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REVIEW

Treatments for obesity in the context of nonalcoholic steatohepatitis and mental health

Aadi Sharma, BA[1] | **Somaya Albhaisi, MBBCh, MD**[2] | **Arun J. Sanyal, MBBCh, MD**[3]

[1]University of Virginia, Charlottesville, Virginia, USA

[2]Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

[3]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia, USA

Correspondence
Somaya Albhaisi, Department of Internal Medicine, Virginia Commonwealth University, 1250 E. Marshall St., Richmond, VA 23298, USA.
Email: somaya.albhaisi@vcuhealth.org

INTRODUCTION

The association between nonalcoholic steatohepatitis (NASH), obesity, and mental health is related to psychological, biological, and inflammatory factors. It has been suggested that treatments for weight loss and other risk factors of NASH may help minimize development of the disease.[1] Because obesity is linked with mental health disorders and is a major risk factor for NASH, weight loss treatment requires multifaceted approaches. In addition to the companion article in this issue of *Clinical Liver Disease*, "Behavioral Health Disorders Related to Nonalcoholic Steatohepatitis," we highlight in this review the nonpharmacological and pharmacological strategies for weight loss in the context of NASH and mental health disorders.[2]

Nonpharmacological strategies

Targeting behaviors through group or individual weight intervention sessions in which patients undergo nutritional education, track calories, increase physical activity, and alter detrimental thinking helps instill habits to resolve weight gain.[1] Studies have shown metabolic and hormonal changes in response to exercise, although no singular exercise strategy is emphasized. Recommendations by the Institute of Medicine of the National Academies of Science entail 60 min of daily exercise, and the American College of Sports Medicine emphasizes 20–60 min of exercise, three to five times a week, with remaining at 55%–90% maximum heart rate. Exercise may increase leptin sensitivity, thus playing a role in moderating inflammation and food intake. A common consensus is that extended duration and moderate intensity are most relevant factors when considering exercise for weight loss.[3] Regarding diet, studies have shown that caloric deficits led to fewer depressive symptoms and weight loss. Within these altered diets, low-carbohydrate and -fat meals rich with fruits, vegetables, nuts, and whole grains are encouraged, as seen in Mediterranean diets. In contrast, western diets with high glycemic loads and processed foods are discouraged. Reduction of fat via lifestyle changes may circumvent inflammatory processes that occur because of accumulation of adipose tissue.[4] However, bidirectional relationships between mood disorders and obesity exist, wherein the presence of one condition increases susceptibility to the other, hence the likelihood for relapse is greater in patients with psychiatric disorders. Psychotherapies such as cognitive-behavioral therapies (CBTs) may target the deficits in weight-management interventions by helping patients manage their anxiety and depression in conjunction with providing weight loss strategies.[1] An alternative or complement to CBT is mindfulness techniques, specifically acceptance and commitment therapy (ACT). So far, ACT has been used in studies only. ACT works to remove behaviors that seek avoidance or control and accentuates behaviors to focus on positive outcomes. Because emotional eating as a result of stress is considered avoidance, ACT targets it for weight management or loss purposes.[5] A lesser studied technique called transcranial direct current stimulation applies a low-intensity current to the left dorsolateral prefrontal cortex, which has a role in

regulating food consumption, food choice, and reward processing. Results have shown a decrease in food craving; however, minimal studies have been done reporting change in body weight.[3] Bariatric surgery is recommended primarily for patients with a body mass index of 40 or at least 35 in the presence of comorbidities such as type 2 diabetes mellitus or obesity-related cardiomyopathy.[1] It is important to note that the rates of suicide are significantly increased after bariatric surgery,[6] and also rates and severity of alcohol use disorder worsen after bariatric surgery.[7,8] Many insurance companies require a battery of psychiatric testing prior to being approved for bariatric surgery. These data underscore the need for careful evaluation of the underlying psychopathology in individual patients with obesity and nonalcoholic fatty liver disease before recommending a specific therapy. Further, the behavioral factors that may affect compliance should be evaluated and addressed to maximize the likelihood of a sustained change in lifestyle. Finally, we have recently demonstrated a high prevalence of NASH in spouses and partners of patients with NASH, including those with cirrhosis, suggesting a role for shared diet and microbiome.[9] It is our clinical experience that engagement with the family unit in lifestyle change has a greater likelihood of long-term success.

Pharmacological strategies

Pharmacotherapies targeting dopaminergic pathways have been proposed because it is hypothesized that excessive or too little dopamine leads to overeating. Dopamine-blocking medications are not recommended because of side effects such as suicidal ideations.[10] Opioid antagonists have been used to mitigate the reward system of the brain with opioid addiction, and similar application to reduce food intake by removing the satisfaction from food has been tested, but their clinical significance is mixed.[10] A combination of naltrexone and bupropion has demonstrated clinical significance in weight loss, where bupropion prevents reuptake of dopamine and naltrexone acts as an opioid agonist.[11,12]

Phentermine/topiramate is a long-acting combination of an appetite suppressant, phentermine, and a drug that acts on the nervous system, topiramate. The exact mechanism of action causing weight loss is not completely clear, but it is thought to be related to appetite suppression and increased satiety through multiple mechanisms, including increased secretion of epinephrine in the hypothalamus, increased γ-amino-butyrate neurotransmitter activity, ion channel modulation, 5 carbonic anhydrase inhibition, and impact on energy intake and thermogenesis.[13,14] Although phentermine/topiramate is US Food and Drug Administration (FDA) approved, the European Medicines Agency refused the approval of the drug because of concerns for long-term side effects and adverse psychiatric and cognitive outcomes.[13,15]

Like drugs targeting dopamine, serotonergic drugs seek to lessen the compulsion for disproportionate eating; however, unlike the former, they are more likely to be considered as possible treatments.[10] Lorcaserin is an anorexic agent that functions as a serotonin agonist and has shown reduction in weight. This drug has, however, been removed from the market because of concerns regarding carconogenecity.[16]

Liraglutide is an injectable glucagon-like peptide 1 (GLP-1) derivative that was approved by the FDA in 2014 for weight management. Liraglutide acts at both central and peripheral levels. Centrally, it acts on the GLP-1 receptor in the hypothalamus and stimulates proopiomelanocortin-, cocaine-, and amphetamine-regulated transcript neurons, leading to suppression of appetite.[13,17,18] It also indirectly inhibits appetite-stimulating neurons, thereby reducing appetite and promoting weight loss.[13,18] Peripherally, liraglutide delays gastric emptying and regulates glucose homeostasis by promoting the balance between insulin and glucagon secretion.[14,19]

Semaglutide is another GLP-1 receptor agonist approved for the treatment of type 2 diabetes, and it received FDA approval in 2021 for use in weight management.[20] Semaglutide has a mechanism of action that is similar to that of liraglutide but with superior metabolic efficacy.[21–23] Previous studies have shown that semaglutide was associated with improvement in body weight and glycemic control in patients with obesity and type 2 diabetes mellitus.[23,24] Semaglutide was also associated with reduced rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes mellitus.[25] Furthermore, semaglutide significantly reduced levels of alanine aminotransferase and markers of inflammation.[26] A phase 2 trial involving patients with NASH showed that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo.[27]

Unfortunately, some medications for mental health disorders can lead to weight gain (Table 1). Second

TABLE 1 Medications associated with weight gain

Weight gain	Little to no weight gain
MAOIs	SSRIs (sertraline, fluoxetine)
SSRIs (paroxetine)	Bupropion
Tricyclic antidepressants (nortriptyline, imipramine, doxepin, amitriptyline)	
Lithium	
Mirtazapine	
Second generation antipsychotics (atypical antipsychotics)	

generation antipsychotic–induced changes of hormone regulation, such as that of leptin, have been implicated in weight gain, in addition to potentially increasing triglyceride storage, altering hypothalamic serotonin function, or leading to insulin resistance.[28]

CONCLUSION

Obesity and mental health in the setting of NASH may be combatted through pharmacological or nonpharmacological methods, and finding the balance between the two is necessary to mitigate detrimental side effects and ensure consistent results.

CONFLICT OF INTERESTS

A.S. and S.A. have no conflicts of interest. A.J.S. is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, and Hemoshear. He has served as a consultant to Astra Zeneca, Conatus, Coherus, Bristol Myers Squibb, Blade, Tobira, Takeda, Siemens, Merck, Genentech, Tern, Gilead, Lilly, Poxel, Artham, Boehringer Ingelhiem, Novo Nordisk, NGM Bio, Birdrock, Novartis, Pfizer, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Perspectum, Immuron, Galectin, Fractyl, Affimune, Chemomab, and Nordic Bioscience. His institution has received grant support from Gilead, Salix, Tobira, Intercept, Bristol Myers, Shire, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Novartis. He receives royalties from Elsevier and UptoDate.

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