



How to control weight gain when prescribing antidepressants

Address diet and exercise first, then consider switching antidepressants or prescribing an adjunctive agent

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The prevalence of undesired weight gain in the United States has reached an all-time high, with 68.5% of adults identified as overweight (body mass index [BMI] ≥ 25) or obese (BMI ≥ 30), 34.5% considered obese, and 6.4% considered extremely obese (BMI ≥ 40).¹ Reasons for weight gain include various physical and nutritional factors in a patient's life, but sometimes weight gain is iatrogenic. Many medications we prescribe are associated with weight gain, including most antidepressants and atypical antipsychotics. Clinicians might minimize or overlook the risk of weight gain when prescribing antidepressants.

Patients with major depression often have associated weight loss. Regaining weight can be seen as sign of successful treatment of depressive symptoms. If weight gain after treatment exceeds the amount of weight loss attributed to depression, however, medication could have caused the excessive gain. This is considered a side effect, or iatrogenic weight gain, and should not be considered normal or clinically acceptable.

Patients who are overweight or obese when beginning antidepressant treatment might be at greater medical risk when placed on a medication that can cause additional weight gain. The time to onset of weight gain during treatment can predict weight gain patterns; those affected in the first month are most at risk of future excessive weight gain.²

In this article, we discuss:

- considerations when prescribing antidepressants
- ways to approach weight gain
- medications available to assist in weight loss.

continued



Weight gain with antidepressants

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Provide education and encouragement about eating a healthy diet and exercising, or refer the patient to a nutritionist



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Our general recommendations

Screen. The United States Preventive Services Task Force maintains a Class-B recommendation for screening all patients for obesity. This means that the Task Force's review panel determined that such screening is at least moderately or substantially beneficial.³ Screening is important in a setting of potential weight gain in patients taking an antidepressant.

Educate and treat. Provide at least some education and encouragement about eating a healthy diet and exercising, or refer the patient to a nutritionist or dietician. Next, initiate psychotherapy (motivational interviewing, cognitive-behavioral therapy [CBT]) as needed. Reserve anti-obesity medications for those who do not respond to weight loss efforts or who might be taking an antidepressant for the long term.

The need for medical management of weight gain has given rise to specialists who treat this complicated, multifactorial condition. Whether psychiatrists should be seen as a substitution for their specialty is not the purpose of this review; rather, how we might more effectively (1) work on our patients' behalf to mitigate potential weight gain from the treatments that we prescribe and (2) participate in consultations that we've provided on their behalf.

BMI is not an absolute marker of health

BMI likely should not be viewed as a marker with absolute prognostic certainty of overall health of an overweight or obese person: An overweight person considered healthy from a cardiovascular and metabolic perspective could still benefit from preventing further weight gain.

Tomiyaama et al⁴ concluded that BMI itself was insufficient to stratify health in a meaningful way—and that such a focus would lead to overweight and obese people in otherwise good health being penalized unfairly through higher health insurance premiums, and would divert focus on those with less optimal health but a normal BMI. The researchers' goal was to use blood pressure, lipid levels, and glycemic markers

as surrogate markers of health, and then statistically compare results with patients' corresponding BMI. Their findings showed that approximately one-half of people who are overweight and 29% of obese people can be considered healthy.⁴

Potential causes of weight gain

There may be more than one reason for weight gain during depression treatment, so a multifactorial management approach might be necessary, depending on the patient's medication regimen. Appetite might be influenced by physical (chemical, metabolic) and psychological (cultural, familial) factors. The following sections focus on specific antidepressant classes and their proclivity for weight gain.

Serotonergic antidepressants

Many patients with depression are treated with medications that alter serotonin levels in the body, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). This neurotransmitter often is affected through depression treatment, and therefore might be a factor contributing to unintended weight gain. In mice bred to lack serotonin 5-HT_{2c} receptors in proopiomelanocortin (POMC) neurons, the expected anorectic reaction to serotonergic agents often is reversed, causing a robust increase in hyperphagia and obesity.⁵ This effect indicates that 5-HT_{2c} receptor stimulation might control appetite and feeding.

After SSRI or SNRI treatment, accumulation of serotonin over time in the synaptic cleft is thought to result in down-regulation of 5-HT_{2c} receptors. This may cause a relative absence of 5-HT_{2c} receptors, similar to what is seen in mice who lack them biologically. The loss of these receptors or their activity often will result in excessive weight gain. Some sedating antidepressants (mirtazapine) and some second-generation antipsychotics (SGAs) (olanzapine, quetiapine) directly block 5-HT_{2c} receptors and might cause more rapid weight gain. Lorcaserin, a selective 5-HT_{2c} receptor agonist, theoretically could reverse this proposed weight

gain mechanism and suppress appetite by activating the POMC pathway in the hypothalamus.

Among SSRIs and SNRIs, paroxetine might be one of the worst for provoking long-term weight gain; a study showed an average increase of 2.73 kg over a 4-month period.⁶

Theoretically, SNRIs have the ability to increase noradrenergic tone. This might be associated with nausea and a decline in appetite or it might generally curb appetite. These agents likely will cause less future weight gain. SNRIs typically induce more noradrenergic tone at increasingly higher dosages. There may be a dose-response curve in this manner. Levomilnacipran likely is the most noradrenergic of the SNRIs; recent regulatory studies suggest no statistically significant weight gain over the long term.⁷

Sedating antidepressants

Mirtazapine has receptor-blocking effects on noradrenergic α -2 and serotonergic 5-HT_{2a} and 5-HT_{2c} receptors. Additionally, histamine blocking of H₁ receptors can contribute to additional weight gain, similar to what is seen with some SGAs. H₁ antagonism dampens satiety response, resulting in increased caloric intake. In that case, or when specific SGAs are used for managing depression, appetite increases (H₁ antagonism) and metabolism slows (possibly 5-HT_{2c} antagonism, muscarinic receptor antagonism, etc.), thus allowing for greater adipose tissue growth and leptin insensitivity.

In a meta-analysis, mean weight increased by 1.74 kg ($P < .0001$) in the first 4 to 12 weeks of mirtazapine treatment, with greater variability in periods >4 months.⁶ Among the more novel antidepressants released since the era of tricyclic antidepressants (TCAs) or monoamine oxidase inhibitor, mirtazapine might have the greatest weight gain potential.

Trazodone and nefazodone block 5-HT_{2a} and 5-HT_{2c} receptors, as well as serotonin reuptake transporters. Compared with trazodone, nefazodone has a more potent effect on 5-HT_{2a} receptor antagonism and a less potent effect on 5-HT_{2c} receptors, and

also mildly inhibits uptake of norepinephrine—meaning that this drug might have less weight gain potential. These medications are not used frequently for treating depression, but trazodone is used as an adjunctive agent for insomnia. Used even at off-label low dosages, trazodone exerts H₁-histaminic and α -1 adrenergic antagonistic properties, decreasing the level of consciousness and allowing sedation and somnolence. Because of its fast onset and relatively short duration of action, it can improve depression symptoms by promoting restful sleep as well as by facilitating monoamine neurotransmission. It also might add to weight gain because of its pharmacodynamic receptor profile.

Tricyclic antidepressants

Amitriptyline can be associated with release of tumor necrosis factor- α , which is implicated in causing weight gain. Many TCAs block H₁ (amitriptyline, imipramine, clomipramine), likely causing weight gain. Most TCAs antagonize muscarinic receptors as well. The more noradrenergic TCAs could curb appetite (nortriptyline, desipramine, protriptyline) similar to SNRIs, therefore countering some of the weight gain drive.

As an example, in a meta-analysis examining weight gain with antidepressants, amitriptyline was associated with weight gain of 1.52 kg above baseline in the acute period (4 to 12 weeks) and 2.24 kg above baseline at 4 to 7 months.⁶ These results of the acute phase should be viewed cautiously because the authors reported high heterogeneity among these studies, and the possibility of publication bias (Egger test, $P < .0001$). In the same meta-analysis, the even the more noradrenergic nortriptyline was associated with an increase of 2.0 kg on average over baseline during acute treatment, with that number dropping to 1.24 kg over baseline at ≥ 4 months.⁶

Newer antidepressants

Vilazodone is a weak SSRI that aggressively partially agonizes pre-synaptic and post-synaptic 5-HT_{1a} receptors in the CNS. This dual site 5-HT_{1a} action is somewhat

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SNRIs can increase noradrenergic tone, which might be associated with nausea and a decline in appetite



Weight gain with antidepressants

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Eating smaller portions, combined with restricting foods high in calories and fat, should be the first step in managing weight gain

unique among antidepressants. This type of agent sometimes is called multimodal,⁸ or could be considered an “SSRI +” antidepressant. These drugs are SSRIs at the core but have additional 5-HT receptor modulating capabilities. Vilazodone has a favorable weight gain profile, as suggested in a 52-week trial reporting 1.7 kg gain over 52 weeks, compared with an average of 6.8 to 10 kg for long-term SSRI therapy.⁹

Vortioxetine is a stronger SSRI that also partially agonizes presynaptic 5-HT_{1a} receptors. In addition, it antagonizes 5-HT_{1d}, 5-HT₃, and 5-HT₇ receptors, giving it a unique pharmacodynamic profile.¹⁰ Vortioxetine also had minimal impact on drug-induced weight gain in 52-week studies, with data from 2 trials indicating either minimal weight gain in 6.1% of patients (mean increase of 0.41 kg over 52 weeks)¹¹ or gain that was not statistically significant.¹²

Levomilnacipran is unique in that it has the most aggressive norepinephrine reuptake inhibition of all SNRIs.¹³ Again, increased noradrenergic tone might curb appetite and caloric intake. Many SNRIs cause low-grade nausea, which could account for decreased appetite. Long-term, 52-week data for this drug also shows minimal proclivity for weight gain, with the trial participants reporting a slight decrease of 4.34 kg on average from baseline.¹⁴

Addressing weight gain

Lifestyle modification. Eating smaller portions, combined with restricting foods high in calories and fat, should be the first step. A simple suggestion to a patient to eat the same foods, but remove 20% of the portion, is a simple intervention akin to that of suggesting sleep hygiene practices for insomnia management. Under medical supervision or with referral to a dietician or nutritionist, more rigid caloric restrictions could be employed.

Commercial weight-loss programs, such as Weight Watchers or Curves, can be helpful; some insurers will only cover medications for weight loss if one of these programs have been tried or is used

in combination with medication. Some patients might ask about extreme weight-loss measures, such as low-calorie diets combined with intense exercise programs that have been popularized in the media. Although the motivation to initiate and maintain meaningful weight loss should be encouraged, doing so in a more gradual manner should be the goal.

Addressing portion size is a good approach in the early stages of managing obesity. Restaurants often serve portions that have more calories than should be consumed in one meal. Visual cues can influence this trend; using smaller plates can help reduce caloric intake.¹⁵

Exercise, sustained for at least 45 minutes, can have long-lasting effects, with a small study showing an increase in metabolic rate of 190 ± 71.4 kcal ($P < .001$) above baseline for 14 hours after exercise.¹⁶ Endurance exercise training is associated with a significant decrease in total cholesterol, triglycerides, and low-density lipoprotein cholesterol, as well as an increase in the high-density lipoprotein level over a 24-week period.¹⁷

Encouraging an exercise regimen that is appropriate for your patient can help maintain weight loss. In small trials,^{18,19} high-intensity exercise was shown to help suppress appetite and decrease 24-hour caloric consumption by 6% to 11%.¹⁸

Psychotherapy can become an important intervention for initiating and maintaining weight loss. CBT can help patients recognize and modify lifestyle components, and reinforce behaviors that promote weight loss. This can come from setting realistic weight loss goals; preventing triggering factors that lead to overeating; encouraging portion control during meals; and promoting exercise habits.

In a small, randomized controlled trial (RCT) examining weight loss in obese women, those who underwent CBT and psychoeducation for 2 hours a week for 10 weeks in addition to dietary changes and exercise showed an average weight loss of 10.4 kg at 18-month follow-up, compared with weight gain of 2.3 kg in the control group.²⁰ The short duration of treatment in this study might be desirable to reduce cost



Weight gain with antidepressants

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CBT can help patients recognize and modify lifestyle components, and reinforce behaviors that promote weight loss

Table 1

FDA-approved medications for treating obesity

Drug (mechanism of action)	Dosage	Evidence of efficacy and safety
Bupropion-naltrexone (NDRI curbs appetite via DA and NA activation of POMC; μ -opioid receptor antagonist dampens reward pathway and removes endogenous POMC activation negative feedback ligand)	Bupropion, 90 mg-naltrexone, 8 mg, 2 tablets taken twice a day	\downarrow 5.2% baseline body mass in first year ²² ; safety and efficacy beyond 1 year is undetermined ^{22,23}
Lorcaserin (selective 5-HT _{2c} receptor agonist, causing anorectic effect via POMC neurons activation in the hypothalamus)	10 mg, twice a day	\downarrow 3 kg from baseline in first year; safety and efficacy beyond 1 year is undetermined ²⁴
Phentermine-topiramate ER (topiramate inhibits appetite stimulation via \uparrow GABA and \downarrow glutamate release, which $\downarrow\downarrow$ NPY and AgRP pathway; phentermine then \uparrow POMC via DAT and NET inhibition, to $\downarrow\downarrow$ appetite further)	Phentermine, 7.5 mg-topiramate, 46 mg, or phentermine, 15 mg-topiramate, 92 mg	For 7.5/46 mg or 15/92 mg: \downarrow 6.8% or 8.8% baseline body mass in first year, respectively ²⁵ and in second year \downarrow 7.8% or 8.7% respectively ²⁶ ; safety and efficacy beyond 2 years is undetermined ²⁵
Liraglutide (GLP-1 receptor agonist, causes more insulin to be released and suppression of glucagon; results in decreased appetite, less energy storage)	3 mg/d subcutaneous	\downarrow 5.4 kg average in first year; safety and efficacy beyond 1 year is undetermined ²⁷
Orlistat (reversible direct pancreatic and gastric enzyme inhibitor, preventing fat breakdown and absorption)	60 to 120 mg, with meals	\downarrow 3 kg in 1 year ²⁸ ; safety and efficacy beyond 4 years is undetermined ²⁹

AgRP: agouti-related protein; DA: dopamine; DAT: dopamine transporter; GABA: γ -aminobutyric acid; GI: gastrointestinal; GLP-1: glucagon like peptide-1; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MEN: multiple endocrine neoplasia; NA: noradrenaline; NDRI: norepinephrine dopamine reuptake inhibitor; NE: norepinephrine; NET: norepinephrine transporter; NPY: neuropeptide Y; POMC: proopiomelanocortin

and utilization of services. Group formats also could be employed.

Motivational interviewing is a useful tool in addiction psychiatry and shows promise for treating obesity and over-eating as well. The approach may differ slightly because weight-loss therapy involves behavior modification rather than behavior cessation. In a meta-analysis of data from RCTs exploring motivational interviewing and its use as an intervention for weight loss, those in the intervention groups experienced significant weight loss as indicated by BMI decreasing a standardized mean difference of -0.51 , compared with control groups.²¹

Medical management considerations

Diagnostics. Recognition and early intervention are instrumental in successfully

treating medication-associated weight gain. It is important to obtain any family history of obesity, diabetes, hypertension, and hyperlipidemia. This will likely indicate a patient's risk for weight gain before initiating medication.

Obtain vital signs at every visit, including blood pressure. Monitoring weight at every clinical visit can be used to calculate and monitor BMI, while also asking the patient to maintain a log of weight measurements obtained at home. Measuring abdominal girth is important to watch for metabolic syndrome, although often this is the least measured variable.

Laboratory testing is helpful. Obtaining a baseline lipid panel and a fasting glucose level (consider measuring hemoglobin A_{1c} in patients with diabetes) is warranted. Including thyroid markers, such as thyroid-stimulating hormone and thyroxine (free T₄), might be important considerations, because

Adverse effects	Comments
Nausea, headaches, constipation	Consider if a patient is stopping smoking; contraindicated in patients with anorexia, a history of seizures, or are taking opioids
Nausea, vomiting, diarrhea	Theoretical risk of serotonin syndrome (avoid serotonergic medications); contraindicated during pregnancy
Xerostomia, constipation, paresthesias	Evaluate after 12 weeks to discontinue or to increase dosage (can gradually increase to phentermine, 15 mg-topiramate, 92 mg). Raise or discontinue gradually. Pregnancy category X (congenital malformation risk). Use cautiously in patient with history of kidney stones
Nausea, vomiting, diarrhea, anorexia, hypoglycemia; rare risk of pancreatitis	Avoid in patients with personal or family history of MEN type 2, or medullary thyroid cancer
Largely GI (diarrhea, fecal urgency)	↓triglycerides, cholesterol (total and LDL) ↑ HDL cholesterol. Supplement with multivitamin

inadequate management of hypothyroidism can complicate the clinical picture.

Follow-up testing should be ordered every 3 to 12 months to monitor progress if your patient is showing signs of rapid weight gain, or if BMI nears ≥ 30 kg/m². These guidelines generally are assigned for prescribing of SGAs, but can be applied when using any psychotropic with weight gain potential.

Medications to consider

When considering the medication regimen as an intervention point, consider changing the antidepressant to one that is not associated with significant weight gain. Although not specifically indicated as a monotherapy for weight loss, switching to or augmenting therapy with bupropion could aid weight loss through appetite suppression.²⁰ Some newer antidepressants, such as vilazodone,

vortioxetine, and levomilnacipran, might have less propensity to cause weight gain. In patients with severe depression, augmenting with medications containing amphetamine or methylphenidate could cause some weight loss, but greater care should be taken because of cardiovascular effects and dependency issues.

Discussing with your patient the possibility of changing or worsening depressive symptoms when adding or switching medications allows them to be aware and engaged in the process and can encourage them to notice and report changes. Developing a sensible schedule to taper an existing medication slowly over several weeks and allowing a new one to build up gradually to a therapeutic level can help minimize adverse effects or a discontinuation syndrome.

If switching antidepressants is not possible, or is ineffective, an anti-obesity medication (*Table 1*²²⁻²⁹) can be considered. These medications should not be considered first-line in weight loss management, but reserved for more difficult or refractory weight loss challenges and in patients who are not able to participate in weight loss or dieting programs because of cognitive disorders, a history of nonadherence, financial or travel limitations, or in those with poor social support systems such as homelessness.

Some of these medications are not reimbursed by insurance companies; therefore, consider the financial burden to the patient and their capacity for adherence to therapy, and discuss this challenge before initiating treatment. There is some evidence for using medications off-label to treat obesity (*Table 2*,³⁰⁻³⁴ *page 47*).

Anti-obesity medications typically are considered for patients with a BMI >30 or in any overweight patient with diabetes, hyperlipidemia, or cardiovascular disease. As always, discuss with patients and their primary care provider the potential benefits and risks of adding any of these or other medications to an existing treatment regimen.

If weight loss goals are not met, consider discontinuing anti-obesity therapy. Patients and physicians should be cognizant of the need to continue long-term maintenance

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Recognition and early intervention are instrumental in successfully treating medication-associated weight gain

Table 2

Medications used off-label to treat obesity

Drug (mechanism of action)	FDA-approved indication and dosage	Evidence of efficacy and safety	Adverse effects	Comments
Metformin (biguanide antihyperglycemic)	Type 2 diabetes mellitus (850 mg, twice a day)	↓2 kg in 1 year ³⁰ ; safety and efficacy beyond 10 years is undetermined ³¹	Risk of lactic acidosis	Weight loss is modest
Exenatide (GLP-1 receptor agonist; causes more insulin to be released and suppression of glucagon. Results in decreased appetite, less energy storage)	Type 2 diabetes mellitus (10 µg subcutaneous injection, before breakfast and dinner)	↓2.49 kg in 35 weeks; longer efficacy is undetermined; safety longer than 3 years is undetermined ³²	Nausea	Requires injection twice daily. Avoid in those with personal or family history of MEN type 2, or medullary thyroid cancer; small trial size
Zonisamide (anticonvulsant)	Partial seizures (400 mg/d)	↓3.3 kg greater than diet and lifestyle intervention; safety and efficacy beyond 1 year is undetermined ³³	Headache, nausea, vomiting	Moderate weight loss, but high adverse effect rate
Pramlintide (synthetic human amylin analogue)	Types 1 and 2 diabetes mellitus (120 to 360 mcg, twice or 3 times a day ³⁴)	↓2.27 kg in first year; safety and efficacy beyond 1 year is undetermined ³⁴	Nausea, headache, anorexia	Those randomized to drug in trial had ↑ 1.8 times likely to report nausea. Requires subcutaneous injection twice daily

GLP-1: glucagon like peptide-1; MEN: multiple endocrine neoplasia

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If switching antidepressants is not possible, or is ineffective, an anti-obesity medication can be considered

nance on these medications after successful treatment—perhaps indefinitely, because patients frequently regain weight after medication is discontinued.

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Weight gain with antidepressants

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Some newer antidepressants, such as vilazodone, vortioxetine, and levomilnacipran, might be less likely to cause weight gain

Related Resource

- Crayton JW. How to manage depression in overweight or obese patients. *Current Psychiatry*. 2012;11(7):33-39.A.

Drug Brand Names

Amitriptyline • Elavil	Nefazodone • Serzone
Bupropion • Wellbutrin, Zyban	Nortriptyline • Pamelor
Clomipramine • Anafranil	Olanzapine • Zyprexa
Desipramine • Norpramin	Orlistat • Xenical
Exenatide • Byetta, Bydureon	Paroxetine • Paxil
Imipramine • Tofranil	Phentermine/topiramate
Levomilnacipran • Fetzima	• Qsymia
Liraglutide • Victoza, Saxenda	Pramlintide • Symlin
Lorcaserin • Belviq	Protriptyline • Vivactil
Metformin • Glucophage	Quetiapine • Seroquel
Methylphenidate • Ritalin, Methylin	Trazodone • Desyrel, Oleptro
Mirtazapine • Remeron	Vilazodone • Viibryd
Naltrexone/bupropion	Vortioxetine • Trintellix
• Contrave	Zonisamide • Zonegran

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Bottom Line

Many antidepressants are known to increase the risk of excessive weight gain, although risk of weight gain varies among antidepressant classes. First, advise changes in diet and exercise; next, initiate psychotherapy as indicated, and then consider referral to a nutritionist. Consider switching to an antidepressant with less potential for causing weight gain or adding bupropion, which could lead to weight loss, if your patient can tolerate it. If these strategies are unsuccessful, consider an anti-obesity medication.