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Psychological and Psychiatric Aspects of Treatment of Obesity and Nonalcoholic Fatty Liver Disease

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Chronic illnesses incur a tremendous cost to American lives in both dollars and quality of life. Outcomes in these illnesses are often affected by psychological, behavioral, and pharmacologic issues related to mental illness and psychological symptoms. This article focuses on psychological and psychiatric issues related to the treatment of obesity and NAFLD, including available weight-loss interventions, the complex relationship between psychiatric disorders and obesity, and special considerations in the use of psychiatric drugs in patients with or at risk for NAFLD and obesity. Recommendations for collaborative care of individuals with comorbid NAFLD and psychological disorders/symptoms are discussed.

OBESITY AND NAFLD

NAFLD affects an estimated 20% to 30% of adults living in Western countries, with up to 80% of obese individuals being affected.¹ Prospective studies have documented that among individuals initially free of NAFLD, persons who developed NAFLD over the course of a 7-year follow-up had higher baseline body mass index (BMI; calculated as weight in kilograms divided by height in meters squared, ie, kg/m²) and gained more weight than those who did not.² In persons with documented NAFLD, weight gain is associated with progression of liver fibrosis over long-term (13.8 ± 1.2 years) follow-up,³ and weight loss, whether achieved through lifestyle change or medication, is associated with improvements in liver histopathology. Specifically, weight losses of 7% and more are associated with improved NAFLD Activity Score (NAS; a scoring system comprising 14 histologic features) whereas losses of 5% and greater are associated with improvement in steatosis only.⁴ Thus, weight management is a critical component of care for the patient with NAFLD.

Obesity is a complex condition that calls for a multidisciplinary approach. Many disciplines (eg, genetics, neuroscience, endocrinology, psychology, public health) have identified factors that contribute to the risk of developing obesity; however, considerable work remains in determining its optimal prevention and treatment. Available treatment options for obesity

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include bariatric surgery, medications, and behaviorally based lifestyle interventions. Each of these options presents unique benefits and drawbacks, and each carries a risk of long-term weight regain, emphasizing the need for further research in promotion of long-term weight management.

WEIGHT-LOSS INTERVENTIONS

Weight-loss medications serve to reduce body weight by reducing appetite, increasing satiety, reducing absorption of nutrients, or increasing energy expenditure. On average, these medications can produce statistically significant, albeit modest weight loss (generally 2–7.9 kg compared with placebo); however, the lost weight most often is regained after the medication is discontinued. No weight-loss medication has been demonstrated to be safe, effective, and well-tolerated for long-term use. Many of these medications have suffered unfavorable risk-benefit profiles or serious adverse events over long-term use, and have ultimately been removed from the market (eg, fenfluramines, rimonabant, dinitrophenol, aminorex, and sibutramine). Several medications have been prescribed off-label for weight loss (fluoxetine, bupropion, topiramate), but randomized clinical trial data are lacking. At present, diethylpropion (an amphetamine-like analogue) and phentermine (a 5-hydroxytryptamine agonist) are approved by the Food and Drug Administration (FDA) for short-term use (up to 12 weeks), and only orlistat (a lipase inhibitor) is approved for long-term use. Unfortunately, weight loss with orlistat is relatively modest, and is not well tolerated because of unpleasant gastrointestinal side effects.⁵ In comparing patients with nonalcoholic steatohepatitis (NASH) receiving diet and vitamin E therapy with or without the addition of orlistat, the orlistat group lost slightly more weight than the comparison group (8.3% vs 6.0% of initial body weight); however, this difference was not significant nor did the groups differ in their improvement in serum aminotransferases, steatosis, necroinflammation, ballooning, or NAS scores.⁶

Bariatric surgery is a treatment for high-risk individuals with clinically severe obesity. Current standards remain consistent with the 1991 recommendations delivered by the National Institutes of Health Consensus Development Conference Panel.⁷ These guidelines recommend that to be a surgical candidate, a patient should have a BMI of 40 or greater, or a BMI of at least 35 if the individual has serious weight-related comorbidities (eg, severe obstructive sleep apnea, type 2 diabetes mellitus, or obesity-related cardiomyopathy). Weight loss after bariatric surgery varies according to type of surgery, and ranges from 48% of excess body weight (gastric banding) to 70% of excess body weight (bypass procedures).⁸ Pooling across surgery types, approximately 92% of patients demonstrate improvement or resolution of steatosis following surgery, with 82% experiencing resolution or improvement of NASH and 66% experiencing improvement in fibrosis.⁹

Behaviorally based weight-management interventions commonly include weekly group or individual sessions for 6 months to a year. These programs focus on energy balance by increasing physical activity and reducing calorie intake, and teach specific behavioral skills for achieving these goals. Specifically, these interventions combine nutritional education with behavioral interventions including self-monitoring, changing environmental cues for overeating and inactivity, problem solving, goal setting, planning, restructuring maladaptive

thinking patterns, and relapse prevention. Self-monitoring (ie, writing down one's daily food intake and physical activity, and tracking one's weight) is a central component of these interventions and appears to be an important predictor of long-term maintenance of weight loss.¹⁰ Weight loss in such programs averages 9 kg or approximately 10% of initial body weight.¹¹ Weight regain commonly occurs when the intervention ends; however, extended contact with the provider can help sustain lifelong adherence to healthy eating and physical activity behaviors. Thus, obesity must be considered a chronic health problem, and some level of ongoing support is likely necessary to maintain treatment effects in the long term.¹² These interventions can be translated into Internet-based delivery systems and are capable of producing meaningful weight loss, although the average weight loss in such programs appears to be modest (4–7 kg) compared with traditional in-person behavioral programs.¹³ Internet and mobile technologies nonetheless represent a ripe area for wide dissemination of such interventions. Another important priority in behavioral weight-management research is on improving outcomes by tailoring interventions to individual patient need.

SUBOPTIMAL WEIGHT LOSS AND WEIGHT REGAIN IN WEIGHT-LOSS PROGRAMS

In each of these types of weight-loss programs, a significant proportion of individuals either fail to achieve significant weight loss or regain weight following the initial stages of treatment. For example, fewer than 50% of individuals in 2 randomized clinical behavioral weight-loss trials in NAFLD achieved the 7% weight loss associated with improved outcomes.^{14,15} Weight loss following bariatric surgery is maximal at 1 year, at which point progressive weight regain commonly begins (eg, $38\% \pm 7\%$ of initial body weight following gastric bypass at 1 year becomes $25\% \pm 11\%$ net loss at 10 years after gastric bypass). A deterioration in some of the specific health benefits of weight loss seems to accompany this weight regain, although an overall reduced risk of mortality is seen in bariatric samples compared with matched individuals receiving usual care of obesity.^{16,17} These findings highlight the need for a greater understanding of the psychosocial forces that contribute to suboptimal weight loss and weight regain.

RELATION BETWEEN PSYCHIATRIC DISORDERS AND OBESITY

Weight-loss intervention trials typically exclude individuals with severe psychopathology (defined, eg, by Lazo and colleagues¹⁵ as hospitalization for depression within the past 6 months and current diagnosis of psychotic or bipolar disorder; and by Promrat and colleagues¹⁴ as psychiatric problems significant enough to prevent participation). Less severe psychiatric problems and eating disorders are often not tracked or reported in these trials, and the presence of these conditions may partially account for weight-loss outcomes. The following sections review the relation between different psychiatric conditions and obesity and the impact of these conditions on outcomes in weight-management programs.

Mood/Anxiety Disorders

Relation to obesity—Mood disorders are associated with a greater risk of obesity after controlling for the use of psychotropic medications that can cause weight gain.¹⁸ Unipolar

depression and obesity demonstrate a bidirectional relationship; that is, the presence of either condition at baseline confers a greater risk of developing the other condition in prospective analyses.^{19,20} Increased prevalence of overweight has been noted in an Italian sample of drug-naïve patients with bipolar disorder (40.8% compared with the national rate estimated to be ~16% during the time of data collection).²¹

A past-year diagnosis with an anxiety disorder is also associated with increased risk of obesity.¹⁸ A large population-based sample recently demonstrated that a past-year diagnosis of posttraumatic stress disorder (PTSD) is associated with increased risk of obesity compared with individuals with no lifetime history of PTSD after adjusting for psychotropic medication use, sociodemographic factors, and depression.²² Obesity was associated with a past-year history of panic attacks in men participating in a large Canadian nationally representative survey. For women participating in this survey, obesity was associated with a past-year history of social phobia or lifetime history of agoraphobia without panic disorder.²³

Impact on outcomes in weight-loss interventions—Depression is relatively common in individuals seeking behavioral weight-management services, and depressed individuals have poorer weight-loss outcomes when participating in these interventions. In one clinic-based program, 17% of treatment-seeking obese individuals were diagnosed with major depression. Only 16% of depressed individuals met the program goal of losing 7% or more of initial body weight, compared with 38% of nondepressed participants meeting this goal. Depressed individuals may be more likely to drop out of a weight-loss program,²⁴ and depressive symptoms are a risk factor for weight regain.¹⁰ Fortunately, it appears that depressed individuals experience a significant reduction in depressive symptoms when participating in a behavioral weight-management program. Exercise-only interventions also appear to have a slightly more modest, but significant positive impact on depressive symptoms.²⁵

Eating Disorders

Relation to obesity—Binge-eating disorder (BED) and night-eating syndrome (NES) are commonly associated with increased BMI. BED is not a formal diagnosis in the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised) (DSM-IV), but is included as a diagnosis for further study.²⁶ BED, a condition characterized by binge eating without the use of compensatory strategies (eg, vomiting, laxative use, over-exercising) has been recommended by the Eating Disorders Workgroup for inclusion in the forthcoming DSM-V.²⁷ BED is estimated to occur in 2% of the general population, and in from 10% to 20% of patients in obesity clinics. Rates of BED in patients seeking bariatric surgery have been variable (6%–47%).²⁸ This variability likely is due to inconsistencies in assessment methods and diagnostic criteria, and these rates are much lower when gold-standard assessment tools and strict diagnostic criteria are used (eg, 4.2%–6.6% in a rigorously assessed bariatric sample).²⁹ Although obesity is not required for a diagnosis of BED, the two are closely related, with 42.4% of individuals with BED qualifying as obese (BMI ≥ 30) in a national comorbidity study.³⁰

NES is a condition not currently included in the DSM-IV. The core feature of this condition is excessive nighttime eating defined as at least 25% of food intake occurring after the evening meal and/or waking during the night to eat. This condition is frequently accompanied by morning anorexia, sleep difficulties, and worsening mood during evening hours.³¹ NES is estimated to occur in 1.5% of the general population, in 9% to 14% of treatment-seeking obese individuals, and in 9% to 42% of bariatric surgery candidates.²⁸ As with BED, rates of NES are typically lower in samples where strict diagnostic criteria and rigorous assessment methods are used (eg, 1.9%–8.9% in a bariatric sample).²⁹ Although rates of NES are elevated in samples of persons with weight problems, the prevalence of obesity in those with NES remains equivocal, partly because of variability in defining this condition.³²

Impact on outcomes in weight-management interventions—The presence of BED is associated with poorer weight-loss outcomes in weight-loss studies.²⁴ However, individuals with BED have reported rather unstable recent weight histories on enrolling in treatment cohorts. For example, participants reported gaining an average of 4.3 kg (range –18.1 kg to +28.1 kg) in the year before initiating therapy. Thus, maintaining a stable weight or losing a modest amount of weight might represent a significant improvement for individuals with BED as they gain control over their eating patterns.³³ CBT for BED is superior to behavioral weight management in achieving abstinence from binge eating; however, weight-loss outcomes in CBT are poorer than those seen in weight-management interventions.³⁴ A recent study compared CBT with behavioral weight loss and a sequenced CBT followed by behavioral weight-loss intervention. As expected, CBT was superior for abstinence from binge eating, behavioral weight loss was superior for weight loss, and the sequenced program did not improve results on either outcome. Thus, patients will likely benefit most from either CBT or behavioral weight loss, and treatment selection may best be determined by the patient's preferred treatment goal.

Other Psychiatric Disorders

Relation to obesity—Whether schizophrenia contributes to risk of obesity independent of the effect of the use of psychotropic medication remains uncertain. One study has documented increased BMI, visceral fat, and plasma cortisol in drug-naïve and drug-free schizophrenics compared with age-matched healthy controls. This sample was small (n = 15 schizophrenics, 7 were drug naïve and 8 were drug free), however, and drug free was defined as no oral neuroleptics for 6 weeks and no intramuscular treatments for 6 months,³⁵ so the generalizability of these findings is limited.

Attention-deficit/hyperactivity disorder (ADHD) has also been demonstrated to be associated with greater likelihood of being overweight or obese in a nationally representative sample, and the relationship between ADHD and obesity appears to be partially accounted for by associated BED.³⁶

Impact on outcomes in weight-management interventions—Individuals with schizophrenia are often not included in standard weight-management programs, although several studies have evaluated medications to prevent/treat antipsychotic medication-related

weight gain. Metformin has shown the greatest weight-loss potential (mean -2.94 kg) compared with placebo in these patients.³⁷ Some of these studies have combined lifestyle intervention with medication treatment, and this combination appears to improve outcomes more than medication therapy alone.³⁸

POTENTIAL MECHANISMS LINKING MENTAL HEALTH AND OBESITY

In addition to weight gain associated with psychotropic medications, several common factors may contribute to the risk of both obesity and psychiatric disorders, including habitual inactivity, neuroinflammation, insufficient access to health care, alterations in neurometabolism, and oxidative stress.³⁹ Psychiatric illnesses also alter behavioral patterns in ways that could increase the risk of obesity. A large study using United States national representative data found that the link between major depression and obesity in women may be accounted for by shifts in food intake and physical activity levels.⁴⁰ Analysis of the 1999 Large Health Survey of Veterans ($N = 501,161$) revealed that compared with their healthy peers, veterans with schizophrenia, PTSD, or bipolar disorder were at elevated risk of reporting a pattern of poor health behaviors, defined as the co-occurrence of obesity, inactivity, and current smoking.⁴¹

PSYCHOTHERAPIES

The evidence base for cognitive-behavioral therapies (CBT) for mood, anxiety, and eating disorders is quite strong (see Ref.⁴² for a review of meta-analyses). CBT emphasizes the links between thoughts, feelings, and behaviors, and seeks to guide patients to bring about improvements in mood and psychosocial functioning through altering maladaptive patterns of thought and behavior. One meta-analysis of direct comparisons of CBT against psychiatric medications for the treatment of anxiety and depression concluded that these 2 treatment modalities appear to have roughly comparable short-term outcomes, with an advantage for CBT in the treatment of panic disorder and a small nonsignificant advantage for medication in the treatment of social anxiety.⁴³ Other types of efficacious psychotherapies include interpersonal psychotherapy, problem-solving therapy, nondirective supportive therapy, behavioral activation therapy,⁴⁴ social skills training, and psychodynamic therapies.⁴⁵

THE USE OF PSYCHIATRIC DRUGS IN PATIENTS WITH NASH

The major relevant clinical issues regarding the use of psychiatric drugs in patients with NASH include the effects of liver disease on pharmacokinetics; the potential adverse effects of hepatotoxicity, weight gain, glucose intolerance, and hyperlipidemia; and potential drug interactions with statins and other hypolipidemic drugs.

Effects of Liver Disease on Pharmacokinetics

Most psychiatric drugs are eliminated via metabolism by the liver and/or excretion by the kidney. There are 2 phases of hepatic metabolism: phase I metabolism consists of oxidation (ie, cytochrome P450 system), reduction, or hydrolysis, and phase II metabolism consists of conjugation (glucuronidation, acetylation, and sulfation). Clearance of drugs may be limited

by either the rate of delivery (ie, hepatic blood flow) of the drug to the liver or the capacity of hepatic enzymes to metabolize the drug. Clinically significant decreases in hepatic blood flow occur only in severe cirrhosis, whereby portosystemic shunting reduces metabolic capacity.

Early fatty liver disease (steatosis) usually does not require dose alteration of psychiatrics, but steatohepatitis may require dosage adjustment depending on the severity of liver dysfunction. In patients whose disease has progressed to cirrhosis, drug dosing will require significant modification. All plasma proteins are synthesized in the liver, so protein binding is altered in liver disease. The main clinical significance of this is that in chronic severe liver disease, blood levels of psychiatrics that bind to plasma proteins (eg, tricyclic antidepressants and α 1-acid glycoprotein) must be interpreted while taking into account the reduction in protein binding. When prescribing hepatically metabolized psychiatric drugs to patients with impaired liver function, it is advisable to reduce the initial dose and titrate more slowly. For more detailed reviews of these principles, see Ferrando and colleagues,⁴⁶ Crone and colleagues,⁴⁷ and Owen.⁴⁸

Antidepressants

Antidepressant drugs are used to treat mood, anxiety, eating, and some somatoform disorders as well as insomnia, enuresis, incontinence, headaches, and chronic pain. All antidepressants rarely can cause idiosyncratic hepatotoxicity. Because severe hepatotoxicity appeared to be more common with nefazodone, it was removed from the market in many countries (it is still available generically in the United States), and it should not be used in patients with preexisting liver disease.⁴⁹ Reports of duloxetine-associated hepatotoxicity in 1% of patients prompted product warnings, but a subsequent review suggests hepatotoxicity is no more common with duloxetine than with other antidepressants.⁵⁰

Weight gain is a relatively common problem during both acute and chronic treatment with antidepressants. Tricyclic antidepressants (TCAs) and mirtazapine most commonly cause weight gain, which is less common with serotonin reuptake inhibitors (SSRIs), and even less so with serotonin-norepinephrine reuptake inhibitors (SNRIs). Bupropion is the only antidepressant that appears to never cause weight gain.⁵¹

In the absence of weight gain, antidepressants do not cause glucose intolerance, but there is reason to think that SSRIs might (slightly) improve glucose metabolism. However, in diabetic patients with neuropathic pain, TCAs or SNRIs are preferred for their analgesic effects.

Several antidepressants, including mirtazapine, paroxetine, and sertraline, have been reported to increase low-density lipoprotein (LDL) cholesterol, but this effect appears to be linked to weight gain.^{52,53}

All antidepressants are extensively metabolized by the liver, resulting in decreased clearance and prolonged half-life in patients with significant hepatic dysfunction. In such patients the starting dose should be reduced 50% and maintenance doses should also be reduced.

Fluoxetine has an especially long half-life (because of the long half-life of its

pharmacologically active metabolite norfluoxetine), and may require dosing less often than daily. Anticholinergic TCAs may precipitate or aggravate hepatic encephalopathy in patients with cirrhosis through anticholinergic central nervous system effects and through slowing gastrointestinal transit.

Lithium

Lithium is used to treat bipolar disorder, and in treatment-resistant depression to augment antidepressant response. Lithium does not have any hepatotoxicity. Weight gain is the second most common reason cited by patients for lithium noncompliance.⁵⁴ Increased thirst and polyuria are nearly universal side effects caused by lithium's blockade of antidiuretic hormone in the kidney, and some of the weight gain in patients taking lithium has been attributed to increased consumption of high-calorie fluids in response to thirst.⁵⁵ Another possible contribution to weight gain with chronic lithium treatment is overt (8%–10%) or subclinical hypothyroidism (20%). In the absence of weight gain and hypothyroidism, lithium does not cause glucose intolerance or hyperlipidemia.

Although lithium is excreted entirely by the kidney, its use may be difficult in patients with advanced cirrhosis because of fluid shifts due to ascites, diuretics, secondary hyperaldosteronism, and gastrointestinal bleeding, as well as other changes in renal function.

Anticonvulsant Mood Stabilizers

Anticonvulsant mood stabilizers (not all anticonvulsants) are used to treat bipolar disorders as well as chronic pain. Valproate, carbamazepine, and oxcarbazepine are the most commonly used anticonvulsant mood stabilizers for the treatment of mania, and lamotrigine for bipolar depression. Anticonvulsants commonly cause transient elevations in liver enzymes.⁵⁶ Significant changes in liver function are usually reversible with dosage reduction or discontinuation, but fatal hepatotoxicity has been reported with valproate and carbamazepine. The risk of hepatic failure may be increased by combination therapy and/or the presence of chronic liver disease.⁵⁷

Weight gain is a common cause of noncompliance, especially with valproate. Carbamazepine less commonly causes weight gain, lamotrigine has little effect on weight, and topiramate causes a small weight loss.^{58–60} In the absence of weight gain, anticonvulsants appear to have little effect on glucose or lipid metabolism.

Most anticonvulsants are extensively metabolized by the liver, resulting in decreased clearance and prolonged half-life in patients with significant hepatic dysfunction. Lower starting and maintenance doses are advisable. Oxcarbazepine requires less dose reduction than carbamazepine. Gabapentin and pregabalin are renally excreted, and dose adjustment is not necessary unless renal function is impaired.

Antipsychotics

Antipsychotics are used to treat schizophrenia, bipolar disorder, treatment-resistant depression and anxiety disorders, delirium, and psychosis in patients with dementia. Liver enzyme elevations during antipsychotic therapy have long been reported but seldom require

drug discontinuation. If present, mild to moderate elevations in hepatic aminotransferases and alkaline phosphatase usually occur early in treatment and are unlikely to result in hepatic dysfunction. Cholestatic jaundice is a rare idiosyncratic reaction reported with phenothiazines.

Almost all antipsychotics can cause weight gain, to varying degrees. Among the older typical antipsychotics, the greatest risk of weight gain is with low-potency agents such as thioridazine and chlorpromazine. Molindone appeared to be the only typical antipsychotic that did not cause weight gain, but this agent is no longer available in the United States. With some of the newer atypical antipsychotics, substantial weight gain has been a serious clinical problem. The greatest to least likelihood of weight gain is: clozapine > olanzapine >> quetiapine > risperidone = paliperidone > aripiprazole > ziprasidone.⁶¹

The atypical antipsychotics have been reported to cause hyperglycemia, new-onset type 2 diabetes, and occasionally ketoacidosis. These effects are not solely explained by weight gain. Patients may also be at risk because schizophrenia and bipolar disorder are themselves associated with increased risk for type 2 diabetes. Similar to the risk for weight gain, the relative risk for causing or aggravating glucose intolerance is: clozapine = olanzapine > quetiapine > risperidone.⁶² It is not clear that ziprasidone and aripiprazole cause hyperglycemia, but the FDA warning has been applied to the entire class of atypical antipsychotics.

Phenothiazines (eg, chlorpromazine), but not butyrophenones (eg, haloperidol) have long been known to elevate serum levels of cholesterol and triglycerides. The risk of hyperlipidemia among atypical antipsychotics is highest with clozapine, olanzapine, and quetiapine, and lowest with risperidone, ziprasidone, and aripiprazole.⁶³ Thus, in a patient with NASH the preferred antipsychotics would be those least likely to cause weight gain, glucose intolerance, and hyperlipidemia, for example, ziprasidone and aripiprazole among the atypical antipsychotics, and haloperidol and fluphenazine among the typical antipsychotics. Guidelines for the use of atypical antipsychotics jointly developed by the American Diabetes Association and the American Psychiatric Association⁶⁴ require regular monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profile.

All antipsychotics are extensively metabolized by the liver, resulting in decreased clearance and prolonged half-life in patients with significant hepatic dysfunction. Lower starting and maintenance doses are advisable with all antipsychotics.

Benzodiazepines and Nonbenzodiazepine Sedatives

Benzodiazepines are used to treat anxiety disorders, sleep disorders, and alcohol withdrawal. Nonbenzodiazepine sedatives (eszopiclone, zopiclone, zolpidem, zaleplon) are prescribed for insomnia. Neither is associated with hepatotoxicity, weight gain, glucose intolerance, or hyperlipidemia. However, in patients with cirrhosis, benzodiazepines and nonbenzodiazepine sedatives (including barbiturates) can precipitate hepatic encephalopathy. Most benzodiazepines and nonbenzodiazepine sedatives are extensively metabolized by the liver. The exceptions are lorazepam, temazepam, and oxazepam, because they are metabolized predominantly by phase II conjugation, which is relatively preserved in

chronic liver disease, making them the preferred sedatives in patients with impaired liver function.

Buspirone

Buspirone is used to treat generalized anxiety disorder, and has no significant effects on hepatic function, weight, glucose, or lipid metabolism. Buspirone is extensively metabolized by the liver, so lower starting and maintenance doses are advisable in patients with impaired liver function.

Psychostimulants

Psychostimulants are used in the treatment of ADHD, narcolepsy, treatment-resistant depression, apathy, and analgesia augmentation in severe pain. The commonly prescribed psychostimulant medications include methylphenidate, various amphetamines, atomoxetine, modafinil, and armodafinil. Pemoline has been withdrawn in many countries including the United States because of its potentially fatal hepatotoxicity. Although psychostimulants may cause appetite suppression and weight loss, this is uncommon at therapeutic doses. Psychostimulants at therapeutic doses have no appreciable effects on hepatic function, glucose, or lipid metabolism. All psychostimulants are extensively metabolized by the liver, requiring dose reduction in patients with significant hepatic dysfunction. The exception is methylphenidate, which appears to be predominantly metabolized in the bloodstream.

Cholinesterase Inhibitors and Memantine

Tacrine is now rarely prescribed because of frequent reversible hepatotoxicity.⁶⁵ Other cholinesterase inhibitors and memantine are well tolerated, with no appreciable effects on hepatic function, weight, glucose, or lipid metabolism. While all of the cholinesterase inhibitors require hepatic metabolism, donepezil requires less dose adjustment than galantamine and rivastigmine. Memantine is primarily eliminated by the kidney and does not require dose adjustment in patients with liver disease.

Drug Interactions Between Hypolipidemic and Psychiatric Drugs

The statins are all substrates for CYP 3A4. Nefazodone and carbamazepine are potent 3A4 inhibitors and can raise statin levels significantly. Less strong inhibition of 3A4 occurs with norfluoxetine (primary metabolite of fluoxetine) and oxcarbazepine. Lovastatin, simvastatin, atorvastatin, and fenofibrate are inhibitors of P-glycoprotein, and can increase absorption of buspirone by a factor of 5 to 10.^{48,49} A summary of the potential hepatotoxicity, weight gain, glucose intolerance, hyperlipidemia, and metabolism/excretion with psychiatric medication is given in Table 1.

RECOMMENDATIONS FOR CLINICAL DECISION MAKING

NAFLD is a serious obesity-related condition, and bariatric surgery should be considered for patients with NAFLD and BMI of 35 or greater, as this treatment currently offers the greatest long-term potential for weight loss. Patients with a BMI less than 35 or who prefer nonsurgical weight loss should be referred for behavioral weight-management services. Group interventions or individual therapy with a behaviorally trained mental health

professional with experience in health behavior change can be effective in promoting and maintaining weight loss. Although individuals with depression and/or BED may have poorer weight-loss outcomes than others, they can lose weight and they may benefit both psychologically and physically by participating in a weight-management program. Interventions that sequence treatment to focus first on BED and then weight loss do not appear to enhance either weight loss or abstinence from binge-eating outcomes, thus patients should be referred for either BED treatment or weight-management–focused treatment according to their preference. Individuals with severe mental illness (eg, suicidal ideation, avolition, psychotic symptoms, severe anxiety) should, of course, be referred for psychological/psychiatric evaluation and treatment. Medications for weight loss are not recommended, as no existing options have been demonstrated to be both safe and effective for long-term use.

Optimal management of comorbid mental health and chronic illness problems requires a shift in our current treatment paradigm. Models that integrate medical and mental health care in the clinic setting have received growing interest in recent years and have been demonstrated to provide superior outcomes compared with usual care. Collaborative care models vary in their specific structure, but a program implemented at the University of Washington serves as an excellent example. In their intervention group, nurses, primary care physicians, a psychiatrist, and a psychologist collaborated in providing structured visits with patients with diabetes, coronary heart disease, or both conditions, and comorbid depression. Compared with usual care, the patients receiving collaborative care showed greater improvement in all 4 disease-outcome measures (glycated hemoglobin, systolic blood pressure, LDL cholesterol, and depressive symptoms). Collaborative care patients were also more satisfied with their care,⁶⁶ and satisfaction has been previously linked to better self-care behaviors and better outcomes.⁶⁷

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KEY POINTS

- Chronic illnesses incur a tremendous cost to American lives in both dollars and quality of life.
- Multiple psychiatric conditions are associated with increased risk of obesity and these conditions can interfere with efforts at weight loss.
- The major relevant clinical issues regarding the use of psychiatric drugs in patients with nonalcoholic steatohepatitis include the effects of liver disease on pharmacokinetics; the potential adverse effects of hepatotoxicity, weight gain, glucose intolerance, and hyperlipidemia; and potential drug interactions with statins and other hypolipidemic drugs.
- Optimal management of comorbid mental health and chronic illness problems requires a multidisciplinary approach and a shift in our current treatment paradigm.

Table 1

Psychiatric drugs in patients with NASH

Drug	Potential Hepatotoxicity	Weight Gain	Glucose Intolerance	Hyperlipidemia	Metabolism/Excretion
Antidepressants					
Tricyclics	Rare	++	-	-	Hepatic
SSRIs, SNRIs	Rare	+	-	-	Hepatic
Bupropion	Rare	-	-	-	Hepatic
Mirtazapine	Rare	++	-	-	Hepatic
Trazodone	Rare	++	-	-	Hepatic
Mood Stabilizers					
Lithium	-	++	-	-	Renal
Valproate	+	++	-	-	Hepatic
Carbamazepine	+	+	-	-	Hepatic
Oxcarbazepine	Rare	+	-	-	Hepatic
Lamotrigine	Rare	-	-	-	Hepatic
Antipsychotics					
Chlorpromazine	+	++	-	-	Hepatic
Haloperidol	Rare	+	-	-	Hepatic
Clozapine	+	+++	++	++	Hepatic
Olanzapine	Rare	+++	++	++	Hepatic
Quetiapine	Rare	++	+	+	Hepatic
Risperidone	Rare	+	-	-	Hepatic
Aripiprazole	Rare	rare	-	-	Hepatic
Ziprasidone	Rare	-	-	-	Hepatic
Sedative-Hypnotics					
Lorazepam, temazepam, oxazepam	Hepatic encephalopathy in cirrhosis	-	-	-	Hepatic phase II conjugation
Other benzodiazepines	Hepatic encephalopathy in cirrhosis	-	-	-	Hepatic phase I and II
Eszopiclone, zopiclone, zolpidem, zaleplon	Hepatic encephalopathy in cirrhosis	-	-	-	Hepatic
Buspirone	Rare	-	-	-	Hepatic
Stimulants					

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Drug	Potential Hepatotoxicity	Weight Gain	Glucose Intolerance	Hyperlipidemia	Metabolism/Excretion
Methyphenidate	-	-	-	-	Bloodstream
Amphetamines	-	-	-	-	Hepatic