of liver histology remains unknown. Unfortunately, most NAFLD patients are unable to achieve sustained weight loss. Although pharmacologic therapies such as orlistat, topiramate, and phentermine to facilitate weight loss are available, their role in the treatment of NAFLD remains experimental.

Pharmacologic Therapies Several drug therapies have been tried in both research and clinical settings. No agent has yet been approved by the FDA for the treatment of NAFLD. Hence, this remains an area of active research. Because NAFLD is strongly associated with the metabolic syndrome and type 2 diabetes **(Chaps. 417 and 418)**, the efficacy of various insulin-sensitizing agents has been examined. *Metformin*, an agent that mainly improves hepatic insulin sensitivity, has been evaluated in several small, open-label studies in adults and a recent larger, prospectively randomized trial in children (dubbed the TONIC study). Although several of the adult NASH studies suggested improvements in aminotransferases and/or liver histology, metformin did not improve liver histology in the TONIC study of children with NASH. Thus, it is not currently recommended as a treatment for NASH. Uncontrolled open-label studies have also investigated *thiazolidinediones (pioglitazone and rosiglitazone)* in adults with NASH. This class of drugs is known to improve systemic insulin resistance. Both pioglitazone and rosiglitazone reduced aminotransferases and improved some of the histologic features of NASH in small, uncontrolled studies. A large, National Institutes of Health–sponsored, randomized placebo-controlled clinical trial, the PIVENs Study (Pioglitazone vs Vitamin E vs Placebo for the Treatment of 247 Nondiabetic Adults with NASH), demonstrated that resolution of histologic NASH occurred more often in subjects treated with pioglitazone (30 mg/d) than with placebo for 18 months (47 vs 21%, p = .001). However, many subjects in the pioglitazone group gained weight, and liver fibrosis did not improve. Also, it should be noted that the long-term safety and efficacy of thiazolidinediones in patients with NASH has not been established. Five-year follow-up of subjects treated with rosiglitazone demonstrated no reduction in liver fibrosis, and rosiglitazone has been associated with increased long-term risk for cardiovascular mortality. Hence, it is not recommended as a treatment for NAFLD. Pioglitazone may be safer because in a recent large meta-analysis it was associated with reduced overall morality, myocardial infarction, and stroke. However, caution must be exercised when considering its use in patients with impaired myocardial function.

Antioxidants have also been evaluated for the treatment of NAFLD because oxidant stress is thought to contribute to the pathogenesis of NASH. *Vitamin E*, an inexpensive yet potent antioxidant, has been examined in several small pediatric and adult studies with varying results. In all of those studies, vitamin E was well tolerated, and most showed modest improvements in aminotransferase levels, radiographic features of hepatic steatosis, and/or histologic features of NASH. Vitamin E (800 IU/d) was also compared to placebo in the PIVENs and TONIC studies. In PIVENs, vitamin E was the only agent that achieved the predetermined primary endpoint (i.e., improvement in steatohepatitis, lobular inflammation, and steatosis score, without an increase in the fibrosis score). This endpoint was met in 43% of patients in the vitamin E group (p = .001 vs placebo), 34% in the pioglitazone group (p = .04 vs placebo), and 19% in the placebo group. Vitamin E also improved NASH histology in pediatric patients with NASH (TONIC trial). However, a recent population-based study suggested that chronic vitamin E therapy may increase the risk for cardiovascular mortality. Thus, vitamin E should only be considered as a first-line pharmacotherapy for nondiabetic NASH patients. Also, given its potentially negative effects on cardiovascular health, caution should be exercised until the risk-to-benefit ratio and long-term therapeutic efficacy of vitamin E are better defined. Ursodeoxycholic acid (a bile acid that improves certain cholestatic liver diseases) and *betaine* (metabolite of choline that raises SAM levels and decreases cellular oxidative damage) offer no histologic benefit over placebo in patients with NASH. Experimental evidence to support the use of *omega-3 fatty acids* in NAFLD exists; however, a recent large, multicenter, placebo-controlled study failed to demonstrate a histologic benefit. Other pharmacotherapies are also being evaluated in NAFLD (e.g., *probiotics, farnesoid X receptor agonists, anticytokine agents, glucagon-like peptide agonists, dipeptidyl IV antagonists*); however, sufficient data do not yet exist to justify their use as NASH treatments in standard clinical practice.

Statins are an important class of agents to treat dyslipidemia and decrease cardiovascular risk. There is no evidence to suggest that statins cause liver failure in patients with any chronic liver disease, including NAFLD. The incidence of liver enzyme elevations in NAFLD patients taking statins is also no different than that of healthy controls or patients with other chronic liver diseases. Moreover, several studies have suggested that statins may improve aminotransferases and histology in patients with NASH. Yet, there is continued reluctance to use statins in patients with NAFLD. The lack of evidence that statins harm the liver in NAFLD patients, combined with the increase risk for cardiovascular morbidity and mortality in NAFLD patients, warrants the use of statins to treat dyslipidemia in patients with NAFLD/NASH.

Bariatric Surgery Although interest in bariatric surgery as a treatment for NAFLD exists, a recently published Cochrane review concluded that lack of randomized clinical trials or adequate clinical studies prevents definitive assessment of benefits and harms of bariatric surgery as a treatment for NASH. Most studies of bariatric surgery have shown that bariatric surgery is generally safe in individuals with well-compensated chronic liver disease and improves hepatic steatosis and necroinflammation (i.e., features of NAFLD/NASH); however, effects on hepatic fibrosis have been variable. Concern lingers because some of the largest prospective studies suggest that hepatic fibrosis might progress after bariatric surgery. Thus, the Cochrane review deemed it premature to recommend bariatric surgery as a primary treatment for NASH. There is also general agreement that patients with NAFLD-related cirrhosis and portal hypertension should be excluded as candidates for bariatric surgery. However, given growing evidence for the benefits of bariatric surgery on metabolic syndrome complications in individuals with refractory obesity, it is not contraindicated in otherwise eligible patients with NAFLD or NASH.

Liver Transplantation Patients with NAFLD in whom end-stage liver disease develops should be evaluated for liver transplantation **(Chap. 368)**. The outcomes of liver transplantation in well-selected patients with NAFLD are generally good, but comorbid medical conditions associated with NAFLD, such as diabetes mellitus, obesity, and cardiovascular disease, often limit transplant candidacy. NAFLD may recur after liver transplantation. The risk factors for recurrent or de novo NAFLD after liver transplantation are multifactorial and include hypertriglyceridemia, obesity, diabetes mellitus, and immunosuppressive therapies, particularly glucocorticoids.

GLOBAL HEALTH CONSIDERATIONS

The epidemic of obesity is now a global and accelerating phenomenon. Worldwide, there are over 1 billion overweight adults, of whom at least 300 million are obese. In the wake of the obesity epidemic follow numerous comorbidities, including NAFLD. NAFLD is the most common liver disease identified in Western countries and the fastest rising form of chronic liver disease worldwide. Present understanding of NAFLD natural history is based mainly on studies in whites who became overweight/obese and developed the metabolic syndrome in adulthood. The impact of the global childhood obesity epidemic on NAFLD pathogenesis/progression is unknown. Emerging evidence demonstrates that advanced NAFLD, including cirrhosis and primary liver cancer, can occur in children, prompting concerns that childhood-onset NAFLD might follow a more aggressive course than typical adult-acquired NAFLD. Some of the most populated parts of the world are in the midst of industrial revolutions, and certain environmental pollutants seem to exacerbate NAFLD. Some studies also suggest that the risk for NASH and NAFLD-related cirrhosis may be higher in certain ethnic groups such as Asians, certain Hispanics, and Native Americans and lower in others such as African Americans, compared with whites. Although all of these variables confound efforts to predict the net impact of this obesity-related liver disease on global health, it seems likely that NAFLD will remain a major cause of chronic liver disease worldwide for the foreseeable future.