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FATTY LIVER DISEASE (V AJMERA, SECTION EDITOR)

Medical Approach for Weight Loss in Nonalcoholic Fatty Liver Disease

Albert Do[1] · Ysabel C. Ilagan-Ying[2] · Wajahat Z. Mehal[1]

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Abstract

Purpose of Review Nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions due to obesity in the modern world. Although treatments are in development, weight loss remains the most definitive and impactful approach to treating this disease and with it the other multisystemic complications of obesity. In this review, we summarize the current medical therapies for weight loss in NAFLD, including patient evaluation, counseling, and incorporation of medications for obesity.

Recent Findings Despite need for weight loss as treatment for NAFLD, few achieve successful weight loss. Weight loss medications lead to weight loss of 5 to 10%, the amount expected to improve NAFLD steatosis and fibrosis. Ultimately, a multimodal approach is necessary to achieve successful weight loss.

Summary Medical management for weight loss in NAFLD requires fibrosis staging and developing a patient-centered approach to assessment of patient weight and behavioral change goals.

Keywords Steatohepatitis · Obesity · Pharmacology · Weight loss medications · Diet · Exercise

Abbreviations

BMI	Body mass index
CP	Child Pugh
EBT	Endoscopic bariatric therapies
FDA	Food and Drug Administration
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is now the most common chronic liver disease in the world with an estimated prevalence of 24% globally and is occurring in the setting of the obesity epidemic [1••, 2]. NAFLD is now the second-leading but fastest growing indication for liver transplantation in the USA [3, 4]. Its severe form, nonalcoholic steatohepatitis (NASH), is associated with cardiovascular disease, hepatic fibrosis, cirrhosis, and associated complications including portal hypertension and hepatocellular carcinoma [5•]. These patients may also suffer from other medical issues throughout liver transplant assessment, including ethical considerations for transplant candidacy in the setting of obesity, sarcopenia, prolonged operative times, and posttransplantation weight gain [6, 7••]. As there are currently no US Food and Drug Administration (FDA)-approved drugs for NAFLD, screening for NASH even in high-risk populations at this time is not recommended due to low cost-effectiveness [8]. Although promising medications to treat steatohepatitis are forthcoming, weight loss is currently the only curative treatment for this disease. Thus, treatment currently focuses on addressing the underlying pathogenic factors for NAFLD, including excess weight, obesity, and insulin resistance. This review aims to summarize and provide updated evidence for the medical management of weight loss, including use of medications for weight loss and indications for referral to advanced endoscopic and surgical management. We also aim to provide practical management strategies for weight loss patients with NAFLD.

This article is part of the Topical Collection on *Fatty Liver Disease*

✉ Albert Do
albert.do@yale.edu

[1] Section of Digestive Diseases, Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, 1080 LMP, PO Box 208019, New Haven, CT, USA

[2] Yale School of Medicine, New Haven, CT, USA

Assessing, Counseling, and Planning for Weight Loss

Instilling Motivation for Weight Change

Lifestyle and medical treatment for weight loss requires patient-centered, informed decision making. Thus, it is essential to develop a strong patient-clinician relationship and focus counseling on weight loss treatments congruent with patient preferences. The transtheoretical model for behavior change is a framework based on six stages through which an individual progresses when coping with a major life stressor or engaging in behavior change [9] and has been adapted for lifestyle management for weight loss. It has been reported to be effective for weight loss from a population standpoint [10]. Assessment of the patient's current stage may allow for a standardized and systematic assessment of a patient's motivation, allowing targeted actions from the provider to facilitate behavior change for weight loss (Fig. 1). This framework is simple and establishes definitions for the different stages of change and has been associated with modest (3 to 5%) weight loss, though the Cochrane systematic review including 5 studies and 3910 patients also did not reveal evidence of sustainable weight loss [11]. Thus, despite potential utility of the transtheoretical model in determining targeted management based on stage of change and given the uncertainty of its efficacy for weight loss, all patients with NAFLD should at least receive counseling regarding their liver disease and its relation to excess weight, regardless of their stage of behavioral change.

Fibrosis stage has been found to be the only independent factor associated with long-term overall mortality, liver transplantation, and liver-related events for patients with NAFLD [12]. Counseling on fibrosis as the primary indicator of disease progression and mortality risk is essential for patient understanding of the timeframe whereby weight loss is needed before severe fibrosis and symptomatic disease may occur. NAFLD-associated fibrosis was prior thought to progress approximately one stage every decade (with stage 4 fibrosis defining cirrhosis), and though the natural history is highly heterogenous, up to 33% of patients expected to have disease progression [13, 14]. Additionally, the estimate of "one stage per decade" in those with nonalcoholic steatohepatitis may not reflect the variability of disease progression, as evidenced by the recent study of two investigations of simtuzumab found cirrhosis progression after just 96 weeks of follow-up in 48 (22%) of 217 patients with Ishak stage 3 fibrosis, and decompensation in 50 (19%) of 258 patients with compensated cirrhosis [15••]. Thus, identification of any fibrosis indicates an urgency with which weight loss should be pursued, especially in younger patients whereby the abundance of lead time allows for increased risk of advanced disease progression. Thus, patients should receive individualized counseling regarding their diagnosis of NAFLD and hepatic fibrosis stage. Even in those with steatosis but not steatohepatitis, the previous notion that nonalcohol fatty liver without NASH is a nonprogressive entity is likely inaccurate, as progressive liver disease still likely occurs. McPherson and colleagues found that on median follow-up of 6.6 years, 44% of patients with baseline

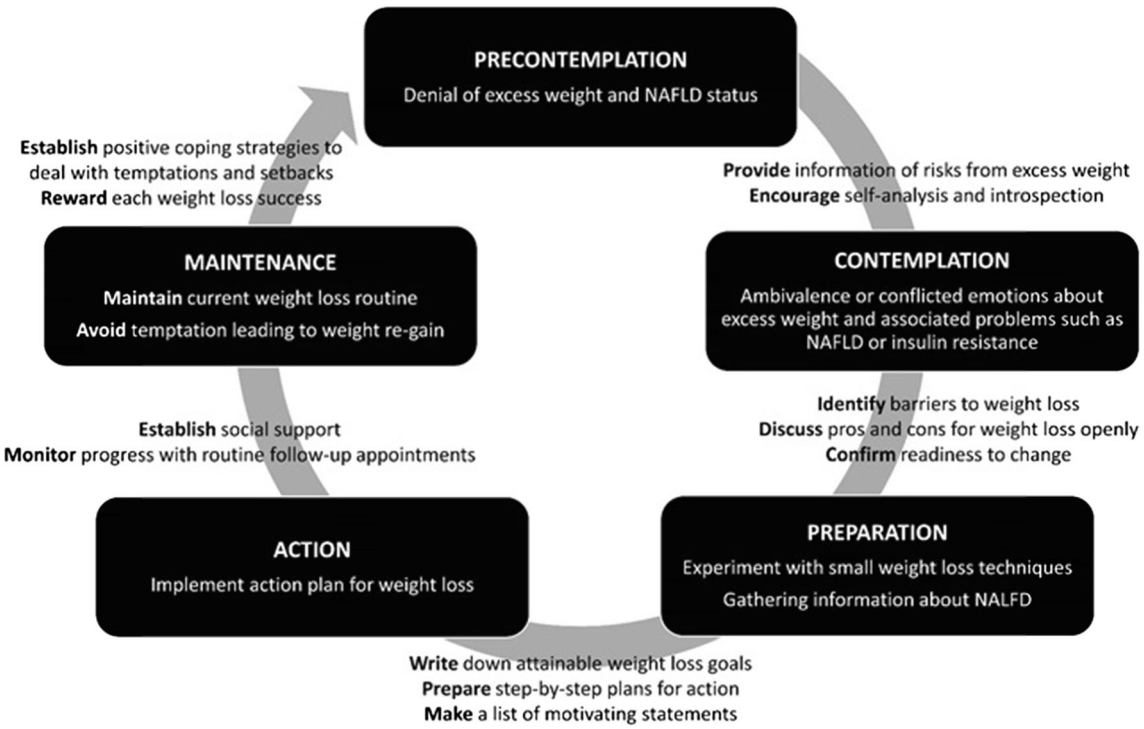

Fig. 1 The transtheoretical model of behavior change for nonalcoholic fatty liver disease

NAFLD had progressed to NASH, and even 22% of these patients reaching stage 3 fibrosis on liver biopsy [16, 17••].

NAFLD is an independent risk factor for cardiovascular disease, and to this effect, the most common cause of mortality is thought to be cardiovascular disease rather than hepatic complications [18, 19]. Patients should be counseled to treat NAFLD as the hepatic manifestation of the metabolic syndrome, the cluster of conditions including insulin resistance, dyslipidemia, visceral obesity, and hypertension, which in turn increase the risk of cardiovascular disease. Particularly, insulin resistance and diabetes are processes directly involved in the pathogenesis of hepatic steatosis [20], and so early interventions for glycemic control and lifestyle modifications like weight loss have the combined benefit of reversing NALFD while also treating comorbid diabetes.

Goals for Weight Loss in NAFLD

Current practice guidelines from the American Association for the Study of Liver Diseases (AASLD) state that weight loss of 3 to 5% of body weight improves steatosis, though greater weight loss (7 to 10%) is needed to improve histopathological NASH and fibrosis [21••]. Vilar-Gomez and colleagues found that in 261 patients with NASH and paired biopsies who were encouraged to lose weight through lifestyle modification, degree of weight loss after 1 year was independently associated with improvements in NASH-related histology. Additionally, of those who lost ≥ 10% body weight, 45% had fibrosis regression, 90% had NASH resolution, and all patients demonstrated 2-point reduction in NAFLD activity score [22]. Thus, weight loss of smaller magnitudes can still result in clinically meaningful improvements in NAFLD, even if one does not cross weight classes (i.e., even if reduction in body weight did not move a patient's class weight to something other than obesity). Hence, the goal of 10% body weight loss should be used as a clinical goal to treat NASH, while monitoring for serum aminotransferase normalization. As part of initial evaluation, assessing longitudinal clinical and laboratory data for periods with normal aminotransferases and cross-referencing associated weights may allow for individualized weight loss goals for patients, where steatohepatitis may be expected to resolve.

Common Mistakes in Medical Weight Loss

The process of planning and treating weight loss should be approached like any chronic disease. At time of diagnosis, managing expectations can help create small, attainable goals with the main focus of promoting overall health, while also establishing rapport in the patient-clinician relationship. When discussing potential treatment options for weight loss, clinicians should take care to fully elaborate the timing, mechanism, and side effect profiles of each type of intervention. Often, patients may seek the quickest fix for losing weight, sometimes resorting to dangerous use of non-FDA approved over-the-counter weight loss aids, some which are hepatotoxic [23]. Weight loss should also be a lifestyle change, not a temporary fix. Patients who pursue medication or surgery to weight loss without the associated psychological and behavioral modifications may have unrealistic expectations for weight loss goals, which may be interpreted as treatment failure but rather was due to exaggerated expectations. For example, there is an overemphasis of exercise, as campaigned by major food corporations to justify moderate intake of calorically dense, sugary products [24•]. Though resistance training may increase muscle mass and subsequent metabolic rate, the shifting of basal metabolic rate to meet the increased energy demands makes exercise the primary mechanism for weight loss initiation—but does not overshadow the powerful effects of diet.

With shrinking clinic time slots and increased pressure to see more patients, the role of dedicated nutrition and weight loss counseling has shifted from the physician to dedicated support staff. In the setting of limited physician time, simply noting a patient's body mass index (BMI) or obesity status and instructing them to lose weight without linking to disease goals leaves the patient without achievable goal points nor motivation to improve their disease status. A similar consequence in high-volume settings is the overlooking of the effects of common medications, particularly across subspecialties. Potent antipsychotics are known to cause high degrees of metabolic dysfunction and subsequent weight gain [25], but there are also other common medications which can cause weight gain, even drugs paradoxically used to treat diabetes and hypertension, components of the metabolic syndrome [26].

The approach to treating weight gain is often intertwined with management for substance use disorders. Patients may similarly exhibit an over-reliance on willpower, utilizing short-term interventions like extreme calorie-restriction or other novelty diets and quick fixes, which ultimately may prove harmful and unsustainable to maintain with ultimate return to baseline behaviors. From the provider perspective, each patient should be treated as a unique individual rather than being given a prescriptive approach of what to do to lose weight. Overgeneralized approaches to weight loss fail to recognize the underlying physiological, genetic, cultural, and psychological barriers unique to each patient's identity and community to prevent weight loss [27, 28, 29••]. Misinformation from media and among patients, coupled with lack of trust among historically underrepresented populations, may lead to a disproportionate increase in adverse outcomes or failed attempts at losing weight [30•]. Additionally, the preoccupation with fad diets or overemphasis on macronutrient distribution and food groups in elimination and restriction diets may result in nutrient deficiencies and caloric

compensation with worse food alternatives, detracting from the goal of overall reduction in energy intake for weight loss.

Perspectives and Misconceptions about NAFLD and Obesity

Patients should be counseled on current knowledge regarding both obesity and NAFLD. A variety of myths and presumptions about obesity and NAFLD may be held by patients, and exploration of these factors may help to correct unhealthy behaviors [31]. Patients should also be informed that weight loss is the most effective therapy for NAFLD, as there are currently no medications FDA-approved medications for NASH. Furthermore, obesity is associated with numerous, multisystemic complications, and thus, weight loss would be expected to improve patient health concurrently across many conditions and organ systems, not just NAFLD [32].

Recognition of perceptions relating to weight stigma and their effects on both provider care quality and patient lifestyle behaviors may potentially allow for recognition of triggers of excess nutritional intake or reduced motivation for exercise. Weight stigma exists towards individuals with obesity, with surveys of nurses revealing 24% reporting feeling "repulsed" by obesity, and 28% of teachers reporting that becoming obese is the worst thing that can happen to a person [33, 34]. Even for individuals with excess weight, increased BMI has been associated with avoidance and delay of healthcare, including feelings of not wanting to "get weighed on the provider's scale," and knowing they would be told to "lose weight" [35]. Even for individuals with obesity, exposure to weight stigma persist have been associated with increased caloric intake and reduced sense of dietary control in women with obesity [36, 37]. Understanding personal and societal cues related to lifestyle behaviors is key to achieving the long-term, sustainable lifestyle changes that are necessary for successful weight loss and maintenance.

Behavioral Modification for Weight Loss in NAFLD

Lifestyle modifications to treat NAFLD should include behavior changes in diet and exercise, as the combination of both is effective for weight loss [38••]. Furthermore, any long-term sustainable behavioral modification should be considered. Thoma and colleagues performed a systematic review of lifestyle interventions for NAFLD, which included only five studies combining diet and exercise interventions and finding 9.7 to 10.6% weight loss over 6 months, associated with alanine aminotransferase reductions by 18 to 41% [39]. Thus, patients should be counseled that irrespective of any medical or surgical modalities pursued for treatment of NAFLD and obesity, the cornerstone of effective therapy is sustained lifestyle changes addressing diet and physical activity.

Diet

No specific dietary intervention has proven superior beyond calorie restriction for total energy reduction, and diet adherence has been found to be an important factor predicting weight loss irrespective of type of diet [40]. A hypocaloric diet with reduction in energy consumption leading is thought to be the most efficacious therapy for weight loss in NAFLD. Meal replacement programs are generally thought to be safe and have been reported to decrease intrahepatic fat content after as little as 6 weeks [41].

Exercise

Exercise is a low-cost intervention for weight loss for treatment of obesity and has been found to be helpful for NAFLD. However, with increasing exercise intensity, total body energy expenditure has been found to plateau above moderate activity levels, thus requiring long periods of exercise to consume large quantities of energy for weight loss [42]. To this effect, the US Health and Human Services physical activity guidelines have recommended prolonged moderate-intensity exercise (at least 300 min/week) for weight loss [43•]. However, exercise is thought to improve NAFLD even in the absence of weight loss. Resistance training has been reported to decrease liver lipid content 13% compared to usual treatment, independent of magnitude of weight loss [44]. Additionally, a systematic review and meta-analysis including 12 studies found benefit of exercise for reduction in liver fat with minimal to no weight loss and at levels below current exercise recommendations for obesity management [45]. Thus, although weight loss is the most important factor modifiable through dietary modification, the role of exercise to treat NAFLD still is important, and patients should pursue healthy exercise habits independent of the concurrent need for weight loss.

The Role of Medications in Weight Loss

Weight Loss Medications are Helpful in NAFLD

Despite the need for lifestyle modification to achieve and sustain weight loss in NAFLD, only an estimated 20% of patients ultimately achieve successful weight loss maintenance, defined as ≥ 10% weight loss sustained for at least 1 year [46]. Thus, weight loss medications should be viewed as valuable tools to treat this disease and are indicated for those with BMI ≥ 30 or ≥ 27 mg/kg^2 with associated weight-related condition, including NAFLD. Some practical considerations need to be made when initiating weight loss medications (Table 1). Some

Table 1 Practical considerations and use of common weight loss medications

Medication name	Dosing	Mechanism of action	Contraindications	Common side effects	Monitoring	Use in cirrhosis
Naltrexone/Bupropion (Contrave®)	32 mg/360 mg daily divided in 2 doses; dose-titrated over 4 weeks	Opioid-receptor antagonist, antidepressant	Pregnancy, uncontrolled hypertension, seizure disorder, eating disorder, chronic opioid use, use within 14 days of taking MAOI, use with other bupropion-containing products	Nausea, headache, constipation, vomiting, insomnia, dizziness, dry mouth	Neuropsychiatric effects; Risk of suicidality in young adults (18–24 years) undergoing treatment for psychiatric disorder	Maximum dose: one tablet daily (naltrexone 8 mg/bupropion 90 mg) Bupropion: CP 7 to 15 use lower dose dependent on formulation (75 to 150 once daily) Naltrexone: mild to moderate impairment-no dose adjustment; Severe impairment-no dose adjustment available; has not been studied
Lorcaserin (Belviq®)	10 mg BID, evaluate efficacy by 12 weeks	Selective serotonin 2C receptor agonist for appetite suppression	Pregnancy, concomitant use of other serotonergic drugs, drugs with CYP2D6 substrates (e.g., dextromethorphan)	Headache, upper respiratory infection, nasopharyngitis, dizziness, nausea, hypoglycemia in diabetes	Neuropsychiatric effects	CP class A/B: no dosage adjustment necessary CP class C: no dose adjustment available; has not been studied, generally avoid
Phentermine (Adipex-P®, Lomaira®)	15–37.5 mg/day (Adipex-P) or 8 mg TID (Lomaira)	Sympathomimetic amine for appetite suppression	Pregnancy, breast-feeding, hypersensitivity to phentermine/sympathomimetic amines, cardiovascular disease, hyperthyroidism, glaucoma, history of drug abuse, within 14 days of taking MAOI	Sedation, myocardial toxicity, primary pulmonary hypertension, valvular disease	Abuse potential, tolerance to anorectic effect	No dose adjustments provided; has not been studied
Phentermine/ Topiramate (Qsymia®)	3.75/23 mg for 14 days, then increase to 7.5/46 mg; if < 5% weight loss then can increase to 11.25/69 mg for 14 days, then 15/92 mg	Sympathomimetic amine appetite suppressant, anti-seizure via voltage-dependent sodium channel blocker, enhancement of GABA activity, NMDA-glutamate receptor antagonism	Fetal orofacial clefts in first trimester pregnancy, hyperthyroidism, glaucoma, use within 14 days of taking MAOI	Dry mouth, constipation, paresthesia, dose-related increase in psychiatric/cognitive events, risk of renal stones, topiramate withdrawal-induced seizures if abruptly discontinued	Neuropsychiatric effects, hyperchloremic, non-anion gap metabolic acidosis and increase in serum creatinine	CP A: no dosage adjustment necessary CP B: maximum dose phentermine 7.5 mg/topiramate 46 mg QD CP C: avoid use; has not been studied Phentermine: as above

Table 1 (continued)

Medication name	Dosing	Mechanism of action	Contraindications	Common side effects	Monitoring	Use in cirrhosis
						Topiramate: no dose adjustments provided, however clearance may be reduced in hepatic impairment
Liraglutide (Saxenda®)	3.0 mg SQ QD, start from 0.6 mg QD and increase by 0.6 mg/week to maximum tolerated dose	GLP1 receptor agonist	DPP-4 inhibitor use	Nausea, vomiting, diarrhea, hypoglycemia risk increased with concomitant diabetes medication use	Acute pancreatitis, gallbladder disease	No dose adjustment necessary; use with caution due to limited experience
Orlistat (Xenical®, Alli®)	120 mg TID, omit dose if meal is missed or contains no fat	Pancreatic lipase inhibitor	Pregnancy, chronic malabsorption, cholestasis, history of calcium oxalate stones	Gastrointestinal discomfort, bloating, fat-soluble vitamin malabsorption	Pruritus, jaundice, pale stools	No dose adjustments provided; has not been studied; however unlikely needed due to low systemic absorption

AKI acute kidney injury, *BID* twice daily, *CP* Child-Pugh, *DPP-4* dipeptidyl peptidase 4, *GLP1* glucagon-like peptide-1, *MAOI* monoamine oxidase inhibitor, *SQ* subcutaneous, *TID* three times daily

medications may even have overlapping indications in patients with obesity. For example, liraglutide, a glucagon-like peptide-1 receptor (GLP-1), has been approved for the treatment of both diabetes mellitus (as Victoza®) and for weight loss (Saxenda®). As a class, weight loss medications are associated with a 5 to 10% total body weight loss, within the scale of the recommended initial weight loss threshold needed to treat NAFLD [47••]. Incorporation of both lifestyle changes and pharmacotherapy has been found to be associated with more weight loss than either medications or lifestyle modification alone [48].

Medication-Induced Weight Gain

Iatrogenic weight gain may occur when patients are placed on common medications which are known to cause weight gain as an adverse effect. Concurrently reviewing a patient's home medications during evaluation for weight loss may identify offending drugs which could be discontinued or substituted in order to prevent further weight gain or even promote weight loss.

Table 2 summarizes practical considerations of commonly used approved weight loss medications, along with contraindications and common side effects. Additionally, we have previously discussed incorporation of weight loss medications into hepatology care, summarizing the current literature regarding expected weight loss with these medications [49••]. Response assessment for all long-term medications requires evaluation of weight loss after 12 weeks at maximal drug dosage. If the weight loss threshold needed to determine efficacy (5% starting weight) is not achieved on a given medication after 12 weeks, then it will be unlikely that result in further weight loss, and the patient should either be increased in dose (as for phentermine/topiramate) or be changed to another medication (all others). However, nonresponse to one medication does not predict inefficacy of another medication, and there is heterogeneity regarding expected a given patient's response to a particular medication. Thus, patients should trial different weight loss medications as one may work even if others before did not.

NASH Cirrhosis and Weight Loss

Patients with cirrhosis should be counseled that fibrosis stage is the strongest predictor of disease-specific mortality in NAFLD [50•, 51]; thus, the development of cirrhosis demands an urgency for definitive treatment with weight loss. Muscle wasting is independently associated with mortality in cirrhosis [52, 53], and many patients with cirrhosis also suffer from sarcopenia [6]. Additionally, cirrhosis is associated with higher risk for sarcopenia for a variety of reasons including impaired anabolic capability and protein-calorie malnutrition [54].

Table 2 Common medications associated with weight gain and potential substitutions

Medication class	Associated with Weight gain	Weight loss or *neutral substitution
Antidepressants and mood stabilizers	MAOIs (isocarboxazid, phenelzine, tranylcypromine) Mirtazipine SSRI (paroxetine) TCAs (amitriptyline, doxepin, imipramine) Lithium	Bupropion MAOIs* (selegiline) SSRIs* (fluoxetine, sertraline, citalopram, escitalopram) SNRIs* (desvenlafaxine, duloxetine, venlafaxine) TCA* (nortryptiline)
Antiepileptics	Carbamazepine Gabapentin Pregabalin Valproic acid	Lamotrigine* Levetiracetam* Phenytoin* Topiramate Zonisamide
Antihistamines	1st generation antihistamines (diphenhydramine, cyproheptadine)	2nd or 3rd generation antihistamines* (cetirizine, fexofenadine, loratadine)
Antihypertensive	α-Blockers (doxazosin, prazosin, terazosin) β-Blockers, nonselective (atenolol, metoprolol, propranolol)	ACE inhibitor* (enalopril, lisionpril) ARB* (losartan, valsartan) β-Blockers, selective* (carvedilol) CCB* (amlodipine, diltiazem, nifedipine, verapamil) Thiazides* (chlorthalidone, hydrochlorothiazide)
Antipsychotics	1st generation (thorazine, haloperidol) 2nd generation (clozapine, olanzapine, risperidone)	2nd generation (aripiprazole, lurasidone, ziprasidone)
Diabetes Medications	Insulin (all types) Sulfonylurea (glimepiride, glipizide, glyburide) Thiazolidinediones (pioglitazone, rosiglitazone) Meglitinides (nateglinide, repaglinide)	α-Glucosidase inhibitors* (acarbose, miglitol) DPP-4 inhibitors* (saxagliptin, sitagliptin) GLP-1 agonists (dulaglutide, exenatide, albiglutide, liraglutide) Metformin Pramlintide SGLT2 inhibitors (canagliflozin, empagliflozin)
Glucocorticoids	Glucocorticoids (dexamethasone, methylprednisolone, prednisolone, prednisone)	Inhaled steroids Topical steroids Alternative medications (NSAIDs)
Hormone-based drugs	Progestin-only contraceptives	Barrier methods Intrauterine devices Surgical sterilization

Adapted from Saunders et al. [26]

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *CCB* calcium channel blocker, *DPP-4* dipeptidyl peptidase 4, *GLP-1* glucagon-like peptide-1, *MAOI* monoamine oxidase inhibitor, *NSAID* nonsteroidal anti-inflammatory drug, *SGLT2* sodium-glucose cotransporter-2, *SNRI* serotonin norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant

Lifestyle changes to improve diet and exercise are needed irrespective of whether a patient has cirrhosis but if present, weight loss medication options are more limited. However, most medications are not contraindicated in cirrhosis unless the patient has Child-Pugh class C disease (Table 2). Bariatric surgery is still an option in the setting of cirrhosis, and for some patients may hold opportunity to achieve successful weight loss. Child-Pugh (CP) class and Model of End-Stage Liver Disease (MELD) scores have been associated with preoperative risk; CP A disease is thought to not result in higher risk for liver-specific complications with surgery compared to those without cirrhosis and thus these patients should be considered for bariatric surgery [55, 56].

Patients with cirrhosis have limitations on interventions to achieve weight loss, in particular owing to impaired hepatic metabolism of drugs, but also due to the higher risk of mortality among patients with cirrhosis undergoing bariatric surgery [57]. However, bariatric surgery in compensated patients is considered safe and has been associated with weight loss of up to 67.7% excess weight after 12 months [58]. Thus, addressing weight before hepatic decompensation occurs is key in preventing of further morbidity from NASH cirrhosis. In those with decompensated cirrhosis, meal replacement therapy is a consideration; however, noting that the prevalence of malnutrition is high in patients with cirrhosis and is associated with increased mortality [53, 59]. Thus, nutritional needs will vary based on both the patient's metabolic needs relative to risks associated with cirrhosis during weight loss [60].

Referral for Bariatric Endoscopy or Surgery

The decision to pursue endoscopic surgical treatment for weight loss is highly personalized and requires patient-

centered decision making. However, patients should also understand that referral for bariatric endoscopy or surgery evaluation is not simply a commitment to undergo surgery, but rather is the initiation of a discussion to better understand the nature and risks associated with these procedures before any decision is made. Financial payment structures for bariatric endoscopy is emerging but is overall still in development, whereas bariatric surgery coverage eligibility has been standardized in the setting of obesity (BMI ≥ 35 with obesity complication, or BMI ≥ 40), in the setting of failure of initial weight loss efforts after a patient-defined time period.

Endoscopic bariatric therapies (EBTs) are being developed as a nonsurgical treatment for obesity and have been found to be additionally effective for NAFLD. On a single-center study, Nguyen and colleagues found 11.3 kg weight loss, BMI reduction by 4.1 kg/m^2, and improvements in ALT and insulin resistance in 135 patients with obesity and NAFLD 6 months after endoscopic intragastric balloon placement [61]. A recent clinical practice update established best practices, including consideration of EBT as a bridge to traditional bariatric surgery [62••].

Bariatric surgery is associated with marked benefits for NAFLD, including histological improvement in steatosis, steatohepatitis, and fibrosis. In a systematic review and meta-analysis of 15 studies, Mummadi and colleagues observed high pooled improvement or resolution rates for steatohepatitis (91.6%), steatohepatitis (81.3%), and fibrosis (65.5%) after bariatric surgery [63]. Bariatric surgery additionally can provide improvements in other cardiovascular risk factors including insulin sensitivity, diabetes mellitus, hypertension, and dyslipidemia [64–67]. No specific bariatric surgery has been found to be superior for NAFLD, as no differences were reported in a prospective study of 381 patients followed for 5 years after biliointestinal bypass, gastric bypass, or gastric band surgery, though the NAFLD cure rate (reduction to ≤ F1 fibrosis) was found to be 95.7% [68]. Although no clear surgery has been found to be more effective for NAFLD, taken as a class, the bariatric surgeries are associated with marked weight loss (≥ 20%), and with cure of multiple comorbidities including diabetes, dyslipidemia, hypertension, and hyperuricemia [64–67]. Depending on the patient's weight loss goal, more weight loss would lead to a higher likelihood of NAFLD cure, in conjunction to other obesity-related complications. As weight loss is urgent in those with advanced fibrosis or cirrhosis, and patients may be in a narrow window of opportunity to receive surgery before their comorbidity renders them ineligible due to high risk. Unfortunately, one of the biggest barriers to bariatric surgery is insurance-mandated preoperative weight loss requirements, which have not been shown to improve postoperative weight loss outcomes, but may delay surgery—often to the detriment of patients [69]. In these patients, early referral is key.

Weight Loss Maintenance and Preventing Regain

The challenging nature of weight loss, even with medical interventions, is underscored by the finding that successful weight loss of ≥ 5% is ultimately achieved by only approximately 20% of patients [46]. Several factors have predicted successful weight loss maintenance, defined as weight loss of ≥ 1 year, which has included physical exercise ≥ 30 min/day [69, 70], self-monitoring [71, 72], reduced television time < 10 h/week [73], and support groups or continued contact from providers [74, 75•]. Further contributing to the challenges of sustained lifestyle changes for weight loss, with initial weight loss, metabolic adaptation occurs whereby counter-regulatory hormones are secreted to re-establish higher body weight as well as adaptive thermogenesis (collectively termed the metabolic "set point"), and have been found to persist for years [76–78]. This "set point" phenomenon is thought to be a contributing factor for weight regain and may hinder weight loss maintenance, resulting in weight fluctuations or "cycles" after initial weight loss. For patients using medications for weight loss, long-term medication use is often required as weight regain after discontinuation is common. In a large systematic review and meta-analysis of 80 studies of long-term follow-up after weight loss interventions, Franz and colleagues found that addition of weight loss medications modestly enhances weight loss maintenance at 24 months [79]. Weight loss medications could therefore be considered in patients experiencing weight regain or plateau in the course of weight loss efforts.

Conclusion

NAFLD is the most common liver disease in the world, owing to its underlying pathogenic relationship to obesity. Even as future therapies become available, it remains essential to address excess weight as the underlying etiologic factor of this disease. With optimization of patient lifestyle changes, leveraging behavioral and pharmacological interventions to treat excess weight, patients can achieve improvement in not just liver disease, but in multiple realms given the numerous, multisystemic conditions which are known to be due to excess weight.

Medical management for weight loss includes a patient-centered approach including establishing a therapeutic alliance, assessing patient weight loss and behavioral change goals, as well as counseling regarding hepatic fibrosis staging, weight loss goals in NAFLD, and lifestyle changes including diet and exercise. Weight loss medications can be helpful in patients who desire additional weight loss and who are unable to achieve success with lifestyle changes alone, or in the setting of weight loss plateau or regain. Consideration for bariatric endoscopy or surgery evaluation should be made for eligible patients meeting coverage criteria and who are at high risk

for complications associated with NAFLD (advanced fibrosis, cirrhosis, other medical complications associated with excess weight). After successful weight loss, weight loss maintenance is key and can generally be achieved with a combination of sustainable behavioral changes, exercise, and addition of medications if weight loss plateau or weight regain occurs. Finally, even as medications for NASH are developed, management for weight loss is still needed to provide added hepatic benefit while additionally treating the multisystemic complications associated with excess weight.

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Compliance with Ethical Standards

Conflict of Interest Albert Do, Ysabel C. Ilagan-Ying, and Wajahat Z. Mehal each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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