Symptoms of Fatigue and Sleepiness in Major Depressive Disorder

David S. Baldwin, D.M., F.R.C.Psych., and George I. Papakostas, M.D.

Fatigue and sleepiness (hypersomnia) are symptoms that are highly prevalent in patients with major depressive disorder (MDD). Individuals who complain of fatigue but do not have diagnosable depression are at a higher risk for developing MDD later in life than individuals who do not complain of fatigue. Fatigue and sleepiness also appear to be particularly difficult to treat, as they are often encountered as residual symptoms among MDD patients who have remitted following treatment with standard antidepressants. There are 3 main approaches for addressing fatigue and sleepiness in depression: first, prescribing antidepressant medications that are less likely to exacerbate these particular symptoms; second, prescribing antidepressant medications that are more likely to resolve these symptoms; third, the use of adjunctive treatments to specifically target residual fatigue and sleepiness in depression. *(J Clin Psychiatry 2006;67[suppl 6]:9–15)*

PREVALENCE OF FATIGUE AND SLEEPINESS IN VARIOUS SAMPLES

Fatigue and sleepiness are complaints that appear to be commonly encountered in the community. In surveys[1–3] of the point prevalence of fatigue in the general population, rates of fatigue between 10% and 30% have been reported. Similarly, surveys[4–6] of the lifetime prevalence of fatigue report comparable prevalence rates, between 20% and 25%.

Fatigue is also common in clinical samples. Surveys[7–9] of primary care patients report that as many as 10% to 35% were experiencing fatigue at any given point in time. There is also evidence to suggest that fatigue may be underreported in this population. For example, in one survey,[9] more than 30% of patients reported experiencing fatigue when specifically asked by the survey taker, compared with fewer than 10% of patients who spontaneously reported that same symptom to their physician.

Fatigue appears to be much more common in depressed patients than in the general population or in primary care samples. In a large epidemiologic study[10,11] of 1884 European patients from 6 countries who consulted their physician about depression, 73% of patients reported feeling tired as one of their symptoms. Of these patients, 76% complained of low mood at some point, which is a core symptom of major depressive disorder (MDD). Sleep problems, including insomnia and hypersomnia, were the third most common symptom and were, in fact, more commonly reported than anxious symptoms of depression. Other studies such as those by Maurice-Tison and colleagues[12] and Baker et al.[13] reported even higher rates of fatigue (94%–97%) in patients with MDD. Furthermore, a study by Posternak and Zimmerman[14] reported rates of "leaden paralysis," which is an extreme form of fatigue, among 21.8% of patients with MDD and as high as 60.8% among patients with atypical MDD. Leaden paralysis appears to be more common in women than men (32.4% compared with 19.9%) and is associated with a greater severity and duration of severe major depressive episodes.[15]

Although hypersomnia does not appear to be as common as fatigue in MDD, it is far from rare. Posternak and Zimmerman,[14] Horwath et al.,[16] and Reynolds and Kupfer,[17] for example, reported rates of hypersomnia between 10% to 20% among patients with MDD and as high as 36.2% among patients with atypical MDD.[14] In addition, sleepiness appears to be more common in women than in men with MDD (20.9% compared with 13.9%) and more common in younger than older MDD patients.[15]

Fatigue and hypersomnia are particularly prevalent in MDD and atypical depression, but there also seems to be prognostic value for these 2 symptoms in patients who are not currently depressed. In a survey by Addington and colleagues,[4] individuals with a history of unexplained

From the Faculty of Medicine, Health, and Life Sciences, University of Southampton, U.K. (Dr. Baldwin); and the Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (Dr. Papakostas).

This article is derived from the planning roundtable "The Role of Dopamine and Norepinephrine in Depression and Antidepressant Treatment," which was held July 22, 2005, in Taplow, Berkshire, U.K., and supported by an educational grant from GlaxoSmithKline.

Corresponding author and reprints: George I. Papakostas, M.D., Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, 15 Parkman Street, WACC#812, Boston, MA 02114 (e-mail: gpapakostas@partners.org).

Table 1. Risk for Depression in Patients Asked About Their Experience With Unexplained Fatigue[a]

Experience With Unexplained Fatigue	N	Relative Risk for Depression
Never	1380	1.0
Remitted	195	4.5
Recurrent	47	28.4

[a]Data from Addington et al.[4]

fatigue were at markedly increased risk for new-onset MDD. For patients who did not have depression at baseline but who reported recurrent unexplained fatigue, the risk of developing depression at follow-up was 28.4 times higher than among patients who did not have fatigue (Table 1). Similar to fatigue, the presence of excessive sleepiness among nondepressed subjects also appears to predict the subsequent onset of a major depressive episode.[18,19]

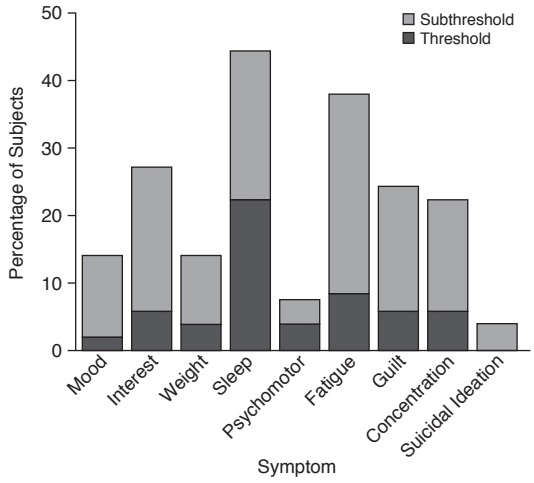
A possible explanation for such findings is that individuals who complain of excessive sleepiness or fatigue, particularly unexplained sleepiness or fatigue, may, in fact, be experiencing prodromal symptoms of MDD, as first proposed by Fava et al.[20] Therefore, clinicians should specifically elicit for other depressive symptoms as well as arrange for frequent follow-up with patients who complain of unexplained symptoms of excessive sleepiness and fatigue in order to increase their chances of detecting and treating MDD should it emerge.

FATIGUE AND SLEEPINESS IN TREATMENT-RESISTANT DEPRESSION

Not only are complaints of fatigue and sleepiness common among patients with MDD, but these symptoms appear to be particularly difficult to treat, since they are often encountered as residual symptoms among patients with remitted MDD.

Nierenberg et al.,[21] for instance, studied 215 patients who had achieved remission following open-label treatment with fluoxetine (20 mg for 8 weeks) and found that as many as 44% of patients continued to complain of sleep disturbances (including insomnia and hypersomnia), 38% continued to complain of fatigue, 27% of reduced interest and pleasure, 25% of guilt, and 24% of poor concentration (Figure 1). Worthington et al.[22] examined the same data set while taking into account the baseline prevalence of each depressive symptom. Specifically, the authors examined the proportion of patients who presented with a specific depressive symptom and who continued to complain of that symptom following remission of their depressive episode. The most "refractory" symptom was found to be hypersomnia: 70% of patients who presented with excessive sleepiness were still complaining of this symptom after achieving remission with fluoxetine. Other highly "refractory" symptoms identified in that study included reduced interest (39%), fatigue (35.8%), and guilt (32.2%).

Figure 1. Frequency of Residual Major Depressive Disorder Symptoms in Responders to Fluoxetine (N = 108)[a]



[a]Reprinted with permission from Nierenberg et al.[21]

Fatigue has also been found to respond less favorably to psychotherapy than other depressive symptoms. In a study by Kopta et al.,[23] symptoms of loss of energy and interest were slower to respond to treatment than predominantly cognitive symptoms of depression, including hopelessness and guilt. Similarly, a study by Barkham et al.[24] found that fatigue, as measured by the Beck Depression Inventory, was the item that showed the least change of all the depressive symptoms during a time-limited psychotherapy.

The benefits of treating sleepiness and fatigue go beyond the resolution of the symptoms themselves. Alertness is required for many cognitive functions that people perform during the day at work and at school. Cognitive symptoms, along with fatigue, often persist following treatment for MDD. A study by Alexopoulos et al.[25] examined the response to treatment with citalopram among 112 geriatric patients with MDD. The authors found that the likelihood of resolving depressive symptoms among patients with a greater burden of cognitive dysfunction at baseline was significantly lower than for patients with a lesser burden of cognitive dysfunction at baseline ($p = .0006$).

GENERAL APPROACHES FOR RESOLVING FATIGUE AND SLEEPINESS IN DEPRESSION

The general population is well aware of the importance of treating fatigue and sleepiness in depression. In a survey of the general public in the United Kingdom in 1995,[26] participants were asked to suppose that they were receiving treatment for depression and choose from a list of

options which would be the most important to them. The items that were most commonly endorsed as the most important consideration were "to be able to think clearly" (46% of respondents), "to remain calm and not become aggressive or agitated" (34%), and "to be able to perform manual tasks without difficulty" (12%).

In a different poll also conducted in 1995,[27] individuals who had been treated for depression in the previous 12 months were asked to comment on their experience with antidepressant treatment. While 12% of respondents felt that they had more energy while taking antidepressants than they did before they started taking them, 16% felt that they were usually more tired than they had been prior to the onset of depression.

Unfortunately, despite the widespread prevalence and importance of fatigue and hypersomnia in depression as well as among patients with remitted MDD, very few studies have been published specifically focusing on the treatment of fatigue and hypersomnia in depression. In general, clinicians often use 1 of 3 approaches when treating depressed patients who present with prominent fatigue and/or hypersomnia.

Avoiding Antidepressant Medications That Are Likely to Worsen Sleepiness and Fatigue

First, there is the most clinically intuitive approach, which is to do no harm when it comes to fatigue and sleepiness. This strategy involves avoiding agents that have been consistently shown to result in greater reports of fatigue and sleepiness as a side effect than placebo, including the tricyclic antidepressants and mirtazapine,[28] duloxetine,[29] and trazodone,[30] in favor of agents that appear to have a similar incidence of fatigue and sleepiness compared with placebo in clinical trials. The latter agents include the selective serotonin reuptake inhibitors (SSRIs),[31] bupropion,[32] venlafaxine,[31] reboxetine,[33] agomelatine,[34] tianeptine,[35] and the monoamine oxidase inhibitors.[36]

Choosing Antidepressant Medications That Are More Likely to Help to Resolve Sleepiness and Fatigue in Depression

The second approach is to select an agent that would be most likely to resolve excessive sleepiness and fatigue. Unfortunately, very few studies specifically reporting on the impact of standard pharmacotherapies on these 2 specific depressive symptoms have been published.

Fluoxetine. Judge and colleagues[37] published a pooled analysis of double-blind, placebo-controlled trials of fluoxetine involving a total of 1231 patients randomly assigned to fluoxetine and 844 to placebo. Fluoxetine showed greater efficacy than placebo in resolving retardation factor scores, which was statistically significant beginning at week 3 and continuing through endpoint at week 6 ($p < .001$). In elderly patients with depression,[37] fluoxetine showed greater efficacy than placebo in resolving these symptoms, which was statistically significant starting at week 4 and continuing through endpoint ($p < .001$). When looking specifically at item 13 in the 17-question version of the Hamilton Rating Scale for Depression (HAM-D-17), which pertains to fatigue, fluoxetine-treated patients showed a significantly ($p < .001$) greater resolution of this symptom than placebo-treated patients at endpoint.

Table 2. Studies Included in Analysis of Bupropion for Sleepiness and Fatigue

Study	Treatment	Duration (wk)	N
Kavoussi et al.[40]	Bupropion SR Sertraline	16	248
Croft et al.[41]	Bupropion SR Sertraline Placebo	8	360
Coleman et al.[42]	Bupropion SR Sertraline Placebo	8	364
Weihs et al.[43]	Bupropion SR Paroxetine	6	100
Data on file, GlaxoSmithKline (protocol 130926)	Bupropion XL Escitalopram Placebo	8	388
Data on file, GlaxoSmithKline (protocol 130927)	Bupropion XL Escitalopram Placebo	8	397

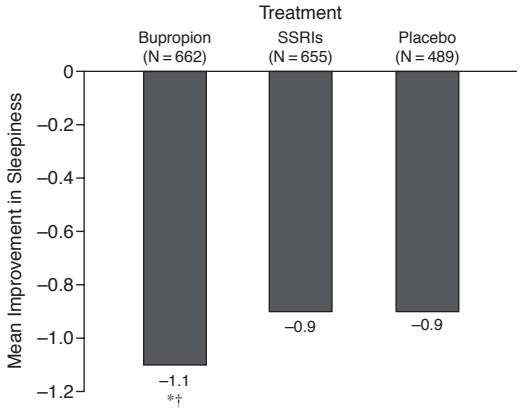
Abbreviations: SR = sustained release, XL = extended release.

Even less is known regarding whether other agents are more effective in resolving excessive sleepiness and fatigue than the SSRIs when used to treat MDD.

Reboxetine. Nelson et al.[38] looked at the data sets of 2 almost identical double-blind studies of reboxetine versus fluoxetine given for 8 weeks. The first study contained 381 patients, and the second study contained 253 patients. These 2 studies were analyzed separately in order to be able to replicate any positive findings and, thus, minimize the likelihood of a chance finding. The HAM-D-17 was used to assess depressive severity, and the 2 active treatments were compared in terms of their ability to resolve each of the 17 individual items. In the first data set, fluoxetine was more effective than reboxetine in reducing early insomnia, whereas reboxetine was more effective in reducing gastrointestinal symptoms. In the second study, reboxetine was more effective than fluoxetine in resolving late insomnia and the general somatic symptoms item (HAM-D item 13), which is a measure of fatigue. Since there was no overlap in the findings between the 2 data sets, the authors concluded that any positive findings were probably due to chance.

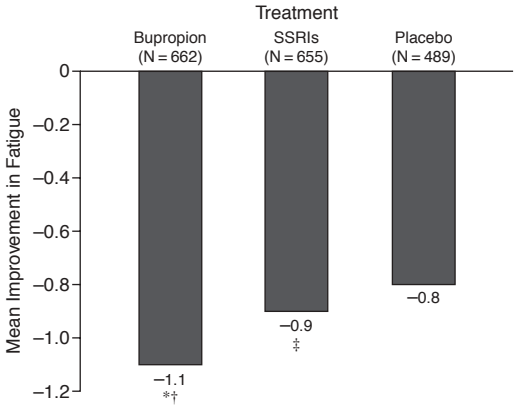
Bupropion. A pooled analysis[39] of double-blind studies compared the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion with SSRIs for the resolution of excessive sleepiness and fatigue. A total of 10 double-blind, randomized clinical trials comparing an SSRI with bupropion for the treatment of MDD have been con-

Figure 2. Improvement in Sleepiness in Intent-to-Treat Group[a]



[a]Reprinted with permission from Papakostas et al.[39] Improvement was measured using Hamilton Rating Scale for Depression items 22, 23, and 24.
*p = .0008 bupropion vs. SSRIs.
†p < .0001 bupropion vs. placebo.
Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

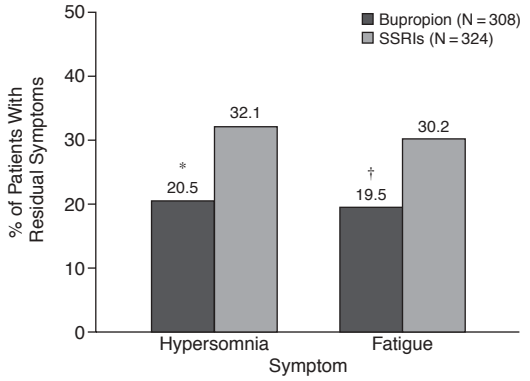
Figure 3. Improvement in Fatigue in Intent-to-Treat Group[a]



[a]Reprinted with permission from Papakostas et al.[39] Improvement was measured using Hamilton Rating Scale for Depression item 13.
*p = .0078 bupropion vs. SSRIs.
†p < .0001 bupropion vs. placebo.
‡p = .0005 SSRIs vs. placebo.
Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

ducted to date; 6[40–43] of these were included in the pooled analysis (Table 2). Four studies (references 32, 44, and 45 and data on file, GlaxoSmithKline), 3 of which were comparisons with fluoxetine (references 32 and 45 and data on file, GlaxoSmithKline) and 1 with paroxetine,[44] were excluded because they involved the use of the 21-question version of the HAM-D, which does not include the hypersomnia items. In the remaining 6 studies, severity of hypersomnia was defined as the sum of scores of items 22, 23, and 24, and severity of fatigue as the score on item 13 of the original HAM-D.

Figure 4. Residual Symptoms Among Treatment Remitters[a]



[a]Reprinted with permission from Papakostas et al.[39]
*p = .0014 bupropion vs. SSRIs.
†p = .002 bupropion vs. SSRIs.
Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

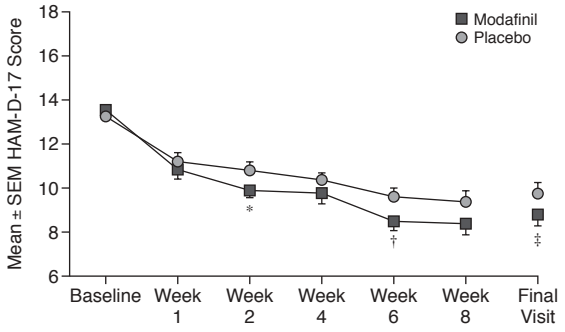
Controlling for hypersomnia scores at baseline, bupropion (mean ± SD change = –1.1 ± 0.06) was more effective than placebo (mean ± SD change = –0.9 ± 0.08, p < .0001) as well as the SSRIs (–0.9 ± 0.07, p = .0008) in resolving hypersomnia.[39] Interestingly enough, the SSRIs were not more effective than placebo in resolving this particular depressive symptom (p > .05) (Figure 2). Treatment with bupropion (–1.1 ± 0.03) was also more effective than treatment with the SSRIs (–0.9 ± 0.03, p = .0078) or placebo (–0.8 ± 0.03, p < .0001) in resolving fatigue. Finally, the SSRIs were also more effective in resolving fatigue than placebo (p = .0005) (Figure 3), which is in accordance with an earlier study by Judge and colleagues.[37]

The authors conducted a second analysis,[39] this time focusing on patients who had remitted following treatment with either bupropion (N = 308) or an SSRI (N = 324). Remission was defined as a HAM-D-17 total score less than 8 at endpoint. Of those patients whose depressive episode remitted following treatment with bupropion, 20.5% continued to complain of hypersomnia compared with 32.1% of patients whose depressive episode remitted following SSRI treatment (p = .0014) (see Figure 4). Similarly, 19.5% of patients whose depressive episode remitted following treatment with bupropion continued to complain of fatigue compared with 30.2% of patients whose depressive episode remitted following treatment with an SSRI (p = .002) (Figure 4).

The Use of Adjunctive Pharmacotherapies to Target Fatigue and Sleepiness in Depression

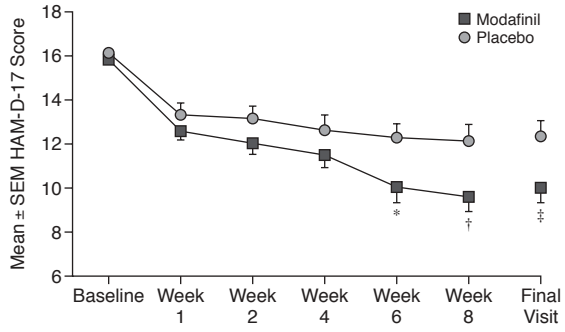
The third strategy is to employ augmentation strategies along with antidepressant treatment to eliminate excessive sleepiness and fatigue and help the patient experience a full remission of symptoms. A number of case reports and open-label trials have been published supporting the use of

Figure 5. Change in 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Scores With Modafinil Augmentation Versus Placebo (all patients)[a]



[a]Reprinted with permission from Fava et al.[58]
*p = .07.
†p = .06.
‡p < .08.
Abbreviation: SEM = standard error of the mean.

Figure 6. Change in 17-Item Hamilton Rating Scale for Depression (HAM-D-17) Scores With Modafinil Augmentation Versus Placebo (patients with baseline HAM-D-17 score ≥ 14)[a]



[a]Reprinted with permission from Fava et al.[58]
*p = .04.
†p = .04.
‡p = .05.
Abbreviation: SEM = standard error of the mean.

agents such as bupropion,[46] the psychostimulants,[47] and modafinil.[48–55]

Bupropion. Green[46] published a case series of 3 outpatients with depression who had experienced partial symptom improvement following treatment with an SSRI but who continued to complain of either persistent or worsening fatigue. Fatigue resolved within 1 to 2 weeks following adjunctive treatment with relatively low doses (75–150 mg/day) of bupropion.

Psychostimulants. Masand et al.[47] published a case series of 7 MDD patients showing partial yet incomplete response following treatment with either an SSRI (N = 6) or venlafaxine (N = 1). A marked improvement in clinical symptoms of depression was noted in all cases following the addition of psychostimulant treatment, with particular improvement in fatigue and apathy.

Atomoxetine. Papakostas et al.[56] conducted an open-label study of adjunctive atomoxetine, a selective norepinephrine reuptake inhibitor, for patients (N = 14) who responded to antidepressants, primarily SSRIs, but experienced residual fatigue. A significant ($p < .05$) decrease in fatigue was noted after the addition of atomoxetine. At baseline, 66.6% of the study participants were considered to have remitted from depression. After treatment with adjunctive atomoxetine, 100% achieved remission. These results underscore the importance of treating residual symptoms to achieve symptom remission in patients with major depressive disorder.

However, placebo-controlled studies examining the safety and efficacy of adjunctive pharmacologic strategies to resolve residual sleepiness and fatigue in depression have only been conducted for modafinil.

Modafinil. Specifically, 2 double-blind studies[57,58] have been published on the use of adjunctive modafinil for the treatment of residual excessive sleepiness and fatigue in MDD. The first study[57] was a double-blind 6-week study of 136 MDD patients who had experienced partial symptom improvement following treatment with standard antidepressants, who were then given modafinil or placebo in addition to their antidepressant regimen. Patients treated with modafinil demonstrated a greater improvement in fatigue than the patients given placebo at week 2; however, there was no difference in the resolution of fatigue between patients treated with modafinil and those given placebo at endpoint. Patients treated with modafinil also demonstrated a greater resolution of excess sleepiness at week 1 than the patients given placebo, but this difference was not significant at week 6. No difference was found between modafinil-treated patients and placebo-treated patients in resolution of depressive symptoms overall. A limitation of this study is that it did not specifically examine patients with residual excessive sleepiness and fatigue, but only patients with incomplete remission in general. The study also involved a relatively small sample size.

A second study[58] was subsequently conducted involving a larger sample size (N = 311), having longer treatment duration (8 weeks), and also specifically focusing on patients with residual sleepiness and fatigue. There was no statistically significant difference between the modafinil- and placebo-treated groups in the resolution of either sleepiness or fatigue as measured by the Epworth Sleepiness Scale, the Fatigue Severity Scale, or the Brief Fatigue Inventory.

Similarly, although there was a numerical difference between modafinil and placebo in the resolution of depressive symptoms, this difference was not statistically significant (Figure 5).[58] However, when the authors conducted a subanalysis of patients with moderate to severe depression, they found that modafinil was significantly ($p \leq .05$) more effective than placebo in resolving depressive symp-

toms at endpoint (Figure 6). Patients taking modafinil also showed greater improvement at endpoint according to the Clinical Global Impressions-Improvement scale than did the patients taking placebo. Thus, while adjunctive modafinil did seem to be an effective strategy in resolving depressive symptoms overall among patients with moderate to severe depression, adjunctive modafinil was not found to be more effective than placebo in resolving residual hypersomnia and fatigue in depression, reinforcing the notion that these symptoms can be particularly difficult to treat.

CONCLUSION

Complaints of excessive sleepiness and fatigue should raise the index of suspicion for depression among clinicians. In addition, these symptoms are highly prevalent in patients with MDD and appear to be particularly difficult to treat. It is not yet known whether any of the available antidepressant classes are particularly effective in treating patients with MDD presenting with high levels of sleepiness and fatigue at baseline. However, there is some evidence to suggest that the NDRI bupropion may be more effective than the SSRIs in resolving sleepiness and fatigue in MDD. Finally, to date, there is a paucity of placebo-controlled studies examining the use of adjunctive pharmacotherapeutic strategies to specifically target residual fatigue and sleepiness in MDD. Although modafinil appears to be effective in resolving depressive symptoms overall among antidepressant partial responders, its efficacy in treating the specific depressive symptoms of sleepiness and fatigue has yet to be established.

REVIEW QUESTION

Ms. B, a 55-year-old married woman, was referred by her primary care physician to you for treatment. She had developed depressive and anxiety symptoms 2 years previously, shortly after stopping tamoxifen treatment for breast cancer. She described her main problems as loss of energy, poor motivation, and the sense that she was simply drifting through life, unable to influence its course. Her symptoms had not responded to treatment with fluoxetine or sertraline, or to amitriptyline, which had been successful in resolving a previous depressive episode, 7 years earlier. At the time of referral, she was prescribed venlafaxine, 150 mg/day, but had been unable to tolerate a higher (225 mg/day) dosage.

What therapeutic strategy or strategies would you recommend for Ms. B?

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro), fluoxetine (Prozac and others), mirtazapine (Remeron and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, atomoxetine and modafinil are not approved by the U.S. Food and Drug Administration for the treatment of fatigue in major depressive disorder.

REFERENCES

1. Hickie I, Davenport T, Issakidis C, et al. Neurasthenia: prevalence, disability, and health care characteristics in the Australian community. Br J Psychiatry 2002;181:56–61
2. Mason P, Wilkinson G. The prevalence of psychiatric morbidity: OPCS survey of psychiatric morbidity in Great Britain. Br J Psychiatry 1996; 168:763–766
3. Pawlikowska T, Chalder T, Hirsch SR, et al. Population based study of fatigue and psychological distress. BMJ 1994;308:763–766
4. Addington AM, Gallo JJ, Ford DE, et al. Epidemiology of unexplained fatigue and major depression in the community: the Baltimore ECA follow-up, 1981–1994. Psychol Med 2001;31:1037–1044
5. Kroenke K, Price R. Symptoms in the community: prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993;153:2474–2480
6. Walker EA, Katon WJ, Jemelka RP. Psychiatric disorders and medical care utilization among people in the general population who report fatigue. J Gen Intern Med 1993;8:436–440
7. Cathebras PJ, Robbins JM, Kirmayer LJ, et al. Fatigue in primary care: prevalence, psychiatric comorbidity, illness behavior, and outcome. J Gen Intern Med 1992;7:276–286
8. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. BMJ 1990;301:1199–1202
9. Fuhrer R, Wessely S. The epidemiology of fatigue and depression: a French primary-care study. Psychol Med 1995;25:895–905
10. Tylee A, Gastpar M, Lepine J-P, et al. Identification of depressed patient types in the community and their treatment needs: findings from the DEPRES II (Depression Research in European Society II) survey. Int Clin Psychopharmacol 1999;14:153–165
11. Tylee A, Gastpar M, Lepine J-P, et al. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. Int Clin Psychopharmacol 1999;14:139–151
12. Maurice-Tison S, Verdoux H, Gay B, et al. How to improve recognition and diagnosis of depressive syndromes using international diagnostic criteria. Br J Gen Pract 1998;48:1245–1246
13. Baker M, Dorzab J, Winokur G, et al. Depressive disease: classification and clinical characteristics. Compr Psychiatry 1971;12:354–365
14. Posternak MA, Zimmerman M. Partial validation of the atypical features subtype of major depressive disorder. Arch Gen Psychiatry 2002;59: 70–76
15. Posternak MA, Zimmerman M. Symptoms of atypical depression. Psychiatry Res 2001;104:175–181
16. Horwath E, Johnson J, Weissman MM, et al. The validity of major depression with atypical features based on a community study. J Affect Disord 1992;26:117–125
17. Reynolds CF III, Kupfer DJ. Sleep research in affective illness: state of the art circa 1987. Sleep 1987;10:199–215
18. Ford DE, Cooper-Patrick L. Sleep disturbances and mood disorders: an epidemiologic perspective. Depress Anxiety 2001;14:3–6
19. Roberts RE, Shema SJ, Kaplan GA, et al. Sleep complaints and depression in an aging cohort: a prospective perspective. Am J Psychiatry 2000;157:81–88
20. Fava GA, Grandi S, Canestrari R, et al. Prodromal symptoms in primary major depressive disorder. J Affect Disord 1990;19:149–152
21. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999;60:221–225
22. Worthington J, Fava M, Davidson K, et al. Patterns of improvement in depressive symptoms with fluoxetine treatment. Psychopharmacol Bull 1995;31:223–226
23. Kopta SM, Howard KI, Lowry JL, et al. Patterns of symptomatic recovery in psychotherapy. J Consult Clin Psychol 1994;62:1009–1016

24. Barkham M, Rees A, Shapiro DA, et al. Outcomes of time-limited psychotherapy in applied settings: replicating the Second Sheffield Psychotherapy Project. J Consult Clin Psychol 1996;64:1079–1085
25. Alexopoulos GS, Kiosses DN, Heo M, et al. Executive dysfunction and the course of geriatric depression. Biol Psychiatry 2005;58:204–210
26. Priest RG, Vize C, Roberts A, et al. Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before its launch. BMJ 1996;313:858–859
27. MORI (Market and Opinion Research International). Depression. Research study conducted for LMB Public Relations on behalf of Bristol-Myers Squibb. May/June 1995, London, UK
28. Bremner JD. A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression. J Clin Psychiatry 1995;56:519–525
29. Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. Psychopharmacol Bull 2002;36: 106–132
30. Halikas JA. Org 3770 (mirtazapine) versus trazodone: a placebo-controlled trial. Hum Psychopharmacol 1995;10(suppl):s125–s133
31. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;20:1166–1174
32. Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther 2001;23:1040–1058
33. Andreoli V, Caillard V, Deo RS, et al. Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. J Clin Psychopharmacol 2002;22:393–399
34. Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of depression. Int Clin Psychopharmacol 2002;17:239–247
35. Costa e Silva JA, Ruschel SI, Caetano D, et al. Placebo-controlled study of tianeptine in major depressive episodes. Neuropsychobiology 1997;35: 24–29
36. Versiani M, Amrein R, Stabl M, for the International Collaborative Study Group. Moclobemide and imipramine in chronic depression (dysthymia): an international double-blind, placebo-controlled trial. Int Clin Psychopharmacol 1997;12:183–193
37. Judge R, Plewes JM, Kumar V, et al. Changes in energy during treatment of depression: an analysis of fluoxetine in double-blind, placebo-controlled trials. J Clin Psychopharmacol 2000;20:666–672
38. Nelson JC, Portera L, Leon AC. Are there differences in the symptoms that respond to a selective serotonin or norepinephrine reuptake inhibitor? Biol Psychiatry 2005;57:1535–1542
39. Papakostas GI, Nutt DJ, Tucker VI, et al. Resolution of sleepiness and fatigue in the treatment of major depressive disorder: a comparison of bupropion and the selective serotonin reuptake inhibitors. Presented at the 44th annual meeting of the American College of Neuropsychopharmacology; Dec 11–15, 2005; Waikoloa, Hawaii. Abstract 111
40. Kavoussi RJ, Segraves RT, Hughes AR, et al. Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. J Clin Psychiatry 1997;58:532–537
41. 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
42. Coleman CC, Cunningham LL, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry 1999;11:205–215
43. Weihs KL, Settle EC Jr, Batey SR, et al. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61:196–202
44. Kennedy SH, Fulton K, Rafi-Tari S, et al. Differences in sexual dysfunction between men and women with depression: a comparison before and after treatment with bupropion and paroxetine. Can J Psychiatry. In press
45. Feighner JP, Gardner EA, Johnston JA, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry 1991;52:329–335
46. Green TR. Bupropion for SSRI-induced fatigue [letter]. J Clin Psychiatry 1997;58:174
47. Masand PS, Anand VS, Tanquary JF. Psychostimulant augmentation of second generation antidepressants: a case series. Depress Anxiety 1998; 7:89–91
48. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000;61: 378–381
49. Berigan TR. Augmentation with modafinil to achieve remission in depression: a case report [letter]. Prim Care Companion J Clin Psychiatry 2001;3:32
50. Schwartz TL, Leso L, Beale M, et al. Modafinil in the treatment of depression with severe comorbid medical illness [letter]. Psychosomatics 2002;43:336–337
51. Even C, Thuile J, Santos J, et al. Modafinil as an adjunctive treatment to sleep deprivation in depression. J Psychiatry Neurosci 2005;30:432–433
52. Markovitz PJ, Wagner S. An open-label trial of modafinil augmentation in patients with partial response to antidepressant therapy. J Clin Psychopharmacol 2003;23:207–209
53. DeBattista C, Lembke A, Solvason HB, et al. A prospective trial of modafinil as an adjunctive treatment of major depression. J Clin Psychopharmacol 2004;24:87–90
54. Keller Ashton A. Modafinil augmentation of phenelzine for residual fatigue in dysthymia [letter]. Am J Psychiatry 2004;161:1716–1717
55. Lundt L. Modafinil treatment in patients with seasonal affective disorder/winter depression: an open-label pilot study. J Affect Disord 2004;81: 173–178
56. Papakostas GI, Petersen TJ, Burns AM, et al. Adjunctive atomoxetine for residual fatigue in major depressive disorder. J Psychiatry Res. In press
57. DeBattista C, Doghramji K, Menza MA, et al. Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003;64:1057–1064
58. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005;66:85–93