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REVIEW

A structured literature review of interventions used in the management of nonalcoholic steatohepatitis (NASH)

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Abstract

Nonalcoholic steatohepatitis (NASH) is a chronic, progressive disease, that can advance to fibrosis, cirrhosis, and hepatocellular carcinoma. Despite being a leading cause of liver transplantation, there are no approved pharmacological treatments. Our aim was to identify literature on management options in NASH. Our structured review of interventions treating NASH patients from English language publications between 1 January 2007 and 25 September 2017 elicited 48 eligible references. Lifestyle management was identified as the mainstay of NASH therapy. Vitamin E and pioglitazone reported reductions in steatosis; however, although recommended for some, no therapies are indicated in NASH. Multiple investigational treatments reported efficacy in mild-to-moderate fibrosis in Phase II/III NASH trials. Lifestyle management, although the focus of clinical guidelines, is insufficient for patients progressing to advanced fibrosis. With no clear guidelines for patients requiring interventions beyond lifestyle modification, long-term outcomes data are needed, particularly in patients with moderate-to-severe fibrosis.

KEYWORDS

clinical outcomes, management options, NASH, nonalcoholic steatohepatitis, treatment interventions

Abbreviations: AASLD, American association for the study of liver diseases; ACC, acetyl-CoA carboxylase; Acetyl-CoA, acetyl coenzyme A; ALT, alanine transaminase; ARBs, angiotensin II receptor antagonists; ASBT, apical sodium-dependent bile acid transporter; ASK, apoptosis signal-regulating kinase 1; AST, aspartate aminotransferase; BIB, bioenterics intragastric balloon; BID, twice a day; BMI, body mass index; BP, blood pressure; CCR2/5, C-C chemokine receptor type 2 or 5; CI, confidence interval; CR, calorie-restricted; CRN, clinical research network; CVD, cardiovascular disease; CYP, cytochrome; EASD, European association for the study of diabetes; EASL, European association for the study of the liver; ESLD, end stage liver disease; F3/F4, fibrosis stage 3/4; FBS, fasting blood sugar; FDA, food and drug administration; FGF21, fibroblast growth factor 21; FGFR4, fibroblast growth factor receptor 4; FMT, faecal microbiota transplant; FXR, farnesoid X receptor; GGT, gamma-glutamyltransferase; GLP-1, glucagon-like peptide 1; HbA1c, glycosylated haemoglobin, type AC1; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance; HS, hepatic steatosis; HVPG, hepatic venous pressure gradient; IBG, intragastric balloon; IQR, interquartile range; ISPOR, International society for pharmacoeconomics and outcomes research; IU, international unit; LDL-C, low-density lipoprotein cholesterol; LDL, low-density lipoprotein; LFC, liver fat content; LNP, lipid nanoparticle; LOXL, lysyl oxidase like; LTD4, leukotriene D4; LT, liver transplantation; MD, mean difference; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NAS, NAFLD activity score; NR, not reported; OCA, obeticholic acid; OR, odds ratio; PBO, placebo; PHC, Paris Hepatology Conference; PIO, pioglitazone; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PTX, pentoxifylline; PUFA, poly-unsaturated fatty acid; QD, once a day; QoL, quality of life; QW, once a week; r, correlation coefficient; RCT, randomised controlled trial; SF-36, short form-36; SGLT2, sodium-glucose transport protein 2; SLR, systematic literature review; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TGR5, takeda G-protein receptor 5; TG, triglycerides; TID, three times a day; TIMP-1, tissue inhibitor of metalloproteinase 1; UDCA, ursodeoxycholic acid; US, United States; vs, versus; WMD, weighted mean difference.

1 | INTRODUCTION

Nonalcoholic steatohepatitis (NASH) is a chronic and progressive liver disease, and is considered the progressive phenotype of nonalcoholic fatty liver disease (NAFLD), the most prevalent chronic liver disease worldwide.[1] NASH is characterized by the accumulation of fat in the liver (steatosis), inflammation and liver damage, which can progress to high-burden conditions such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[2] An estimated 3%-7% of the adult population develop NASH, of which approximately 15%-20% progress to advanced fibrosis, namely bridging fibrosis (F3) or cirrhosis (F4).[3] NASH frequently progresses undetected due to the early nonspecific symptoms of the disease, leading to serious patient consequences, such as end-stage liver disease (ESLD), an increased need for liver transplantation (LT), and death.[4,5]

The burden of NASH on healthcare systems is high; in 2016 NASH overtook hepatitis C as a leading indication for LT in the Unites States (US).[6] The annual cost of NAFLD and NASH-related LT in the US is estimated at $161 567 727 and its burden is expected to grow.[7] Despite the high burden, guideline recommendations regarding effective diagnosis and management are limited—there are currently no effective noninvasive diagnostic tests, and no recommended or approved pharmacological therapies for NASH.[5,8] Available therapies focus solely on treating NASH comorbidities, such as obesity, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD),[9] while NASH management options focus on lifestyle changes, based on diet and exercise, and control of the associated comorbidities.[2,10] Lifestyle changes have demonstrated greatest benefit in improving steatosis and mild fibrosis;[2,10] however, as patients with advanced fibrosis due to NASH are at a significantly higher risk of liver-related mortality, pharmacological treatments are urgently needed, especially in this population.[11] Fibrosis is considered the strongest predictor of adverse clinical outcomes, including liver-related death.[12,13] Therefore, fibrosis improvement has been identified as an important endpoint in clinical trials by regulatory agencies—the Food and Drug Administration (FDA) has recently developed draft guidance detailing that Phase II trials should provide evidence of efficacy on a histological endpoint such as reduction in inflammatory changes, improvement in fibrosis, or both.[13] This guidance showcases the need for approved therapies in NASH, specifically in fibrosis due to NASH.

In order to understand the current treatment landscape in NASH, this structured literature review aimed to identify all management options in use for patients with NASH and examine the clinical outcomes achieved.

2 | METHODOLOGY

A structured literature review was conducted to identify literature on the current management and treatments in NASH, including all available safety and efficacy data. A pre-agreed search protocol was used, following the principles of the Cochrane handbook for systematic literature reviews (SLRs).[14] The OVID search engine was used to search for publications across 4 databases: EconLit, Embase, PsycINFO, and Medline. The search strategy used a combination of free-text searching and "subject headings" to ensure that the most relevant literature was identified (see Appendix S1). Searches were limited to English language publications between 1 January 2007 and 25 September 2017. Publications were included in the full-text review if they reported on the efficacy or safety of treatments or lifestyle management in adult patients (≥18 years) with NASH.

To ensure all relevant publications were captured, a "grey literature" search was performed. This included an internet-based search using a combination of efficacy, safety and management keywords and incorporated both nonpeer-reviewed, publicly available information and peer-reviewed publications that may not yet be indexed in OVID databases, due to their recent publication date, or because they were published in journals that are not indexed within these databases. In addition, conference proceedings from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), American Association for the Study of Liver Diseases (AASLD), European Association for the Study of Diabetes (EASD), European Association for the Study of the Liver (EASL), Paris Hepatology Conference (PHC), and third Paris NASH Symposium were reviewed for relevant nonpeer-reviewed publications.

During the title and abstract screening, 250 of the 268 retrieved abstracts were excluded, based on the predefined inclusion criteria (see Appendix S2). The full-texts of 18 potentially relevant publications were assessed and an additional 4 publications were excluded, resulting in 14 full-text inclusions. The grey literature search identified 34 conference abstracts and posters which were deemed relevant for inclusion into the evidence base and thus, a total of 48 publications were included into this structured literature review. A full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is presented in Figure 1. The list of captured publications is presented in Appendix S3. Due to the significant amount of captured publications consisting of reviews, and to ensure robustness of the data points presented, original research publications cited in review papers were referenced in results tables where these data were presented. The list of original research publications cited here is presented in Appendix S4.

3 | RESULTS

There was a wide range of study types identified, including meta-analyses, randomized controlled trials (RCTs), narrative reviews, and observational studies. The publications identified varied in robustness; small studies with short follow-up, and RCTs of limited quality were the most frequently identified. Where available, the study design and number of included patients have been reported in this manuscript for clarity.

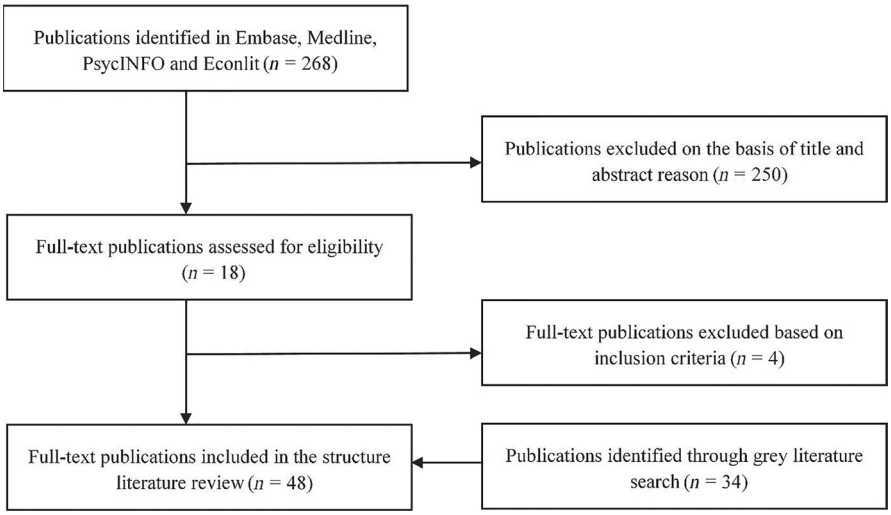

FIGURE 1 PRISMA diagram of included and excluded publications. PRISMA, preferred reporting items for systematic reviews and meta-analyses

The captured publications confirmed that the current management of NASH includes lifestyle modification, off-label treatments, bariatric surgery, and LT. Lifestyle modification was the most commonly reported management strategy in NASH and was the mainstay of treatment in the absence of approved therapies.[10,15-25] Multiple publications also discussed off-label therapy use; however, as these focused on the treatment of comorbidities due to NASH, relevant data were limited.[10,15,20,23,26,27] In contrast, few publications reported on bariatric surgery and LT, with ten reporting on these interventions.[16,28-36] An overview of the NASH management strategies identified in this review are presented in Figure 2.

3.1 | Lifestyle modification

Lifestyle modification was identified as the main method for the nonclinical management of NASH, with 12 publications reporting on this.[10,15-25] Outcomes related to weight loss were reported in 5 publications, including a Phase III RCT (n = 31), a narrative review, and a prospective (n = 293), retrospective (n = 45) cohort study, and Practice Guidance.[15,16,18,21,24] The publications indicated that weight loss was associated with several clinical improvements, including improvements in liver histology, lobular inflammation, fibrosis resolution, and fibrosis progression.[15,18,21,24] The specific outcomes achieved with lifestyle modification are shown in Table 1. Four original research publications are referenced in Table 1 to support the data points cited in the captured publications. [37-40]

In addition to the clinical improvements of weight loss, the AASLD Practice Guidance, which provides a data-supported approach to the diagnostic, therapeutic, and preventive aspects of NAFLD and NASH care, reported that a weight loss of 3%-5% improved steatosis, but a greater weight loss of 7%-10% showed a significant improvement in all features of NASH, including portal inflammation and fibrosis.[16] One narrative review suggested that a weight loss of ≥7% may improve liver histology in NASH patients based on observations from small studies conducted in patients with fatty liver or coronary heart disease.[15] While weight loss was acknowledged by the Practice Guidance as a good management option to improve steatosis, one narrative review highlighted that a key difficulty in NASH was not achieving weight loss, but rather maintaining it.[17] The authors cautioned that this issue has not been addressed in the context of NASH, which correlated with the findings of this narrative review, as no publication reported on maintaining weight loss in patients with NASH.[17]

Weight loss management was further stratified into diet composition and caloric restriction in the literature. One SLR reported that caloric restriction was the most important lifestyle modification to induce weight loss and improve steatosis.[25] The SLR also reported that diet composition induces the greatest

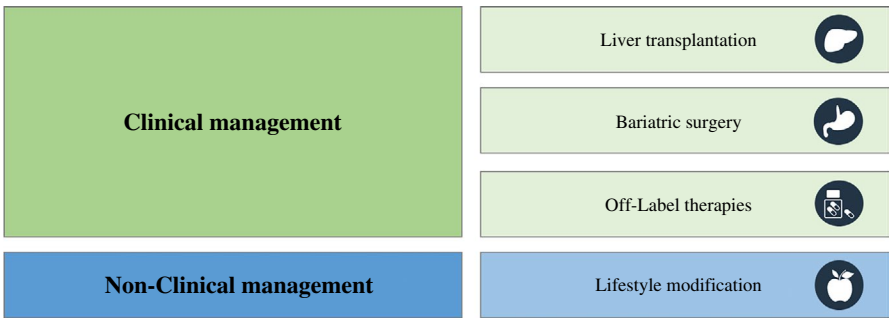

FIGURE 2 Overview of management strategies in NASH described in this review

TABLE 1 Publications reporting on outcomes associated with lifestyle modifications[a]

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes achieved
Combination of diet, physical exercise and behavioural strategies	Promrat et al. 2010[21] (referenced in Issa et al. 2017[10] and Corey et al. 2016[17])	US	RCT	Overweight and obese patients with biopsy-proven NASH	31	Dosage: NR Frequency: NR Length of therapy: 48 weeks	Patients with weight loss ≥ 7% vs patients with weight loss < 7% achieved a reduction from baseline in the following: > NAS (-3.45 vs -1.18, $P < 0.001$) > Steatosis (-1.36 vs -0.41, $P < 0.001$) > Lobular inflammation (0.82 vs -0.24, $P = 0.03$)
Nutritional counselling	Ahmed et al. 2015[15] (referencing Huang et al. 2005[40] and Ueno et al. 1997[37])	NR	Narrative review	Biopsy-proven NASH patients	23	Dosage: NR Frequency: NR Length of therapy: 12 months	Patients with weight loss of ≥ 7% may show an improvement in liver histology
Restricted diet and exercise	Ahmed et al. 2015[15] (referencing Huang et al. 2005[40] and Ueno et al. 1997[37])	NR	Narrative review	Biopsy-proven NASH patients	25	Dosage: NR Frequency: NR Length of therapy: 3 months	Patients with weight loss of ≥ 7% may show an improvement in liver histology
Lifestyle modification or with surgical intervention	Glass et al. 2015[18]	NR	Retrospective cohort study	NASH patients with serial liver biopsy	45	Dosage: NR Frequency: NR Length of therapy: NR	63.2% fibrosis regression in patients who lost ≥ 10% of total body weight vs 9.1% in patients who lost < 10% of total body weight ($P < 0.001$)
Diet intervention and physical activity	Vilar-Gomez et al. 2015[24] (referenced in Issa et al. 2017,[10] Corey et al. 2016,[17] Noureddin et al. 2016[20] and Townsend et al. 2016[23])	Cuba	Prospective cohort study	Histologically-proven NASH patients	293	Dosage: NR Frequency: NR Length of therapy: 52 weeks	Patients with weight loss of > 10% vs patients with < 10% weight loss achieved the following: > 90% resolution of NASH > 100% reduction in NASH > 45% regression of fibrosis
Lifestyle or diet induced weight loss	Chalasani et al. 2017[16] (referencing Musso et al. 2012[38])	Global	Practical guidance and narrative review	NASH patients	NR	Dosage: NR Frequency: NR Length of therapy: NR	Patients who were able to lose at least 5% of body weight had improvements in HS, whereas ≥ 7% body weight reduction was associated with NAS improvement
Calorie-restricted diet and aerobic exercise or calorie-restricted diet alone	Nikroo et al. 2015[19]	Iran	RCT	NASH patients	25	Dosage: NR Frequency: NR Length of therapy: 12 weeks	> Physical function, performance limitations due to illness, physical component score, general health, and vitality showed significant changes.* > In the diet alone group, general health and vitality improved after the intervention. > A significant reduction was observed in ultrasonographic features of fatty liver of those who also had aerobic exercise.*

(Continues)

TABLE 1 (Continued)

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes achieved
Calorie-restricted diet and aerobic exercise or calorie-restricted diet alone	Sima et al. 2014[22]	NR	RCT	NASH patients	25	Dosage: NR Frequency: NR Length of therapy: 12 weeks	> A significant improvement in BP, FBS, TG, HOMA-IR, ultrasonogrphic grading of steatosis and QoL was observed only in patients who received aerobic exercise. (*P* 0.021, 0.005, 0.006, 0.042, 0.010 and 0.012, respectively).
1 of 4 lifestyle modification: standard care, low-fat diet and moderate exercise, moderate-fat/low-processed-carbohydrate diet and moderate exercise, or moderate exercise only	Younossi et al. 2014 (referencing Eckard et al. 2013[39])	US	SLR	Biopsy-proven NAFLD with NASH patients included	56	Dosage: NR Frequency: NR Length of therapy: 6 months	Significant difference to the histopathological profile overall (*P* < 0.001).

BP, blood pressure; FBS, fasting blood sugar; HOMA-IR, homeostasis model of insulin resistance; HS, hepatic steatosis; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NR, not reported; QoL, quality of life; RCT, randomized controlled trial; TG, triglycerides; US, United States; vs, versus.

[a]Primary publications are referenced where applicable. Promrat et al. 2010 and Vilar-Gomez et al. 2015 data are reported in 4 narrative reviews (Corey et al. 2016, Issa et al. 2017, Noureddin et al. 2016, and Townsend et al. 2016), therefore these reviews were not reported individually in the table, but are referenced alongside the relevant data.

[b]Number of patients.

*P-value not reported.

benefit in patients with NASH and comorbidities, namely a low-carbohydrate diet was shown to improve hepatic insulin sensitivity in patients with NASH and comorbid T2DM, and a low-fat diet improved LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) in patients with NASH and high cholesterol.[25] Despite the hepatic benefits reported, the impact of diet composition on fibrosis due to NASH was not discussed.

In addition to diet, one narrative review reported that both aerobic and anaerobic exercise induce a decrease in intrahepatic fat accumulation; however, a greater effect was observed with aerobic exercise.[20] This was supported by another narrative review, which reported that a 24-week moderate-intensity aerobic programme in patients with NASH demonstrated histological improvements, with greater benefits observed in patients who also made dietary modifications; however, due to the narrative nature of this review, the specific modifications made were not reported.[23] An SLR and meta-analysis noted that there are significant obstacles to patients performing exercise: the authors cautioned that lack of confidence was a key barrier for patients with NASH.[25]

Two publications reported aerobic exercise in combination with a low-calorie diet results in a greater improvement in quality of life (QoL) compared to diet alone ($P = 0.012$), as measured by the short form-36 (SF-36) questionnaire.[19,22] Significant changes in physical function, general health and vitality were observed; therefore, the authors concluded that aerobic exercise in combination with a low-calorie diet was more effective at improving QoL compared to dietary modifications alone.[19]

3.1.1 | Conclusions

Primary lifestyle modification for NASH patients was based on dietary changes, such as caloric restriction or changes in dietary composition, and exercise. The aim of lifestyle modification was to induce weight loss, with a 7%-10% weight reduction reported to lead to significant improvements in liver chemistry and histologic activity of NASH. Despite the reported benefits of dietary modification and exercise in achieving weight loss and improving steatosis and fibrosis in NASH, the long-term impact on NASH progression was not reported in any of the publications.

3.2 | Off-label treatments in NASH

There are currently no therapies indicated for use in patients with NASH; therefore, all captured publications reported on their off-label therapy use only. While the identified AASLD Practice Guidance recommended the consideration of pioglitazone (PIO) and/or vitamin E as pharmacological options for some patients with NASH, these are also not indicated in NASH and are used off-label.[16] There was a range of outcomes captured for these therapies and the specific outcomes reported (where available) are presented in Table 2. Ten original research publications are referenced in Table 2 to support the data points cited in the captured publications.[41-50]

TABLE 2 Publications reporting safety and efficacy outcomes for available off-label and investigational treatments in NASH[a]

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes Achieved
Off-label treatments							
Vitamin E	Sato et al. 2015[27] (referencing Dufour et al. 2006[41] and Sanyal et al. 2010[42])	Japan	Meta-analysis of 5 RCTs	NASH patients treated with vitamin E vs PBO	401	Dosage: 400 IU Frequency: BID Length of therapy: 2 years Dosage: 800 IU Frequency: QD Length of therapy: 96 weeks	Patients treated with vitamin E had reductions in: > Steatosis (vitamin E vs PBO (MD = −0.67, > 95% CI -0.9-(−0.43), $P < 0.00001$) > Lobular inflammation (vitamin E vs PBO > (MD = −0.20, 95% CI −0.38-(−0.01), $P = 0.04$) > Fibrosis (vitamin E vs PBO (MD = −0.30, 95% CI −0.59-(−0.01), $P = 0.04$)
	Issa et al. 2017[10] (referencing Sanyal et al. 2010,[42] Miller et al. 2005,[43] and Rimm et al. 1993[44])	Global	Narrative review	Nondiabetic NASH patients treated with vitamin E vs PBO	247	Dosage: 800 IU Frequency: QD Length of therapy: 96 weeks Dosage: NR Frequency: NR Length of therapy: NR Dosage: NR Frequency: NR Length of therapy: NR	Patients treated with vitamin E had: > Histological improvement in vitamin E (43%) vs PBO (19%, $P = 0.001$) > Increase in all-cause mortality in vitamin E vs PBO (risk difference: 39/10 000 with > 400 IU) > Increased mortality linked to haemorrhagic stroke and prostate cancer
	Townsend et al. 2016[23] (referencing Chan et al. 2016[45])	Global	Narrative review	NASH patients treated with vitamin E vs selenium vs PBO	NR	Dosage: 400 IU Frequency: QD Length of therapy: NR	Patients treated with vitamin E showed: > Relative risk of 17% > Absolute risk of 1.6 per 1000 patient-years
PIO	Ratziu et al. 2010[53]	NR	Open label extension of the FLIRT II trial[c]	NASH patients treated with rosiglitazone	40 who completed extension phase	Dosage: 8 mg Frequency: QD Length of therapy: 2 years	No significant reduction in steatosis ($P = 0.16$) or necroinflammation and fibrosis ($P = 0.74$)
	Townsend et al. 2016[23] (referencing Lincoff et al. 2007[46])	Global	Narrative review	NASH patients with T2DM treated with PIO vs PBO	NR	Dosage: NR Frequency: NR Length of therapy: NR	An 18% reduction in death, myocardial infarction, and stroke for PIO vs PBO*
	Musso et al. 2017[54]	NR	Meta-analysis	NASH patients with advanced fibrosis treated with 4-8 mg of rosiglitazone or 30-45 mg of PIO	516	Dosage: NR Frequency: NR Length of therapy: NR	PIO was associated with increased odds of improvement in advanced fibrosis vs PBO (OR 2.95, 95% CI 1.04-10.90, $P = 0.02$)
	Issa et al. 2017[10] (referencing Cusi et al. 2016[47])	Global	Narrative review	NASH patients treated with PIO vs PBO	NR	Dosage: 45 mg Frequency: QD Length of therapy: 18 months	Patients achieved 2-point decrease in NAS without worsening of fibrosis after 18 months in PIO (65%) vs PBO (19%)*

(Continues)

TABLE 2 (Continued)

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes Achieved
Liraglutide	Issa et al. 2017[10] (referencing Armstrong et al. 2016[48])	Global	Narrative review	NASH patients randomized to receive subcutaneous injections of liraglutide (1.8 mg daily) vs PBO	52	Dosage: 1.8 mg Frequency: QD Length of therapy: 48 weeks	> Patients met the primary endpoint of resolution of NASH with liraglutide (39%) vs PBO (9%) (relative risk 4.3, 95% CI1.0-17.7; $P = 0.019$). > Significant improvement in steatosis ($P = 0.009$) and hepatocellular ballooning ($P = 0.05$) in NASH patients with liraglutide vs PBO
OCA	Noureddin et al. 2016[20] (referencing Neuschwander-Tetri et al. 2015[49])	Global	Narrative review	Noncirrhotic NASH patients treated with OCA vs PBO	219	Dosage: 25 mg Frequency: QD Length of therapy: 72 weeks	> Improvement in liver histology with OCA (45%) vs PBO (21%)* > Similar improvements in steatosis, hepatocellular ballooning, lobular inflammation > Pruritus with OCA (23%) vs PBO (6%)* > Statistically significant increases in TG, LDL and a decrease in HDL with OCA group vs PBO*
	Liberman et al. 2017[55]	US	Post-hoc analysis of the FLINT trial[d]	Noncirrhotic NASH patients with T2DM treated with OCA vs PBO	283	Dosage: 25 mg Frequency: QD Length of therapy: 72 weeks	Improvement in NAS without worsening of fibrosis with OCA (57%) vs PBO (21%)*
	Sanyal et al. 2017a[56]	NR	Secondary analysis of the FLINT trial[d]	Noncirrhotic NASH patients treated with OCA vs PBO	198	Dosage: 25 mg Frequency: QD Length of therapy: 72 weeks	Significant increase in LDL-C in OCA group vs in PBO group (25.0 vs −6 mg/dL, $P < 0.0001$)
UDCA	Pietu et al. 2012[57]	NR	Retrospective cohort study	NASH patients treated with UDCA + vitamin E.	101	Dosage: 1000 mg Frequency: QD Length of therapy: NR	Improved long-term liver function tests (1.39 ± 0.74 to 0.78 ± 0.34 for AST and 1.72 ± 0.92 to 0.91 ± 0.69 for ALT)
PTX	Sharma et al. 2012[51]	India	RCT	NASH patients treated with PTX vs PIO	60	Dosage: 400 mg Frequency: TID Length of therapy: 6 months	> Significant improvements in hepatic steatosis ($P = 0.02$) with PTX and ($P = 0.005$) with PIO > Ballooning, lobular inflammation and portal inflammation were improved with PIO vs PTX
	Alam et al. 2017[60]	Bangladesh	RCT	NASH patients treated with PTX vs PBO	35	Dosage: 400 mg Frequency: TID Length of therapy: 6 months	> Significant improvements in NAS for PTX vs PBO (2.10 ± 1.07 vs 0.90 ± 0.99, $P = 0.006$) > Minimum side effects including abdominal pain and dyspepsia
	Cernea et al. 2017[59] (referencing Du et al. 2014[50])	Global	Narrative review	NASH patients with fibrosis treated with PTX vs PBO	147	Dosage: NR Frequency: NR Length of therapy: NR	Significant improvements in: > NAS in PTX group vs PBO group (WMD = −1.16, 95% CI −1.51-(−0.81), $P < 0.00001$) > Lobular inflammation vs PBO (WMD = −0.43, 95% CI −0.64-(−0.23), $P < 0.0001$)

(Continues)

TABLE 2 (Continued)

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes Achieved
Investigational treatments							
Aramchol	Issa et al. 2017[10] (referencing Safadi et al. 2014[62])	Global	Narrative review	NASH patients treated with 100 mg daily aramchol vs PBO	66	Dosage: 100 mg or 300 mg Frequency: QD Length of therapy: 3 months	Significant decrease in liver fat in patients treated with 100 mg aramchol vs PBO (12.57 ± 22.14% vs 6.39 ± 36.27%, $P = 0.02$)
BMS-986263	Lawitz et al. 2017[67]	NR	RCT	NASH patients with advanced fibrosis treated with BMS-986263	11	Dosage: NR Frequency: NR Length of therapy: NR	> ISHAK and METAVIR scores improved in 5/9 and 3/9 subjects > FibroScan showed a > 10% decrease in fibrosis in 48% of patients
BMS-986036	Abdelmalek, 2017a[66]	NR	Post-hoc analysis	Biopsy-confirmed NASH patients treated with BMS-986036 (10 or 20 mg) vs PBO	48	Dosage: 10 mg Frequency: QD Length of therapy: NR Or Dosage: 20 mg Frequency: QW Length of therapy: NR	High baseline levels of pro-C3 associated with biomarker improvements for liver stiffness and fibrosis (median % change = −34.9% vs −23.1%, $P = 0.08$)
	Sanyal et al. 2017b[65]	Global	RCT	Biopsy-confirmed NASH patients treated with BMS-986036 (10 or 20 mg) vs PBO	74	Dosage: 10 mg Frequency: QD Length of therapy: NR Or Dosage: 20 mg Frequency: QW Length of therapy: NR	> Reductions in MRI-PDFF > Significant reduction in liver fat: 10 mg (absolute change from baseline = −6.8, $P = 0.004$), 20 mg (−5.2, $P = 0.008$) vs PBO (−1.3) Improvement in biomarkers of fibrosis (MRE and pro-C3) > 17% diarrhoea vs 8% in PBO group* > 15% nausea vs 8% in PBO group*
Cenicriviroc	Cassidy et al. 2016[26]	Global	Narrative review	NASH patients with fibrosis treated with cenicriviroc vs PBO	NR	Dosage: NR Frequency: NR Length of therapy: NR	> Failed primary endpoint in CENTAUR[e] of a 2-point reduction in NAS > Met secondary endpoint of 20% improved fibrosis by ≥ 1 stage vs 10% in PBO group ($P = 0.023$)
	Abdelmalek, 2017b[68]	Global	Cohort study	NASH patients treated with cenicriviroc	1022	Dosage: NR Frequency: NR Length of therapy: NR	2.8% fatigue and 2.1% diarrhoea in NASH patients
Elafibranor	Chalasani et al. 2017[16] (referencing Ratziu et al. 2016[63])	Global	Practice guidance	NASH patients treated with elafibranor 120 mg/day	NR	Dosage: 120 mg Frequency: QD Length of therapy: 12 months	Exhibited an efficacy signal for improving NASH without fibrosis worsening over a 12-month study period
GS-0976	Loomba, 2017a[69]	Global	RCT	Biopsy-confirmed NASH patients treated with GS-0976 (20 or 5 mg QD) vs PBO	NR	Dosage: 5 mg or 20 mg Frequency: QD Length of therapy: 12 weeks	> Significant reductions in MRI-PDFF for GS-0976 vs PBO: 20 mg (−28.9% to −8.4%, $P = 0.002$) > Significant improvement in TIMP-1 for GS-0976 vs PBO ($P = 0.022$) > Minimal side effects including nausea for GS-0976 (14% with 20 mg)

(Continues)

TABLE 2 (Continued)

Intervention	Reference	Country	Study	Adult Population	N[b]	Dosage and frequency	Outcomes Achieved
Imm124-E	Issa et al. 2017[10] (referencing Mizrahi et al. 2012[64])	Global	Narrative review	Biopsy proven NASH patients with T2DM treated with Imm124-E	10	Dosage: 600 mg Frequency: TID Length of therapy: 30 days	> Reduction in haemoglobin A1C, insulin resistance with mild improvements in cholesterol levels for Imm124-E > No adverse events reported
NGM282	Loomba, 2017c[70]	NR	Post-hoc analysis	NASH patients treated with NGM282 vs PBO	NR	Dosage: 3 mg or 6 mg Frequency: NR Length of therapy: 12 weeks	Reduction in absolute liver fat content by −9.7% and −11.9% at 3 mg and 6 mg ($P < 0.001$) for NGM282 vs −0.9% with PBO
Selonsertib	Loomba et al. 2017d[71]	Global	RCT	Biopsy-confirmed NASH patients treated with selonsertib (6 or 18 mg); simtuzumab (125 mg) or simtuzumab alone	72	Dosage: 6 mg or 18 mg Frequency: QD Length of therapy: 24 weeks	> Significant reduction in fibrosis with selonsertib 6 mg (30%, 95% CI 14-50) and 18 mg (43%, 95% CI 26-63) vs simtuzumab alone (20%, 95% CI 3-56) > Improvement in liver stiffness by MRE vs simtuzumab alone > The majority of patients in all treatment groups experienced at least 1 adverse event (mild-to-moderate)

ALT, alanine transaminase; AST, aspartate transaminase; BID, twice a day; CI, confidence interval; HbA1c, glycosylated haemoglobin, type AC1; HDL, high-density lipoprotein; IU, international unit; LDL, low-dose lipoprotein; LDL-C, LDL-cholesterol; MD, mean difference; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging–proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NR, not reported; OCA, obeticholic acid; OR, odds ratio; QD, once a day; QW, once a week; PBO, placebo; PIO, pioglitazone; PTX, pentoxifylline; RCT, randomised controlled trial; T2DM, type 2 diabetes mellitus; TG, triglycerides; TID, 3 times a day; TIMP-1, tissue inhibitor of metalloproteinase 1; UDCA, Ursodeoxycholic acid; US, United States; WMD, weighted mean difference.

[a]Primary publications are referenced where applicable.

[b]Number of patients.

[c]FLIRT was a one-year randomised, double-blind, placebo-controlled Phase II study investigating rosiglitazone (4 mg/day for the first month and 8 mg/day thereafter) in NASH.

[d]FLINT was a randomised, double-blind, placebo-controlled Phase II study investigating OCA (25 mg) in NASH over 72 weeks.

[e]CENTAUR was a one-year randomised, double-blind, placebo-controlled Phase II study investigating cenicriviroc (150 mg) in NASH.

*P-value not reported.

3.2.1 | Vitamin E

Three publications reported on clinical outcomes of vitamin E in NASH.[10,23,27] Comparison of reported outcomes was limited, due to varying inclusion criteria, different doses of vitamin E, the additional use of other drugs, and limited histological data.[10,23,26,27] Despite these limitations, the authors reported that vitamin E was associated with improvements in steatosis, inflammation, and ballooning in nondiabetic patients with NASH; this was supported by a meta-analysis (n = 401) (Sato et al., 2015) and a narrative review (n = 247) which also showed improvements in steatosis (see Table 2).[10,27] However, discrepancies were identified as to whether vitamin E leads to fibrosis improvement: the meta-analysis reported that vitamin E improved both hepatic histology and fibrosis,[27] whereas the narrative review reported no change in fibrosis with vitamin E.[10] In addition, this review raised concerns about the safety profile of vitamin E due to possible increases in mortality and prostate cancer; however, the authors noted that the studies reporting this were small in size, and were not powered to test safety hypotheses.[10]

3.2.2 | Thiazolidinediones (including Pioglitazone)

The thiazolidinedione, pioglitazone (PIO), was the most frequently reported off-label treatment in NASH, and was captured in 6 publications.[10,23,51-54] In these publications, PIO showed an improvement in steatosis and inflammation and a smaller improvement in fibrosis in patients with NASH (see Table 2).[10,23,52] However, variable efficacy was reported: a narrative review (n = 247) in patients with nondiabetic NASH reported that PIO did not meet the primary endpoint of significant changes in histological features, as assessed by the CRN classification in a Phase III RCT suggesting the use of PIO may be limited in NASH.[23] Despite its failure to reach the primary endpoint, a reduction in hepatic steatosis ($P < 0.001$) and lobular inflammation ($P < 0.001$) was observed.[23] This was also seen in another Phase III RCT (n = 60) of PIO versus (vs) pentoxifylline (PTX), where significant improvements in hepatic steatosis were reported (see section 3.2.7).[51] In a meta-analysis, PIO was associated with increased odds of advanced fibrosis improvement (odds ratio (OR), 2.95; 95%CI, 1.04-10.90) vs placebo (PBO) ($P = 0.02$), suggesting PIO may be one of the few therapies identified that are efficacious in this population.[54]

Additional long-term safety concerns in NASH were discussed based on studies conducted in patients with diabetes: a narrative review reported that PIO was associated with an increased risk of heart failure, bone fracture, oedema, and weight gain;[23] however, another narrative review found that PIO reduced the risk of major cardiovascular events (myocardial infarction, stroke and cardiovascular death), suggesting that the long-term safety profile of PIO remains to be established in NASH.[10]

Conflicting data were also reported on the clinical use of thiazolidinediones; one Phase II RCT (n = 40) reported no significant benefit with long-term use of the thiazolidinedione, rosiglitazone (which has subsequently been withdrawn from use).[53] Additionally, a narrative review reported that discontinuation of thiazolidinediones resulted in a return to pretreatment NASH histology, suggesting that PIO therapy would have to be maintained indefinitely to sustain a treatment response; however, no efficacy or safety data were reported.[52]

3.2.3 | Liraglutide

A narrative review (n = 52) and the AASLD Practice Guidance reported on the efficacy of liraglutide in patients with NASH.[10,16] Both publications showed patients had improved resolution of NASH as well as small improvements in fibrosis progression (see Table 2).[10,16] In addition, the Practice Guidance noted that although liraglutide was associated with weight loss, gastrointestinal effects were reported.[16]

3.2.4 | Metformin

One narrative review reported on clinical outcomes of metformin in NASH.[15] The identified review described improvements in serum aminotransferases for patients treated with metformin; however, no results were presented.[15] Additionally, the review described no significant benefit of metformin in improving liver histology in patients with NASH.[15] No other efficacy and safety data were reported.

3.2.5 | Obeticholic acid

Three publications reported on clinical outcomes of obeticholic acid (OCA), showing improvements in steatosis, inflammation, and fibrosis for patients with noncirrhotic NASH as well as patients with NASH and comorbid T2DM (see Table 2).[20,55,56] However, a secondary analysis of the FLINT trial (n = 198) reported that these improvements were associated with significant increases in LDL-C in patients with noncirrhotic NASH, which was a concern due to NASH alone being associated with increased cholesterol synthesis.[56]

One narrative review (n = 219) examining both OCA and intestinal-specific Farnesoid X receptor (FXR) agonists in NASH reported that intestinal-specific FXR may reduce obesity, improve peripheral, and hepatic insulin resistance and reduce liver inflammation in patients with NASH.[20] However, the authors concluded that further studies and long-term data are required to assess the clinical efficacy of this treatment in improving hepatic fibrosis in patients with NASH.[20] The authors also suggested that this treatment may not have an associated increase in LDL-C and HDL-C observed with OCA; however, the treatments were not directly compared and thus require further investigation.[20]

3.2.6 | Ursodeoxycholic acid

One retrospective cohort study (n = 101), one SLR and the AASLD Practice Guidance reported on clinical outcomes of ursodeoxycholic acid (UDCA) (Table 2).[16,57,58] The retrospective cohort study (n = 101) reported that UDCA in combination with vitamin E showed an improvement in long-term liver function tests.[57] This was supported by

the SLR, reporting that the same combination therapy significantly improved liver function in 5 small proof-of-concept studies in patients with NASH.[58] The Practice Guidance concluded that despite promising results, UDCA has so far only been investigated in proof-of-concept studies with a small number of participants and with surrogate endpoints; therefore, the efficacy data should be interpreted with caution.[16]

3.2.7 | Pentoxifylline

Two RCTs (n = 60 and n = 35) and a narrative review reported that PTX improved histological features of NASH, but showed no significant benefit in improving fibrosis (see Table 2).[51,59,60] The first Phase II RCT (n = 35) examined PTX vs PBO, with PTX showing significant improvements in liver histology with minimal side effects, including abdominal pain.[60] The other Phase II RCT (n = 60) examined PTX vs PIO and while both treatments showed significant improvements in hepatic steatosis, the authors concluded that due to greater improvements in patients with NASH, PIO should be used ahead of PTX.[51]

3.2.8 | Statins

A narrative review and a cross-sectional study (n = 347) reported on clinical outcomes of statins.[33,61] The review showed that statins had potential beneficial effect in patients with NASH cirrhosis, as an improvement in liver function tests was observed in this population, possibly delaying decompensation.[33] However, the cross-sectional study reported worsening of fibrosis and NASH progression in patients with NASH and comorbid T2DM (although the results were not significant).[61] In addition to the above studies, a Phase II RCT investigating the effects of atorvastatin and L-carnitine co-administration vs atorvastatin was identified. (ClinicalTrials.gov Identifier: NCT01617772) This trial is currently ongoing with no clinical outcomes reported, and has an estimated completion date of December 2019 (ClinicalTrials.gov Identifier: NCT01617772).

3.2.9 | Angiotensin II receptor antagonists

One narrative review reported on clinical outcomes of angiotensin II receptor antagonists (ARBs).[59] In the review, ARBs were shown to improve serum transaminases in patients with NASH and hypertension.[59] It also reported on telmisartan, an ARB which has shown beneficial effects on steatosis, ballooning, lobular inflammation, and fibrosis in small studies, although the authors cautioned more histological data are required to confirm this.[59]

3.2.10 | Conclusions

Off-label treatments in NASH are focused on treating comorbidities such as T2DM and obesity. PIO and vitamin E are the only pharmacological therapies currently recommended off-label for NASH patients. Marketed therapies (ie metformin, liraglutide, angiotensin II receptor antagonists, statins, OCA, pentoxifylline and UDCA) are often used off-label; however, due to lack of data, are not currently recommended in NASH patients.

3.3 | Investigational treatments

A number of investigational treatments were identified for the treatment of NASH, including: aramchol, BMS-986036, BMS-986263, cenicriviroc, elafibranor, GS-0976, Imm-124E, NGM282, and selonsertib. These investigational treatments had limited efficacy and safety data available (details of the reported safety and efficacy outcomes are presented in Table 2).[10,16,26] Three original research publications are referenced in Table 2 to support the data points cited in the captured publications.[62-64]

A narrative review showed that aramchol significantly decreased liver fat content in patients treated with 100 mg daily vs PBO in a Phase II RCT (n = 66) (Table 2).[10] However, minor adverse events were reported, namely mild abdominal pain and mild upper respiratory tract infection.[10]

Preliminary data from a Phase II RCT (n = 74) and a post-hoc analysis (n = 48), showed a beneficial effect of BMS-986036 on steatosis, liver injury, and fibrosis in NASH; however, no safety data were reported (Table 2).[65,66] Preliminary data from a Phase Ib/II RCT (n = 11) for a similar therapy, BMS-986263, have shown an improvement in advanced fibrosis in patients with NASH, with no dose-limiting toxicities reported (Table 2).[67]

A narrative review reported that cenicriviroc failed to meet the primary endpoint of a 2-point reduction in NAFLD activity score (NAS) in a Phase IIb trial; however, an improvement in fibrosis by at least one stage without worsening of steatosis was described.[26] Additionally, one cohort study (n = 1,022) noted that cenicriviroc had demonstrated a positive safety profile in patients with NASH, although long-term efficacy data were not reported for this (Table 2).[68] The narrative review also reported on another therapy, elafibranor which failed to meet its primary endpoint of percentage disappearance of NASH without worsening of fibrosis in a Phase II RCT.[26] The endpoint was met in a sub-population of patients with mild-to-moderate fibrosis (NAS > 4) only; however, no further efficacy results were reported.[16,26] In the AASLD Practice Guidance, elafibranor was associated with improving NASH without the worsening of fibrosis over a 12-month period.[16] Additionally, although elafibranor was associated with improved cardiometabolic profiles, there was a mild, reversible increase in serum creatinine.[16]

In a Phase II RCT of GS-0976 (n = 49) vs PBO (n = 26), GS-0976 showed a significant reduction in magnetic resonance imaging-proton density fat fraction (MRI-PDFF) in patients with NASH (Table 2).[69] Furthermore, treatment with GS-0976 was associated with minimal side effects, the most frequent being nausea, abdominal pain, and diarrhoea.[69]

A narrative review (n = 10) identified Imm124-E as an investigational treatment with very limited results: it was reported to mediate a reduction in haemoglobin A1C, insulin resistance and cause a mild

improvement in cholesterol levels and liver enzymes in patients with NASH and comorbid T2DM (Table 2).[10] NGM282 was another investigational treatment identified with limited results.[70] A post-hoc analysis (n = 82) reported that NGM282 showed significant reductions in hepatic steatosis, liver fat content and other NASH biomarkers; however, no safety data were captured.[70]

In a Phase II RCT of selonsertib with simtuzumab (n = 62) vs simtuzumab alone (n = 10), selonsertib demonstrated a reduction in liver fibrosis in patients with NASH (Table 2).[71] The majority of patients treated with selonsertib and simtuzumab experienced at least 1 mild-to-moderate adverse event, the most frequent being headache, nausea, and sinusitis.[71]

An additional 12 investigational treatments were identified as being in early phases (Phase I/II) of development, with no safety or efficacy data reported. These treatments are summarized in Appendix S5.

3.3.1 | Conclusions

Overall, 21 investigational therapies for the treatment of NASH were identified in this review. Only nine investigational therapies (aramchol, BMS-986036, BMS-986263, cenicriviroc, elafibranor, GS-0976, Imm-124E, NGM282, and selonsertib) have shown efficacy in NASH patients and are currently being evaluated in Phase II and Phase III clinical trials. Other pharmacological therapies are in early phases of development, where efficacy and safety data have not yet been published.

3.4 | Surgical treatments

3.4.1 | Bariatric surgery

In comparison to interventions used and described thus far, bariatric surgery was reported as a high cost treatment option used only in selected eligible patients with NASH to facilitate weight loss.[72] Six publications, including 3 prospective cohort studies (n = 109, n = 44 and n = 28), one meta-analysis, one narrative review, and the AASLD Practice Guidance discussed bariatric surgery.[16,28-32] In all publications identified, bariatric surgery was reported to improve steatohepatitis, inflammation, and hepatocellular ballooning, as well as induce remission of T2DM, and NASH disappearance in morbidly obese patients and patients with cirrhotic NASH (see Table 3).[28-30,32] In the meta-analysis of 766 paired liver biopsies, bariatric surgery was also reported to improve fibrosis due to NASH.[31] Despite the above results, the AASLD Practice Guidance recommended restricting the use of bariatric surgery to eligible obese patients with NASH only; therefore, limiting its use to a very small population.[16]

One narrative review reported on emerging endoscopic bariatric therapies, including intragastric balloon therapy, which has been associated with equal weight loss and lower morbidity compared to conventional bariatric surgery.[10] Intragastric balloon therapy in combination with diet and exercise (n = 8) showed significant improvement in NAS at 6 months compared to a sham balloon placement (P = 0.03), as well as an improvement in QoL in obese patients (n = 119) after balloon placement ($P < 0.05$).[10] However, no change in hepatic inflammation, ballooning or fibrosis was reported.[10]

3.4.2 | Liver transplantation

LT in NASH was reported in 5 publications, including 2 retrospective cohort studies (n = 39,124 and n = 48), 2 narrative reviews and the AASLD Practice Guidance, where it was considered as an option for patients with NASH and ESLD or HCC only.[16,33-36] There were no efficacy data reported in any of the publications; however, 40% of patients with NASH were identified to be at risk of developing renal dysfunction within 1 month of LT, suggesting serious safety issues with LT in this patient population.[16,35] Additional evidence from a clinical review suggested that reduction in risk factors for post-LT metabolic syndrome may impose a significant survival benefit in post-LT patients.[36]

3.4.3 | Conclusions

Surgical treatments were identified as high-cost strategies for managing limited eligible groups of patients in NASH, compared to lifestyle management and off-label therapies. These included bariatric surgery and LT, and despite reported improvements in inflammation and steatohepatitis with bariatric surgery, and survival benefits of LT, these therapies are limited to specific NASH populations of eligible obese patients and patients with ESLD and HCC only.[16,26]

4 | DISCUSSION AND CONCLUSIONS

A total of 48 publications were included in this literature review, which reported on the management strategies in NASH and the outcomes achieved with lifestyle modification, off-label therapies, investigational therapies, bariatric surgery, and LT. The majority of the publications presented were narrative reviews; therefore, the discrete data for the efficacy and safety of pharmacological therapies were limited or often lacking. In addition, the majority of the identified eligible publications (n = 34) were identified as grey literature, most were early findings in abstracts and were not yet peer-reviewed.

Although several publications reported that weight loss through lifestyle modification was associated with improvements in NASH, a reduction of 7%-10% was required to improve fibrosis, with greater improvements observed with increased weight loss: in patients who achieved weight loss of > 10%, almost half achieved fibrosis regression.[15,18,21,24] With several difficulties associated with weight loss, including fatigue, lack of confidence to perform exercise and the high inability of maintaining weight loss long-term, it would appear that this management strategy is effective in the short-term only.[23,25] There was a general lack of data on the long-term effects of lifestyle modification on NASH progression; therefore, further

TABLE 3 Publications reporting safety and efficacy outcomes of bariatric surgery in NASH[a]

Reference	Country	Study	Adult population	N[b]	Outcomes ACHIEVED
Mummadi et al. 2008 [31]	Global	SLR and meta-analysis	NASH patients with paired liver biopsies	766 paired biopsies	After treatment with bariatric surgery: > 81.3% pooled improvement in steatohepatitis (95% CI 61.9-94.9) > 65.5% pooled improvement or resolution of fibrosis (95% CI 38.2-88.1)
Estep et al. 2014 [28]	NR	Prospective cohort study	Obese NASH undergoing bariatric surgery	44	After treatment with bariatric surgery: > Fibrosis was negatively correlated with ALT ($r = -0.36$, $P < 0.05$) and AST ($r = -0.43$, $P < 0.05$)
Lassailly et al. 2015a [32]	France	Prospective cohort study	Morbidly obese NASH patients	109	After treatment with bariatric surgery: > 85.4% NASH disappearance (95% CI 5.8-92.2) > Rate of disappearance was 94.2% higher in mild NASH vs 70.0% in moderate or severe NASH ($P = 0.007$) > 84.2% improvement in hepatocellular ballooning (95% CI 74.4%-91.3%) > 67.1% improvement in lobular inflammation (95% CI 55.8%-77.1%) > 33% improvement in fibrosis > Decrease in steatosis from 60% (IQR 40%-80%) to 10% (IQR 2.55-21.3%) > Lower weight loss with gastric banding vs gastric bypass (decrease in BMI 6.4 ± 0.7 vs 14.0 ± 0.5, $P < 0.0001$)
Lassailly, 2015b [30]	France	Prospective cohort study	Cirrhotic NASH patients	28	One year after bariatric surgery: > Improved BMI (49.8 to 39.1) > Improved steatosis (50% to 10%) > Improved NAS score (4.0 to 1.5) > Comparable survival vs controls (95.5% ±0.04 vs 98.9% ±0.01, $P = 0.32$)
Chalasani et al. 2017 [16] (referencing Mosko et al. 2011 [73])	US	Guidelines	Cirrhotic NASH patients	3,888	> 0.3% higher mortality in patients undergoing bariatric surgery with cirrhosis vs 0.9% with no cirrhosis > 16.3% higher mortality in patients undergoing bariatric surgery with decompensated cirrhosis vs patients with no cirrhosis
Shouhed et al. 2017 [29] (referencing Mathurin et al. 2009 [74])	Global	Narrative review	NASH patients treated with bariatric therapy vs conventional therapy	6,131	Five years after surgery: > Patients with liver steatosis had decreased from 37% at baseline to 16%, with the improvement mostly occurring in the first year. > Severe steatosis persisted in only 8.8% of patients. > Patients diagnosed with probable or definite NASH had significantly decreased from 27.4% to 14.2%.* > 95.7% of patients maintained a fibrosis score of ≤F1.
Issa et al. 2017 [10] (referencing Lee et al. 2012 [75])	Global	Narrative review	NASH patients treated with IBG plus diet and exercise;	8	> At 6 months after procedure, improvement in NAS was significantly better vs sham balloon (2 vs 4; $P = 0.03$) > There was a trend toward improvement in steatosis ($P = 0.075$) but no change in hepatic inflammation, ballooning, or fibrosis in both groups after treatment.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CI, confidence interval; IBG, intragastric balloon; IQR, interquartile range; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NR, not reported; r, correlation coefficient; RCT, randomized controlled trial; SLR, systematic literature review; T2DM, type 2 diabetes mellitus; US, United States.

[a]Original publications are referenced where applicable.

[b]Number of patients.

*P-value not reported.

research is required before any conclusions can be drawn regarding its efficacy in NASH.

Importantly, there was a lack of clear guidelines for managing patients with advanced fibrosis due to NASH, who require an intervention beyond diet and exercise. With the increased burden of fibrosis due to NASH, effective long-term therapies and guidelines are needed; therefore, further research is required in this population of patients with NASH. Alongside the lack of guidance, there was also a paucity of clinical trial data, reflecting an absence of licensed treatments for NASH. Both these limitations were recently acknowledged by the FDA, who published draft guidance for NASH clinical trial development—this has been developed specifically to encourage research into novel therapies for NASH, and ensure the inclusion of fibrosis endpoints into trial design, confirming the need for treatments that effectively target fibrosis due to NASH.[13]

Overall, the publications reporting on off-label treatments captured a wide range of outcomes and a significant variability in the target populations, making comparisons across treatments challenging. Vitamin E and PIO were the only therapies identified and recommended by the AASLD Practice Guidance for consideration as pharmacological options in selected patients with NASH.[16] This recommendation is further supported by the EASL-EASD Practice Guidelines, which outline that while no firm recommendations could be made, vitamin E or PIO could be used in selected patients with NASH based on available efficacy and safety data.[76] These treatments were the most frequently captured in this review, with 7 publications reporting on their clinical outcomes in NASH.[10,23,26,27,51-53] Despite this, the results of this review show that vitamin E use appears to be limited to patients with nondiabetic NASH due to lack of data in the overall NASH population.[16] Therefore, further research is required on the efficacy and safety of vitamin E before firm conclusions can be made regarding its use in NASH. Similarly, further research is required to address long-term safety concerns associated with PIO, as it was associated with an increased risk of heart failure, bone fracture, oedema and weight gain.[23] Conflicting data on the long-term efficacy of PIO may limit its use further, with the discontinuation of PIO therapy in patients reportedly leading to a return of pretreatment NASH histology, suggesting PIO may not be a reliable treatment for patients with NASH.[52,53]

Other off-label therapies were reported less frequently and 4 of these therapies (metformin, PTX, statins and UDCA) did not show or report improvements in fibrosis. As this is now considered a key efficacy endpoint in NASH, it would appear that most therapies require more research to show efficacy in this disease.[13] Only PIO has been studied in patients with advanced fibrosis due to NASH; however, it has also shown limited efficacy, warranting further clinical research for these patients.[10,27]

For investigational therapies in development for the treatment of NASH, the majority of data were small studies (n < 100), had short-term follow-ups and included a range of different outcomes and target populations, highlighting the difficulties in comparisons across studies. Further investigation on these therapies is needed before their efficacy in NASH can be determined. Overall, the data suggested that 4 investigational therapies (BMS-986036, cenicriviroc, elafibranor, and selonsertib) may be efficacious in patients with mild-to-moderate fibrosis due to NASH.[10,26] However, there was a lack of data for patients with NASH in advanced stages of fibrosis (F3/F4), with only one RCT reporting on BMS-986263, which demonstrated a decrease in fibrosis in approximately half the patients studies.[67] This paucity may have been due to the majority of publications being narrative reviews, which may not have adequately reported on the NASH population examined. Additionally, as these therapies are still in the early stages of development it is likely that sub-population data in NASH are yet to emerge; therefore, ongoing trials should confirm which therapies are best suited for use in the overall NASH population vs patients with advanced fibrosis due to NASH.

There was a particularly limited evidence base for LT found as part of this review, with no publications reporting on the efficacy of LT in patients with NASH and one publication quoting safety concerns post-LT.[16] This may be due to studies rarely classifying NASH as the primary cause of LT, rather quoting liver disease, cancer or liver failure as reasoning for transplantation. Therefore, further research into the primary cause of LT is needed to understand its efficacy in NASH patients.

New techniques in endoscopic bariatrics, such as intragastric balloon therapy, have also been investigated due to the decrease in morbidity compared to bariatric surgery.[10] As these are relatively new potential options in NASH, further research is needed to determine their long-term effects and validate their cost-effectiveness. Should long-term effects be demonstrated, the NASH population eligible to receive these therapies will still remain extremely limited, further demonstrating a need for effective pharmacological therapies in early and later stages of NASH. Only one meta-analysis reported an improvement of bariatric surgery on liver fibrosis due to NASH, suggesting a lack of research in later stages of NASH with current surgical treatments. Due to the serious consequences associated with advancing NASH, including ESLD and HCC, new pharmacological therapies are needed to treat, reverse and halt fibrosis progression, thus reducing the costly consequences of this burdensome condition.[7]

Due to the structured nature of this review, its methodology lacked a critical appraisal of data for each examined publication—this could lead to a skewed weighing of evidence (eg results from a network meta-analysis and a narrative review could be considered of equal quality); however, by reporting study design and size throughout the manuscript and only contrasting evidence within studies, we limited this bias. While not directly searched for through the search strategy, one Practice Guidance document was identified as part of this review; as guidance documents provide evidence-based recommendations for disease management, further research into guidance-specific evidence would be useful to understand the recommended NASH management options across countries and identify any discrepancies in recommendations.

There was a range of methodologies reported in the publications captured in this review, and a difference in the robustness of evidence must be acknowledged. The majority of the publications were

narrative reviews, which did not report primary data regarding the efficacy and safety of pharmacological therapies. There was also little evidence from quality-controlled trials and the captured RCTs were generally low quality and reported only in abstracts. Many of the publications included in this review were from grey literature sources, indicating that a significant proportion of the currently available evidence base was preliminary and was not yet peer reviewed. While this reflects the early stages of development of many pharmacological therapies in NASH, the reported results and evaluations were limited and varied significantly across treatments. This highlights the current lack of robust evidence on the efficacy and safety of treatments in NASH, and further emphasizes the need for additional generation of quality evidence in this disease. Importantly, more comparable data are required to assess the true effectiveness of each pharmacological therapy in NASH—the recent FDA draft guidance (Food and Drug Administration, 2018) should ensure the standardization of outcomes in future clinical trials, increasing the comparability of data.

This structured literature review found that NASH management currently focuses on dietary modification, exercise, and managing of comorbidities, which has shown positive results in patients with mild-to-moderate fibrosis due to NASH. However, there is a significant lack of evidence on both short- and long-term outcomes with these management strategies, and evidence shows that they do not always provide the level of control needed to provide sustained improvements for patients with NASH. Several investigational treatments are currently in development but equally lack long-term safety and efficacy data—this reflects the relatively new research area of NASH pharmacological therapies and the fact that many studies are still ongoing. The majority of available and upcoming therapies focus on treating, halting or reversing NASH with mild-to-moderate fibrosis. Very limited data were reported in advanced fibrosis due to NASH, with only 2 therapies showing improvements in this population. Further research is needed in treating patients with advanced stages of fibrosis due to NASH, where the highest morbidity and mortality burden of NASH lies.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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