REVIEW

RASHMI DESHMUKH, MD
Department of Psychiatry and Psychology, The Cleveland Clinic

KATHLEEN FRANCO, MD*
Head, Section of Consultation-Liaison Psychiatry, Department of Psychiatry and Psychology, The Cleveland Clinic

Managing weight gain as a side effect of antidepressant therapy

ABSTRACT

Weight gain caused by antidepressant drugs is a major reason for patient noncompliance with treatment and poor treatment outcome. Knowing which drugs are more likely to cause weight gain in the short term and the long term is essential to any discussion with the patient about the risks vs the benefits of antidepressant therapy. Informing the patient up front about the chances of weight gain and what can be done if it occurs helps build a strong physician-patient relationship and promotes good treatment outcomes.

KEY POINTS

Tricyclic antidepressants and irreversible monoamine oxidase inhibitors (MAOIs) are more likely to cause weight gain in both the short term (< 6 months) and the long term (≥ 1 year). Reversible MAOIs are less likely to cause weight gain but are not available in the United States.

Selective serotonin reuptake inhibitors (SSRIs) are not likely to cause weight gain if used for 6 months or less. Opinions vary as to whether they cause weight gain when used for 1 year or longer. Paroxetine may be more likely than other SSRIs to cause weight gain.

For long-term therapy, nefazodone is less likely to cause weight gain than SSRIs and tricyclic compounds.

In general, bupropion is more likely to cause weight loss, and for long-term therapy it is less likely than SSRIs to cause weight gain.

*The author has indicated that she is on the speakers' bureau of the Pfizer company.

WEIGHT GAIN IS A SERIOUS concern for patients starting or already taking an antidepressant. Weight gain as a side effect of antidepressant therapy [1–5] in the short term (3 to 6 months) and the long term (1 year or longer) contributes to the reluctance of patients to continue or start treatment.[2]

Knowing how likely an antidepressant is to cause weight gain (TABLE 1) helps the physician select the best drug for the individual patient. Informing the patient about the chances of weight gain and what can be done about it helps build a strong physician-patient relationship and improves the effectiveness of treatment.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) inhibit an enzyme involved in the metabolism of biogenic amines (eg, norepinephrine, epinephrine, dopamine, serotonin) and xenobiotic amines (eg, tyramine, ephedrine, phenylephrine). They are effective against depression and anxiety.

MAOIs that bind irreversibly to receptors (eg, phenelzine, isocarboxazid, tranylcypromine) typically cause weight gain, and this is perhaps more common with phenelzine than with isocarboxazid and tranylcypromine.[2,6–8] Reversible MAOIs are less likely to cause weight gain but are currently unavailable in the United States.[2]

TRICYCLIC ANTIDEPRESSANTS

Weight gain is a common and well-known adverse effect of short-term and long-term treatment with tricyclic antidepressants,[2] primarily as a result of excessive appetite. Possible

TABLE 1

Effect of antidepressant drugs on body weight

DRUG	EFFECT ON WEIGHT
Monoamine oxidase inhibitors (irreversible type)	Weight gain likely in short term (< 6 months) and long term (≥ 1 year)
Tricyclic compounds	Weight gain likely in short term and long term
Selective serotonin reuptake inhibitors (SSRIs) other than paroxetine	Weight gain in short term less likely Weight gain in long term possible, but evidence is varied
Paroxetine	Weight gain in short and long term more likely than for other SSRIs
Nefazodone	Likely to have no effect on weight
Bupropion	Likely to cause weight loss
Mirtazapine	More likely than placebo to cause weight gain in short term, but less likely than tricyclics
Venlafaxine	Likely to have no effect on weight

A strong patient-physician alliance is integral to positive outcome

mechanisms include blockade of histamine H_1 and serotonin 2C receptors, carbohydrate craving caused by alpha-noradrenergic activity or histamine blockade, changes in the regulation of body fat stores by modulating neurotransmitter systems at the hypothalamic level, and recovery from clinical depression.[2,5,9,10]

Because tertiary tricyclic antidepressants such as amitriptyline, imipramine, and doxepin are stronger histamine blockers than are secondary tricyclics such as desipramine and nortriptyline, the tertiary tricyclic drugs are more likely to cause weight gain.

In a randomized study of hospitalized depressed patients, Fernstrom and Kupfer[10] reported that treatment with three tricyclic compounds promoted weight gain, with amitriptyline adding more weight than nortriptyline and desipramine. In the same study, most patients treated with zimelidine (a tricyclic antidepressant, not available in the United States) showed no weight gain and often demonstrated weight loss.

A study by Frank et al[11] indicated that 13% to 15% of imipramine-treated patients gained 10 or more pounds by week 16 or 33 of treatment. In contrast, at least one study of nursing home residents found no measurable difference in weight outcomes after treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), or no antidepressant treatment.[12] All drug groups showed mean weight changes of less than 2.1 lb after 6 months of therapy. Whether or not these findings can be generalized to community patients is unclear.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Weight gain is less likely with SSRIs when they are used for 6 months or less. There are diverse opinions about whether increases in body weight occur in patients using them for 1 year or longer. Paroxetine may be more likely than other SSRIs to cause weight gain during short-term or long-term treatment.

Weight change induced by SSRIs is probably related to alteration in serotonin 2C receptor activity, appetite increase, carbohydrate craving, or recovery from clinical depression.[8,13,14]

In one large placebo-controlled study,[15] outpatients with depression treated with fluoxetine for 12 weeks lost 0.3 kg on average. Croft et al[16] documented a loss of 0.8 kg with sertraline vs 1.1 kg with bupropion in a placebo-controlled 12-week comparison. On the other hand, Mackle and Kocsis,[17] in a study lasting fewer than 8 weeks, reported a weight gain of

0.5% in patients taking the SSRI citalopram vs 0.9% in those taking placebo. Bouwer and Harvey,[14] in an open-label study without placebo control, reported a rapid appetite increase and an average weight gain of 7.1 kg with citalopram, which is well known to have a marked affinity for histamine H_1 receptors and, therefore, stimulates the appetite.

In nursing home patients, SSRIs are as likely to cause weight gain as they are to cause weight loss, but the magnitude of the effect is generally small.[12] Studies of short-term antidepressant therapy have suggested that weight gain is less likely to occur when SSRIs are used in the short term (3 to 6 months). When weight gain does occur, the rates are comparable with those of placebo.[2]

Clearly, there is uncertainty about whether unexpected increases in body weight occur during long-term treatment as opposed to short-term treatment with SSRIs.[18] In its revised practice guideline for the treatment of major depressive disorder,[19] the American Psychiatric Association acknowledges that the literature differs as to whether patients taking SSRIs beyond the acute phase experience weight gain as a medication side effect.[19] Six-month placebo-controlled studies have found no significant difference in weight gain with fluoxetine[15] or citalopram.[17] A 12-month study of citalopram reported 4.7% of 541 patients with depression experienced weight gain of greater than 5 kg.[20] Another placebo-controlled study of the prophylactic effect of citalopram in unipolar, recurrent depression at 48 to 77 weeks reported no weight gain with citalopram.[21]

Whether long-term SSRI use leads to weight gain is still unclear

Weight gain more likely with long-term paroxetine

Fava et al[22] presented data from a 6-month double-blind non–placebo-controlled study of paroxetine, sertraline, and fluoxetine. The rate of emergence of significant weight gain, defined as a 7% or greater increase in body weight, was 25.5% for paroxetine vs 4.2% with sertraline and 6.8% with fluoxetine.

A 24-week double-blind study of paroxetine and sertraline[23] showed significantly more weight gain with paroxetine but failed to report the percentage of patients who exhibited at least a 7% change in weight, the accepted standard of clinical significance.

NEFAZODONE

Nefazodone seems to be less associated with weight gain than other antidepressants in studies of both short-term and long-term therapy. It is a phenylpiperazine with selective serotonin and norepinephrine reuptake inhibition.

A 36-week placebo-controlled study[24] reported weight gain associated with nefazodone to be similar to placebo (7.6% vs 8.6%).

Sussman et al[25] conducted a pooled analysis of three clinical trials comparing nefazodone with SSRIs and three clinical trials comparing nefazodone with imipramine.[7,18,25] Using 7% or greater weight change as a measure of clinical significance, results indicated that 4.3% of SSRI-treated patients had lost weight at some point in the acute phase (6 to 8 weeks) vs 1.7% with nefazodone. During longer treatment (16 to 46 weeks), weight gain occurred more often in patients taking an SSRI than in patients taking nefazodone (17.9% vs 8.3%). Patients taking imipramine also had a greater increase in body weight than patients taking nefazodone in both short-term and long-term phases, indicating that nefazodone may be less likely to cause weight gain than both SSRIs and tricyclic antidepressants when used longer than 1 year.

BUPROPION

Bupropion is essentially devoid of antihistaminic effects and is commonly associated with weight loss. This aminoketone weakly blocks postsynaptic serotonin and norepinephrine uptake, in addition to inhibiting presynaptic dopamine reuptake.

A number of studies have compared bupropion with placebo, sertraline, tricyclic antidepressants, or trazodone.[16,26–29] All showed that bupropion was associated with weight loss (mean 2.5 lb), whereas the other drugs were associated with weight gain. In placebo-controlled studies, depressed outpatients treated for 12 weeks lost, on average, 0.3 kg with fluoxetine,[15] 0.8 kg with sertraline[16] or 1.1 kg with bupropion.[16] In a separate 52-week double-blind placebo-controlled study, Weihs et al[29] showed a mean weight loss of 1.2 kg in patients treated with bupropion.

MIRTAZAPINE

Through blockade of histamine H_1 and serotonin 2C receptors, mirtazapine is likely to be related to weight gain in both the short term and the long term.[1] A piperazine-azepine compound, it enhances central noradrenergic and serotonergic activity. It is a potent antagonist of H_1, serotonin 2, and serotonin 3, and a moderate antagonist of peripheral alpha-1 adrenergic and muscarinic receptors.

A meta-analysis of four US studies found that patients gained weight during the first 4 weeks of treatment.[30]

Mirtazapine is more likely to cause weight gain than placebo but may be less likely to cause weight gain than tricyclic antidepressants such as amitriptyline.[31,32] A comparison of mirtazapine and venlafaxine in the treatment of severely depressed hospitalized patients with melancholic features identified a significant weight gain of 2.0 ± 3.7 kg in the mirtazapine group and a loss of 0.5 ± 2.9 kg in the venlafaxine group.[33]

VENLAFAXINE

Treat weight gain with behavior modification, dietary changes, another drug

Venlafaxine, a potent inhibitor of serotonin and norepinephrine reuptake, is sometimes prescribed for patients with psychomotor retardation, hypersomnia, or resistance to other antidepressants.[34]

A short-term study comparing venlafaxine with fluoxetine found no significant weight gain with either agent.[35] Thus, like SSRIs and unlike mirtazapine, venlafaxine is less likely to cause weight gain in the short term,[33] although there are not enough data to comment on its long-term effects.

RECOMMENDATIONS FOR MANAGEMENT

Many patients prematurely discontinue their medication as a result of increased appetite or weight gain and may fall back into depression. On the other hand, fighting weight gain once it has occurred can be very difficult, and it is advisable to consider the likelihood and potential consequences of weight gain when choosing an antidepressant.[36,37]

Educating the patient about the chances of weight gain as a side effect of treatment and its management is best accomplished through a strong patient-physician alliance and is integral to positive outcome.

Preventing weight gain in patients on antidepressants is the ideal strategy. It typically involves caloric restriction and increased caloric expenditure through aerobic exercise.[1] Patients may benefit from a nutritional consultation and participation in a low-cost commercial weight-loss program. Individuals can be asked to record weekly weights, and thus both clinician and patient can be alerted to small increases in weight before the problem becomes too difficult. Maintaining a food diary and behavioral techniques such as increasing meal frequency, smaller meals, or decreasing the pace of eating can help.

Switching to another drug with a lower risk of weight gain is an alternative approach, although this carries a risk of loss of clinical effect.

Addition of another agent such as a stimulant (methylphenidate, amphetamines), an H_2 receptor antagonist (famotidine), triiodothyronine, topiramate, bupropion, or naltrexone may help diminish weight gain.[1,37] Although none has been tested systematically, low doses have been prescribed along with an antidepressant in an effort to avoid weight gain associated with antidepressant therapy.

In our practice, we have found that adding low-dose bupropion (100 to 150 mg/day) or topiramate (25 to 50 mg/day) may help weight loss when used in addition to diet control and exercise.

REFERENCES

1. **Janicak PG, Davis JM, Preskorn SH, Ayd Fj Jr.** Principles and Practice of Psychopharmacology. Baltimore: Williams & Wilkins, 1997:219–273.
2. **Fava M.** Weight gain and antidepressants. J Clin Psychiatry 2001; 61(suppl 11):37–41.
3. **Kaplan HI, Sadock BJ.** Mood disorders. In: Kaplan and Sadock's Synopsis of Psychiatry: behavioral sciences, clinical psychiatry. 8th ed. Baltimore: Williams & Wilkins, 1998:524–580.
4. Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV). Washington DC: American Psychiatric Association Press.
5. **Malhotra S, McElroy SL.** Medical management of obesity associated with mental disorders. J Clin Psychiatry 2002; 63:(suppl 4):24–32.
6. **Rabkin J, Quitkin F, Harrison W, Tricamo E, McGrath P.** Adverse reactions to monoamine oxidase inhibitors. Part 1: a comparative study. J Clin Psychopharmacol 1984; 4:270–278.
7. **Cantu TG, Korek JS.** Monoamine oxidase inhibitors and weight gain. Drug Intell Clin Pharm 1988; 22:755–759.

8. **Sussman N, Ginsberg D.** Effects of psychotropic drugs on weight. Psychiatr Ann 1999; 29:580–594.
9. **Pijl H, Meinders AE.** Bodyweight change as an adverse effect of drug treatment: mechanisms and management. Drug Saf 1996; 14:329–342.
10. **Fernstrom MH, Kupfer DJ.** Antidepressant-induced weight gain: a comparison study of four medications. Psychiatry Res 1988; 26:265–271.
11. **Frank E, Kupfer DJ, Bulik CM, Levenson JA.** Imipramine and weight gain during the treatment of recurrent depression. J Affect Disord 1990; 20:165–172.
12. **Rigler SK, Webb MJ, Redford L, Brown EF, Zhou J, Wallace D.** Weight outcomes among antidepressant users in nursing facilities. J Am Geriatr Soc 2001; 49:49–55.
13. **Benazzi F.** Weight gain in depression remitted with antidepressants: pharmacological or recovery effect? Psychother Psychosom 1998; 67:271–274.
14. **Bouwer CD, Harvey BH.** Phasic craving for carbohydrate observed with citalopram. Int Clin Psychopharmacol 1996; 11:273–278.
15. **Michelson D, Amsterdam JD, Quitkin FM, et al.** Changes in weight during a 1-year trial of fluoxetine. Am J Psychiatry 1999; 156:1170–1176.
16. **Croft H, Settle E Jr, Houser T, Batey SR, Donahue RM, Ascher JA.** A placebo-controlled comparison of the antidepressant efficacy and effects of sexual functioning of sustained release bupropion and sertraline. Clin Ther 1999; 21:643–658.
17. **Mackle M, Kocsis J.** Effects on body weight of the SSRI citalopram. Presented at the 37th annual meeting of the American College of Neuropsychopharmacology; Dec 14-18, 1998: Las Croabas, Puerto Rico.
18. **Sussman N, Ginsberg D.** Rethinking side effects of the selective serotonin reuptake inhibitors: sexual dysfunction and weight gain. Psychiatr Ann 1998; 28:89–97.
19. **American Psychiatric Association.** Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry 2000; 157(suppl 4):1–45.
20. **Wade A, Overo KF, Lemming O, et al.** Weight monitoring during two long term trials of citalopram. Presented at the 12th Congress of the European College of Neuropsychopharmacology; Sept 21–25, 1999; London, England.
21. **Hochstrasser B, Isaksen PM.** Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. Br J Psychiatry 2001; 178:304–310.
22. **Fava M, Judge R, Hoog SL, Nilsson ME, Koke SC.** Fluoxetine vs sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 2000; 61:863–867.
23. **Agren H, Aberg-Wistedt A, Akerblad AC, et al.** Sertraline vs paroxetine in major depression: a multicenter double blind 24 week comparison. Presented at the 152nd annual meeting of the APA; May 1999, Toronto, Ontario, Canada.
24. **Fieger AD, Bielski RJ, Bremner J, et al.** Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. Int Clin Psychopharmacol 1999; 14:19–28.
25. **Sussman N, Ginsberg DL, Bikoff J.** Effects of nefazodone on body weight: a pooled analysis of SSRI and imipramine controlled trials. J Clin Psychiatry 2001; 62:256–260.
26. **Weisler RH, Johnston JA, Lineberry CG, Samara B, Branconnier RJ, Billow AA.** Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol 1994; 14:170–179.
27. **Feighner J, Hendrickson G, Miller L, Stern W.** Double-blind comparison of doxepin versus bupropion in outpatients with major depressive disorder. J Clin Psychopharmacol 1986; 6:27–32.
28. **Chouinard G.** Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983; 44:121–129.
29. **Weihs K, Houser T, Batey S, et al.** Long-term treatment of depression with sustained release bupropion. Presented at the 152nd annual meeting of the American Psychiatric Association; May 2000; Chicago, Il.
30. **Goodnick PJ, Kremer C.** Weight gain during mirtazapine therapy. Prim Psychiatry 1998; 3:103–108.
31. **Smith WT, Glaudin V, Panagides J, Gilvary E.** Mirtazapine vs amitriptyline vs placebo in the treatment of major depressive disorder. Psychopharmacol Bull 1990; 26:191–196.
32. **Montgomery SA, Reimitz PE, Zivkov M.** Mirtazapine versus amitriptyline in the long-term treatment of depression: a double blind placebo-controlled study. Int Clin Psychopharmacol 1998; 3:103–108.
33. **Guelfi JD, Ansseau M, Timmerman L, Korsgaard S.** Mirtazapine vs venlafaxine in hospitalized severely depressed patients with melancholic features. Mirtazapine-Venlafaxine Study Group. J Clin Psychopharmacol 2001; 21:425–431.
34. **Stahl SM.** Psychopharmacology of antidepressants. London, UK: Dunitz 1998.
35. **Silverstone PH, Ravindran A.** Once daily venlafaxine extended release compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry 1999; 60:22–28.
36. **Zajecka JM.** Clinical issues in long term treatment with antidepressants. J Clin Psychiatry 2000; 61(suppl 2):20–25.
37. **Masand PS.** Weight gain associated with psychotropic drugs. Review. Expert Opinion on Pharmacotherapy 2000; 1:377–389.

ADDRESS: *Kathleen Franco, MD, Section of Consultation-Liaison Psychiatry, Department of Psychiatry and Psychology, P57, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*