Faridpur Med. Coll. J. 2026;21(2):51-60 DOI: https://doi.org/10.3329/fmcj.v21i2.90822

Reveiw Article

Pharmacological Management of Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)

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Abstract:

Background: *Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD), is the most prevalent chronic liver disease worldwide and a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation. Despite its growing burden, pharmacological treatment options remain limited, and existing evidence is heterogeneous. This systematic review aimed to critically evaluate the efficacy and safety of pharmacological therapies in improving histological and metabolic outcomes among adults with MASLD/NAFLD.*

Materials & Methods: *A systematic search of PubMed, Scopus, Cochrane Library, and ClinicalTrials.gov was conducted, following PRISMA 2020 guidelines. Eligible studies included comparative clinical trials and cohort studies evaluating pharmacological interventions in adults with MASLD/NAFLD and reporting histological, metabolic, efficacy, or safety outcomes. Methodological quality was assessed using the NIH Study Quality Assessment Tools. A narrative synthesis was performed due to clinical and methodological heterogeneity.*

Results: *Twenty-three studies met the inclusion criteria, encompassing randomized controlled trials, phase II–III studies, and real-world cohorts. Pharmacological agents targeting metabolic pathways, particularly incretin-based therapies, fibroblast growth factor analogues, and thyroid hormone receptor-β agonists, demonstrated the most consistent improvements in hepatic steatosis, metabolic parameters, and composite efficacy endpoints. Histological benefits, including resolution of steatohepatitis and improvement in fibrosis, were most evident in longer-duration trials with biopsy-confirmed populations. Safety profiles were generally acceptable, with predominantly mild to moderate gastrointestinal adverse events; serious adverse events were uncommon.*

Conclusions: *Pharmacological therapies targeting systemic metabolic dysfunction offer the greatest therapeutic promise for MASLD. While several agents demonstrate meaningful histological and metabolic benefits with acceptable short-term safety, long-term outcomes and optimal treatment strategies require further investigation.*

Keywords: NAFLD, MASLD, Pharmacological management.

1. Introduction:

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is now recognized as the most common chronic liver disorder globally, affecting nearly one-third of adults and strongly associated with obesity, type 2 diabetes mellitus, dyslipidaemia, and insulin resistance.[1–3] MASLD encompasses a disease spectrum ranging from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH/NASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma, and is now a leading indication for liver transplantation globally.[4–6]

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Despite its substantial clinical and public health burden, effective pharmacological management of MASLD remains a major unmet need. Lifestyle modification

remains the cornerstone of treatment; however, long-term adherence is poor and often insufficient to halt disease progression, particularly in patients with advanced fibrosis or high metabolic risk.[7,8] Over the past two decades, multiple pharmacological agents targeting metabolic pathways, inflammation, oxidative stress, and fibrogenesis, including insulin sensitizers, lipid-modifying agents, nuclear receptor agonists, incretin-based therapies, and novel antifibrotic compounds, have been evaluated in clinical trials with varying degrees of success.[9–12] Recently, the approval of resmetirom for at-risk MASH has further intensified interest in drug-based therapeutic strategies.[13]

However, the existing evidence base is heterogeneous and fragmented. Individual trials differ substantially in study design, patient populations, diagnostic criteria, endpoints, and follow-up duration. Moreover, while many studies report improvements in metabolic parameters or non-invasive biomarkers, fewer provide robust data on histological outcomes, which remain the regulatory gold standard for disease modification. Safety and tolerability profiles also vary across pharmacological classes and are critical considerations, given the chronic nature of MASLD therapy.[14–16] As a result, clinicians and policymakers face challenges in interpreting the cumulative evidence and translating it into informed clinical decision-making.

Previous reviews have often focused on specific drug classes, surrogate outcomes, or emerging therapies, and many predate recent advances in MASLD nomenclature, trial design, and therapeutic development.[2,11,12,14] A comprehensive synthesis that systematically evaluates both efficacy and safety of pharmacological interventions across histological and metabolic outcomes in adult MASLD/NAFLD populations is therefore warranted.

This systematic review aimed to critically evaluate the efficacy and safety of pharmacological therapies in improving histological and metabolic outcomes among adults with MASLD or NAFLD, based on evidence from comparative clinical studies. By synthesizing the available clinical data, this review seeks to clarify the therapeutic value of current pharmacological strategies and to inform future research and clinical practice.

Materials & Methods:

Study Design and Reporting Standards:

The present systematic review was conducted to evaluate the efficacy and safety of pharmacological interventions in enhancing histological and metabolic outcomes among adults with MASLD and NAFLD. The review methodology and reporting adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[17] A PRISMA flow diagram was employed to illustrate the process of study identification, screening, eligibility assessment, and inclusion.

Search Strategy:

A thorough search of several electronic databases, including PubMed, Scopus, and the Cochrane Library, was carried out in December 2025. Additionally, the researchers used "clinicaltrials.gov" to look for registered trials. Pre-selected keywords and phrases served as the foundation for this stringent search technique, which sought to identify the most pertinent and qualifying papers and trials. The search strategy was designed to identify studies evaluating pharmacological treatments for MASLD/NAFLD and their histological, metabolic, efficacy, and safety outcomes. The following search terms were applied:

“("Metabolic Dysfunction-Associated Steatotic Liver Disease" OR "MASLD" OR "Non-Alcoholic Fatty Liver Disease" OR "NAFLD") AND ("pharmacological therapy" OR "medications" OR "drug treatment") AND ("histological outcomes" OR "liver biopsy" OR "liver fibrosis" OR "metabolic outcomes" OR "efficacy" OR "safety" OR "side effects")”

Eligibility Criteria:

Studies were eligible if they: (i) included adults (≥18 years) with metabolic dysfunction–associated steatotic liver disease (MASLD) or non-alcoholic fatty liver disease (NAFLD), including non-cirrhotic or presumed non-alcoholic steatohepatitis (NASH); (ii) evaluated pharmacological interventions; (iii) reported at least one relevant histological, metabolic, efficacy, or safety outcome; (iv) used a comparative clinical design (randomized controlled trials, controlled trials, or cohort studies); (v) were published in English; and (vi) were published between 2000 and 2025.

Studies were excluded if they: (i) involved participants ≤ 17 years; (ii) assessed non-pharmacological interventions (e.g., lifestyle, surgery, supplements, herbal products); (iii) lacked relevant outcomes; (iv) were preclinical, protocol-only, genetic/Mendelian randomization, or non-comparative studies; or (v) were reviews, guidelines, editorials, or had high risk of bias.

Search Process:

A structured, multi-stage search process was employed to identify studies eligible for inclusion in this systematic review. First, a comprehensive search of electronic bibliographic databases was conducted to identify published studies using predefined keywords and Boolean operators. The databases searched included PubMed, Scopus, and the Cochrane Library. In parallel, ClinicalTrials.gov was searched to identify trials.

Second, manual screening of reference lists from all included studies and relevant review articles was performed to identify additional eligible studies not identified through electronic database searches.

All retrieved records were imported into the Rayyan AI, a cloud-based systematic review platform, which was used to manage the review process from duplicate removal through title and abstract screening to full-text assessment.[18] After initial screening of titles and abstracts, potentially relevant articles underwent full-text review to determine eligibility based on predefined inclusion and exclusion criteria (Figure 1).

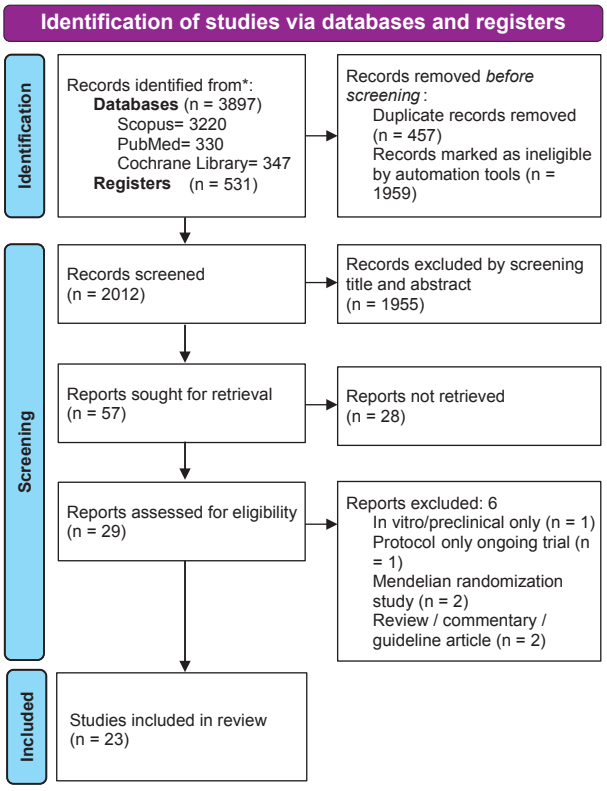

Figure 1: Flow diagram of the literature search and articles selection (adapted from PRISMA 2020 guidelines for systematic reviews)

Quality Assessment:

The methodological quality of the included studies was evaluated using the National Institutes of Health (NIH) Study Quality Assessment Tools.[19,20] The Quality Assessment Tool for Controlled Intervention Studies was applied to randomized controlled trials, whereas observational cohort and cross-sectional studies were assessed using the corresponding NIH Quality Assessment Tool for Observational Designs. Each domain within the NIH tools was evaluated and categorized as "Yes," "No," "Not Reported (NR)," "Cannot Determine (CD)," or "Not Applicable (NA)", as appropriate. The NR category was used when relevant information was potentially applicable but not reported, CD when assessment was unclear due to insufficient detail, and NA when a criterion was not applicable to the study design.

Quality assessment was performed independently by two reviewers, with disagreements resolved through discussion and consensus. Each study was subsequently classified as exhibiting good, fair, or poor methodological quality.

Data Extraction:

Data from the included studies were extracted using a standardized, pilot-tested data extraction form. The extracted data encompassed study characteristics (first author, year of publication, country, and study design) and participant characteristics (sample size, age, and diagnostic criteria), details of the pharmacological intervention (drug class, dosage, and treatment duration), comparator characteristics, and reported outcomes related to histological findings, metabolic parameters, treatment efficacy, and safety and tolerability. Data extraction was performed independently, and the extracted information was cross-checked to ensure accuracy and completeness.

Data Synthesis:

Given the heterogeneity in study designs, pharmacological agents, outcome measures, and follow-up durations, a qualitative narrative synthesis was conducted. Findings were synthesized and summarized according to pharmacological class and mechanism of action, with emphasis on histological outcomes, metabolic effects, efficacy, and safety profiles. Where appropriate, results were compared across studies to identify consistent trends and clinically relevant patterns.

Results:

Study Selection:

The comprehensive database search identified 3,897 records from PubMed, Scopus, and the Cochrane Library, with an additional 531 records retrieved from ClinicalTrials.gov. Following duplicate removal and title–abstract screening, 29 studies were selected for full-text assessment. Six studies were excluded at this stage due to preclinical design, review or guideline format, genetic or Mendelian randomization methodology, or the absence of retrievable outcome data. Ultimately, 23 studies fulfilled the predefined eligibility criteria and were included in the qualitative synthesis. The study selection process and reasons for exclusion are summarized in the PRISMA flow diagram (Figure 1).

Study Characteristics:

The 23 included studies represented a heterogeneous body of evidence comprising randomized controlled trials, phase II and phase III interventional studies, and registered clinical trials. Fifteen studies were peer-reviewed articles.[21–32,32–35] while eight were clinical trial registry records with available protocol-level or interim information.[36–42]

All studies enrolled adult participants (≥18 years) diagnosed with NAFLD, NASH/MASH, or MASLD. Disease severity varied substantially, ranging from simple steatosis and early-stage disease to advanced fibrosis (F2–F3) and compensated cirrhosis. Study duration ranged from very short-term pharmacodynamic assessments (2 weeks)[36] to long-term interventions extending to 52 weeks or longer.[23,24,28,37] Sample sizes varied widely, from small early-phase trials evaluating novel agents[27,32] to large multi-center trials and real-world cohorts involving several thousand participants.[24,35]

Table 1: Included studies: design and population summary (n = 23)

Study (Author, Year)/Identifier	Design	Population	Diagnosis basis	Cirrhosis status	Follow-up
Kessoku, 2018	Study protocol (DB RCT design)	Adults NAFLD +constipation	NR	NR	NR
CENTRAL Trial Record (CN-020 25947)	Trial registry record	Adults NASH	NR	NR	NR
Torres, 2011	Randomized, open-label	Adults NASH	Histology/ biopsy (typical for Hepatology NASH trials)	Non-cirrhotic (likely)	48 weeks (≈12 months)
Harrison, 2022	Randomized, DB, placebo-controlled Phase IIa	Adults compensated NASH cirrhosis	Biopsy-confirmed NASH cirrhosis	Compensated cirrhosis	16 weeks (primary biopsy window)
NCT03486899 (FALCON 1)	Trial registry	Adults NASH + stage 3 fibrosis	NR	Non-cirrhotic (F3)	NR
NCT04006145	Trial registry	Adults NAFLD or NASH	NR	NR	NR
NCT06256926 Sanyal, 2024	Trial registry Randomized, DB, placebo-controlled Phase 2	Adults NAFLD Adults MASH + fibrosis	NR Histology/ biopsy	NR (trial Non-cirrhotic endpoint)	NR 48 weeks (per NEJM phase 2 format)
Emricasan trial, 2019	Randomized, placebo-controlled	Adults NASH F1–F3	Biopsy	Non-cirrhotic	NR
Nakajima, 2021	Randomized, placebo-controlled	Adults NAFLD (high-risk)	NR	NR	NR
Safadi, 2021	Randomized, DB Phase 2	Adults NAFLD/NASH	NR	NR	NR
NCT03912532 (ALPINE 2/3)	Trial registry	Adults NASH F2–F3	Biopsy (typical for F2/F3)	Non-cirrhotic	NR
Harrison, 2024	Phase 3 program design paper	Adults "presumed NASH" (program)	Presumed + biopsy endpoints (design	Mixed	52 weeks biopsy + longer outcomes)
Pedrosa, 2020	Trial design paper	Adults NASH + fibrosis	Biopsy (design)	Non-cirrhotic	NR
Loomba, 2021	Randomized, placebo-controlled Phase 2a	Adults NASH	Imaging/ biomarkers + fibrosis evidence	Non-cirrhotic	12 weeks
NCT04480710 (AMBITION)	Trial registry	Adults NASH F2–F3	NR	Non-cirrhotic	NR
Calle. A., 2021	Randomized, placebo-controlled Phase 2a	Adults NAFLD	Imaging/ biomarkers (typical)	NR	NR
Hu, 2023	Randomized, placebo-controlled Phase Ib/IIa	Adults NAFLD	NR	NR	28 days
Zein, 2011	Randomized, placebo-controlled	Adults biopsy-confirmed NASH	Biopsy	Non-cirrhotic	1 year
NCT03513588	Trial registry	Adults NAFLD	NR	NR	2 weeks
Ratziu, 2022	Randomized, DB, placebo-controlled Phase 2	Adults fibrotic NASH	NR	Non-cirrhotic	NR
Suki, 2025	Real-world cohort (propensity matched)	Adults MASLD	ICD coding	Mixed	1 year

Note: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; RCT, randomized controlled trial; DB, double-blind; NR, not reported; AE, adverse event; SAE, serious adverse event.

Pharmacological Interventions:

A broad spectrum of pharmacological agents targeting distinct pathogenic pathways in MASLD/NAFLD was evaluated. These included insulin-sensitizing and metabolic agents such as rosiglitazone-based regimens[3] and pentoxifylline[33,38]; fibroblast growth factor 21 (FGF21) analogues and related metabolic regulators, including efruxifermin and aldafermin[23,37,39]; incretin-based therapies such as semaglutide and survodutide[24,35]; nuclear receptor and bile acid pathway modulators, including pemafibrate, elobixibat, tropifexor, cenicriviroc, and resmetirom[26,28,29,40]; and agents targeting apoptosis, inflammation, and fibrosis pathways such as emricasan and CRV431.[25,41]

Additionally, several studies evaluated inhibitors of de novo lipogenesis and lipid metabolism, including TVB-2640 and acetyl-CoA carboxylase (ACC) inhibitors with or without DGAT2 inhibition.[30,31] Novel or repurposed agents, such as lubiprostone, namodenoson, and the pan-phosphodiesterase inhibitor ZSP1601, were also investigated in early-phase trials.[21,27,32] The therapeutic landscape was dominated by metabolic and hormonal modulators, reflecting the systemic nature of MASLD rather than liver-specific targeting alone, as shown in Table 2.

Table 2: Pharmacological Interventions Categorized by Mechanistic Theme

Pharmacological class/theme	Representative agents	Number of studies	Targeted pathway/ rationale
GLP-1–based and dual incretin agonists	Semaglutide, Survodutide	2	Weight reduction, improved insulin sensitivity, anti-inflammatory effects
FGF analogues	Efruxifermin, Aldafermin, Pegbelfermin	3	Regulation of lipid metabolism, fibrosis modulation
Thyroid hormone receptor-β agonists	Resmetirom	1	Reduction of hepatic steatosis via lipid oxidation
FXR agonists/ bile acid modulators	Tropifexor, EDP-305, Elobixibat	3	Bile acid signalling, inflammation, fibrosis
Lipid synthesis and metabolism inhibitors	ACC inhibitors, DGAT2 inhibitors, TVB-2640, Pemafibrate	4	Suppression of de novo lipogenesis and triglyceride synthesis
Anti-inflammatory/ anti-fibrotic agents	Pentoxifylline, Emricasan, CRV431	3	Cytokine suppression, apoptosis and fibrosis modulation
Novel signalling pathway modulators	ZSP1601, Namodenoson	2	PDE inhibition, adenosine receptor signalling
Adjunct or gut–liver axis–targeted agents	Lubiprostone	1	Modulation of intestinal permeability and inflammation

Histological Outcomes:

Histological outcomes, assessed through liver biopsy or validated fibrosis-related surrogate measures, were reported in a subset of the included studies, particularly those enrolling patients with biopsy-confirmed NASH/MASH or advanced fibrosis. In patients with compensated NASH cirrhosis, efruxifermin demonstrated improvements in fibrosis- and steatohepatitis-related endpoints, supporting its potential disease-modifying role in advanced disease.[23] Similarly, survodutide showed histology-aligned improvements in patients with MASH and fibrosis, with evidence of fibrosis regression and steatohepatitis resolution reported in a randomized phase II trial.[24]

Pentoxifylline was evaluated in biopsy-confirmed NASH and demonstrated modest improvements in histological features alongside reductions in inflammatory markers.[33] In contrast, emricasan, despite targeting apoptotic pathways, showed limited histological benefit in patients with NASH and fibrosis, highlighting the complexity of translating mechanistic effects into meaningful histological improvement.[25]

Agents primarily targeting hepatic lipid synthesis and metabolism, including TVB-2640, ACC/DGAT2 inhibitors, and ZSP1601, were generally assessed using liver fat content and fibrosis-related biomarkers rather than repeat biopsy. These studies reported reductions in hepatic fat and favorable trends in fibrosis-related markers, although consistent evidence of biopsy-confirmed fibrosis regression was limited.[30–32] Histological benefits were most consistent when metabolic improvements were achieved, supporting MASLD as a metabolically driven liver disease, as shown in Table 3.

Table 3: Summary of Histological and Metabolic Outcomes Across Therapeutic Themes

Outcome domain	Evidence pattern	Drug classes showing	Key observations benefit
NASH resolution	Moderate to strong	GLP-1/dual agonists, FGF analogues, THR-β agonists	Histological resolution is primarily seen in metabolic and hormonal therapies
Fibrosis improvement (≥1 stage)	Moderate	FGF analogues, resmetirom, selected FXR agonists	Fibrosis regression was observed mainly in longer-duration trials
Steatosis reduction	Strong	GLP-1 agonists, lipid metabolism inhibitors, THR-β agonists	Consistent reductions in liver fat by biopsy or imaging
Inflammation and ballooning	Variable	Anti-inflammatory agents, FGF analogues	Less consistent than steatosis outcomes
Liver enzymes (ALT/AST)	Strong	GLP-1 agonists, FXR agonists, lipid modu lators	Enzyme reduction typical but not always linked to histological change
Glycemic control and insulin sensitivity	Strong	GLP-1 agonists, TZDs, metabolic agents	Improvements often paralleled histological benefit
Weight and lipid profile	Strong	GLP-1 agonists, pemafibrate, resmetirom	Weight loss and triglyceride reduction are prominent

Metabolic Outcomes

Across the included studies, metabolic outcomes were the most frequently reported, including measures of body weight, body mass index, lipid profiles, insulin resistance, and glycaemic control. Incretin-based therapies exhibited the most consistent and pronounced metabolic effects. Notably, semaglutide was linked to significant weight reduction, improved HbA1c and lipid parameters, and favorable cardiovascular outcomes in a large real-world MASLD population.[35] Survodutide was likewise associated with meaningful metabolic improvements and favorable liver-related outcomes in patients with MASH and fibrosis.[24]

Pemafibrate improved lipid parameters in patients with NAFLD, particularly triglyceride levels, reflecting its targeted action on lipid metabolism[26] Rosiglitazone-based regimens improved insulin sensitivity and glycaemic markers but were accompanied by weight-related considerations.[22] Pentoxifylline showed modest improvements in metabolic and inflammatory parameters across trials.[33,38](Table 3)

Efficacy Outcomes

Overall treatment efficacy was evaluated using composite endpoints incorporating histological, metabolic, and biochemical outcomes. FGF21 analogues (efruxifermin and aldafermin) demonstrated improvements across multiple outcome domains, including fibrosis-related markers and metabolic parameters, suggesting broader disease-modifying potential[23,37] Incretin-based therapies also showed consistent efficacy across metabolic and liver-related outcomes, particularly in populations with high cardiometabolic risk[24,35]

Large development programs, most notably the MAESTRO phase III program evaluating resmetirom, provided evidence of efficacy in improving steatohepatitis resolution and fibrosis-related endpoints[28] Other agents demonstrated selective efficacy confined to metabolic or biochemical improvements without consistent histological benefit, underscoring variability in therapeutic response across pharmacological classes.

Safety and Tolerability

Safety and tolerability outcomes were reported across all included studies, although the depth and granularity of reporting varied. Overall, the included pharmacological therapies showed favorable tolerability profiles, with adverse events largely limited to mild or moderate severity. Gastrointestinal adverse events were the most frequently reported across multiple drug classes, particularly with incretin-based therapies, bile acid pathway modulators, and repurposed agents[21,24,26,34,35,40]

The pan-phosphodiesterase inhibitor ZSP1601 was associated with common but mostly mild adverse events, including diarrhea, transient elevations in creatinine, and headache, with no serious adverse events reported in early-phase trials[32] FXR and bile acid pathway modulators, such as EDP-305, were evaluated with safety and tolerability as key outcomes, reflecting known class-related concerns such as pruritus and lipid alterations.[35]

Serious adverse events were uncommon across studies and rarely resulted in treatment discontinuation. However, long-term safety data remained limited for several novel agents and for studies with short treatment durations or registry-only reporting, highlighting the need for extended follow-up in future trials.[36,37,39–42]

Discussion:

This systematic review summarizes findings from 23 clinical studies assessing the efficacy of pharmacological interventions for metabolic dysfunction–associated steatotic liver disease (MASLD) and non-alcoholic fatty liver disease (NAFLD). Collectively, the findings demonstrate a clear evolution in therapeutic strategy, moving away from isolated anti-inflammatory or hepatocyte-targeted approaches toward agents that address the systemic metabolic drivers of disease. This shift reflects advances in understanding MASLD as a multisystem disorder rooted in insulin resistance, dyslipidemia, and chronic low-grade inflammation.

Among the included studies, agents targeting metabolic and hormonal pathways showed the most consistent efficacy. Incretin-based agents, including GLP-1 receptor agonists and dual incretin agonists, showed improvements in liver enzymes, metabolic parameters, and disease progression, supported by findings from randomized trials and real-world settings.[24,35] These findings align with broader evidence indicating that weight loss and improved insulin sensitivity are among the strongest predictors of histological improvement in steatohepatitis.[7,43]

FGF analogues, particularly FGF19 and FGF21-based therapies, showed promising antifibrotic and steatosis-reducing effects in biopsy-confirmed populations[23,37] These agents exert pleiotropic metabolic effects, including enhanced lipid oxidation and reduced hepatic lipogenesis, which may explain their ability to influence fibrosis, an outcome historically resistant to pharmacotherapy. Similar antifibrotic signals have been reported in prior phase II programs, supporting the consistency of these findings.[44]

In contrast, therapies focused primarily on inflammation or apoptosis, such as pentoxifylline and emricasan, yielded variable results.[25,33,38] While some studies reported improvements in inflammatory markers or modest histological changes, the overall efficacy was inconsistent. These observations support the emerging consensus that inflammation alone is insufficient as a therapeutic target in MASLD, particularly in the absence of meaningful metabolic improvement.[11]

Histological endpoints remain central to regulatory approval and clinical decision-making. In this review, histological improvement was most evident in studies with longer follow-up durations and biopsy-confirmed enrollment, particularly those targeting metabolic pathways.[23,24,28,33] This pattern further emphasizes the critical role of sustained intervention and careful patient selection in the evaluation of disease-modifying potential.

However, many early-phase and short-duration studies relied on surrogate markers such as liver enzymes or imaging-based fat quantification[30,32] While useful for proof-of-concept, these measures do not consistently correlate with fibrosis regression or long-term clinical outcomes. This limitation echoes prior critiques of NAFLD drug development and underpins regulatory emphasis on fibrosis improvement and steatohepatitis resolution as primary endpoints.[14,45]

A key theme across included studies is the tight coupling between metabolic improvement and hepatic benefit. Reductions in body weight, triglycerides, and insulin resistance were frequently accompanied by reductions in liver fat and disease activity.[22,24,26,30,35] This relationship reinforces MASLD as a metabolic disease with hepatic manifestations rather than a purely liver-limited pathology.

Notably, lipid-targeting therapies such as pemafibrate and ACC inhibitors achieved meaningful reductions in hepatic fat but sometimes induced unfavorable lipid profiles, including hypertriglyceridemia.[26,31] These findings highlight the importance of evaluating systemic metabolic consequences alongside hepatic efficacy, particularly given the elevated cardiovascular risk in this population.[46]

Pharmacological treatments were generally well tolerated in the short term, with gastrointestinal adverse events being the most commonly reported class-wide issue, particularly for incretin-based and FXR-targeted therapies.[24,29,34,35] Although often mild to moderate, these effects contributed to treatment discontinuation in some trials and may influence real-world adherence.

Class-specific safety concerns were also observed. FXR agonists were frequently associated with pruritus[29,34], while older insulin sensitizers were linked to weight gain and fluid retention.[22] Importantly, serious adverse events were uncommon; however, the lack of long-term

safety data limits conclusions regarding chronic use, particularly in patients with advanced fibrosis or cirrhosis. This concern is consistent with broader safety discussions in MASLD pharmacotherapy.[47]

Strengths and Limitations:

This review includes a comprehensive search across multiple databases and trial registries, thematic synthesis of outcomes, and explicit separation of histological, metabolic, efficacy, and safety domains. However, limitations include reliance on published and registry-reported data, heterogeneity across studies, and limited long-term safety evidence.

Clinical and Research Implications:

Clinically, the findings support prioritizing metabolic-centric pharmacological strategies, particularly incretin-based therapies, FGF analogues, and thyroid hormone receptor-β agonists, while carefully considering safety and patient comorbidities. Combination therapies targeting complementary pathways may represent the next step in improving efficacy.

From a research perspective, there is a need for long-term, head-to-head comparative trials, integration of validated non-invasive fibrosis markers, and clearer linkage between surrogate endpoints and clinical outcomes. Addressing these gaps will be critical to translating pharmacological advances into durable clinical benefit.

Conclusion:

Current pharmacological therapies for MASLD demonstrate the greatest efficacy when targeting systemic metabolic dysfunction rather than isolated hepatic pathways. While several agents show promising histological and metabolic benefits with acceptable safety profiles, substantial gaps remain regarding long-term outcomes and optimal therapeutic strategies. Continued high-quality clinical trials and integrated treatment approaches are essential to advancing effective pharmacological management of MASLD.

Abbreviations:

ACC, acetyl-CoA carboxylase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CD, cannot determine; DB, double-blind; DGAT2, diacylglycerol O-acyltransferase 2; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; NA, not applicable; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NEJM, *New England Journal of Medicine*; NIH, National Institutes of Health; NR, not reported; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SAE, serious adverse event; THR-β, thyroid hormone receptor beta; TZD, thiazolidinedione.

References:

1. Powell EE, Wong VWS, Rinella M. Non-alcoholic fatty liver disease. *The Lancet*. 2021;397(10290):2212-2224. doi:10.1016/S0140-6736(20)32511-3

2. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of Hepatology*. 2020;73(1):202-209. doi:10.1016/j.jhep.2020.03.039

3. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;77(4):1335-1347. doi:10.1097/HEP.0000000000000004

4. Rinella ME. Nonalcoholic Fatty Liver Disease: A Systematic Review. *JAMA*. 2015;313(22):2263. doi:10.1001/jama.2015.5370

5. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018;67(1):123-133. doi:10.1002/hep.29466

6. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology*. 2017;65(5):1557-1565. doi:10.1002/hep.29085

7. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology*. 2015;149(2):367-378.e5.doi:10.1053/j.gastro.2015.04.005

8. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67(1): 328-357.doi:10.1002/hep.29367

9. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med*. 2010;362(18):1675-1685. doi:10.1056/NEJMoa0907929

10. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679-690. doi:10.1016/S0140-6736(15)00803-X

11. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24(7):908-922. doi:10.1038/s41591-018-0104-9

12. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10(11):686-690. doi:10.1038/nrgastro.2013.171

13. Harrison SA, Bedossa P, Guy CD, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med*. 2024;390(6):497-509. doi:10.1056/NEJMoa2309000

14. Ratziu V, Goodman Z, Sanyal A. Current efforts and trends in the treatment of NASH. *J Hepatol*. 2015;62(1 Suppl):S65-75. doi:10.1016/j.jhep.2015.02.041

15. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395

16. Younossi ZM, Corey KE, Alkhouri N, et al. Clinical assessment for high-risk patients with non-alcoholic fatty liver disease in primary care and diabetology practices. *Aliment Pharmacol Ther*. 2020;52(3):513-526. doi:10.1111/apt.15830

17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Published online March 29, 2021:n71. doi:10.1136/bmj.n71

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. doi:10.1186/s13643-016-0384-4

19. Celaya M, Zahlan AI, Rock C, et al. Individual- and community-level risk factors for maternal morbidity and mortality among Native American women in the USA: a systematic review. *BMJ Open*. 2024;14(11):e088380. doi:10.1136/bmjopen-2024-088380

20. National Institute of Health.(nd). Quality assessment tool for observational cohort and cross-sectional studies. April 21, 2023. https://www.nhlbi.nih.gov/health-topics/assessing-cardiovascular-risk

21. Kessoku T. Efficacy, safety, and tolerability of lubiprostone for the treatment of non-alcoholic fatty liver disease in adult patients with constipation_ The LUBIPRONE, double-blind, randomised, placebo-controlled study design. *Contemporary Clinical Trials*. Published online 2018.

22. Torres DM, Jones FJ, Shaw JC, Williams CD, Ward JA, Harrison SA. Rosiglitazone versus rosiglitazone and metformin versus rosiglitazone and losartan in the treatment of nonalcoholic steatohepatitis in humans: A 12-month randomized, prospective, open- label trial. 2011; 54(5).

23. Harrison SA. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. 2023;5.

24. Sanyal AJ, Bedossa P, Fraessdorf M, et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. *N Engl J Med*. 2024;391(4):311-319. doi:10.1056/NEJMoa2401755

25. Harrison SA, Goodman Z, Jabbar A, et al. A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis. *Journal of Hepatology*. 2020;72(5):816-827. doi:10.1016/j.jhep.2019.11.024

26. Nakajima A, Eguchi Y, Yoneda M, et al. Randomised clinical trial: Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), versus placebo in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2021;54(10):1263-1277. doi:10.1111/apt.16596

27. Safadi R, Braun M, Francis A, et al. Randomised clinical trial: A phase 2 double-blind study of namodenoson in non-alcoholic fatty liver disease and steatohepatitis. *Aliment Pharmacol Ther*. 2021;54(11-12):1405-1415. doi:10.1111/apt.16664

28. Harrison SA, Ratziu V, Anstee QM, et al. Design of the phase 3 MAESTRO clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. *Aliment Pharmacol Ther*. 2024;59(1): 51-63.doi:10.1111/apt.17734

29. Pedrosa M, Seyedkazemi S, Francque S, et al. A randomized, double-blind, multicenter, phase 2b study to evaluate the safety and efficacy of a combination of tropifexor and cenicriviroc in patients with nonalcoholic steatohepatitis and liver fibrosis: Study design of the TANDEM trial. *Contemporary Clinical Trials*. 2020;88: 105889. doi:10.1016/j.cct.2019.105889

30. Loomba R, Mohseni R, Lucas KJ, et al. TVB-2640 (FASN Inhibitor) for the Treatment of Nonalcoholic Steatohepatitis: FASCINATE-1, a Randomized, Placebo-Controlled Phase 2a Trial. *Gastroenterology*. 2021;161(5): 1475-1486. doi:10.1053/j.gastro.2021.07.025

31. Calle RA, Amin NB, Carvajal-Gonzalez S, et al. ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials. *Nat Med*. 2021;27(10):1836-1848. doi:10.1038/s41591 -021-01489-1

32. Hu Y. ZSP1601, a novel pan-phosphodiesterase inhibitor for the treatment of NAFLD, A randomized, placebo-controlled phase Ib/IIa trial. *Nature Communications*. Published online 2023.

33. Zein CO, Yerian LM, Gogate P, et al. Pentoxifylline improves nonalcoholic steatohepatitis: A randomized placebo-controlled trial. Hepatology. 2011;54(5):1610-1619. doi:10.1002/hep.24544

34. Ratziu V, Rinella ME, Neuschwander-Tetri BA, et al. EDP-305 in patients with NASH: A phase II double-blind placebo-controlled dose-ranging study. Journal of *Hepatology*. 2022;76(3):506-517. doi:10.1016/j.jhep.2021. 10.018

35. Suki M, Amer J, Milgrom Y, et al. Semaglutide in MASLD Patients: Improved Survival and Liver Outcomes. *Pharmaceuticals*. 2025;18(7):1075. doi:10.33 90/ph18071075

36. A phase 1b, randomized, double-blind (sponsor-open), placebo-controlled, parallel group study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of multiple oral doses of pf- 06865571 for 2 weeks in adults with nonalcoholic fatty liver disease. Published online April 19, 2018. Accessed June 21, 2018. https://clinicaltrials. gov/study/NCT03513588

37. A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of NGM282 Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH). Published online April 9, 2019. Accessed May 16, 2019. https://clinicaltrials.gov/study/NCT03912532

38. The Effect of Pentoxifylline on Nonalcoholic Steatohepatitis (NASH). Published online December 12, 2005. Accessed March 1, 2005. https://clinicaltrials.gov/study/NCT00267670

39. A Phase 2B Randomized Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of BMS-986036 (PEG-FGF21) in Adults With Nonalcoholic Steatohepatitis (NASH) and Stage 3 Liver Fibrosis. Published online March 30, 2018. Accessed June 19, 2018. https://clinicaltrials.gov/ study/NCT03486899

40. A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults With Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH). Published online June 29, 2019. Accessed June 6, 2019. https://clinicaltrials.gov/study/NCT04006145

41. AMBITION: A Phase 2A, Multiple-Center, Single-Blind, Placebo-Controlled Study To Evaluate The Safety and Tolerability of CRV431 Dosed Once Daily in NASH Induced F2 and F3 Subjects. Published online July 9, 2020. Accessed June 23, 2020. https://clinicaltrials.gov/study/ NCT04480710

42. A Prospective, Randomized, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Curcuvail® of K Patel Phyto Extractions Pvt. Ltd. in Patients With Non-alcoholic Fatty Liver Disease (NAFLD). Published online December 8, 2021. Accessed January 8, 2021. https://clinicaltrials.gov/study/ NCT06256926

43. Lassailly G, Caiazzo R, Ntandja-Wandji LC, et al. Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis. *Gastroenterology*. 2020;159(4):1290-1301.e5. doi:10.1053/ j.gastro.2020.06.006

44. Sanyal A, Charles ED, Neuschwander-Tetri BA, et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet*. 2019;392(10165): 2705-2717.doi:10.1016/S0140-6736(18)31785-9

45. Harvey BE. NASH: regulatory considerations for clinical drug development and U.S. FDA approval. Acta Pharmacol Sin. 2022;43(5):1210-1214. doi:10.1038/s41 401-021-00832-z

46. Targher G, Byrne CD, Tilg H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. *Gut*. 2020;69(9):1691-1705. doi:10.1136/ gutjnl-2020-320622

47. An J, Sohn JH. Pharmacological advances in the treatment of nonalcoholic fatty liver diseases : focused on global results of randomized controlled trials. *Clin Mol Hepatol*. 2023;29(Suppl):S268-S275. doi:10.3350/cmh.2022.0437