Pharmacologic Considerations for MASLD and MASH

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In 2023, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) replaced the former nomenclature of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). The purpose of the update was to remove exclusionary and stigmatizing language of the previous terminology. Additionally, a new diagnosis (MetALD) helps to recognize patients who have features of MASLD along with increased alcohol intake.

MASLD is the most common chronic liver disease around the world, likely impacting more than 30% of the global population. By the year 2040, the prevalence rate of MASLD in adults is expected to increase to over 55%. Despite the growing prevalence, less than 5% of patients with MASLD are aware of their liver disease. A more aggressive form of MASLD is MASH, which is the leading cause of liver cancer and number one cause for liver transplantation among women.[1-3]

Current guidelines for the diagnosis and management of MASLD and MASH include the 2023 American Association for the Study of Liver Diseases (AASLD) Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease and the 2024 EASL/EASD/EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease.[4,5] Additionally, guidelines were recently published to address the FDA approval of resmetirom.[6]

Diagnosing MASLD may mean recognizing several aspects of the history and physical exam, including the presence of steatotic liver disease identified by imaging or biopsy, at least one cardiometabolic criteria defined in the guidelines, and no other identified causes of steatosis. The diagnosis of MetALD incorporates the same three diagnostic criteria as MASLD in addition to alcohol intake of ≥20 grams per day (females) or ≥30 grams per day (males).[5] Of note, a standard drink – 12 ounces of regular beer, 5 ounces of wine, 1.5 ounces of distilled spirits – typically contains 14 grams of alcohol. On average, 20% of patients with MASLD progress to MASH, which is hepatic steatosis with inflammation and hepatocyte ballooning on imaging. Progression of disease is relatively slow; however, progression may be faster in patients with cardiometabolic risk factors of type 2 diabetes mellitus (T2DM) and obesity.[1]

In primary care settings, patients suspected to have MASLD based on metabolic risk factors or imaging should undergo primary risk assessment. The fibrosis-4 (FIB-4) index is a non-invasive tool used to identify patients who may advance to fibrosis and is calculated using a patient's age in years, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in units/L, and platelet count in 10^9/L. The score is calculated as:

$$\text{FIB-4} = \frac{(\text{age} \times \text{AST})}{\text{platelet count} \times \sqrt{\text{ALT}}}$$

The FIB-4 score should be used to screen patients with T2DM, obesity, and ≥1 cardiometabolic risk factor, or persistently elevated liver enzymes. If the FIB-4 score is <1.3, then the score should be reassessed every one to three years based on T2DM diagnosis and number of metabolic risk factors, and every one to two years for patients with T2DM or pre-T2DM or if they have ≥2 metabolic risk factors.

Previous terminology referenced throughout the article matches terminology utilized in clinical trials prior to updated nomenclature.

The FIB-4 score can be reassessed every two to three years if the patient does not have T2DM or has <2 metabolic risk factors. If the FIB-4 score is between 1.3 and 2.67, intensified management of comorbidities is warranted including lifestyle interventions, treatment of comorbidities, or bariatric procedures. For scores >2.67, a referral to a hepatologist is recommended. See Table 1 for a summary of management recommendations. All patients with clinical suspicion of MASLD should have ongoing assessment of alcohol intake, lifestyle management, and cardiometabolic risk reduction and preferential use of medications with potential MASLD benefit.[4,5]

The management of MASLD is multi-faceted and incorporates both non-pharmacologic and pharmacologic interventions. For those with overweight/obesity, weight loss of 3% to 5% has been shown to improve steatosis; however, weight loss of >10% is generally required to improve MASH and fibrosis.

The Mediterranean diet has been associated with cardiovascular health and reduction in liver fat. If unable to follow the Mediterranean diet, a diet leading to a caloric deficit with limited carbohydrates and saturated fat, and enriched with high fiber and unsaturated fats, should be recommended. Studies have shown regular moderate exercise at least five times per week for a total of 150 minutes per week or an increase in activity level by more than 60 minutes per week can prevent or improve MASLD. Exercise should be routinely recommended and individualized to the patient's physical abilities.[4-7]

Several medications may improve parameters of MASLD; however, the only FDA-approved agent currently on the market for the treatment of MASLD or MASH is resmetirom. Non-FDA-approved agents that may have some benefit in MASLD or MASH include pioglitazone, vitamin E, injectable semaglutide, and tirzepatide (see Table 2 on page 82).

Resmetirom is a partial agonist of thyroid hormone receptor-beta (THR-β), which is the predominant thyroid hormone receptor in the liver. The stimulation of THR-β in the liver reduces intrahepatic triglycerides. Resmetirom is FDA approved for noncirrhotic MASH with moderate to advanced fibrosis (F2-F3). If the patient's actual body weight is less than 100 kg, then 80 mg by mouth once daily is recommended. If the patient's actual body weight is 100 kg or more, the recommended dose is 100 mg once daily.[8] If patients are utilizing a concomitant moderate cytochrome P450 2C8 inhibitor (e.g., clopidogrel), the recommended dosage is 80 mg daily for those 100 kg or more or 60 mg daily for those who weigh less than 100 kg.[6]

Resmetirom therapy is recommended in patients with liver histology showing MASH with stage 2 to 3 liver fibrosis or stipulated on their imaging-based non-invasive liver disease assessment. If a biopsy is not available, the preference is to use a liver stiffness test measuring vibration-controlled transient elastography and/or magnetic resonance elastography, based on the MAESTRO-NASH trial and AASLD guidelines. Resmetirom is not recommended in patients with concomitant active liver disease, excess alcohol use, active thyroid disease, or cirrhosis. Patients with other liver stiffness measurements could be considered by a specialist experienced in liver fibrosis for the initiation of resmetirom therapy.[4,6,9,10]

Routine monitoring for safety and efficacy is recommended for patients on resmetirom. Before treatment initiation, a hepatic function panel, thyroid function tests, lipid panel, and a non-invasive measurement of liver stiffness is recommended. After three months of treatment, a hepatic function panel should be obtained. After six months of treatment, a hepatic function panel, thyroid function panel, and lipid panel are recommended, and at 12 months an assessment of response. If there is worsening of non-invasive liver disease assessment or a consistent increase in ALT, resmetirom therapy should be stopped.

Resmetirom therapy may be continued if a beneficial response is shown after 12 months of therapy. A beneficial response to resmetirom therapy is defined as either an improvement in liver stiffness measure or the normalization or significant improvement in ALT (defined as a decrease in ALT by 17 units or a 20% decline). Improvement in liver stiffness measure is defined as an improvement in vibration-controlled transient elastography by ≥25% or magnetic resonance elastography by ≥20% from baseline.[6,10]

Statin therapy can be utilized while patients are on resmetirom therapy but may need to be modified. While taking resmetirom, it is recommended not to exceed a daily dose of 40 mg of atorvastatin or pravastatin, and 20 mg of rosuvastatin and simvastatin.[6]

In the MAESTRO-NAFLD-1 trial, resmetirom 80 mg and 100 mg were compared to placebo over the course of 52 weeks in patients with NAFLD and presumed NASH. The primary endpoint of the study was the incidence of treatment-emergent adverse events

Table 1. **FIB-4 Risk Stratification and Referral to GI**[3]

FIB-4 Score	Presence of Cardiometabolic Comorbidities*	Management	Reassessment Interval
<1.3	No presence of diabetes *and* <2 metabolic risk factors	Manage by PCP	Every 2-3 years
<1.3	T2DM *or* ≥2 metabolic risk factors	Manage by PCP	Every 2-3 years
1.3 - 2.67	Any	Consider referral to GI/liver specialist	n/a
>2.67	Any	Refer to GI/liver specialist	n/a

** Cardiometabolic criteria*

1. *Body mass index ≥25 kg/m² (≥23 for Asian patients)* ***or*** *waist circumference >94 cm (male) or >80 cm (female) or ethnicity adjusted.*
2. *Fasting serum glucose ≥100 mg/dL* ***or*** *two-hour post-load glucose levels ≥140 mg/dL* ***or*** *HbA1c ≥5.7%* ***or*** *type 2 diabetes* ***or*** *treatment for type 2 diabetes.*
3. *Blood pressure ≥130/85* ***or*** *specific antihypertensive drug treatment.*
4. *Plasma triglycerides ≥150 mg/dL* ***or*** *lipid-lowering treatment.*
5. *Plasma HDL cholesterol ≤40 mg/dL (male) and ≤50 mg/dL (female)* ***or*** *lipid-lowering treatment.*

over 52 weeks. Secondary endpoints included LDL-C, apoB, triglycerides, hepatic fat, and liver stiffness. The study found resmetirom was well tolerated among the participants. Resmetirom was also found to improve markers of liver injury and reduce the levels of LDL-C, apoB, and triglycerides.[11]

In the phase 3 MAESTRO-NASH trial, resmetirom 80 mg and 100 mg were compared to placebo over the course of 52 weeks in patients with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3. The two primary endpoints were NASH resolution with no worsening of fibrosis and an improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score. The study found 25.9% of participants in the 80 mg group, 29.9% of participants in the 100 mg group, and 9.9% of participants in the placebo group demonstrated NASH resolution with no worsening of fibrosis.

Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of participants in the 80 mg group, 25.9% in the 100 mg group, and 14.2% of participants in the placebo group. Both primary endpoints were found to be statistically significant, and resmetirom was found to be superior to placebo. The study concluded both doses of resmetirom were superior to placebo with respect to resolution of NASH and improvement in liver fibrosis by at least one stage.[9]

Pioglitazone is a thiazolidinedione that acts as a peroxisome proliferator-activated receptor (PPAR)-γ activator. It improves insulin sensitivity and causes lipid metabolism within the adipose tissue, liver, and muscles. Historically, it is indicated for the management of T2DM.[12] In a 2006 study, pioglitazone was compared to placebo in patients with biopsy-confirmed NASH over a six-month period. The study found pioglitazone provided improvement in liver histology for those with NASH and T2DM. Conversely, the study found a significant increase in weight gain with pioglitazone therapy as compared to placebo.[13]

Vitamin E is an antioxidant that has been shown to reduce hepatocellular injury due to oxidative stress. A 2019 study completed with patients within the U.S. Department of Veterans Affairs compared vitamin E 400 units orally twice daily with or without pioglitazone 45 mg daily to placebo over the course of 18 months. The study found the combination of vitamin E and pioglitazone provided significant benefit regarding the improvement of liver histology for patients with NASH and T2DM. The study authors suggest that monotherapy of vitamin E should not be recommended for patients with NASH because it does not improve liver histology compared to placebo.[14]

In patients with biopsy-confirmed NASH without T2DM, a 2010 study compared the use of pioglitazone, vitamin E, or placebo over the course of 96

Table 2. Review of Current Literature on the Pharmacologic Management of MASLD/MASH		
Agents	**MASH Benefits with T2DM**	**MASH Benefits without T2DM**
Resmetirom	X (FDA approved)	X
Pioglitazone	X	X
Vitamin E		X
Injectable Semaglutide	X	X
Tirzepatide	X	X

weeks. Participants received pioglitazone 30 mg daily, vitamin E 800 units daily, or placebo. In comparison to placebo, vitamin E was superior for the treatment of NASH in adults without T2DM. The study authors found pioglitazone did not provide significant improvement in histologic features of NASH, but it did provide a significant improvement in inflammation and steatosis.[15]

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Mechanistically, GLP-1 receptor agonists act within the incretin pathway to decrease appetite, insulin resistance, and liver fat, which are all advantageous in MASLD and MASH. Semaglutide currently has FDA-approved indications in T2DM and weight management.[16] In a phase 2 trial, injectable semaglutide was compared to placebo in patients with biopsy-confirmed NASH and fibrosis, with or without T2DM, and a BMI of greater than 25 kg/m^2. Participants were randomized to receive either a 0.1 mg, 0.2 mg, or 0.4 mg subcutaneous daily dose of semaglutide, or a placebo. The 72-week-long trial found a significant resolution of NASH in patients with or without T2DM as compared to placebo. There was no significant improvement in fibrosis in the semaglutide group as compared to placebo. The use of semaglutide was found to cause a weight loss of 13% from baseline, while placebo led to only 1% weight loss.[17]

Tirzepatide is a novel agent that is a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonist.[18] The phase 2 SYNERGY-NASH trial compared tirzepatide to placebo in patients with biopsy-confirmed NASH and stage F2 or F3 (moderate or severe) fibrosis. Participants received either 5 mg, 10 mg, or 15 mg once weekly of tirzepatide as compared to placebo for 52 weeks. The study found tirzepatide was more effective in resolution of NASH without worsening of fibrosis as compared to placebo after 52 weeks.[19]

The use of sodium glucose cotransporter 2 (SGLT-2) inhibitors as a MASH-targeted therapy in patients with MASH is not recommended. There is currently insufficient evidence to support utilizing SGLT-2 inhibitors for MASH. For patients with MASLD, SGLT-2 inhibitors are safe to use and are recommended to be used for the appropriate comorbid conditions of T2DM, heart failure, or chronic kidney disease.[6]

The pipeline of medications for the management of MASLD and MASH is promising with new clinical targets. Approaches under investigation include hepatic lipid accumulation and the resultant metabolic stress. Agents to target this include PPAR agonists (lanifibranor, saroglitazar); another approach focuses on targeting fibrosis, oxidative stress, and inflammation. These agents include tumor necrosis α pathway regulators (emricasan, ZSP1601) and immune modulators (cenicriviroc, belapectin). An additional approach for MASLD management targets the gut. These agents include solithromycin and IMM-124e.[20]

As the prevalence of MASLD and MASH continues to increase, the detection and early screening of these are crucial to control contributing comorbid conditions and prevent progression to fibrosis or cirrhosis. Routine risk reassessment, lifestyle interventions, and intensive management of metabolic comorbid conditions may prevent further complications.

The pharmacologic management of MASLD and MASH is evolving. There is currently only one FDA-approved agent for the management of MASH, but several agents have been shown to improve disease markers for patients. Agents focusing on new clinical targets suggest a promising future in the management of MASLD and MASH.

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