Japanese Journal of Gastroenterology and Hepatology[R] ISSN 2435-1210|Volume 11

Review Article Open Access

Emerging Pharmacological Therapies for Metabolic Dysfunction-Associated Steatohepatitis: Clinical Efficacy, Safety, Drug Interactions and Future Perspectives

Pedhapudi Shakthi Amrutha[1*] and Seelam Harshitha[2]

[1]Department of Pharmacy Practice, Aditya College of Pharmacy (A), Aditya University, Surampalem, East Godavari, Andhra Pradesh, India

[2]Department of Pharmacy Practice, Aditya College of Pharmacy (A), Aditya University, Surampalem, East Godavari, Andhra Pradesh, India

***Corresponding author:**

Pedhapudi Shakthi Amrutha,
Department of Pharmacy Practice, Aditya College of Pharmacy (A), Aditya University, Surampalem, East Godavari, Andhra Pradesh, India

Received: 10 Nov 2026
Accepted: 18 Nov 2026
Published: 21 Nov 2026
J Short Name: JJGH

Copyright:

©2026 Pedhapudi Shakthi Amrutha. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits Pedhapudi Shakthi Amrutha unrestricted use, distribution, and build upon your work non-commercially

Keywords:

MASH; MASLD; Pharmacotherapy; Resmetirom; Semaglutide

Citation:

Pedhapudi Shakthi Amrutha, Emerging Pharmacological Therapies for Metabolic Dysfunction-Associated Steatohepatitis: Clinical Efficacy, Safety, Drug Interactions and Future Perspectives. Japanese Jour of Gastro and Hepatology® 2026; V11(1): 1-5

1. Abstract

1.1. Objectives

To review the current clinical evidence on pharmacological therapies for metabolic dysfunction-associated steatohepatitis (MASH), focusing on efficacy, safety, drug interactions, monitoring requirements and implications for clinical pharmacy practice.

1.2. Methods

A structured narrative review approach was adopted. Relevant literature was identified through searches of PubMed/MEDLINE, Scopus and the Cochrane Library, supplemented by clinical trial registries, regulatory documents and professional guidelines. Publications evaluating pharmacological interventions in adults with MASH or non-alcoholic steatohepatitis were considered. Evidence was assessed according to study design, clinical relevance, efficacy outcomes and safety findings. [Insert the final search dates, exact search strategy and screening details before submission.

1.3. Key Findings

Resmetirom and semaglutide have demonstrated histological benefits in phase III clinical trials and have received United States regulatory approval for selected adults with non-cirrhotic MASH and moderate-to-advanced fibrosis. Tirzepatide has demonstrated promising phase II results, while fibroblast growth factor 21 analogues and other emerging agents remain under investigation. Gastrointestinal adverse events, clinically significant drug interactions and patient-specific treatment considerations remain important.

1.4. Conclusions

Pharmacological management of MASH is evolving towards individualised treatment based on fibrosis stage and cardiometabolic risk. Clinical pharmacists can contribute through medication reconciliation, interaction screening, adverse drug reaction monitoring and patient counselling. Further long-term evidence is required to establish clinical outcomes and optimal treatment strategies.

2. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is an increasingly recognised cause of chronic liver disease. Its progressive inflammatory form, metabolic dysfunction-associated steatohepatitis (MASH), was previously termed non-alcoholic steatohepatitis (NASH). MASH is characterised by hepatic steatosis, lobular inflammation and hepatocellular ballooning, with varying degrees of fibrosis.

The disease is closely associated with obesity, insulin resistance, type 2 diabetes mellitus, dyslipidaemia and metabolic syndrome. Progressive hepatic fibrosis may lead to cirrhosis, portal hypertension, hepatocellular carcinoma and liver-related mortality. In addition, patients with MASLD have an increased burden of cardiovascular and other metabolic complications.

Lifestyle modification, including dietary changes, weight reduction and regular physical activity, remains the foundation of management. However, lifestyle interventions alone may not be sufficient for all patients, particularly those with significant hepatic fibrosis.

Recent advances in pharmacological research have introduced therapies targeting hepatic lipid metabolism, thyroid hormone signalling, incretin pathways and fibrogenesis. Resmetirom and semaglutide represent important developments because both have received United States Food and Drug Administration (FDA) approval for selected adults with non-cirrhotic MASH and fibrosis stages F2–F3.

Despite these advances, treatment selection requires careful consideration of disease severity, comorbidities, concomitant medications, adverse effects and long-term treatment outcomes.

This review discusses the pharmacological management of MASH, with particular emphasis on clinical efficacy, safety, drug interactions and the contribution of clinical pharmacists to optimising medication use.

3. Review Approach and Literature Search

3.1. Review Design

A structured narrative review approach was used to evaluate the current evidence concerning pharmacological therapies for MASH. The review focused on clinical trial findings, regulatory information, treatment safety and practical implications for clinical pharmacy practice.

3.2. Review Questions

The review aimed to address the following questions:

1. What pharmacological therapies have demonstrated clinical efficacy in MASH?
2. What evidence supports their effects on MASH resolution and liver fibrosis?
3. What are the important adverse effects and clinically significant drug interactions?
4. What monitoring and counselling considerations are relevant to clinical pharmacy practice?
5. Which emerging therapies may influence future MASH management?

3.3. Information Sources and Search Strategy

Literature was searched using PubMed/MEDLINE, Scopus and the Cochrane Library. ClinicalTrials.gov, regulatory documents and relevant professional guidelines were also considered.

Search terms included combinations of the following:

- "Metabolic dysfunction-associated steatohepatitis"
- "Metabolic dysfunction-associated steatotic liver disease"
- "Non-alcoholic steatohepatitis"
- Pharmacotherapy
- Drug therapy
- Resmetirom
- Semaglutide
- Tirzepatide
- Efruxifermin
- Pegozafermin
- Denifanstat
- Fibroblast growth factor 21
- Glucagon-like peptide-1 receptor agonists

The search covered literature from database inception to [insert final search date]. English-language publications were considered.

Note: The exact database-specific search strings, search dates and retrieved publication counts must be recorded before submission.

3.4. Literature Selection and Quality Considerations

Clinical trials, peer-reviewed research articles, systematic reviews, meta-analyses, regulatory documents and professional guidelines were considered according to their relevance to the review questions.

Randomised controlled trials and phase II or phase III clinical studies were given priority when evaluating treatment efficacy and safety. Regulatory documents were considered for approved indications, dosage information, contraindications and drug interactions.

Animal studies, in-vitro studies, unrelated clinical studies, editorials and publications without relevant pharmacological information were not considered in the clinical evidence synthesis. Reviews were used for background and contextual information rather than treated as original clinical trial evidence.

The strength of evidence was interpreted according to study design, sample size, duration of follow-up, outcome definitions and limitations.

4. Pathophysiology and Pharmacological Targets

MASH develops through interactions between metabolic dysfunction, hepatic lipid accumulation, inflammation, oxidative stress and fibrogenesis.

Insulin resistance promotes increased free fatty acid delivery to the liver and hepatic triglyceride accumulation. Lipotoxicity and cellular stress contribute to hepatocyte injury and inflammatory signalling. Persistent inflammation activates hepatic stellate cells, promoting extracellular matrix deposition and fibrosis.

Several pharmacological approaches have therefore been investigated:

1. Thyroid hormone receptor-beta activation to improve hepatic lipid metabolism.
2. Incretin-based therapies to improve glycaemic control, body weight and metabolic function.
3. Fibroblast growth factor signalling to influence lipid and glucose metabolism.
4. Peroxisome proliferator-activated receptor pathways to regulate lipid metabolism and inflammation.
5. Inhibition of de novo lipogenesis to reduce hepatic fat accumulation.

These mechanisms provide the basis for current and emerging pharmacological treatments.

Table 1: Summary of selected clinical trials evaluating pharmacological therapies for MASH.

Medicine	Clinical trial	Phase	Main efficacy findings
Resmetirom	MAESTRO-NASH	III	Improved MASH resolution and fibrosis outcomes
Semaglutide	ESSENCE	III	Improved MASH resolution and fibrosis outcomes at week 72
Tirzepatide	SYNERGY-NASH	II	Improved MASH resolution and fibrosis outcomes
Efruxifermin	SYMMETRY	IIb	Investigated in patients with MASH-related cirrhosis; primary week-36 fibrosis endpoint was not met

The results of these trials should not be directly compared as if they were head-to-head studies. Differences in patient populations, trial duration, fibrosis stages, outcome definitions and statistical methods may influence the reported treatment effects.

Table 2: Important safety and clinical pharmacy considerations.

Medicine	Important adverse effects	Clinical pharmacy considerations
Resmetirom	Diarrhoea, nausea, pruritus and vomiting	CYP2C8 interactions, statin dose limitations and liver-related monitoring
Semaglutide	Nausea, vomiting, diarrhoea and constipation	Hypoglycaemia with insulin or sulfonylureas, dehydration, gallbladder and pancreatitis precautions
Tirzepatide	Nausea, diarrhoea and vomiting	Review concomitant antidiabetic medicines and monitor gastrointestinal tolerance
FGF21 analogues	Trial-dependent adverse effects	Monitor emerging safety data and investigational status

5. Pharmacological Therapies for MASH

5.1. Resmetirom

Resmetirom is an orally administered, liver-directed thyroid hormone receptor-beta agonist. Activation of thyroid hormone receptor-beta promotes hepatic lipid metabolism and reduces liver fat.

The MAESTRO-NASH phase III trial evaluated resmetirom in patients with MASH and liver fibrosis. At week 52, MASH resolution without worsening of fibrosis occurred in 25.9% of patients receiving 80 mg and 29.9% receiving 100 mg, compared with 9.7% receiving placebo. Improvement in fibrosis by at least one stage without worsening of the non-alcoholic fatty liver disease activity score occurred in 24.2%, 25.9% and 14.2%, respectively.

Resmetirom also demonstrated reductions in low-density lipoprotein cholesterol. Diarrhoea and nausea were more frequent in the treatment groups than in the placebo group.

The FDA granted accelerated approval for resmetirom in March 2024 for adults with non-cirrhotic MASH and moderate-to-advanced fibrosis, corresponding to F2–F3 stages, alongside diet and exercise.

Clinical pharmacy considerations

Resmetirom requires attention to clinically significant drug interactions. Strong CYP2C8 inhibitors such as gemfibrozil are not recommended for concomitant use. Dosage adjustment is required with moderate CYP2C8 inhibitors such as clopidogrel. Increased exposure to certain statins may require dosage limitations and monitoring.

Patients should be monitored for gastrointestinal adverse effects, liver-related safety concerns and potential statin-associated adverse reactions. Resmetirom should not be used in patients with decompensated cirrhosis.

5.2. Semaglutide

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA). It improves glucose-dependent insulin secretion, reduces appetite, delays gastric emptying and promotes weight reduction.

The ESSENCE phase III trial evaluated semaglutide 2.4 mg once weekly in patients with biopsy-confirmed MASH and fibrosis stages F2–F3. In the planned week-72 interim analysis, MASH resolution without worsening of fibrosis occurred in 62.9% of the semaglutide group compared with 34.3% of the placebo group. Improvement in fibrosis without worsening of steatohepatitis occurred in 36.8% and 22.4%, respectively.

Mean body weight reduction was also greater with semaglutide than with placebo. Gastrointestinal adverse events were more common in the semaglutide group.

In August 2025, the FDA approved Wegovy (semaglutide) for adults with non-cirrhotic MASH and moderate-to-advanced fibrosis under accelerated approval.

Clinical pharmacy considerations

Common adverse effects include nausea, vomiting, diarrhoea, constipation and abdominal discomfort. Important precautions include acute pancreatitis, gallbladder disease, dehydration-related kidney injury and hypoglycaemia when used with insulin or insulin secretagogues.

Semaglutide delays gastric emptying and may affect the absorption

of concomitant oral medicines. Patients should receive counselling regarding gradual dose escalation, gastrointestinal symptoms, hydration and treatment adherence.

5.3. Tirzepatide

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist. It improves glucose regulation and promotes weight reduction.

The SYNERGY-NASH phase II trial evaluated tirzepatide in patients with MASH and fibrosis stages F2–F3. At week 52, MASH resolution without worsening of fibrosis occurred in 44%, 56% and 62% of patients receiving 5 mg, 10 mg and 15 mg, respectively, compared with 10% receiving placebo.

Fibrosis improvement was also observed in the treatment groups. Gastrointestinal adverse events were the most commonly reported adverse events and were generally mild or moderate.

Although these findings are promising, the phase II results should not be interpreted as equivalent to established phase III evidence. Tirzepatide should not be described as an FDA-approved MASH-specific treatment on the basis of this trial alone.

5.4. Clinical Pharmacy Considerations

Patients should be monitored for gastrointestinal intolerance, dehydration and gallbladder-related symptoms. Hypoglycaemia risk may increase when tirzepatide is used with insulin or sulfonylureas. Medication review and dose optimisation of concomitant antidiabetic therapy may therefore be required.

5.6. Fibroblast Growth Factor 21 Analogues

Fibroblast growth factor 21 (FGF21) is involved in glucose and lipid metabolism and has attracted interest as a therapeutic target in MASH.

FGF21 analogues, including efruxifermin and pegozafermin, have been investigated for their potential effects on hepatic steatosis, inflammation and fibrosis.

Clinical studies have reported promising histological and metabolic findings. However, these agents remain investigational, and further phase III evidence and long-term safety data are needed before their role in routine MASH treatment can be established.

5.7. Other Emerging Pharmacological Approaches

Several additional therapeutic approaches are being investigated:

Peroxisome proliferator-activated receptor agonists: These agents influence lipid metabolism, insulin sensitivity and inflammatory pathways.

De novo lipogenesis inhibitors: Drugs targeting fatty acid synthesis may reduce hepatic lipid accumulation.

Sodium-glucose cotransporter-2 inhibitors: These agents are primarily used for diabetes and cardiorenal indications. Their potential hepatic benefits are being investigated, but they should not be considered established MASH-specific therapies solely on the basis of metabolic improvements.

Combination therapies: Combining agents with complementary mechanisms may provide additional benefits. However, routine combination of MASH-targeted medicines requires stronger evidence regarding efficacy, safety and long-term outcomes.

6. Safety Profile and Drug Interactions

Medication safety is a major consideration in MASH because affected patients frequently have diabetes, obesity, dyslipidaemia, hypertension and cardiovascular disease. Consequently, polypharmacy and potential drug interactions are common.

6.1. Polypharmacy and Medication Reconciliation

Patients with MASH frequently receive multiple medicines for metabolic comorbidities. Medication reconciliation helps identify duplicate therapy, unnecessary medication use and potential interactions.

6.2. Adverse Drug Reaction Monitoring

Patients should be assessed for treatment-related adverse events during follow-up. Suspected adverse drug reactions should be documented and reported through the appropriate pharmacovigilance system.

6.3. Patient Counselling

Counselling should include the purpose of treatment, administration schedule, common adverse effects, warning symptoms, adherence and the importance of lifestyle modification.

7. Clinical Pharmacy Implications

Clinical pharmacists have an important role in supporting safe and effective pharmacological management of MASH.

Key responsibilities include:

- Reviewing medication histories and identifying potential drug interactions.
- Assessing concomitant antidiabetic and lipid-lowering therapy.
- Monitoring treatment-related adverse drug reactions.
- Supporting appropriate laboratory and clinical monitoring.
- Educating patients about medicine administration and adherence.
- Identifying contraindications and treatment-related precautions.
- Communicating relevant medication safety concerns to the multidisciplinary team.

A structured clinical pharmacy approach may help improve medication safety and treatment adherence in patients receiving MASH pharmacotherapy.

8. Future Perspectives

Future MASH treatment is likely to involve individualised pharmacotherapy based on fibrosis stage, metabolic phenotype and associated comorbidities.

Long-term clinical trials are required to determine whether improvements in histological surrogate endpoints translate into reductions in cirrhosis progression, liver-related complications, transplantation and mortality.

Further research should also evaluate combination therapies, treatment duration, long-term safety, cost-effectiveness and access to medicines.

The role of clinical pharmacists in treatment monitoring and pharmacovigilance also deserves further investigation.

9. Limitations of the Review

This review has limitations. Differences in trial designs, study populations, treatment durations and histological outcome definitions may affect comparisons between pharmacological interventions. Some emerging therapies have limited long-term clinical evidence. In addition, regulatory approvals differ between countries, and United States approval should not automatically be interpreted as approval by Indian regulatory authorities.

10. Conclusion

The pharmacological management of MASH has advanced considerably with the development of therapies targeting hepatic lipid metabolism and metabolic dysfunction. Resmetirom and semaglutide have demonstrated histological benefits and received FDA approval for selected adults with non-cirrhotic MASH and fibrosis stages F2–F3. Tirzepatide and FGF21 analogues represent promising areas of ongoing research.

Treatment selection should be individualised according to disease stage, comorbidities, concomitant medicines and safety considerations. Clinical pharmacists can contribute through medication reconciliation, drug interaction screening, adverse drug reaction monitoring and patient education. Further long-term studies are required to establish sustained clinical benefits and optimal treatment strategies.

11. Limitations

This systematic review has certain limitations. The included studies showed variations in study design, sample size, treatment duration, patient characteristics, and outcome measures, which may limit direct comparisons between pharmacological interventions. Additionally, differences in diagnostic criteria and disease classification across studies may have influenced the interpretation of findings. The availability of published evidence and the possibility of publication bias may also affect the comprehensiveness of the review. Furthermore, some potentially relevant studies may not have been identified despite the systematic search strategy. Therefore, the findings should be interpreted with consideration of these limitations.

12. Acknowledgement

The authors would like to express their sincere gratitude to the Department of Pharmacy Practice, Aditya College of Pharmacy, Aditya University, Kakinada, Andhra Pradesh, India, for providing the academic support and encouragement necessary for completing this review.

13. Patient Consent

Patient consent was not applicable to this systematic review, as it was based exclusively on previously published studies and did not involve the recruitment of human participants, collection of individual patient data, or direct interaction with patients.

14. Ethics Approval

Ethical approval was not required for this review because it involved the analysis of previously published literature and did not involve human participants, animal experiments, or the collection of identifiable personal data.

15. Conflict of Interest

The authors declare that they have no conflicts of interest related to the publication of this systematic review.

16. Author Contributions

All authors contributed to the development of this review.

- Conceptualisation: [Pedhapudi Shakthi Amrutha, Seelam Harshitha].
- Literature search and data collection: [Pedhapudi Shakthi Amrutha, Seelam Harshitha].
- Data screening and selection: [Pedhapudi Shakthi Amrutha, Seelam Harshitha].
- Data extraction and analysis: [Pedhapudi Shakthi Amrutha, Seelam Harshitha].
- Writing – Original Draft Preparation: [Pedhapudi Shakthi Amrutha].
- Writing – Review and Editing: [Seelam Harshitha].

References

1. Harrison SA, Bedossa P, Guy CD. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med. 2024; 390: 497-509.
2. Sanyal AJ, Newsome PN, Kliers I. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025; 392: 2089-2099.
3. Loomba R, Hartman ML, Lawitz EJ. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med. 2024.
4. US Food and Drug Administration. FDA approves treatment for serious liver disease known as MASH. 2025.
5. US Food and Drug Administration. Rezdiffra (resmetirom) prescribing information.
6. US Food and Drug Administration. Wegovy (semaglutide) prescribing information.
7. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. Clinical practice guidance on the use of resmetirom and semaglutide as MASH-targeted therapy. 2026.
8. Gallage S, Govaere O, Anstee QM. Current therapeutic landscape and future treatment perspectives of MASH. Nature. 2026; 657: 76-91.