Current Pharmacologic Therapy for Nonalcoholic Fatty Liver Disease

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KEYWORDS

• NASH • Pharmacologic therapy • Weight loss • Lifestyle modification
• Insulin sensitizers • Fatty acids • Antioxidants

KEY POINTS

- Modest but sustained weight loss, regular exercise, and diet composition modification seem to improve biochemical and histologic abnormalities.
- Other therapies directed at insulin resistance, oxidative stress, cytoprotection, and fibrosis may also offer benefits, but further studies are required.
- A multifaceted approach of lifestyle modifications, weight loss, and pharmacotherapy can be used in combination, but no single treatment approach has proved universally applicable to the general population with nonalcoholic steatohepatitis (NASH).
- Continuous clinical and preclinical studies on existing and potential drugs are needed to improve treatment of nonalcoholic fatty liver disease/NASH, which is a burgeoning health care problem.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is now the most frequent chronic liver disease in Western countries, affecting more than 30% of the general population, and has emerged as a serious public health burden. The prevalence of this syndrome is increasing worldwide in parallel with the increase in obesity (**Table 1**).[1] Recent surveys indicate that NAFLD may account for approximately 80% of cases, and that 1 in 4 or 5 American adults has NAFLD.[2,3]

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Table 1
Summary: pharmacologic therapies in the treatment of Non Alcoholic Steatohepatitis (NASH)

Treatment	Mechanism	Biochemical Effects	Histologic Effects	Comments
Orlistat	Weight loss	↓ LFTs and insulin resistance	↓ Steatosis, inflammation, NAS score	Improvement in inflammation and NAS seen if weight loss ≥9%
Rimonabant	Weight loss, possible peripheral effects	↓ Insulin resistance, triglyceride levels, LFTs ↑ HDL and adiponectin levels	↓ Steatosis	Animal data, psychiatric side effects
Incretin analogues (exendin-4)	Weight loss	↓LFTs, insulin resistance, hemoglobin A_1C levels	↓ Steatosis	Animal and pilot studies in NAFLD; extensively studied in type 2 diabetes mellitus
TZDs	PPAR-γ agonists	↓ LFTs, insulin resistance, and TNF-α levels ↑ Adiponectin levels	↓ Steatosis, inflammation and fibrosis	Side effects: weight gain, peripheral edema, cardiac, fractures, need for maintenance therapy
Metformin	↑ AMP kinase	↓ LFTs and insulin resistance No effect on adiponectin levels	+/− improvement in steatosis, inflammation, and fibrosis	Data conflicting; no RCTs
Vitamin E	↓ Oxidative stress	↓ LFTs	Uncertain	Large trials with histologic follow-up evaluation required
Betaine	↓ Oxidative stress	↓ LFTs	↓ Steatosis, inflammation, fibrosis	Pilot study only
UDCA	Hepatoprotective	No change	No change	Not beneficial in large RCT
Pentoxifylline	Hepatoprotective	↓ LFTs, TNF-α levels	↓ Steatosis, inflammation	Pilot study only
HMG CoA-reductase inhibitors	Improve lipid panel	? LFTs	Uncertain	Conflicting studies
Ezetimibe	Blocks cholesterol absorption in intestine	? LFTs	↓ Steatosis and fibrosis	Animal data
Angiotensin receptor blockers	? Inhibits stellate cells	↓ LFTs	↓ Fibrosis	Animal and pilot studies

The symbol "↓" indicates a decrease, "↑" indicates an increase, and "?" indicates that the effect is uncertain.

Abbreviations: AMP, adenosine 5′-monophosphate; HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LFTs, liver function tests; PPAR; peroxisome proliferator–activated receptor; TNF, tumor necrosis factor, TZDs, thiazolidinediones.

From Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. Gastroenterology 2008;134:1689; with permission.