with survodutide and a trend towards improvement in fibrosis (34% of the participants in the survodutide 6.0-mg group vs. 22% of those in the placebo group). Since hepatocytes lack GLP1 receptor, theoretically, dual agonism of glucagon receptor and GLP-1 receptors is expected to be very effective for treating MASH [37]. This would lead to the combination of the extrahepatic beneficial effects of GLP-1 receptor agonism including glycemic and weight reduction and control of appetite, and the direct hepatic effects of glucagon on the liver including enhanced energy expenditure, lipolysis, and hepatic fat mobilisation [38, 39]. Adverse effects and discontinuation rates were high with survodutide, the most common being gastrointestinal disorders. Those receiving survodutide also reported a higher frequency of fatigue and asymptomatic elevation in pancreatic enzymes, though significantly higher rates of pancreatitis were not reported. Grade 1 and grade 2 hypoglycaemia were reported with survodutide. Other dual agonists with receptor ratios between 1:3 and 1:5 have been halted before for high incidence of adverse effects including gastrointestinal issues, increase in heart rate and thrombocytopenia [40, 41]. It is necessary to achieve appropriate ratio of glucagon receptor to GLP-1 receptor activation and slow dose escalation to achieve minimal side effects. The drug is currently being evaluated in five phase III studies—the SYNCHRONISE group of studies for obese people with different co-morbidities [42].

Cotadutide and efinopegdutide

Cotadutide is a novel dual GLP-1 and glucagon receptor (GLP-1R/GCGR) that has been shown to decrease body weight and improve glycaemic control, serum liver enzymes, and non-invasive fibrosis biomarkers in individuals with T2DM and overweight or obesity, and histological features of MASH and fibrosis amongst animal models [43]. Its GLP-1 receptor agonist activity reduces body weight, food intake, and improves glycaemic control. Cotadutide attenuates liver fibrosis to a greater extent than liraglutide or obeticholic acid, despite adjusting the dose to achieve similar degree of weight loss in experimental animal models. Cotadutide, via direct hepatic glucagon agonism and extrahepatic GLP-1 receptor mediated effects, could be a promising therapeutic option for the treatment of MASH [44]. In a phase 2b study on 834 overweight and obese adults, cotadutide 100, 200 and 300 mcg subcutaneous injections were found to improve transaminase levels and fibrosis scores, though liraglutide was not [45]. TB001, another dual GLP-1R/GCGR agonist, could retard the progression of liver fibrosis in various rodent models through blocking of NFκB–IKBα/JNK signalling axis, and it might be a promising therapeutic candidate for the treatment of multiple causes of hepatic fibrosis [46]. Efinopegdutide (MK-6024) is a dual agonist of the glucagon and GLP-1 receptors. In a phase IIa RCT with semaglutide as the active comparator, amongst 145 randomised participants with MASLD, one-third had T2DM. Efinopegdutide 10 mg weekly led to significantly greater reduction in LFC compared to semaglutide 1 mg weekly [47].

Dipeptidyl peptidase 4 (DPP-4) inhibitors

There is no data on the efficacy of DPP-4 inhibitors on liver histology amongst patients with biopsy-proven MASH. Levels of DPP-4 are high in more severe MASLD. [48]. One small open-label trial showed improved histologic MASLD activity scores with sitagliptin in patients with MASLD. [49]. Another 26-week multicentre trial showed that sitagliptin, combined with metformin, can lead to reduced body weight and hepatic fat content and improve glycaemic control in patients with T2DM and MASLD [50]. The findings were not confirmed in other trials [49]. One small phase 2 RCT demonstrated improvement in ultrasonography-detected hepatic fat content with vildagliptin [51]. However, vildagliptin must be used with caution in those with liver cirrhosis.

SGLT2 inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are novel oral glucose-lowering agents that have received attention due to their unique mechanism of inhibiting glucose reabsorption in the proximal renal tubules and increasing urinary glucose excretion. This type of anti-hyperglycemic method does not depend on insulin and reduces body weight. SGLT2 inhibitors can improve MASLD and reduce AST and liver fat in patients with T2DM and MASLD [52]. The tissue characteristics of MASLD are predominantly hepatic lipid accumulation, which is caused by an imbalance between hepatic triglyceride synthesis and fatty acid oxidation. SGLT2 inhibitors (SGLT2i) induce a metabolic shift from carbohydrate oxidation to fatty acid oxidation, thus possibly prevent lipid accumulation by increasing fatty acid oxidation in adipose tissues and the liver [53]. In addition, they can reduce energy by excreting glucose in the urine. This energy loss may promote β-oxidation in liver and visceral fat, induce liver fat metabolism, and reduce visceral fat. There is decreased transport of fatty acids from adipose tissues to

the liver, correction of hyperinsulinemia, and increase in adiponectin levels. The adenosine monophosphate-activated protein kinase pathway is activated by adiponectin, which inhibits fat formation and accelerates the oxidation of fatty acids in the liver [54, 55]. SGLT2 inhibitors lower the blood glucose and gradually correct hyperinsulinemia whilst improving insulin resistance and reducing hepatic lipogenesis. Additional pathogenesis of MASLD includes oxidative stress, mitochondrial dysfunction and endoplasmic reticulum homeostasis. SGLT2 inhibitors directly inhibited the enhanced expression of dipeptidyl peptidase-4 in the liver, reduced the plasma FGF21 levels, and improved the mitochondrial function or reduced endoplasmic reticulum stress in the liver [56]. The major positive effect of SGLT2i in reducing hepatic lipid content is mediated by reduced de novo lipid synthesis (reduced blood glucose and insulin levels) and increased beta-oxidation of fatty acids. Treatment with SGLT2i decreases both glucose and insulin levels (especially in those with T2DM), which leads to a large decrease in hepatic de novo lipid synthesis. Glucagon-secreting alpha cells of pancreatic islets express SGLT2, and inhibition of the cotransporter results in increased glucagon secretion. The high glucagon levels (and elevated glucagon/insulin ratio) lead to stimulation of β-oxidation (and hepatic ketone production and elevated blood ketone levels) and cause a shift from carbohydrate to fatty acid metabolism and help reduce liver triglyceride content [57, 58].

An open-label RCT was conducted amongst 66 patients with T2DM and MASLD to compare the efficacy and safety of ipragliflozin (50 mg) versus pioglitazone (15–30 mg). The primary outcome was a change from baseline in the liver to spleen attenuation ratio (L/S ratio) on computed tomography (CT) at week 24. Compared to pioglitazone, ipragliflozin was equally beneficial for MASLD and glycemic control. Furthermore, ipragliflozin significantly reduced body weight and abdominal fat area [59].

In another RCT, luseogliflozin (2.5 mg) was compared with metformin (1500 mg) amongst 32 patients with T2DM and MASLD. The primary outcome was change in liver to spleen attenuation ratio (ΔL/S) obtained by CT at 6 months. Change in L/S in the luseogliflozin group was significantly greater than that in the metformin group, indicating that luseogliflozin could effectively improve liver fat deposition compared to metformin in T2D patients with MASLD [60].

EFFECT-II was randomised placebo-controlled, double-blind parallel-group study aimed to investigate the effects of dapagliflozin 10 mg and omega-3 carboxylic acids (OM-3CA) 4 gm, individually or combined, on LFC in individuals with T2DM and MASLD. The primary endpoint was LFC assessed by MRI-derived proton density fat fraction (MRI-PDFF). Combined treatment with dapagliflozin and OM-3CA significantly reduced LFC. Dapagliflozin monotherapy reduced all measured hepatocyte injury biomarkers and FGF21, suggesting a disease-modifying effect in MASLD [61].

E-LIFT trial (Effect of Empagliflozin on Liver Fat) was a prospective, open-label, randomised clinical study to examine the effect of empagliflozin 10 mg/day when included in the standard treatment of T2DM versus standard treatment without empagliflozin amongst 50 patients with T2DM and MASLD. Hepatic steatosis was measured by MRI-PDFF. Compared to baseline, significant reduction was found in the end-of-treatment MRI-PDFF for the empagliflozin group (16.2–11.3%; $P < 0.0001$) and a non-significant change was found in the control group (16.4–15.5%; $P = 0.057$) [62].

Metformin

Metformin is an inexpensive drug that improves insulin sensitivity. In a small open-label trial involving 26 patients with MASH, metformin therapy lead to reduction in serum aminotransferase levels, improvements in insulin sensitivity and liver histology. However, there was no significant decrease in liver fibrosis scores and the beneficial effects were presumed to be mediated through weight loss [63]. A systematic review and meta-analysis of 11 randomised control trials that included 671 participants (27% with diabetes) revealed that metformin was unable to improve liver histology compared with placebo [64]. Similarly, Li et al. in their meta-analysis of 9 RCTs found that metformin failed to improve hepatocyte steatosis, ballooning and fibrosis. Significant improvement in the biochemical and metabolic parameters was, however, noted [65]. In the light of present evidence, metformin is not recommended for the treatment of MASLD. It is worth mentioning, however, that the use of metformin in people with T2D results in 50% reduction in the incidence of HCC [66].

A recent systematic review of ten population-based studies investigating the effects of different anti-hyperglycaemic agents on liver-related outcomes in T2DM concluded that whilst SGLT2is led to the strongest reduction in the incidence of MASLD, progression to cirrhosis, and composite liver-related events, thiazolidinediones also reduced the risk of developing MASLD and cirrhosis but did not significantly lower the incidence of hepatocellular carcinoma. GLP-1 RAs were significantly associated with reduced liver-related mortality [67].

MASLD-specific medications

Several classes of drugs that target either metabolic pathways, fibrosis or oxidative stress are being evaluated for their efficacy in MASLD and MASH and are in phase IIb and phase III trials. Possible mechanisms of benefit of drugs that act on the metabolic pathways include inhibition of de novo

lipogenesis, improved insulin sensitivity, correction of the links between de novo lipogenesis and bile acid metabolism, increased mitochondrial fatty acid oxidation and modulation of the uptake of fatty acids in the liver. The different agents with their beneficial effects on different parameters of MASH as evidenced in different trials are summarised in Table 1.

Vitamin E

Vitamin E is a fat-soluble vitamin that works as an antioxidant. Current data support the use of vitamin E in non-diabetic patients with MASLD. The PIVENS study showed that compared to placebo, vitamin E at a dose of 800 IU/day significantly reduced hepatic steatosis and alanine aminotransferase (ALT) levels. No significant changes in fibrosis were noted [7]. Though vitamin E was found to be superior to placebo for the treatment of MASH in adults without diabetes, there was an increase in insulin resistance indices. Long-term safety of vitamin E is of concern since several meta-analyses suggest increased mortality and up to 20% increased risk of haemorrhagic stroke and a possible increase in the risk of prostate cancer in men over the age of 50 years [68].

Some other trials have also shown that vitamin E alone, or in combination with silymarin significantly reduced fatty liver index scores compared to placebo [69, 70]. Vitamin E has also been found to improve non-invasive surrogate markers of liver fibrosis like the AST to platelets ratio (mean, 0.55–0.4; $P < 0.001$) or the MASLD fibrosis score (mean, −1.6 to −2.1; $P < 0.05$) [70, 71]. Treatment with vitamin E decreased levels of pro-inflammatory cytokines like IL-6, TNF-α or chemokines (CCL-2/monocyte chemo-attractant protein 1) [69, 72]. In addition, vitamin E treatment has been found to improve levels of adiponectin (+3.81 in UDCA/vitamin E vs. −1.63 in UDCA/placebo vs. −0.69 ng/mL in placebo/placebo; $P < 0.03$) whilst decreasing leptin levels (−0.48 vs. 2.54; $P < 0.05$) concentrations compared to placebo [73, 74].

Agents affecting metabolic pathways in the liver

Obeticholic acid

Obeticholic acid (OCA) is an FXR agonist. FXR being a bile acid receptor, FXR agonists can contribute to glucose regulation at both the hepatic and the peripheral level by regulating glycogenolysis and gluconeogenesis and modulating insulin sensitivity in the muscle and the adipose tissues, respectively [75]. In addition, FXR agonism balances de novo lipogenesis and fatty acid oxidation whilst exerting anti-inflammatory effects. The phase IIb "FLINT" trial showed the superiority of 25 mg OCA at reducing MASLD

Table 1 Beneficial effects of the medications on different parameters of MASLD/MASH based on data from available trials

Beneficial effects of pharmacotherapeutic agents seen in trials in MASLD/MASH						
Agents that show histologic improvement	Agents that decrease in hepatic fat content	Agents that decrease MASLD activity scores	Agents that decrease in amino-transferase levels	Agents involved in improvement of metabolic parameters	Agents that reduce development of hepatocellular cancers	Agents that reduce mortality
Pioglitazone, other PPAR agonists ?	Pioglitazone	Obeticholic acid	Pioglitazone	Pioglitazone	Statin	Aspirin
Liraglutide	GLP1Ra	FGF19 analogues	GLP1Ra	GLP1Ra	Aspirin	Statins
Survodutide	Tirzepatide		Tirzepatide	SGLT2i		SGLT2i
Tirzepatide	SGLT2i		Vitamin E	FGF21 analogues		
Resmetirom	FGF21 analogues		UDCA, nor-UDCA	Silymarin		
Vitamin E	Acetyl-CoA carboxylase inhibitors		Silymarin	Statin		
Apoptosis signal-regulating kinase 1 inhibitors	Statins		Probiotics	Probiotics		
?Silymarin	Thyroid hormone receptor β analogues		Statins			
Statins			LOLA			
			Carnitine			

MASLD = non-alcoholic fatty liver disease, MASH = non-alcoholic steatohepatitis, PPAR = peroxisome proliferator-activated receptor. SGLT2i = sodium linked glucose cotransporter, GLP1Ra = glucagon-like peptide receptor agonist, FGF = fibroblast-like growth factor, UDCA = ursodeoxycholic acid, LOLA = L-Ornithine L-Aspartate

activity score (NAS) by two points without worsening fibrosis [76]. Interim results of the phase III REGENERATE trial suggest the superiority of OCA in improving fibrosis [77].

FGF19 analogues

A humanised FGF-19 analogue NGM282 acts on the same downstream pathways as FXR agonists. Fibroblast growth factor (FGF19) is released following the activation of intestinal FXR, with similar downstream effects like that following FXR activation. In a 12-week open-label trial, subcutaneous NGM282 at either 1 or 3 mg doses showed decrease in fibrosis by ≥ 1 stage without MASH worsening and improvement in NAS by ≥ 2 points without fibrosis worsening [78, 79].

Fibroblast growth factor 21 agonists

Fibroblast growth factor 21 (FGF21) is a key mediator of energy homeostasis and lipid and glucose metabolism which co-ordinates the metabolic shift from the fed to fasted states. It also regulates hepatic gluconeogenesis, ketogenesis, and adipose tissue lipolysis, upregulates fatty acid oxidation, attenuates pro-inflammatory signals, and is transcriptionally regulated by PPAR alpha [80]. In a phase IIa trial with subcutaneous injections of the FGF21 analogue pegbelfermin (BMS-986036), both daily and weekly treatments were superior to placebo in achieving the primary outcome of hepatic fat reduction (10 mg daily: − 6.8% vs. 20 mg weekly: − 5.2 vs. placebo − 1.30%, $P_{all} < 0.001$) and reduction in plasma triglycerides, and low-density lipoprotein cholesterol with no difference for those with or without T2DM and with no changes in blood glucose or HbA1c levels [81]. Another FGF21 analogue PF-052313023, whilst reducing lipid levels, also produced dose-dependent changes in bone turnover markers, raising concern over their long-term use [82]. The recent phase IIb trial with a long-acting glycosylated (pegylated with the use of site-specific glycosyltransferases) FGF21 analogue pegozafermin demonstrated that subcutaneous pegozafermin at a dose of 15 mg or 30 mg weekly or 44 mg once every 2 weeks led to improvements in fibrosis and a significantly higher proportion of patients met the criteria for resolution of MASH (37%, 23% and 26% in the 15-mg, 30-mg and 44-mg pegozafermin group, respectively) [83]. Following these results, it has received the FDA Breakthrough Therapy Designation for the treatment of MASH.

Liver-targeted mitochondrial uncouplers

Mitochondrial uncoupling in the liver leads to vanishing of the mitochondrial proton gradient, thereby dissipating stored fat in the liver. In history, the first mitochondrial uncoupler, 2,4-dinitrophenol (DNP), was used as an explosive during World War I and many of the workers who handled this compound were found to significantly lose weight. The medication began to be widely available as an over-the-counter medication for weight loss in the United States, but soon reports of toxic effects, including several deaths, led to its withdrawal from the market [84].

Systemic mitochondrial uncoupling agents like DNP have a narrow therapeutic window. However, liver-targeted mitochondrial uncoupling agents like DNP–methyl ether (DNPME) can both prevent and reverse diet-induced hepatic insulin resistance without significant changes in body weight [85]. Adding an extended-release coating to DNP to generate a controlled-release mitochondrial protonophore can further increase the toxic-to-effective dose ratio and has been found to reverse insulin resistance, hepatic inflammation and hepatic fibrosis in rodent models of T2DM and MASH. Several novel mitochondrial and novel tissue-specific uncoupling agents have been developed, like the small molecule compounds C1 and CZ5, chronic administration of which have been found to improve glucose tolerance, reduce body weight and lipid metabolism in diabetic or HFD-fed mice by increasing whole-body energy expenditure.

Acetyl-CoA carboxylase inhibition

The enzyme acetyl-CoA carboxylase (ACC) has cytosolic and mitochondrial forms. Cytosolic ACC, ACC1, is highly expressed in the liver and catalyses the carboxylation of acetyl-CoA into malonyl-CoA, which is the rate-limiting step in the fatty acid synthesis. Mitochondrial membrane-bound ACC2 is expressed in oxidative tissues like muscle and heart, and produces localised malonyl-CoA, which, via inhibition of carnitine palmitoyltransferase (CPT1), prevents the transfer of long-chain CoAs into the mitochondria for fatty acid oxidation [86, 87]. Few animal and human studies have demonstrated favourable effects of ACC inhibition on MASLD, MASH, and T2DM. In obese rat models, antisense oligonucleotide (ASO)-mediated reduction of hepatic ACC1 and ACC2 has shown marked reductions in hepatic triglyceride content [88].

However, long-term inhibition of ACC has been found to worsen glucose intolerance and to increase gluconeogenesis likely due to increased levels of hepatic acetyl-CoA causing allosteric activation of pyruvate carboxylase [89]. In spite of reduction in hepatic steatosis, allosteric ACC inhibitors (MK-4074 and GS-0976) have been associated with increases in plasma triglyceride [87]. Interestingly, co-treatment with a PPARα agonist reduced the hypertriglyceridemia associated with ACC inhibition, suggesting the role of combination therapy [89].

Anti-apoptosis/anti-inflammatory agents

Emricasan

Emricasan, a pan-caspase inhibitor that inhibits necrosis and apoptosis, has the potential to reduce hepatic fibrosis and portal pressure. In a phase III clinical trial of MASH-related cirrhosis with severe portal hypertension, emricasan did not show improvement in hepatic venous pressure gradient (HVPG), but there was a modest trend towards improved HVPG in those with compensated cirrhosis [90]. In another recent phase II clinical trial in histologically confirmed MASH and stage F1–F3 fibrosis, emricasan failed to improve fibrosis [91].

Apoptosis signal-regulating kinase 1 inhibitors

Apoptosis signal-regulating kinase 1 (ASK1) leads to enhanced apoptosis of hepatocytes with inflammation and fibrosis. Selonsertib (GS-4997) is an ASK1 inhibitor. Simtuzumab is an antibody against lysyl oxidase-like molecule 2, which can block the cross-linking of collagen and elastin, which leads to fibrosis. In a phase II study comparing selonsertib 6 or 18 mg daily orally with and without weekly 125 mg simtuzumab injections to simtuzumab alone in adults with stage 2 or 3 MASH-related fibrosis, the authors reported a reduction in stages of liver fibrosis and progression to cirrhosis in those receiving 18 mg selonsertib [92]. The lack of efficacy of simtuzumab had been shown previously [93]. However, the phase III companion trials STELLAR-3 and STELLAR-4 with oral selonsertib in MASH with compensated cirrhosis failed to show any differences in MASH resolution or progression to cirrhosis.

Galectin inhibitors

Galectins are cytosolic proteins that contribute to inflammation and fibrosis in MASH, especially galectin-3 secreted by macrophages. In a phase IIb double-blinded RCT of the galectin-3 inhibitor belapectin in adults with MASH-related cirrhosis, biweekly infusions of 2 or 8 mg/kg belapectin did not reduce HVPG, although some reduction was seen in those without varices [94].

Antifibrotic medications C–C chemokine receptor 2 and 5 inhibitors

Given the role of C–C chemokine receptors 2 and 5 in the development of fibrosis in MASH, their inhibition offers an attractive treatment target. In the CENTAUR trial, a 2-year phase IIb cross-over RCT of cenicriviroc (CVC), a dual C–C chemokine receptors 2 and 5 antagonist versus placebo, after 1 year, twice as many patients on cenicriviroc (20% on CVC vs. 10% on placebo, $P=0.02$) achieved reduction of ≥ 1 stage of fibrosis but at the end of year 2, the fibrosis reduction was similar in the placebo group [95].

Other agents acting on hepatocytes

Ursodeoxycholic acid

UDCA is a hydrophilic stereoisomer of chenodeoxycholic acid, which increases the secretion of bile acids and other anionic molecules, such as glutathione conjugates or bilirubin glucuronides, thus abrogating cholestasis. Upregulation of hepatobiliary transporter genes such as bile salt export pump and multidrug-resistance proteins 2 and 3 is an important mechanism behind the increased secretion of bile acids with UDCA. Clinical studies to document the hepatoprotective effects of UDCA offer conflicting results. Recently, norursodeoxycholic acid (nor-UDCA), a synthetic side chain-shortened homologue of UDCA, significantly reduced serum ALT levels (-17.2 vs. $+5.3$ U/L; $P<0.0001$), and hepatic fat fraction measured by magnetic resonance spectroscopy (-23.5% vs. -1.0%) within 12 weeks of use [96]. Current evidence suggests that whilst monotherapy with conventional doses of UDCA (13–15 mg/kg/day) has little therapeutic effect in MASH, higher doses of UDCA (28–35 mg/kg/day) or synthetic analogues like nor-UDCA may be beneficial in MASH patients with low severity [97].

Silymarin

There has been very limited data with silymarin in MASLD. One study showed improvements in fibrosis (≥ 1 stage) in the silymarin group compared to the placebo group (22.4% vs. 6.0%; $P=0.023$), though no differences in NAS were observed in this and further studies [98, 99]. Silymarin treatment has improved aminotransferase levels in patients with MASLD in several RCTs and a recent meta-analysis involving 622 patients with MASLD [97, 100]. Also, significant improvements in metabolic parameters, including triglyceride, fasting glucose, and total cholesterol, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and favourable changes in anthropometric parameters like waist circumference and body mass index (BMI) have been reported [101].

L-Ornithine L-Aspartate

Few studies have evaluated L-Ornithine L-Aspartate (LOLA) as a treatment for MASH. Reductions in liver enzymes have been seen in up to 70% of patients, with beneficial outcomes more commonly seen in patients with fatty livers than those with liver cirrhosis due to other aetiologies [102]. LOLA has also improved hepatic microcirculation,

as evaluated by polyhepatography, in the presence of stage 0–1 fibrosis [97]. However, the studies are very few and small, and transaminases are the only outcome measured, demanding further studies to understand the effect of LOLA in patients with MASLD.

Carnitine

Given the effects of carnitine on the reduction in intracellular free fatty acids levels and the improvement of insulin resistance, the effect of a complex of dimethyl-4,4'-dimethoxy-5,6,5′6'-dimethylene dixoybiphenyl-2,2'-dicarboxylate (DDB) with carnitine orotate complex was evaluated in participants with either impaired fasting glucose (IFG) or T2DM. In a double-blind RCT, DDB-carnitine orotate complex in combination with metformin was found to reduce ALT to a greater extent than metformin-placebo combination (mean reduction, 51.5 ± 33.2 IU/L vs. 16.7 ± 31.3 IU/L, $P = 0.001$) amongst the patients with IFG and MASLD ($P = 0.001$) [103]. There were lower oxidative stress markers and greater changes in mitochondrial copy number, suggesting lesser mitochondrial damage in the metformin plus DDB-carnitine orotate complex group. There was a higher rate of ALT normalisation and lower hepatic steatosis in the DDB-carnitine orotate complex treatment group than in placebo (89.7% vs. 17.9%, $P < 0.001$) in patients with T2DM and MASLD. However, no improvement in insulin resistance parameters was observed.

Agents acting via alteration of gut microbiome

Alteration in the microbiome–gut–liver axis, including changes in the gut epithelial permeability, causing increased bacterial translocation, choline metabolism, increased pro-inflammatory cytokines, increased endogenous alcohol production, alterations in bile acid metabolism, and upregulation of hepatic toll-like receptors (TLR) can be mechanisms leading to the progression of MASLD and MASH. Studies have found an abundance of *Prevotella* in patients with obesity and MASH. Another paediatric study showed an increase in *Escherichia,* which is the genus of ethanol-producing bacteria in patients with MASH [104]. The role of gut microbiota-modifying agents like probiotics, prebiotics, synbiotics, and faecal microbiota transplantation is being explored in MASH. These agents can alter intestinal permeability, reduce oxidative stress and bacterial endotoxin release and have been found to reduce hepatic inflammation.

There have been around seven RCTs to study the therapeutic effect of probiotics in patients with MASLD [97]. Despite heterogeneities, overall evidence suggests that probiotic intervention could have a role in reducing liver steatosis. Improvements in liver enzymes, including total and LDL cholesterols, were also seen with probiotics. Unfortunately, the studies were small, with no data on their effects on MASH histologic markers. Similarly, most studies with synbiotics, which are a combination of advantageous gut bacteria (probiotics) and non-digestible fibres that help these bacteria to grow (prebiotics), have demonstrated significant reductions in liver enzymes and steatosis as measured by ultrasound, as well as lower liver stiffness as measured by transient elastography. One study also suggested that synbiotics supplementation may be associated with a greater reduction in fibrosis amongst lean MASLD subjects than lifestyle modification alone (− 1.71 ± 0.25 vs. − 0.71 ± 0.18 kPa; $P < 0.001$) [105]. However, few other studies have failed to demonstrate any improvement in magnetic resonance imaging-based liver fat content or the levels of markers of liver fibrosis. A recent meta-analysis involving 28 clinical trials enrolling 1,555 patients with MASLD revealed that syn-/probiotic therapy had beneficial effects on BMI, ALT (mean difference, − 13.40; 95% CI − 17.03 to − 9.77; $I^2 = 94\%$; $P < 0.001$), AST (mean difference, − 13.54; 95% CI − 17.86 to − 9.22; $I^2 = 96\%$; $P < 0.001$), HOMA-IR (mean difference, − 0.42; 95% CI − 0.73 to − 0.12; $I^2 = 79\%$; $P = 0.007$) and total cholesterol [106]. The effects of various combinations of antibiotics on MASLD were limited to animal models and are believed to be not only due to changes in gut microbiota composition but also altered bile acid metabolism. In humans, rifaximin has shown mixed effects on liver enzymes, microbiome composition, bile acid and inflammatory marker levels. Additional metabolites and molecular targets like short-chain fatty acids (SCFA), bile acids and anti-lipopolysaccharides (anti-LPS) metabolites have also been tried. Butyrate, a SCFA, has been found to reduce inflammation and fat accumulation in animal models of MASLD [104]. Whilst overall evidence looks promising in MASLD, identifying appropriate bacterial strains and proper duration of treatment need further investigation.

IMM-124E

IMM-124E is a colostrum product that can concentrate anti-E. coli lipopolysaccharide IgG and reduce inflammation by binding bacterial endotoxins. Thus, it is a potential intervention of interest due to the role of endotoxins in the pathogenesis of MASLD [107]. Immuron Ltd. (NCT02316717) has completed a phase II trial but has not yet published the results.

Role of statins in MASLD/MASH

Statins are used to reduce LDL-C and overall cardiovascular risk, with no harm to those with baseline liver disease [108]. Patients with MASLD who received atorvastatin had up to 68% reduction in the relative risk of cardiovascular disease (CVD) benefit compared to untreated ones and up to 39%

reduction compared to those without abnormal liver tests [109]. A similar CV benefit of atorvastatin was also seen in the post hoc analysis of the Incremental Decrease in End Points Through an Aggressive Lipid Lowering (IDEAL) study [110]. However, these trials were not designed to study MASLD outcomes, and histology was unavailable. Another prospective, randomised, open-label study Assessing the Treatment Effect in Metabolic syndrome without Perceptible Diabetes (ATTEMPT) on patients with metabolic syndrome found resolution of MASLD on USG in 86% of the patients over a 42-month treatment period [111]. In another prospective study on 20 patients with metabolic syndrome and biopsy-proven MASH, 19 patients receiving rosuvastatin for 1 year had normal liver in the repeat biopsy, even without weight loss or reduction in waist circumference [112]. Few other studies with biopsy-proven MASH from Italy and Finland also found statin used to be inversely related to significant fibrosis (stage 2–4) [113]. Though limited, but experimental data also suggest that rosuvastatin might prevent the development of MASH-related hepatocellular cancers [114].

Though current guidelines do not recommend statins as agents for the treatment of MASLD/MASH, they are reported to be safe in MASLD/MASH patients and are recommended for the primary and secondary prevention of CVD [108].

Role of thyroid hormone analogues in MASLD/MASH

Thyroid hormone (TH) and its analogues have long been tried as therapeutic agents for treating obesity since they increase mitochondrial respiration and basal metabolic rate. However, the impact of TH on glucose metabolism has yielded controversial results. In addition, supraphysiologic concentrations of TH might cause deleterious side effects like tachycardia, cardiomyopathy and sarcopenia [115]. TH is expected to benefit MASLD by increasing fatty acid oxidation, reducing fatty acid synthesis and promoting hepatocyte regeneration. In older studies, several compounds like sobetirome, eprotirome, and MB07811 were seen to reduce liver steatosis. Sobetirome was also reported to prevent the development of HCC induced by activation of the catenin pathway [116].

Liver-selective TH analogues like the cytochrome P450–activated prodrug MB07811 have shown marked reduction in hepatic steatosis and plasma lipids in rats and have shown a reduction in LDL cholesterol and triglycerides in patients with mild hypertriglyceridemia [89, 117]. A novel glucagon–T3 hybrid molecule targeting T3 to the liver was shown to increase energy expenditure, reduce fat mass independent of food intake, and reduce hepatic lipids without causing cardiac or bone toxicity [118].

In people with NASH, the hepatic thyroid hormone receptor-β (THR-β) activity is reduced, disrupting mitochondrial function and β oxidation of fatty acids, thus aggravating the pathway leading to fibrosis [119]. The metabolic advantages of thyroid hormone mediated by the liver, like reducing hepatic fat, lipoproteins, and atherogenic lipids, are possible by selective activation of THR-β. Resmetirom (MGL-3196) is a liver-targeted THR agonist that can be administered orally once daily. Due to its high protein binding nature, it has minimal tissue penetration beyond the liver and displays specific uptake by the liver [120, 121]. Compared to triiodothyronine (T3), resmetirom is 28 times more selective for THR-β than THR-α. Resmetirom can, thus, provide much-needed metabolic benefits whilst preventing any unwanted effects of excess thyroid hormone on the bone and the heart that are primarily mediated via THR-α [122]. In a phase II study of 125 adults with biopsy-confirmed MASH, oral resmetirom at 80 mg daily dose showed a 32.9% relative reduction of hepatic fat assessed by MRI-PDFF, further increasing to 32.9% after 36 weeks, at which time a significant reduction in ALT was also observed. Biopsy-confirmed MASH resolution was observed in a significantly higher proportion of patients on MGL-3196 (27% vs. 6%, $P = 0.02$) [120]. In the most recently published phase III MAESTRO-MASH trial, NASH resolution without worsening of fibrosis was found in 25.9% of the patients who received 80 mg resmetirom and 29.9% of those who received 100 mg resmetirom, as compared with 9.7% of those who received placebo ($P < 0.001$ for both comparisons with placebo). Improvement in fibrosis by at least one stage without worsening of the NAFLD activity score was found in 24.2% of the patients who received 80 mg resmetirom and 25.9% of those who received 100 mg resmetirom, as compared with 14.2% of those who got a placebo ($P < 0.001$ for both comparisons with placebo). Significant reduction in LDL cholesterol was also noted with both resmetirom 80 mg and 100 mg compared to placebo. Diarrhoea and nausea were the prominent adverse effects noted in this trial. Following the impactful results of this trial, resmetirom became the first drug approved by the US-FDA to treat patients with MASH and moderate to advanced liver fibrosis [123].

Benefits have also been reported with 10 mg daily dose of VK2809, another selective THR- β agonist, in a trial of 45 patients with MASLD treated for 12 weeks [124]. Significant reductions in hepatic fat content were also seen with 5 mg daily or 10 mg alternate-day doses of the compound. However, the results of the latter trial have not been published yet. Notably, there was a transient rise in ALT levels at the onset of treatment, though levels were not different from placebo after 12 weeks of administration. A follow-up phase IIb study, the VOYAGE study, on 337 subjects with biopsy-proven MASH (NAS ≥ 4) and MRI-PDFF liver fat fraction ≥ 8% with different doses of tVK2809 is underway [125].

Aspirin

A nationwide cross-sectional study demonstrated that regular aspirin use is associated with a lower prevalence of MASLD (HR, 0.62; 95% CI 0.51–0.74, $P = 0.04$), whilst another prospective cohort study showed that aspirin use reduced the risk of advanced fibrosis (HR, 0.63; 95% CI 0.43–0.85) [126, 127]. Interestingly, a pooled analysis of several studies has shown that aspirin use reduces the risk of HCC development by 32% and 46%. Although the aetiology of liver disease was not specified, it can be assumed that MASLD was one of the chief aetiologies of liver disease in these studies [126].

Weight loss intervention focussing on the role of bariatric surgery

A large prospective study demonstrated a probable deterioration of fibrosis, though the severity of fibrosis increased in ~ 20% of patients during the 1-year follow-up period [128]. However, in another recent study conducted amongst severely obese patients with biopsy-proven MASH, there was resolution of MASH in 84% of patients with progressive and sustained reduction of fibrosis beginning as early as the first year and effects sustained through five years.

Currently, the cornerstone of management for most MASLD patients is conservative and surgical weight loss. Weight loss has been demonstrated to improve liver biochemical tests, histology, serum insulin levels, and quality of life in patients with MASLD, along with improved liver biochemistry after significant weight loss. Whilst bariatric surgery's weight loss and metabolic effects are well established, very few studies and meta-analyses have specifically looked at its effects on MASLD outcomes alone. In one study, Lassailly et al. found that resolution of MASLD/MASH was seen in up to 64.2% of patients undergoing Roux-Y gastric bypass and 5.5% of patients undergoing sleeve gastrectomy with documented regression of already present liver fibrosis [129]. One meta-analysis of 48 studies showed that the combination of pioglitazone and Roux-en-Y gastric bypass surgery demonstrated the best effects on the MASLD activity score. However, a small proportion of patients may actually develop MASH or suffer from aggravation of the disease (MASLD/MASH/ live fibrosis) after bariatric surgery [130].

Combination of newer agents in the therapy of MASH

Several trials have been conducted to study the role of combinations of different treatments targeting multiple pathogenetic mechanisms leading to MASH, especially combining the ones that have, on their own, shown promising results in MASH. These include different combinations of anti-diabetic therapies, MASLD-specific therapies, and combinations of anti-diabetic agents with MASLD-specific therapies.

Many animal studies have shown encouraging results with combination compared to monotherapy, like the effects of a combination of ipragliflozin and pioglitazone on liver fibrosis parameters [131]. A combination of liraglutide and/ or ipragliflozin has been found to reduce hepatic lipid accumulation in mice, but no fibrosis parameters were evaluated in this study [132]. In studies using preclinical models of MASH and fibrosis, combining ACCi with hepatic lipid-modulating agents did not increase anti-fibrotic efficacy compared to monotherapy [133].

Amongst the clinical studies, a combination of pioglitazone with exenatide resulted in a better reduction in ALT and hepatic fat content compared to pioglitazone alone, but effects on liver fibrosis were not evaluated in this study [134]. A study from Japan showed that the combination of pioglitazone and tofogliflozin improved liver stiffness, ALT levels, lipid parameters, adiponectin levels, and liver steatosis compared to tofogliflozin alone in patients with T2DM and MASLD.

A combination of exenatide and dapagliflozin has been studied in a few trials, but the results were contradictory. In one study, the combination was found to improve markers of liver steatosis and fibrosis in patients with T2DM uncontrolled by metformin, but in another study, it failed to demonstrate any additive reduction of hepatocellular lipids despite better glycemic control [135, 136]. In trials using the "MASLD-specific" medications, steatosis was found to be reduced in all studied combination treatments (cilofexor/Firsocostat, cilofexor/selonsertib, and Firsocostat/selonsertib) compared to placebo. However, anti-fibrotic activity was seen only with the combination of cilofexor/Firsocostat, which improved MASH activity and reduced steatosis.

In phase 2 trials, semaglutide has been tried in various combinations with MASLD-specific medications like cilofexor, Firsocostat, or both. A reduction in steatosis documentable by MRI was found only in the semaglutide/Firsocostat group, whilst semaglutide plus cilofexor reduced steatosis evaluated by CAP but not MRI [137, 138]. There were no observed differences in liver stiffness between the groups. Notably, however, the FibroScan-aspartate aminotransferase (FAST) score, which incorporates liver stiffness, liver steatosis and AST levels, was found to be reduced with all combinations except semaglutide plus cilofexor combination.

Practical approach to pharmacotherapy in MASH in the current era

Weight loss forms the cornerstone of the management of MASH. Weight loss of 3%–5% improves steatosis, but greater degrees of weight loss > 10% is required to improve

MASH and fibrosis. Sustained weight loss improves peripheral insulin sensitivity, thus reducing the drive for liver injury in MASH. However, long-term adherence to lifestyle modifications is a challenge. A calorie-deficit diet with limited carbohydrates and saturated fat and enriched with high fibre and unsaturated fats (e.g. Mediterranean diet) should be encouraged, along with increased daily activity levels. Both aerobic and resistance training exercises have been found to reduce liver fat, and exercise prescriptions should consider individual preferences. Pharmacotherapy in MASLD is mostly indicated for progressive MASH and early-stage MASH with additional risk factors of progression to fibrosis like age > 50 years, diabetes, metabolic syndrome, increased alanine aminotransferase (ALT), or active MASH with high necro-inflammatory activity.

Due to the paucity of approved therapies, the existing guidelines focus more on the diagnostic aspects of MASH than pharmacotherapy [5, 139, 140]. Based on available evidence, we have tried to formulate a practical approach to pharmacotherapy in MASH based on the presence of other co-morbidities (Fig. 2). Currently, the only recommended pharmacotherapies potentially improving MASH include vitamin E and resmetirom for people without T2DM and pioglitazone and GLP-1RAs for people with T2DM. However, it is commonplace to see rampant use of multiple other medications with the belief that they would provide benefits in MASH, including metformin, UDCA, silymarin, etc., although they have not demonstrated any benefit in trials. Given that the majority of patients with MASH die of cardiovascular causes than cirrhosis, the focus should rather be shifted to providing adequate cardio-protection with available agents, many of which, like SGLT2i or aspirin, could also have the potential benefit in reducing the progression of MASH or the development of HCC. Statins must be initiated for dyslipidaemia rather than withholding them for concerns about hepatotoxicity and hypertriglyceridemia persisting after adequate dose of statins may benefit from supplementation with omega-3 fatty acids, icosapent-ethyl, or fibrates. It is important to remember that the available data on semaglutide, pioglitazone and vitamin E do not suggest significant anti-fibrotic benefit, and these have not been

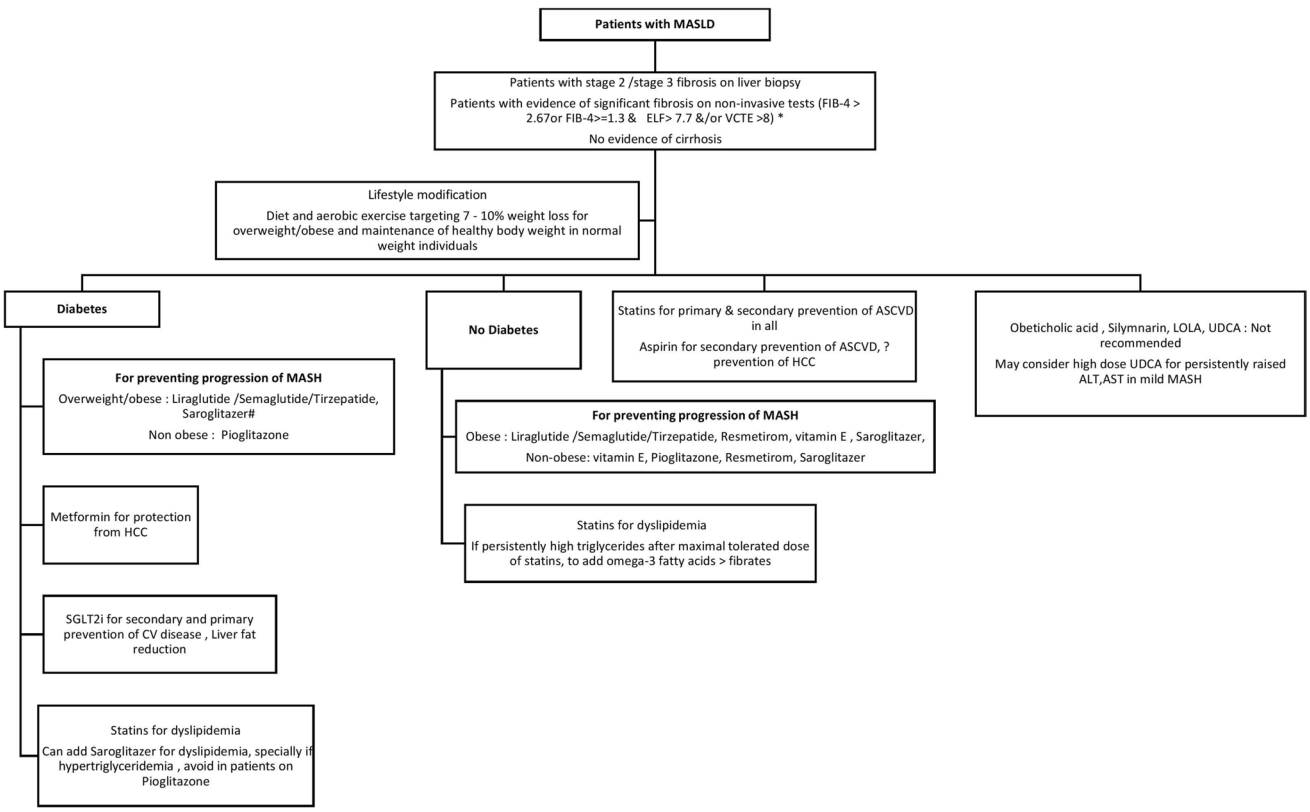

Fig. 2 Practical approach to current-day pharmacotherapy in MASH. Choice of agents to be guided by availability, cost, patient acceptance and adverse effect profile *based on AASLD Guidelines 2023 and AACE guidelines 2022. # Saroglitazar is approved by the DCGI for the treatment of diabetic dyslipidaemia and MASH. Abbreviations used: MASLD = non-alcoholic fatty liver disease, MASH = non-alcoholic steatohepatitisFIB-4 = Fibrosis-4 index, ELF = vibration-controlled transient elastography, ELF = enhanced liver fibrosis, HCC = hepatocellular carcinoma, CV = cardiovascular, ASCVD = atherosclerotic cardiovascular disease, UDCA = ursodeoxycholic acid, ALT = alanine transaminase, AST = aspartate transaminase

Table 2 Medications that have shown benefit in MASH

Medication	Approved for use in	Mode of administration	Appropriate dose for MASH improvement	Adverse effects
Vitamin E	MASH without DM	Oral	800 IU/day in two divided doses	Haemorrhagic stroke, risk of prostate cancer
Pioglitazone	MASH with and without T2DM	Oral	30–45 mg/day	Weight gain, risk of heart failure exacerbation, bone loss
Saroglitazar	MASH with and without T2DM	Oral	4 mg/day	Unclear adverse effect profile due to small studies; high CV risk seen with muraglitazar
Liraglutide	MASH without cirrhosis	Subcutaneous injections	1.8 mg s.c. daily (T2DM) 0.6–3 mg s.c. daily (obesity)	Gastrointestinal, gallstones (related to weight loss), pancreatitis
Semaglutide	MASH without cirrhosis	Subcutaneous injections Oral	0.4 mg s.c. daily, 0.25–2.4 mg sc weekly 3,7 and 14 mg daily (T2DM)	Gastrointestinal, gallstones (related to weight loss), pancreatitis
Tirzepatide	MASLD with T2DM/obesity	Subcutaneous injections	10 or 15 mg once weekly	Gastrointestinal, gallstones related to weight loss, pancreatitis
Resmetirom	MASH without cirrhosis	Oral	80 mg or 100 mg daily	Diarrhoea, vomiting
SGLT2I	MASLD with T2DM	Oral	5 or 10 mg dapagliflozin 10 or 25 mg empagliflozin 100 mg or 300 mg canagliflozin	Risk of genitourinary yeast infection, volume depletion, bone loss
Medication	Mechanism	Mode of administration	Dose	Adverse effects
Other promising agents in the pipeline				
Pegozafermin	Fibroblast growth factor 21 (FGF21) analogue	Subcutaneous injections	15 or 30 mg weekly	Mild-moderate nausea, diarrhoea
Survodutide	Dual glucagon receptor and GLP-1 receptor agonist	Subcutaneous injections	2.4, 4.8 or 6 mg	Gastrointestinal, tachycardia, thrombocytopenia
Cotadutide Efinopegdutide	Dual GLP-1 and glucagon receptor agonist	Subcutaneous injections	Cotadutide 200 & 300 mcg daily Efinopegdutide 10 mg weekly	Gastrointestinal disorders—nausea, vomiting, diarrhoea Anti-drug antibody development, injection-site reaction
Lanifibranor	Pan PPAR agonist	Oral	800 or 1200 mg daily	Nausea, diarrhoea, peripheral oedema, anaemia and weight gain

T2DM = Type 2 diabetes mellitus, MASLD = Non-alcoholic fatty liver disease, MASH = non-alcoholic steatohepatitis, PPAR = peroxisome proliferator-activated receptor. SGLT2i = sodium linked glucose cotransporter, GLP1Ra = glucagon-like peptide receptor agonist, FGF = fibroblast-like growth factor

studied in patients with cirrhosis. The recommended and maximal doses of these agents, along with the need for monitoring, are outlined in Table 2. A reasonable combination of the available agents may also be tried in the absence of improvement of MASH after 1 year of use. A repeat histologic examination to confirm resolution may not be very practical, and in its absence, improvements in the non-invasive surrogates like FIB-4 or Enhanced Liver Fibrosis (ELF) scores or vibration-controlled transient elastography with LSM can be used with their corresponding cut-offs.

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