

# How to manage depression in overweight or obese patients

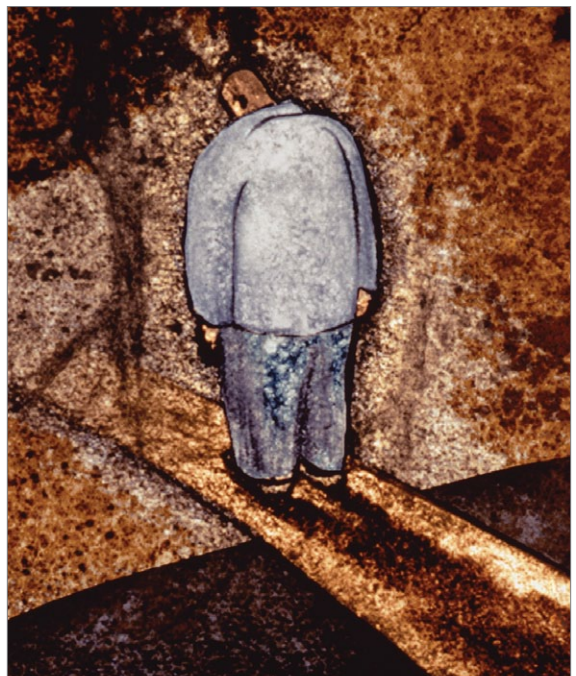
A single, unified treatment plan for both conditions offers the best chance of success

**M**rs. G is a 52-year-old mother and teacher with a 20-year history of recurrent depressive episodes for which she has been treated with various antidepressants, including sertraline, fluoxetine, and citalopram. For some of her depressive recurrences, she also received adjunctive second-generation antipsychotics (SGAs), including quetiapine and olanzapine.

She describes feelings of “being defeated,” hopelessness, and boredom and frustration with her teaching. It takes her approximately 30 minutes to go to sleep each night, but she wakes up after 2 to 3 hours, and the remainder of her night’s sleep is markedly disrupted. Because of her hopeless feelings, she has given up on dieting and going to the gym. When feeling down she has donuts and coffee. She has gained 45 lbs over the past 10 years and now weighs 175 lbs. In addition to her disrupted mood, she complains of frequent headaches and sore muscles.

Mrs. G’s psychiatrist refers her to her primary care physician for evaluation of her physical complaints and recommendations regarding her weight gain. Her waistline measures 90 cm and her body mass index (BMI) is 29.1 kg/m<sup>2</sup>; a BMI of ≥30 is considered obese. Her blood pressure is 145/85 mmHg. Laboratory work reveals a total cholesterol level of 235 mg/dL, low-density lipoprotein of 146 mg/dL, and fasting blood sugar, 135 mg/dL.

Mrs. G’s case illustrates many of the issues psychiatrists face when caring for overweight or obese patients with depression (OW/OB-D). Both conditions can be challenging to manage, and may be especially difficult to treat when they co-occur. When depression and obesity co-occur, their



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## Depression and obesity

### Clinical Point

Incorporate exercise into a depression treatment program for overweight/obese patients from the start



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Table 1

## Pharmacotherapy and weight gain: Antidepressants

Agent	Effect on weight
<b>SSRIs</b>	
Paroxetine	Moderate gain
Fluoxetine	Early: weight loss Long-term: moderate gain
<b>SNRIs</b>	
Duloxetine	Minimal gain
Escitalopram	Moderate gain
<b>Other agents</b>	
Imipramine (TCA)	Moderate gain
Selegiline (MAOI)	Moderate gain
Trazodone (tetracyclic)	Moderate gain
Bupropion (atypical)	Moderate loss
MAOI: monoamine oxidase inhibitor; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant	
Source: References 22,23	

capacity to inflict psychological and physical harm likely is greater than either condition alone. Data point to a “2-way street” of mutually destructive effects of being overweight/obese on depression and vice versa.<sup>1</sup>

This article summarizes ways that depression and obesity aggravate each other, and highlights research that suggests depression and obesity are manifestations of inflammatory processes. It also suggests a stepwise approach to treating OW/OB-D patients.

### Mutually destructive processes

**Self-esteem and body image.** Lowered self-esteem is a hallmark of depression. In popular culture, “you can’t be too rich or too thin,” and the pressure to be slim is great. Therefore, OW/OB-D patients have 2 reasons to feel a depleted sense of self-worth: their psychiatric illness and their weight. Observant clinicians will recognize these dual sources of self-deprecation and tailor treatment to address both.

Increasing numbers of celebrities, performers, and prominent politicians are overweight or obese. Increased social acceptance of OW/OB individuals in our culture may be legitimizing weight gain

and obesity. When OW/OB-D patients justify their weight by pointing to overweight celebrities, clinicians can counter this argument with data on the hazards of obesity on health and well-being, such as premature death, coronary artery disease, diabetes, arthritis, and some forms of cancer.

OW/OB patients tend to interact with other OW/OB individuals. Christakis et al<sup>2</sup> reported that adults with obese friends were more likely to become obese than individuals without obese friends. Valente et al<sup>3</sup> found that overweight teens were twice as likely to have overweight friends as non-overweight teens. This power of social connectedness can be harnessed when treating OW/OB-D patients, where therapeutic groups can help patients address both depression and weight gain.

**Inactivity.** OW/OB-D patients with psychomotor retardation or reduced activity may gain weight because they consume more calories than their body requires. Depressed patients may say they “have no energy” to participate in a clinician-recommended exercise program or that “it won’t do any good anyway.”

These tendencies are best dealt with by incorporating an exercise program into the comprehensive plan for OW/OB-D patients from the start of treatment. Several studies suggest that in addition to helping manage weight, exercise may have antidepressant effects. In a large, well-controlled trial of patients with major depressive disorder (MDD), Blumenthal et al<sup>4</sup> found that an exercise program was as effective as fluoxetine, 20 mg/d, and the antidepressant effects persisted at 10-month follow-up for patients who continued to exercise.<sup>5</sup> In a review of studies of exercise in depressed patients, Helmich et al<sup>6</sup> concluded that in most studies exercise was beneficial. However, Mead et al<sup>7</sup> found that nearly all trials of exercise and depression had substantial design flaws. Based on the 3 well-designed studies they reviewed, Mead et al concluded that the efficacy of exercise was comparable to that of cognitive therapy.

Although the evidence on exercise for treating depression is inconclusive, an exer-

Table 2

## Pharmacotherapy and weight gain: Adjunctive agents

Agent	Use in depression	Effect on weight
<b>SGAs</b>		
Olanzapine	Psychotic depression	Large gain
Clozapine	Adjunct; psychotic depression	Large gain
Quetiapine	Primary; adjunct	Large gain
Aripiprazole	Adjunct	Small gain
Risperidone	Psychotic depression	Small gain
Ziprasidone	Psychotic depression	Small loss
<b>Mood stabilizers</b>		
Divalproex	Treatment resistance, bipolar disorder	Moderate to large gain
Lamotrigine	Treatment resistance	Neutral

SGAs: second-generation antipsychotics  
Source: References 22,23

cise program is essential for OW/OB-D patients because it can help manage weight and improve cardiovascular fitness. Motivation is a key ingredient of successful programs.<sup>8</sup> Encourage patients to make exercise enjoyable, perhaps by using video games or other interactive computer-based programs.<sup>9</sup>

**Sleep disturbances.** Disrupted sleep—another hallmark of depression—appears to be a risk factor for weight gain.<sup>10</sup> Although the basis for this relationship is still under investigation, one possibility is that some patients with insomnia get up to eat more often than those without sleep disturbances. Research has shown that when sleep is curtailed in a sleep laboratory, patients consume approximately 20% more calories from snacks (1,086 calories) than non-sleep-deprived patients (866 calories).<sup>11</sup> Although this 220-calorie increase may seem small, it would amount to approximately 2 lbs of additional weight per month.

**Appetite.** Although weight loss is a cardinal sign of MDD, increased appetite and weight gain can be seen in many depressed patients who do not meet diagnostic criteria for MDD as well as those with seasonal affective disorder and metabolic syndrome, a condition characterized by insulin resistance, glucose intolerance, atherogenic dyslipidemia, visceral adiposity, hyperco-

agulation, chronic inflammation, oxidative stress, and hypertension.<sup>12</sup>

Emerging information about the neuroendocrinology of appetite regulation may lead to a better understanding of weight management in OW/OB-D patients. Leptin, a hormone released by adipose tissue, increases when fat stores are high, leading to reduced appetite and fat stores. Conversely, when fat stores are low, plasma leptin levels decrease, producing increased appetite and reduced energy expenditure.<sup>13</sup>

Researchers have suggested that leptin insufficiency and/or leptin resistance may contribute to vulnerability to depression, and leptin may have antidepressant effects.<sup>14</sup> Lawson et al<sup>15</sup> found that leptin levels were inversely associated with Hamilton Depression Rating Scale scores in normal-weight (BMI ≤25) women.

Leptin levels also are significantly associated with comorbid depressed mood and sleep disturbance.<sup>16</sup> In healthy volunteers, shortening sleep duration to 4 hours produced an approximately 20% reduction in leptin release compared with normal sleep duration.<sup>17</sup> Because of the relationship between sleep disorders and depression, leptin may act on sleep regulatory mechanisms, depressogenic pathways, or both. But studies of leptin's role in obesity, depression, and sleep have not yet found a single role for leptin that ties all 3 conditions to this hormone's known physiological functions.

### Clinical Point

**Increased appetite and weight gain can be seen in many depressed patients who don't meet criteria for major depressive disorder**

continued



## Depression and obesity

### Clinical Point

Evidence suggests that depression and obesity are associated with alterations in immune activity

Box

## Depression and obesity: The ‘inflammation connection’

Research suggests that both depression and obesity are associated with immune dysregulation and inflammation.<sup>a-d</sup> Although the complexities of these interactions are beyond the scope of this article, having a model for understanding the role of inflammation in overweight or obese patients with depression (OW/OB-D) may be useful. Data supporting a role for immune dysregulation in OW/OB-D patients rests on the following findings:

**Fat and muscle are endocrine organs:** Fat is not just a storage organ for energy-rich lipids but also a rich source of cytokines, including monocyte chemoattractant protein-1 (MCP-1), interleukin-2, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). The increase in MCP-1 in fat tissue triggers a cascade of events that leads to chronic inflammation in adipose tissue. These substances can be released into circulation, stimulating inflammatory responses in other tissues. Data suggest that obesity's effects on cardiovascular disease are mediated by these adipose-derived inflammatory hormones. There is a strong relationship between the volume of adipose tissue and the amount of pro-inflammatory hormones released; therefore, reducing weight reduces inflammatory burden on the body.

Pedersen<sup>e</sup> pointed out that muscle also is an endocrine organ. Among the cytokines (or “myokines”) muscle produces are interleukin-6 (IL-6), interleukin-8, and brain-derived neurotrophic factor. During exercise, the amount of IL-6 released from muscles may increase by 100-fold. Although IL-6 usually is considered a pro-inflammatory regulator, it—or other muscle-derived myokines—may be responsible for some of exercise's beneficial effects.<sup>e</sup>

If this hypothesis is correct, patients whose exercise includes resistance training—which increases muscle mass—are not just getting stronger or burning calories but may be facilitating release of hormones that could counteract obesity's inflammatory effects.

**Cytokine levels are elevated in depression and obesity:** A substantial body of evidence shows that depressed patients have elevated circulating levels of inflammation markers. In particular, the proinflammatory cytokines IL-6 and interleukin-1 $\beta$  and the acute phase reactant C-reactive protein (CRP) are elevated in depressed patients.<sup>f</sup> Studies also show that blood levels of IL-6, TNF- $\alpha$ , and CRP are elevated in obese patients.<sup>g</sup>

### Fat-derived cytokines alter metabolic pathways related to mood and inflammation:

Among the many possible pathways linking cytokine actions and depression, the effects of TNF- $\alpha$  on serotonin metabolism have been studied extensively.<sup>h,i</sup> TNF- $\alpha$  activates brain indoleamine 2,3-dioxygenase, leading to rapid depletion of serotonin and exacerbation of depressive symptoms.<sup>j</sup>

Regarding physical problems, evidence suggests adipose-tissue-derived pro-inflammatory agents are involved in development of metabolic syndrome, a condition characterized by insulin resistance, glucose intolerance, atherogenic dyslipidemia, visceral adiposity, hypercoagulation, chronic inflammation, oxidative stress, and hypertension.<sup>k</sup> These conditions are strong risk factors for type II diabetes, coronary artery disease, hypertension, and stroke.

### Anti-inflammatory agents for depression

Data suggest a model in which weight gain leads to an increase in pro-inflammatory cytokines. When released into the circulation, these cytokines produce a variety of deleterious effects, including blockade of serotonin synthesis in the brain that leads to depressive symptoms. Evidence suggests that anti-inflammatory agents might disrupt this process.

**Celecoxib.** The anti-inflammatory agent celecoxib acts by inhibiting cyclooxygenase-2, the rate-limiting enzyme in the synthesis of prostaglandin, a powerful inflammation mediator. Three double-blind, placebo-controlled trials have compared groups of:

- depressed patients receiving reboxetine with and without celecoxib<sup>l</sup> or fluoxetine, 40 mg/d, with and without celecoxib<sup>m</sup>
- bipolar disorder patients taking mood stabilizers or atypical antipsychotics with and without celecoxib, 400 mg/d.<sup>n</sup>

These studies suggest that celecoxib may accelerate improvement in depressive symptoms. Celecoxib's potential for increased cardiovascular risk may limit its use.

**Aspirin.** Mendlewicz et al<sup>o</sup> conducted an open-label study in which 24 depressed patients who failed to respond to 4 weeks of antidepressant treatment received adjunctive acetylsalicylic acid, 160 mg/d, for another 4 weeks. They found that 52% of patients responded when aspirin was added to their regimen, and the improvement was seen during the first week of treatment.

Source: For reference citations see this article at [CurrentPsychiatry.com](http://CurrentPsychiatry.com)

**Nonadherence.** Compared with non-depressed patients, depressed patients are 76% more likely to not adhere to treatment.<sup>18</sup> Patients may report that they are not interested in the treatment program or lack hope that it will be successful. Furthermore, OW/OB-D patients may consider exercise

programs to be too strenuous and diet programs too depriving.<sup>19</sup>

OW/OB-D patients may require special care in monitoring adherence. The presence of depression in patients enrolled in weight loss programs may prompt the treatment staff to modify the usual proto-

col by including the patient in an active depression treatment module.<sup>20</sup>

### Effects of pharmacologic agents

Many antidepressant agents are associated with weight gain.<sup>21</sup> *Tables 1 (page 34) and 2 (page 35)* summarize the effects antidepressants and adjunctive medications used to treat depression have on weight.<sup>22,23</sup> SGAs such as clozapine and olanzapine, which frequently are used as augmenting agents in patients with treatment-resistant depression (TRD), are associated with weight gain.<sup>22</sup> Lamotrigine also is an effective adjunctive medication for TRD and is not associated with significant weight gain.<sup>24</sup>

Bupropion has antidepressant and weight-loss effects and may be a suitable primary medication for OW/OB-D patients.

Early weight gain with olanzapine/fluoxetine combination may be a strong indicator of substantial weight gain with longer-term treatment. A weight gain of >2 kg (4.4 lbs) during the first 2 weeks of treatment is a strong predictor of weight gain of ≥10 kg (22 lbs) at 26 weeks.<sup>25</sup>

Antidepressants may be associated with an increased risk of obesity, and strategies to offset this risk may be useful in clinical practice, particularly patient education on the risks of weight gain and early introduction of a diet and exercise program.

Evidence suggests that depression and obesity are associated with alterations in immune activity (*Box*). This suggests that anti-inflammatory agents might have a role in treating depression by reducing the release of cytokines that may lead to depressive symptoms.

### Cognitive/behavioral approaches

Although large, well-designed studies of OW/OB-D patients are in the planning or pilot phases,<sup>26-28</sup> a substantial database supports incorporating behavioral or cognitive-behavioral therapies when treating these patients.<sup>29</sup> Patients in programs that combine behavioral approaches with diet and exercise achieve the greatest weight loss, and frequently show improved depression scores.<sup>30-32</sup>

In a randomized trial, 203 obese women with moderate to severe depression showed significant weight loss and decreased depression scores whether they were in a behavioral weight-loss program or one that combined behavioral weight loss with cognitive-behavioral depression management.<sup>33</sup> This study raises important questions: Did the behavioral weight-loss program effectively treat depression? Did patients' depressive symptoms improve because of their improved sense of well-being as they lost weight? Did a putative reduction in cytokine production by fat cells improve their mood?

### Treatment implications

Mrs. G has TRD, a BMI that borders on obesity, sleep problems, and lab values that suggest she may have metabolic syndrome. To best manage patients such as Mrs. G, consider the following steps:

1. Select an antidepressant that is unlikely to cause further weight gain, such as bupropion, duloxetine, or fluoxetine.
2. If necessary, add an augmenting agent that is not associated with weight gain, such as bupropion, aripiprazole, or lamotrigine.
3. Verify that your patient is getting adequate sleep. Begin by reviewing the principles of sleep hygiene and, if necessary, prescribe a sedative or hypnotic medication.
4. Although controlled clinical trials are lacking, consider including an anti-inflammatory agent such as aspirin to the pharmacologic armamentarium.
5. Institute an exercise and diet program at the *beginning* of treatment. Exercise can begin with 20 to 30 minutes a day of walking. Tell patients that exercising in groups is a good way to address nonadherence and social isolation and reinforce positive lifestyle changes. Recommend that patients combine aerobic exercise to burn calories with resistance training to build muscle. Suggest that patients try to make exercising fun using video games or interactive computer-based programs.
6. Encourage your patient to keep a journal to record his or her weight, amount and type of exercise, medication taken,

### Clinical Point

**Antidepressants that are unlikely to cause further weight gain include bupropion, duloxetine, and fluoxetine**



## Depression and obesity

### Clinical Point

Encourage patients to keep a journal to record weight, amount of exercise, medications taken, and dietary intake

## Related Resources

- Markowitz S, Friedman MA, Arent SM. Understanding the relation between obesity and depression: causal mechanisms and implications for treatment. *Clinical Psychology: Science and Practice*. 2008;15(1):1-20.
- Burke LE, Wang J, Sevick MA. Self-monitoring in weight loss: a systematic review of the literature. *J Am Diet Assoc*. 2011;111(1):92-102.

### Drug Brand Names

Aripiprazole • Abilify	Olanzapine • Zyprexa
Bupropion • Wellbutrin, Zyban	Olanzapine/fluoxetine • Symbyax
Celecoxib • Celebrex	Paroxetine • Paxil
Citalopram • Celexa	Quetiapine • Seroquel
Clozapine • Clozaril	Risperidone • Risperdal
Divalproex • Depakote	Selegiline • Emsam
Duloxetine • Cymbalta	Sertraline • Zoloft
Escitalopram • Lexapro	Trazodone • Desyrel,
Fluoxetine • Prozac	Oleptro
Imipramine • Tofranil	Ziprasidone • Geodon
Lamotrigine • Lamictal	

### Disclosure

Dr. Crayton reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

and dietary intake. Review this information at every session to reinforce the importance of this integrated exercise and diet program.

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## Bottom Line

Overweight or obese patients with depression will benefit from interventions that target both conditions. Antidepressants and other medications should be selected based in part on their likelihood to increase weight. Initiate a diet and exercise program at the beginning of treatment for depression.

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# This month's instantpoll%

Mr. D, age 47, presents with worsening depression—increasing fatigue, difficulty sleeping, and feelings of worthlessness—despite trials of escitalopram, sertraline, and, most recently, paroxetine, 25 mg/d. He's recently gained 30 lbs. **In addition to encouraging him to diet and exercise, how would you treat him?**

- Continue paroxetine, 25 mg/d, and add lamotrigine
- Switch to bupropion, 200 mg/d
- Increase paroxetine to 50 mg/d
- Switch to duloxetine, 60 mg/d
- Continue paroxetine, 25 mg/d, and add a sedative/hypnotic

See **"How to manage depression in overweight or obese patients"** page 33-39

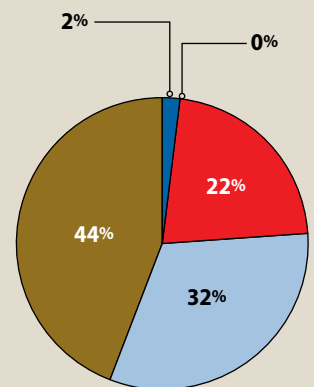
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## MAY POLL RESULTS

Ms. W, age 32, says that for 9 months she's been binge eating 1 or 2 days a week. Her bingeing is triggered by anxiety and frustration. She's gained weight and now has a body mass index of 25 kg/m<sup>2</sup>.

**How would you treat her?**

- 2%** Start escitalopram, 30 mg/d
- 0%** Start orlistat, 120 mg 3 times a day
- 22%** Refer her to group cognitive-behavioral therapy (CBT)
- 32%** Refer her to individual CBT
- 44%** Start fluoxetine, 60 mg/d, and refer her to individual CBT



**SUGGESTED READING:**  
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