



Meeting of the Minds

Web
Cast

Ask Dr. Schwartz about managing weight gain from antidepressant therapy.
For details, see page 54

Current

PSYCHIATRY

How to control weight gain when prescribing antidepressants

Ignoring this side effect can increase medical risk, treatment nonadherence

Weight gain occurs with most antidepressants but is frequently overlooked, perhaps because clinicians are focused instead on metabolic effects of antipsychotics and mood stabilizers. Patients taking antidepressants often complain of weight gain, however, and many of the drugs' FDA-approved package inserts acknowledge this effect.

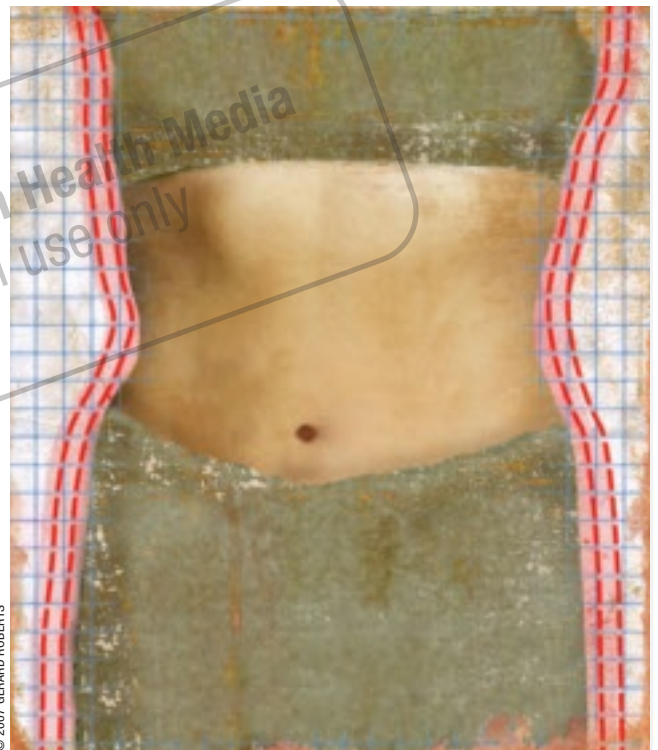
Two-thirds of patients with major depression present with weight loss, and gaining weight can be associated with successful treatment. Weight gain is of concern—and likely to be drug-induced—if it exceeds the disease-induced weight loss and continues after depressive symptoms improve.

Weight may change early or late during antidepressant treatment, and gaining in the first weeks usually predicts future gains.¹ Patients who are overweight when treatment begins are especially at risk if given weight-promoting agents. This article:

- compares antidepressant effects on patient weight
- discusses mechanisms by which antidepressants may cause weight gain
- outlines a plan to prevent excess weight gain when patients start antidepressant therapy
- recommends diet, exercise, cognitive-behavioral therapy (CBT), and medications for overweight patients on long-term antidepressant treatment.

Weight-gain potential by class

Unlike antipsychotics, antidepressants have not been associated in clinical trials with causing metabolic syn-



Thomas L. Schwartz, MD

Associate professor

Zsuzsa S. Meszaros, MD, PhD

Clinical assistant instructor

Rahat Khan, MD

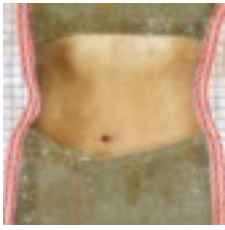
Clinical extern

Nikhil Nihalani, MD

Clinical assistant professor

• • • •

Department of psychiatry
SUNY Upstate Medical University
Syracuse, NY



Weight gain

Clinical Point

Paroxetine seems to be the SSRI most likely to cause weight gain, especially when used with an antipsychotic

Table 1
Long-term effects of antidepressants on body weight, by class*

Class	Effect (gain, loss, or neutral)
MAOIs	Moderate gain overall Phenelzine: greatest gain in MAOI class Transdermal selegiline: appears neutral
Novel antidepressants	Bupropion: weight loss ⁴ Mirtazapine: greatest potential for gain among antidepressants ⁵ Nefazodone: neutral ⁶ Trazodone: modest gain ⁷
SSRIs	Citalopram: modest gain ⁸ Escitalopram: modest gain ⁹ Fluoxetine: modest loss acutely ¹⁰ Fluvoxamine: neutral ¹¹ Paroxetine: greatest gain in SSRI class ¹⁰ Sertraline: modest gain ¹⁰
SNRIs	Duloxetine: modest gain ¹² Venlafaxine: modest gain (controversial) ¹³
TCA s	Amitriptyline: gain ¹⁴ Imipramine: gain ¹⁵ Nortriptyline: neutral ¹⁶

* Information is a general representation of available literature, gathered from many studies with differing designs. Consult original reports for specific data on dosing, patient populations, treatment durations, and weigh changes.

MAOIs: monoamine oxidase inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants

drome and diabetes. Even so, certain antidepressants can cause clinically significant and perhaps more insidious weight gain when compared with some second-generation antipsychotics (SGAs). For example, SGAs on average may cause 2.3 kg/month weight gain during the first 12 weeks of treatment, and mirtazapine caused 3 kg weight gain in a recent 6-week trial.^{2,3}

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) may pose a greater weight-gain risk than newer antidepressants, but selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been clinically noted to cause weight gain over time (*Table 1*).⁴⁻¹⁶

SSRIs. Weight gain associated with long-term SSRI use seems clinically apparent, but the evidence is preliminary.

Paroxetine seems to be the SSRI most likely to cause weight gain. A 26- to 32-week comparison trial by Fava et al¹⁰ showed that weight gain risk with SSRI therapy var-

ies with the drug used. In this trial, 284 patients with major depressive disorder were randomly assigned to double-blind treatment with paroxetine, sertraline, or fluoxetine:

- More of those taking paroxetine gained >7% in weight from baseline, and their weight gain was statistically significant.
- Sertraline-treated patients had modest, non-significant weight gain.
- Fluoxetine-treated patients had modest, non-significant weight loss.

Using paroxetine with an antipsychotic can be especially problematic. Fukowi and Murai¹⁷ described 2 cases in which adding paroxetine to risperidone caused severe weight gain (13.5 kg to >14 kg) in 4 to 5 months.

Citalopram may cause a 1- to 1.5-kg weight gain over 1 year,⁸ whereas fluvoxamine has been shown not to affect weight in obese patients.¹¹ Citalopram (like TCAs) can cause carbohydrate craving and early weight gain.¹⁸ Escitalopram caused a modest (0.5 kg) weight gain in elderly patients during an 8-week trial.¹³

Initial weight loss followed by overall weight gain after 1 year of SSRI treatment is a common clinical finding that was not noted in initial acute SSRI drug trials. In a comparison of fluoxetine's acute and long-term effects,¹⁹ 839 patients experiencing a major depressive episode were first treated with open-label fluoxetine, 20 mg/d. After 12 weeks, 395 patients who met criteria for remission were randomly assigned to continue with placebo or fluoxetine, 20 mg/d, for 14, 38, or 50 weeks.

In the acute phase, a small but statistically significant weight loss (mean 0.35 kg, $P < 0.01$) was noted. In the continuation phase, statistically significant weight gain occurred among

all patients. Mean absolute weight changes were:

- 1.1 kg at 26 weeks (P <0.001)
- 2.2 kg at 38 weeks (P <0.001)
- 3.1 kg at 50 weeks (P <0.001).

The authors concluded that the weight gain—similar with fluoxetine or placebo—was probably associated with recovery from depression rather than fluoxetine treatment, although this was not a controlled variable in the study.

Causes of weight gain

Serotonin. Appetite is controlled by cultural, psychological, neurochemical, and metabolic factors. Among neurochemical factors, serotonin helps regulate appetite and is the neurotransmitter most often manipulated in depression treatment.

Serotonin receptor agonists such as fenfluramine and dexfenfluramine have an acute anorexigenic effect. In rats, 5-HT_{2c} receptor agonism decreases eating behavior, and mice lacking 5-HT_{2c} receptors are obese.²⁰ This may explain why SGAs or antidepressants that block 5-HT_{2c} pose the greatest risk of weight gain.

SSRI or SNRI treatment might increase serotonin in the synaptic cleft, allowing 5-HT_{2c} receptor down-regulation that is slower than—but similar in effect to—the acute 5-HT_{2c} blockade caused by the SGAs.²¹ Weight gain from SSRI use reflects on these medications' multiple serotonergic mechanisms. Serotonin appears to regulate carbohydrate intake and can increase food intake.²²

Nefazodone and trazodone block 5HT_{2a} receptors potently, and the norepinephrine (nefazodone only) and serotonin reuptake pumps (both agents) less potently. Differences in their mechanism (nefazodone increases norepinephrine) and lack of 5-HT_{2c} blockade might be responsible for their reported weight neutrality.

Table 2
Antidepressants' relative long-term effects on body weight

Effect	Antidepressants
Loss	Bupropion, ⁴ fluoxetine ¹⁰
Gain	Modest: citalopram, ⁸ duloxetine, ¹² escitalopram, ⁹ sertraline, ¹⁰ trazodone, ⁷ venlafaxine ¹³ Relatively more: amitriptyline, ¹⁴ imipramine, ¹⁵ mirtazapine, ⁵ paroxetine, ¹⁰ phenelzine
Neutral	Fluvoxamine, ¹¹ nefazodone, ⁶ nortriptyline ¹⁶

Information is a general representation of available literature, gathered from many studies with differing designs. Consult original reports for specific data on dosing, patient populations, treatment durations, and weight changes.

Tricyclics block differing ratios of norepinephrine and serotonin reuptake pumps, resulting in postsynaptic serotonergic and adrenergic receptor desensitization and, later, down-regulation. TCAs with higher serotonin reuptake blockade may increase weight through this desensitization.

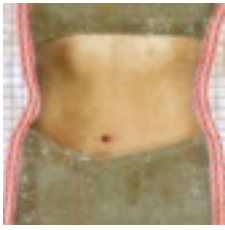
TCAs also affect appetite by blocking histaminergic (H₁) pathways. Drugs with high affinity for blocking H₁ receptors have been associated with carbohydrate craving¹⁸ and low satiety rates that allow increased calorie intake. TCAs have antimuscarinic, antihistaminic, and alpha adrenoceptor-blocking actions, all of which may contribute to weight gain.

In theory, beta-3 adrenergic receptors in adipose tissue may play a role in weight control by converting fat into heat and energy, especially in response to norepinephrine. TCAs or SNRIs that favor a noradrenergic profile may promote weight loss or neutrality. The relatively weight-neutral selegiline patch, which avoids first-pass metabolism and active adverse metabolites, also may use this mechanism.²³

Mirtazapine blocks presynaptic alpha-2 and postsynaptic 5HT_{2a}, 5HT_{2c}, and 5HT₃ serotonin receptors as well as H₁ histamine receptors. Both 5HT_{2c} and H₁ blockade result in weight gain, the drug's most apparent adverse effect. This mechanism is similar to that of the SGA olanzapine.

Clinical Point

Serotonin helps regulate appetite and carbohydrate intake and is the most often manipulated neurotransmitter in depression treatment



Weight gain

Clinical Point

Instruct patients to weigh themselves at home at least weekly in the morning and to report gains >5 pounds

Table 3

Using antidepressants in patients at metabolic risk for weight gain

- **Warn patients** before they begin antidepressant treatment about the risks of weight gain and worsening or onset of comorbid medical conditions
- **Obtain and document** family medical history in addition to the usual family psychiatric history
- **Discuss and initiate** a diet and exercise plan to prevent or treat weight gain before medically significant weight gain occurs
- **Choose a weight-neutral** or weight-negative antidepressant for patients with existing obesity, hypertension, hyperglycemia, or hypercholesterolemia or family history of these comorbidities
- **Discuss the risks and benefits** with your patient if antidepressants that cause weight gain are needed for better efficacy, and document this conversation
- **Monitor patients' weight** as long as they continue taking drugs that may increase weight

TNF- α . Obese persons have increased plasma levels of TNF- α and its soluble receptor (sTNF-R p75), which may induce insulin resistance. Activation of the TNF- α system, such as by amitriptyline or mirtazapine, may promote weight gain.²⁴

Preventing weight gain

Early intervention is key to preventing drug-related weight gain and treating obesity. Provide informed consent and psychoeducation when prescribing antidepressants. In patients at metabolic risk, consider using weight-neutral or weight-loss agents (Table 2, page 45),⁴⁻¹⁶ and monitor for weight gain (Table 3). At-risk patients have:

- abdominal obesity (waist circumference >40 inches [102 cm] in men, >35 inches [88 cm] in women, or waist-to-hip ratio >0.9 in women and >1.0 in men)
- hyperlipidemia
- elevated body mass index (BMI [overweight = BMI 25 to 30 kg/m², obesity = BMI >30 kg/m²])
- hypertension
- diabetes mellitus or impaired glucose tolerance
- history of stroke or cardiovascular disease
- family history of obesity, hypertension, diabetes, or hyperlipidemia.

Use SGA guidelines? Consider following modified American Diabetes Association guidelines for metabolic monitoring of patients treated with SGAs.²⁵ We suggest that you follow SGA guidelines as a de-

fault when using mirtazapine—which is pharmacodynamically the most similar to SGAs—and TCAs. For patients taking other antidepressants, we recommend that you:

- measure blood pressure and weight, and calculate BMI often
- instruct patients to weigh themselves at home at least weekly in the morning and to report gains >5 lbs.

An overall 10-lb weight gain is clinically significant in most patients and calls for a management plan. Abdominal girth often increases as part of metabolic syndrome. If you choose to measure this variable and are uncomfortable reaching around patients while measuring, allow patients to apply the tape measure themselves.

Lab tests. Obtain fasting glucose and lipid levels at baseline for most patients and then quarterly in those with initial weight gain, medical comorbidities, or family history of hypertension, hypercholesterolemia, or diabetes. Many clinicians also screen for hypothyroidism and anemia, and these tests may be added. For patients without metabolic risk factors taking SSRIs and SNRIs, start quarterly draws if weight increases rapidly by >5 lbs or if BMI approaches ≥ 30 kg/m². Tracking fasting triglycerides can serve as a sentinel for metabolic syndrome, which sometimes occurs before substantial weight gain or hyperglycemia.

Dietary measures

If weight gain has occurred, a safe initial goal for patients is to lose 0.5% to 1% initial

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Table 4

Medications indicated for treating obesity

Drug/mechanism	Indication/dosage	Evidence of efficacy, safety	Comment
Sibutramine (sympathomimetic; serotonergic, noradrenergic reuptake inhibitor)	Obesity (5 to 20 mg/d)	↓10% to 15% of body weight in 1 year; ²⁹ safety, efficacy beyond 1 year undetermined	↓ triglycerides, total cholesterol, LDL cholesterol ↑ HDL cholesterol Monitor for serotonin syndrome when used with serotonergic psychotropics
Orlistat (inhibits gastric and pancreatic lipases by binding to these enzymes in the gut)	Obesity (120 mg tid with meals; take other drugs 1 hour pre- or post-orlistat)	↓9% to 10% of body weight in 1 year; ³⁰ safety, efficacy beyond 2 years undetermined	↓ triglycerides, total cholesterol, LDL cholesterol ↑ HDL cholesterol Lower risk of drug interactions than with sibutramine; GI side effects; multivitamin required
Rimonabant (investigational, pending FDA approval; selective type 1 cannabinoid receptor blocker)	Obesity (20 mg/d) (pending approval)	Reduced weight, improved heart disease risk factors in obese patients with metabolic syndrome or >1 cardiovascular risk factors (1-2 years) ³¹	Generally well-tolerated; mild nausea most common side effect

* Many studies in this table were conducted in patients taking second-generation antipsychotics for schizophrenia or bipolar disorder. Results may not apply to antidepressant-induced weight gain.

GI: gastrointestinal; HDL: high-density lipoprotein; LDL: low-density lipoprotein

body weight per week—or 5% to 10% of weight across several months. Diet and exercise produce maximal benefit but require commitment and motivation, which are often difficult or impossible for depressed patients. Encouraging the patient's efforts is worthwhile; if intervention is postponed until remission is achieved, weight gain may be substantially higher and more difficult to treat.

Cutting fat and calories. The first step in losing weight is to restrict high-fat and high-calorie foods and eat smaller portions. If this fails, then switch the patient to a low- or very-low-calorie diet, which provides a quick initial weight loss. This can motivate the patient but should be tried only under a physician's supervision.

Many patients benefit from structured commercial weight-loss programs, but the likelihood of regaining the weight is high if stopped. These programs typically recommend 1,200 kcal/day for women and 1,800 kcal/day for men, with 55% of calories from carbohydrates, about 25% to 35% from protein, and 10% to 25% from fat.

In a study of 100 patients, those on 2 liq-

uid meal replacements per day plus snacks and 1 low-fat meal (approximately 1,200 to 1,500 kcal/day) lost considerable weight in the first 3 months but regained some weight later. Many maintained weight loss on 1 liquid meal replacement per day plus snacks and 2 low-fat meals.²⁶

Low- and very-low-calorie diets are indicated for patients with BMI >35 kg/m²:

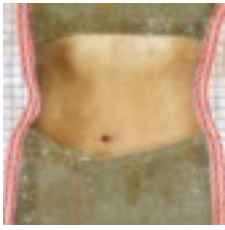
- in whom conservative treatment (a portion-controlled, low-fat diet) has failed
- and who are willing to maintain at least 1 year of treatment and major lifestyle changes.

A low-calorie diet provides ≥1,000 kcal/day; very low-calorie diets may provide ≤800 kcal/day and rely mostly on liquid meal replacements. This semi-starvation can produce fatigue, weakness, lightheadedness, and changes in vital signs, including blood pressure, heart rate, and respiratory rate. For this reason, extreme diets require a team approach with the primary care clinician and a dietitian.

Among mentally healthy patients following very-low-calorie diets in clinical trials, 90% lose ≥10 kg and 50% lose ≥20

Clinical Point

Eating habits can be changed with CBT; behavior modification alone can generate a weight loss of 0.5 to 0.7 kg per week



Weight gain

Clinical Point

Reserve antiobesity drugs for patients with BMI >30 kg/m² (>27 kg/m² in those with diabetes, hyperlipidemia, or heart disease)

Table 5

Medications used 'off label' for treating obesity

Drug/mechanism	Indication/dosage	Evidence of efficacy, safety	Comment
Amantadine (antiviral agent; may potentiate dopaminergic function)	Influenza A prophylaxis and Parkinson's disease (300 mg/d, with olanzapine)	↓3.5 kg over 3 to 6 months (study of 12 patients) ³²	Patients had gained a mean 7.3 kg during olanzapine treatment
Nizatidine (histamine-2 receptor antagonist)	Duodenal ulcer; GERD (600 mg/d as prophylaxis with olanzapine)	↓2.5 kg with nizatidine; ↑5.5 kg with placebo ³³ (16-week RCT)	Unknown effectiveness when used as prophylaxis with antidepressants; can cause delirium, especially in older patients
Naltrexone (opioid antagonist; decreases craving for sweet, fatty foods caused by TCAs and lithium)	Alcohol, narcotics addiction (50 mg/d)	TCA-induced weight gain reversed, then resumed after drug was stopped (8-patient trial) ³⁴	Small mean weight loss compared with previous drug-induced weight gain; no adverse effects seen on depressive symptoms
Topiramate (anticonvulsant)	Epilepsy, migraine (100 to 400 mg/d as adjunct to antipsychotics)	↓10 to 15 lbs in 33% to 55% of bipolar disorder patients ³⁵	May serve dual purpose in treating obese patients with affective disorders; fatigue, cognitive dulling, ataxia, glaucoma, oligohydrosis, acidosis are possible
Metformin (biguanide antihyperglycemic)	Type 2 diabetes (500 mg tid as adjunct to antipsychotics)	15 of 19 patients who gained 10% in body weight taking SGAs lost weight with add-on metformin (12-week, open-label trial)	Sporadic diarrhea in some patients; risk of lactic acidosis (tests unremarkable in this small trial) ³⁶

* Many studies in this table were conducted in patients taking second-generation antipsychotics for schizophrenia or bipolar disorder. Results may not apply to antidepressant-induced weight gain.

GERD: gastroesophageal reflux disease; RCT: randomized, double-blind, placebo-controlled trial; SGAs: second-generation antipsychotics; TCAs: tricyclic antidepressants

kg in the first 4 to 6 months.²⁷ Most weight loss occurs in the first 12 to 16 weeks, after which an ad libitum low-fat, high-fiber diet can be used.

Exercise has physiologic and psychological benefits, including inhibiting food intake and promoting a sense of self-control. Physical exercise increases insulin sensitivity and reduces the risk of secondary medical problems, such as heart disease. Walking ≥40 minutes daily produces maximal benefit, but walking even 30 minutes 3 times a week can help maintain weight.

CBT. Eating habits can be changed through identifying lifestyle behaviors to be modified, setting goals, modifying triggers of excessive eating, and reinforcing desired behavior with CBT. Gradual but consistent

behavior change leads to healthier eating habits, exercise, and weight loss. Behavior modification alone can generate a weight loss of 0.5 kg to 0.7 kg per week.²⁸

A study of 6 schizophrenia patients (mean age 37) examined CBT effects on weight gain associated with clozapine (n=4) or olanzapine (n=2). Mean BMI decreased from 29.6 kg/m² to 25.1 kg/m² after 7 to 9 sessions of individual CBT, followed by 16 biweekly group sessions that focused on weight reduction and weight maintenance. A dietician provided detailed counseling.²⁸

Using medications for weight loss

Switching. To avoid polypharmacy, consider switching the patient to a weight-neutral or weight-losing antidepressant,

such as bupropion. Keep in mind when switching medications, however, that the next agent with less weight-gain potential might not deliver comparable antidepressant efficacy.

Antiobesity drugs. Short of switching, an antiobesity drug (Table 4, page 51)²⁹⁻³¹ or off-label intervention (Table 5)³²⁻³⁶ may be warranted. Antiobesity drugs should not be used as primary therapy for obesity. Their use may be warranted, however, for psychiatric patients who:

- are unable to fully participate in diet and exercise programs because of symptoms (such as cognitive impairment or severe negative symptoms)
- lack social support (such as reflected by financial problems, homelessness, or poor compliance with treatment recommendations).

Generally, we reserve antiobesity drugs for patients with BMI >30 kg/m² (or >27 kg/m² in patients with diabetes, hyperlipidemia, or cardiovascular disease). Before adding these agents to a psychotropic regimen, however, review the relative risks and benefits with the patient and his or her primary care physician.

The goal of pharmacotherapy is for the patient to lose 5% to 10% of baseline weight in 3 to 6 months. Failure to achieve this goal is an indication to stop the medication. A plateau in weight loss after 6 to 9 months is expected and is not cause for discontinuation. If successful, drug treatment may be continued indefinitely, and both physician and patient must understand the intention to treat long-term. Most patients regain weight upon discontinuation.

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Related Resources

- Centers for Disease Control and Prevention. Overweight and obesity: contributing factors. www.cdc.gov/nccdphp/dnpa/obesity/contributing_factors.htm.
- Mathur R. What causes obesity? www.medicinenet.com/obesity_weight_loss/page2.htm.

Drug Brand Names

Amantadine • Symmetrel	Nizatidine • Axid
Amitriptyline • Elavil	Nortriptyline • Pamelor
Bupropion • Wellbutrin	Olanzapine • Zyprexa
Citalopram • Celexa	Orlistat • Xenical
Duloxetine • Cymbalta	Paroxetine • Paxil
Escitalopram • Lexapro	Phenelzine • Nardil
Fluoxetine • Prozac	Selegiline (transdermal) • EMSAM
Fluvoxamine • Luvox	Sertraline • Zoloft
Imipramine • Tofranil	Sibutramine • Meridian
Metformin • Glucophage	Topiramate • Topamax
Mirtazapine • Remeron	Trazodone • Desyrel
Naltrexone • ReVia	Venlafaxine • Effexor
Nefazodone • Serzone	

Disclosures

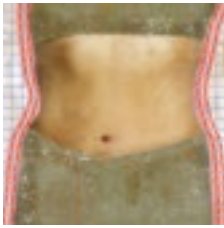
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Clinical Point

Weight gain may be substantially greater and more difficult to treat if you postpone intervention until after depression remission is achieved



Weight gain

Clinical Point

Consider stopping an antiobesity drug if the patient does not lose 5% to 10% of baseline weight in 3 to 6 months

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Bottom Line

Antidepressants may contribute to weight gain, although this effect varies among agents. Pre-existing obesity and metabolic factors increase the weight gain risk. Routinely educate patients, monitor weight and metabolic factors, and encourage diet and exercise management. Consider antiobesity medication, when indicated.

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Thomas Schwartz, MD

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