Weight Gain and Antidepressants

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Weight gain during antidepressant treatment can be either a sign of improvement in patients who have weight loss as a symptom of depression or a residual symptom in patients who overeat when depressed. However, significant weight gain during the acute phase of treatment or weight gain that continues despite achieving full remission of depressive symptoms is likely to be a side effect of antidepressant treatment. Weight gain is a relatively common problem during both acute and long-term treatment with antidepressants, and it is an important contributing factor to noncompliance. This article will review the literature with regard to the relative risk for weight gain of antidepressants. It appears that tricyclic antidepressants (TCAs) and perhaps monoamine oxidase inhibitors (MAOIs) may be more likely to cause weight gain than the selective serotonin reuptake inhibitors (SSRIs) or the newer antidepressants, with the exception of mirtazapine, which may be placed between the SSRIs and the TCAs in terms of relative risk for weight gain. Paroxetine may be more likely to cause weight gain than the other SSRIs during long-term treatment, and bupropion and nefazodone may be less likely to cause weight gain than the SSRIs in the long term, although more studies are necessary to confirm these impressions.
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Decreased appetite and weight loss are common symptoms of depression, particularly among patients with melancholic features. Weight gain following antidepressant treatment may, therefore, be a sign of recovery from depression and may be viewed positively by patients. On the other hand, increased appetite, carbohydrate craving, and weight gain can also be symptoms of depression, in particular among depressed patients with atypical features. Weight gain in the initial phases of antidepressant treatment may be due, in those instances, to the persistence of such reverse neurovegetative symptoms. Weight gain that continues despite achieving remission of depressive symptoms can be either a residual symptom of depression or a side effect of the antidepressant. For all these reasons, a significant methodological issue affecting most studies of the effects of antidepressants on weight is that, typically, all subjects are included in the analyses and all changes in weight are reported, regardless of whether the change in weight reflects an improvement in depressive symptoms. All these issues affect studies that examine the short-term effects of antidepressants on weight in particular, as it is much more difficult to ascertain whether a change in weight is in fact a side effect of the antidepressant. Some of the more recent studies have examined the relationship between rates of significant weight gain and baseline body mass index (BMI), making the assumption that weight gain has to be regarded as a side effect in individuals with BMI within the normal or the overweight/obese range at baseline.

Weight gain, in fact, is a relatively common problem during both the acute and long-term treatment with antidepressants, and it is an important contributing factor to noncompliance. In addition, a risk of significant weight gain may frequently affect the degree of acceptability of a given pharmacologic treatment. Many patients are reluctant to be treated with an antidepressant that may affect their weight. Therefore, clinicians need to consider this issue when presenting patients with the relative risks and benefits of the proposed therapeutic options. Unfortunately, there are very few studies in the literature that have specifically examined this issue, making it quite difficult to estimate the relative risk for weight gain across antidepressant therapies.

MONOAMINE OXIDASE INHIBITORS

Although weight gain is often considered a typical side effect of the irreversible monoamine oxidase inhibitors (MAOIs), few studies have examined this issue in a systematic way. An early study by Caffey et al.[1] suggested that the risk for weight gain during short-term treatment with MAOIs was comparable with that of tricyclic antidepressants (TCAs). A retrospective study of a large cohort of patients treated with either phenelzine or tranylcypro-

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mine showed that weight gain is an adverse event with both drugs, although more commonly with phenelzine.[2] A literature review[3] also suggested that weight gain occurred with phenelzine more commonly than with other MAOIs such as isocarboxazid and tranylcypromine, but the fact that this conclusion was based on the frequency of case reports in the literature indicates that it may simply reflect reporting biases and not the actual frequency of this side effect. Reversible MAOIs such as moclobemide may be less likely to cause weight gain than the older, irreversible MAOIs. In a 7-week trial,[4] significant weight gain was reported with patients taking amitriptyline but not with those taking moclobemide, and in a 6-week study,[5] weight gain was observed in 2.6% of moclobemide-treated patients versus 21.6% of patients treated with maprotiline. Finally, in a large cohort of patients (N = 1120), only 1.4% had a ≥ 10 kg weight gain during long-term treatment with moclobemide.[6] All of these studies seem to support the impression that, while weight gain is a common side effect of irreversible MAOIs, reversible MAOIs such as moclobemide may be less likely to cause weight gain in both the short and long term. Given the paucity of data on other reversible MAOIs and their effect on weight, more studies are necessary to support this view.

TRICYCLIC ANTIDEPRESSANTS

TCAs are well known for their effect on weight, both in the short and long term. Weight gain is a common adverse event after treatment with TCAs, even for 1 month, with amitriptyline having probably the greatest likelihood of causing it.[7] This is supported by a study by Ansseau et al.[8] showing that significant weight gain was more common after 5 weeks of treatment with amitriptyline than with milnacipran. Finally, the short-term effect on weight of TCA treatment is supported by the findings of Fernstrom et al.[9] that 15% of 52 imipramine-treated patients had a weight gain equal to or greater than 10 lb after 16 weeks of treatment. All these studies confirm the clinical impression that tricyclics are associated with a risk of weight gain, even as early as 5 weeks into treatment.

In a review by Garland et al.,[10] weight change in TCA-treated patients varied from 0.57 kg to 1.37 kg per month of therapy. In a continuation therapy study, Berken et al.[11] examined the effect of long-term treatment with TCAs on weight gain and showed that, for an average of 6 months of treatment, the mean weight increase was 1.3 to 2.9 lb per month. These data suggest an increased risk of even further weight gain during long-term treatment with TCAs. Not all patients treated with TCAs in the long term, however, will report substantial increases in weight. Using data from the Pittsburgh study, Frank and colleagues[12] have shown that 13.3% of patients treated with imipramine for an average of 33 weeks had a 10% or more increase in body weight.

Researchers have discussed possible mechanisms by which TCAs may induce weight gain, such as a marked increase in the preference for sweets,[11,13] excessive appetite probably through a blockade of the histamine H_1 receptors,[14] changes in the regulation of body fat stores by modulating neurotransmitter systems at the hypothalamic level,[15] increased energy efficiency,[16] and finally, in some cases, clinical improvement.[17] However, there are no definitive studies on the actual pathophysiology of weight gain as a side effect of TCAs, and the role of serotonin 5-HT_{2C} receptors, known to be involved in the regulation of appetite and body weight,[14] has not yet been investigated in a systematic fashion.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Selective serotonin reuptake inhibitors (SSRIs) had been initially viewed by clinicians and researchers as weight neutral or, in some cases, associated with weight loss. In fact, in a 6-week, acute trial,[18] weight loss was reported with fluoxetine, while weight gain occurred with maprotiline. A significant weight loss (mean = –0.3 kg) was reported following 12 weeks of treatment in a large (N = 832) study of depressed outpatients.[19] In a study by Croft et al.[20] comparing sertraline and bupropion, patients taking both agents had a decrease in weight (0.8 kg on average for sertraline and 1.1 kg on average for bupropion). In a 6-week trial,[21] mianserin was associated with weight gain, while fluvoxamine was not. Finally, in studies with a ≤ 8 week duration, a ≥ 7% increase in body weight was reported in 0.5% of citalopram-treated patients and 0.9% of placebo-treated patients.[22] These acute therapy studies on the effect of SSRIs on weight suggest that weight gain is unlikely to occur when these drugs are used in the short term e–d, when it does occur, it appears to be present at rates that are comparable with those of placebo.

The literature on the effects of SSRIs during long-term treatment is limited mostly to uncontrolled or anecdotal reports.[23] Sussman and Ginsberg[24] have suggested that, at least anecdotally, long-term treatment with SSRIs may be associated with weight gain. A retrospective study of 31 remitted depressed patients on long-term treatment with SSRIs alone showed a 58% rate of weight gain, although weight loss had occurred during the index episode of depression, and the BMI of patients was not reported.[25] In the recently published study by Michelson et al.,[19] after 26 weeks of continuation treatment with fluoxetine, 20 mg/day, 4.8% of the patients had a ≥ 7% increase in body weight, a rate no different from that of placebo, which was 6.3%. Mackle and Kocsis[22] presented similar data concerning citalopram from 6-month duration studies, with the difference in rate of ≥ 7% increase in body weight between citalopram and placebo not being significant (3.9% vs. 2.8%, respectively). Consistent with these find-

ings, a 12-month study[26] of citalopram in depression showed that 4.7% of 541 patients reported a weight gain greater than 5 kg.

My colleagues and I[27] have recently completed a double-blind study of paroxetine, sertraline, and fluoxetine, in which we found that the mean change in weight from baseline to endpoint for up to 6 months of treatment with these 3 SSRIs was significantly different, in that paroxetine had a significant increase of about 3.6% over the 6 months versus a slight increase for sertraline and a slight decrease for fluoxetine. When we examined the rate of emergence of significant weight gain—defined as 7% or more increase in body weight—the rate was about 25.5% for paroxetine, significantly higher than the rates for fluoxetine (6.8%) and sertraline (4.2%). Almost all of the patients who reported significant weight gain in this study were either overweight or their BMI was within the normal range before starting treatment. Given the lack of a placebo arm in the design of the study, one cannot determine whether the rates of weight gain observed with these 3 SSRIs represent a true increased risk for such event. On the other hand, if you consider the 6.3% rate of weight gain with placebo from the Michelson et al.[19] study and the 2.8% rate of weight gain with placebo from the study by Mackle and Kocsis,[22] it would seem unlikely that the 25% rate of weight gain that we observed in patients taking paroxetine during 6 months of treatment was due to the spontaneous rate of weight gain in this population. Still, it is hard to interpret the significance of the rates of weight gain reported with fluoxetine (6.8%) and sertraline (4.2%), as they are more in the range of that seen with placebo. In addition, one cannot establish whether the patients who gained weight in the long term did so because of a return of depressive symptoms, including overeating, or because of the antidepressant treatment itself (e.g., true side effect). However, the higher risk for significant weight gain with paroxetine compared with other SSRIs has been confirmed by a 24-week, double-blind study of sertraline versus paroxetine.[28]

The possible mechanisms for SSRI-induced weight gain are (1) recovery from depression or clinical improvement,[25] (2) appetite increase/carbohydrate craving,[29] and (3) changes in serotonin 5-HT_{2C} receptor activity.[14] There are no definitive studies on the actual pathophysiology of weight gain as a side effect of SSRIs in those individuals in whom it occurs, and the role of the autonomic nervous system in the control of energy metabolism and nutrient partitioning[30] and of other modulators of body weight, such as neuropeptide Y[14] or leptin,[30] have not been investigated either.

ATYPICAL ANTIDEPRESSANTS

Some convincing evidence shows that nefazodone may be relatively weight neutral in both the short and long term. In a 36-week continuation phase study,[31] 7.6% of nefazodone-treated patients reported weight gain versus 8.6% of placebo-treated patients. Data pooled from 6 long-term studies comparing nefazodone with the SSRIs fluoxetine, sertraline, and paroxetine reveal that a significant increase in body weight, defined as a ≥ 7% increase in body weight, was present in 8.8% of nefazodone-treated patients and 17.9% of the SSRI-treated patients,[14] suggesting that nefazodone may be less likely to cause weight gain than the SSRIs in the long term.

Bupropion is an antidepressant associated with weight loss. As mentioned earlier, the study by Croft et al.[20] found that bupropion had a decrease in weight (1.1 kg on average). Weight loss is a relatively common adverse event in many open trials with bupropion,[32] and Weisler et al.,[33] in a 6-week trial, found a 2.5-lb mean weight loss with bupropion treatment, versus a 1.2-lb mean weight gain with trazodone. In 8-week placebo-controlled premarketing clinical trials, a weight loss of greater than 5 lb occurred in 14% and 19% of patients treated with bupropion sustained release (SR) 300 and 400 mg/day, respectively, versus 6% of placebo-treated patients. A weight gain of greater than 5 lb occurred more frequently in patients treated with placebo than in patients treated with bupropion SR. A weight loss of greater than 10 lb occurred in 2% of patients treated with bupropion SR 300 mg/day, 6% of patients treated with 400 mg/day, and 2% of placebo-treated patients (Glaxo Wellcome, data on file). In a double-blind, placebo-controlled discontinuation study over 52 weeks, at the end of the double-blind continuation phase responders to bupropion SR were randomly assigned to either staying on bupropion SR therapy or going on placebo therapy. The subjects in the bupropion SR treatment group had a mean weight loss of 1.2 kg and the subjects in the placebo group had essentially no change (+ 0.02 kg).[34] Finally, in two 13-week trials,[35,36] weight gain was more common in patients taking doxepin and amitriptyline than in those taking bupropion.

In contrast, mirtazapine is an atypical antidepressant with the profile most likely to be associated with weight gain, probably because of its significant histamine H_1 receptor blocking effects. Treatment for 6 weeks with mirtazapine has been shown to be more commonly associated with weight gain than placebo.[37] During a 20-week continuation phase study published by Montgomery and colleagues,[38] weight gain was also more common with mirtazapine (13%) than placebo, but this side effect was less common with mirtazapine than with amitriptyline (22%). So mirtazapine, even though it may be less likely to cause weight gain than tricyclics, is still a drug associated with weight gain, both acutely and in the long term. A meta-analysis[39] of 4 U.S. studies showed that most of the weight gain experienced with mirtazapine took place during the first 4 weeks of treatment.

VENLAFAXINE

A 12-week study by Silverstone and Ravindran[40] comparing venlafaxine and fluoxetine showed no significant weight gain among patients treated with either agent. This finding suggests that venlafaxine, like the SSRIs, is not associated with weight gain in the short term. On the other hand, very little is known about the effect of venlafaxine on weight in the long term. At least anecdotally, some patients complain of weight gain during long-term treatment with venlafaxine, but it is unclear what the relative risk for this side effect with this agent in the long term is. There is a clear need for studies assessing the impact of continuation and maintenance treatment with venlafaxine on weight in comparison with placebo.

ANTIDEPRESSANT COMBINATIONS

Antidepressant combinations (in which 2 or more antidepressants are used at the same time) are commonly used in clinical practice, but they are typically understudied in terms of long-term safety and tolerability. For example, in most of the studies in which the combination of SSRIs and TCAs has been used in refractory populations, patients' side effects were typically monitored only in the short term.[41] Few systematic studies have examined whether weight gain as a side effect is additive if a patient is taking more than one compound that is associated with a risk of weight gain. Similarly, very little is known about the effect on weight of combining antidepressants with other psychotropic drugs associated with a risk for weight gain such as lithium, anticonvulsants, or antipsychotics.[42] For example, Carpenter et al.[43] have assessed the efficacy and tolerability of mirtazapine augmentation of SSRIs in refractory depression in an open, uncontrolled study. Their study suggested the efficacy of this combination in refractory depressed patients, and the most common side effect of the augmentation was weight gain when mirtazapine was added to the SSRIs. Since no arm considered mirtazapine therapy alone in the study, one cannot determine whether the rate of weight gain reported in this open trial was the same as the rate of mirtazapine alone. Similar issues concern the studies that have assessed the efficacy of augmenting agents such as lithium or atypical antipsychotic agents in patients nonresponsive to SSRIs.[41] In some cases, clinicians use antidepressant combinations partly to reduce the risk for weight gain, such as in the case of combining bupropion with SSRIs, but again there are no studies showing a reduced risk for weight gain with this combination compared with SSRIs alone.

COURSE OF WEIGHT GAIN

The course of weight gain as a side effect of antidepressant treatment is poorly studied. Most of the studies that have examined changes in weight during acute and/or continuation treatment with antidepressants do not typically determine whether the risk for weight gain reaches a plateau or continues. In the maintenance treatment Pittsburgh Study,[44] in which patients were randomly assigned to either staying on imipramine therapy or going off imipramine therapy after acute and continuation therapy phases, two thirds of all patients gained some weight (mean gain = 5.5% above baseline body weight), although there was no difference between drug and no-drug conditions in terms of weight gain. On the other hand, the marked difference in prophylactic efficacy between continued imipramine treatment and no treatment with imipramine may have confounded the assessment of the risk for weight gain with imipramine, since more patients in the non-imipramine groups had a return of depressive symptoms, which may have included overeating and carbohydrate craving.

MANAGEMENT APPROACHES

Once clinicians have made the determination that a patient is experiencing weight gain as a side effect of an antidepressant, what are the options? Typically, the first option clinicians consider is that of behavioral modification. Behavioral interventions typically involve caloric restriction or increased caloric expenditure and increased physical exercise. Unfortunately, many patients—even with changes in, or attempts to restrict, their caloric intake—may experience significant weight gain with antidepressants despite increased physical activity. An alternative approach is switching to other antidepressants with a lower risk for weight gain, but one is not necessarily guaranteed that the response will be maintained. Therefore, it is typically easier to consider the relative risk for weight gain early in the decision of which antidepressant to choose and then to start the patient on an antidepressant therapy with a relatively lower risk. Another common management option is that of keeping the same antidepressant and using certain augmentation strategies, such as phentermine, psychostimulants, sibutramine, histamine H_2 receptor antagonists, triiodothyronine, naltrexone, and bupropion. The main problem is that none of these strategies have been tested systematically; many derive primarily from anecdotal observations.

CONCLUSION

In conclusion, weight gain is a common side effect of both acute and long-term treatment with antidepressants. TCAs, and perhaps MAOIs, are more likely to cause weight gain than the SSRIs or the newer antidepressants, with the exception of mirtazapine, which may be placed between the SSRIs and the TCAs in terms of relative risk for weight gain. Paroxetine may be more likely to cause

weight gain than the other SSRIs during long-term treatment, and bupropion and nefazodone may be less likely to cause weight gain than the SSRIs in the long term, although we need further studies to confirm these impressions. There is a clear need to study the emergence of weight gain during antidepressant treatment more closely and determine when weight gain is a true side effect, an effect of clinical improvement, or a reversal of the positive neurovegetative symptoms.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), naltrexone (ReVia), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), phentermine (Fastin and others), sertraline (Zoloft), sibutramine (Meridia), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, fluvoxamine is not approved by the U.S. Food and Drug Administration for the treatment of depression and naltrexone, phentermine, and sibutramine are not approved for weight loss due to psychotropics.

REFERENCES

1. Caffey EM, Rosenblum MP, Klett CJ. Side effects and laboratory findings in a study of antidepressant drugs. Dis Nerv Syst 1962;23:444–449
2. Rabkin J, Quitkin F, Harrison W, et al. Adverse reactions to monoamine oxidase inhibitors, part 1: a comparative study. J Clin Psychopharmacol 1984;4:270–278
3. Cantu TG, Korek JS. Monoamine oxidase inhibitors and weight gain. Drug Intell Clin Pharm 1988;22:755–759
4. Bakish D, Wiens A, Ellis J, et al. A double-blind placebo-controlled comparison of moclobemide and amitriptyline in the treatment of depression. Can J Psychiatry 1992;37(suppl 1):12–17
5. Vaz-Serra A, Figueira ML, Firmino H, et al. Multicenter double-blind study of moclobemide and maprotiline. Clin Neuropharmacol 1994;17(suppl 1): S38–S49
6. Moll E, Neumann N, Schmid-Burgk W, et al. Safety and efficacy during long-term treatment with moclobemide. Clin Neuropharmacol 1994;17 (suppl 1):S74–S87
7. Fernstrom MH, Kupfer DJ. Antidepressant-induced weight gain: a comparison study of four medications. Psychiatry Res 1988;26:265–271
8. Ansseau M, von Frenckell R, Mertens C, et al. Controlled comparison of two doses of milnacipran (F 2207) and amitriptyline in major depressive inpatients. Psychopharmacology (Berl) 1989;98:163–168
9. Fernstrom MH, Krowinski RL, Kupfer DJ. Chronic imipramine treatment and weight gain. Psychiatry Res 1986;17:269–273
10. Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. J Clin Psychopharmacol 1988;8:323–330
11. Berken GH, Weinstein DO, Stern WC. Weight gain: a side-effect of tricyclic antidepressants. J Affect Disord 1984;7:133–138
12. Frank E, Kupfer DJ, Bulik CM, et al. Imipramine and weight gain during the treatment of recurrent depression. J Affect Disord 1990;20:165–172
13. Fernstrom MH, Kupfer DJ. Imipramine treatment and preference for sweets. Appetite 1988;10:149–155
14. Sussman N, Ginsberg D. Effects of psychotropic drugs on weight. Psychiatr Ann 1999;29:580–594
15. Pijl H, Meinders AE. Bodyweight change as an adverse effect of drug treatment: mechanisms and management. Drug Saf 1996;14:329–342
16. Fernstrom MH. Depression, antidepressants, and body weight change. Ann N Y Acad Sci 1989;575:31–39
17. Levitt AJ, Joffe RT, Esche I, et al. The effect of desipramine on body weight in depression. J Clin Psychiatry 1987;48:27–28
18. de Jonghe F, Ravelli DP, Tuynman-Qua H. A randomized, double-blind study of fluoxetine and maprotiline in the treatment of major depression. Pharmacopsychiatry 1991;24:62–67
19. 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
20. Croft H, Settle E Jr, Houser T, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther 1999;21:643–658
21. Moon CA, Jesinger DK. The effects of psychomotor performance of fluvoxamine versus mianserin in depressed patients in general practice. Br J Clin Practice 1991;45:259–262
22. 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
23. Fava M, Rosenbaum JF. Treatment-emergent side effects of the newer antidepressants. In: The Psychiatric Clinics of North America: Annual of Drug Therapy, vol 3. Philadelphia, Pa: WB Saunders Co; 1996:13–29
24. Sussman N, Ginsberg D. Rethinking side effects of the selective serotonin reuptake inhibitors: sexual dysfunction and weight gain. Psychiatr Ann 1998;28:89–97
25. Benazzi F. Weight gain in depression remitted with antidepressants: pharmacological or recovery effect? Psychother Psychosom 1998;67:271–274
26. Wade A, Overo KF, Lemming O. 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
27. Fava M, Rosenbaum JF, Judge RA, et al. Fluoxetine vs sertraline and paroxetine in major depression: long-term changes in weight. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 19, 1999; Washington, DC. Abstract NR430:186
28. Agren H, Aberg-Wistedt A, Akerblad AC. Sertraline versus paroxetine in major depression: a multicenter double-blind, 24-week comparison. Presented at the 152nd annual meeting of the American Psychiatric Association; May 15–20, 1999; Toronto, Ontario, Canada
29. Bouwer CD, Harvey BH. Phasic craving for carbohydrate observed with citalopram. Int Clin Psychopharmacol 1996;11:273–278
30. Tataranni PA. From physiology to neuroendocrinology: a reappraisal of risk factors of body weight gain in humans. Diabetes Metab 1998;24: 108–115
31. Feiger 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
32. Harto-Truax N, Stern WC, Miller LL, et al. Effects of bupropion on body weight. J Clin Psychiatry 1983;44(5, sec 2):183–186
33. Weisler RH, Johnston JA, Lineberry CG, et al. Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol 1994;14:170–179
34. Weihs K, Houser T, Batey S, et al. Long-term treatment of depression with bupropion sustained-release. Presented at the 152nd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
35. Chouinard G. Bupropion and amitriptyline in the treatment of depressed patients. J Clin Psychiatry 1983;44(5, sec 2):121–129
36. Feighner J, Hendrickson G, Miller L, et al. Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. J Clin Psychopharmacol 1986;6:27–32
37. Smith WT, Glaudin V, Panagides J, et al. Mirtazapine vs amitriptyline vs placebo in the treatment of major depressive disorder. Psychopharmacol Bull 1990;26:191–196
38. 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;13:63–73
39. Goodnick PJ, Kremer C, Wingard P. Weight change during mirtazapine therapy. Prim Psychiatry 1998;3:103–108
40. Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry 1999;60:22–28
41. Fava M. New approaches to the treatment of refractory depression. J Clin Psychiatry 2000;61(suppl 1):26–32
42. Ackerman S, Nolan LJ: Body weight gain induced by psychotropic drugs. CNS Drugs 1998;9:135–151
43. Carpenter LL, Jocic Z, Hall JM, et al. Mirtazapine augmentation in the treatment of refractory depression. J Clin Psychiatry 1999;60:45–49
44. Frank E, Kupfer DJ, Buhari A, et al. Imipramine and weight gain during the long-term treatment of recurrent depression. J Affect Disord 1992;26: 65–72