Daytime Sleepiness and Insomnia as Correlates of Depression

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Insomnia and daytime sleepiness are often associated with depression. The possible relationships between sleep difficulties and depression are numerous. Insomnia and other sleep disturbances can be precursors to the onset of major depressive disorder, so they may act as risk factors for or predictors of depression. The symptomatology of depression also prominently includes insomnia, and sleep disturbances may be residual symptoms after response to antidepressant treatment. Insomnia and the resultant daytime sleepiness may be short-term or long-term side effects of antidepressant treatment as well. Whether insomnia is a precursor, symptom, residual symptom, or side effect of depression or its treatment, clinicians must give serious attention to and attempt to resolve sleep disturbances because of the risk of depression onset, worsening of depressive symptoms, and relapse of depression after response to antidepressant treatment. Remission of depression cannot be fully achieved until the associated insomnia and daytime sleepiness are resolved. This article describes the relationships between insomnia and depression and discusses the effects of various antidepressants on sleep. Finally, several different treatment options, including antidepressant monotherapy and augmentation of antidepressants with other medications, are explored. *(J Clin Psychiatry 2004;65[suppl 16]:27–32)*

Dysfunctional sleep conditions, including insomnia, hypersomnia, and excessive sleepiness, are frequently found concurrent with depressive disorders. In some cases, a patient may sleep abnormally long and frequently, while, more often, patients may be plagued with nighttime wakefulness, other aspects of insomnia, and a resultant daytime sleepiness. These sleep disturbances may be symptoms or predictors of depression or side effects of antidepressant treatment, and the relationship between sleep disturbance and depression may be different for every patient. Daytime sleepiness and nighttime wakefulness are associated with depression in various ways, and these relationships should be identified and addressed when treating depressed patients.

SLEEP CONDITIONS ASSOCIATED WITH DEPRESSION

Among the 9 criteria for a major depressive episode as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV)[1] is "insomnia or hypersomnia nearly every day." Although hypersomnia—a condition of excessive sleepiness evidenced by nighttime oversleeping or daytime sleeping on a daily basis—is less common in depression than is insomnia, certain forms of depression, including atypical depression, are especially associated with hypersomnia. Insomnia, an inability to fall asleep at bedtime or after mid-sleep awakenings or a tendency to experience poor efficiency of sleep, is often found concurrent with depression. Individuals with depression typically present with initial, middle, or late insomnia (nighttime wakefulness during the initial, middle, or late stages of the night or other allotted sleep time) and an accompanying daytime sleepiness as a result of the sleep deprivation or poor sleep quality. Because nighttime wakefulness or insomnia and its accompanying daytime sleepiness are a common problem in depressed patients, these sleep disturbances should be of concern to clinicians.

RELATIONSHIPS BETWEEN DEPRESSION AND INSOMNIA

Insomnia can be associated with depression in various ways. Insomnia may be the chief complaint of some depressed patients or the symptom that prompts them to seek clinical diagnosis and treatment. Insomnia may be a risk factor for depression or a predictor of depression onset, as some patients with insomnia later present with depression. Insomnia may also be a residual symptom after an otherwise successful treatment of depression. Lastly, insomnia

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can be a short-term or long-term side effect of antidepressant treatment.

PREVALENCE OF DEPRESSION IN INSOMNIA PATIENTS

Insomnia is often associated with mood disorders and, more specifically, with depression. In a study[2] of comorbid conditions in patients with sleep disorders diagnosed by polysomnography, Coleman and colleagues found that 35% of patients with insomnia also experienced psychiatric disorders. Of that group, half (50%) experienced mood disorders. In a field trial[3] of the sleep disorder rankings and frequencies expressed by the DSM-IV, insomnia due to another mental disorder was the most commonly diagnosed DSM-IV disorder, with 46% of the patients who were diagnosed with chronic insomnia experiencing a comorbid psychiatric disorder. Insomnia has even been associated with depression in children, as described by Johnson and colleagues.[4] In a study of 717 11-year-old children, 25% of subjects who experienced sleep disturbances also had anxiety or depression, while only 5% of those without sleep disturbances experienced one of these disorders. Given this set of data, insomnia is closely associated with depression; therefore, a patient who primarily and repeatedly complains of insomnia may also be suffering from a depressive condition.

INSOMNIA AS A SYMPTOM OF DEPRESSION

Insomnia accompanied by daytime sleepiness is one of the most common manifestations of depression. Sleep abnormalities are experienced by 40% to 60% of outpatients with major depressive disorder.[5] These sleep problems are not restricted to only one type of depression. Insomnia is typically viewed as a characteristic symptom of melancholic forms of depression, but melancholy affects only a portion of those depressed patients who experience insomnia. Among outpatients with major depressive disorder and insomnia, about one third experience initial insomnia, one third experience middle insomnia, and one third experience delayed insomnia; however, some patients experience a combination of all 3.[6]

Insomnia related to depression encompasses sleep initiation and maintenance difficulties and sleep architecture abnormalities.[1,5] Sleep electroencephalographic (EEG) recordings of patients with major depressive disorder who have sleep initiation and maintenance problems most commonly show prolonged sleep latency (sleep onset insomnia), intermittent wakefulness, sleep fragmentation, and, in some cases, early morning awakenings. These patients also experience reduced sleep efficiency, an inability to return to sleep after nighttime awakenings, and decreased total sleep time. Significant sleep architecture abnormalities are also detected by sleep EEG tests of patients with major depressive disorder. These abnormalities include an increase in light, stage I sleep; decreased rapid eye movement (REM) sleep latency; prolonged first REM sleep cycle; an increase in total REM sleep; and a decrease in deep, slow-wave non-REM (NREM) sleep in stages III and IV. The presence of these identifiable sleep abnormalities in major depressive disorder patients may allow clinicians to predict the onset or recurrence of depression, since evidence suggests that these sleep abnormalities may begin before the onset of depression and after clinical remission. A study[6] evaluating the association between the sleep disturbances common in depressed patients and the symptoms experienced in depression found that the greater the REM activity (and, conversely, the shorter the NREM, delta-wave activity), the greater the severity of depression symptoms. EEG evidence also suggests that certain sleep abnormalities may be associated with specific depressive symptoms.[6] While there are clear correlations between depression and abnormal EEG recordings in adults, there are conflicting data[7–9] about whether these correlations also hold true in childhood and adolescent depression. Although studies have shown increased REM activity in adolescent subjects with depression, other sleep aspects (such as stage IV sleep) have not been found to differ from nondepressed controls.[8,10] Overall, EEG sleep abnormalities appear to occur less frequently in adolescents and children with depression than in adult depression patients.[7]

INSOMNIA AS A RISK FACTOR OR PREDICTOR FOR DEPRESSION

While insomnia is included in depressive symptomatology, it is also an initial condition that may predict the onset of depression and even make depression onset more likely. Epidemiologic reports[11–13] have shown that people may develop insomnia first and depression later. In a prospective study[14] of sleep difficulties experienced by 2370 subjects in Alameda County, Calif., subjects experiencing sleep difficulties in 1994 were more likely to have depression in 1995 compared with controls without sleep complaints, and individuals experiencing sleep difficulties in 1995 had a substantially higher rate of depression than those without sleep problems in the same year. Similarly, Ford and Kamerow[12] found that subjects with insomnia at baseline had a greater risk for depression at 1-year follow-up than those without insomnia; the risk was even greater for subjects experiencing insomnia at baseline and 1 year. Conversely, subjects whose insomnia had resolved before the 1-year follow-up had a much lower chance of developing depression, underlining the importance of treating insomnia as a way of preventing the onset of depression. Breslau and colleagues[11] found similar results in a cohort of young adults. Among a random sample of 21- to 30-year-old members of a large health maintenance organiza-

tion in Michigan who were interviewed in 1989 and again in 1992, the risk for subsequently developing depression among subjects with a history of insomnia at baseline was 4 times higher than that of subjects without a history of insomnia, after adjusting for gender.

Sleep factors play a significant role in predicting depression in children and adolescents. Longer sleep latencies predict lifetime depression in adolescents, and decreased sleep efficiency and delayed sleep onset in depressed children and adolescents in remission predict recurrence of depression. In a study[15] of patients experiencing delayed sleep onset, these patients were more than twice as likely as those without delayed sleep onset to have a recurrence of their depression. Since decreased sleep continuity, REM latency, and NREM sleep and increased REM sleep are characteristic sleep features in depressed patients, these measures may also predict onset or relapse of depression in adults and adolescents.

It is clear that sleep difficulties, especially nighttime wakefulness, are risk factors and predictors of depression, so a viable opportunity for prevention of depression may arise. With the assumption that resolving sleep problems may decrease the likeliness of depression onset, clinicians might view the timely treatment of sleep difficulties as a depression prevention initiative. However, more research is needed to determine whether this type of treatment indeed lowers the occurrence of depression among patients with sleep problems. Eaton and colleagues[16] differentiated between *precursors*, or signs and symptoms that precede a disorder, and the period before the full-blown disorder manifests itself, called *prodrome*, during which some signs and symptoms are present. Since precursors can never predict a disorder with certainty and a prodrome can only be deemed such retrospectively, it is important to distinguish between risk factors and precursors (which may later be deemed prodromal if the disorder does occur) by adequately screening patients who present with risk factors. The strong link between sleep problems and subsequent depression should lead clinicians to treat and attempt to resolve these risk factor conditions in their patients while continuing to monitor them for possible depression onset.

INSOMNIA AS A RESIDUAL SYMPTOM OF MAJOR DEPRESSIVE DISORDER

Although antidepressant therapy is effective in bringing about depression remission for many patients, some residual symptoms often persist despite clinical remission of many aspects of depression. While about one third of patients achieve full remission from antidepressant therapy, approximately one third experience partial response, and one third are nonresponders.[17] Partial response occurs when a patient responds to treatment but still has significant residual symptoms. When the improvement in symptoms is substantial, but remission is not obtained, the term *response without remission* is typically used. Insomnia and other sleep disturbances are common residual symptoms among responders without remission or with remission in major depressive disorder.[18–20]

As a residual symptom, sleep disturbances predict a relapse of depression.[21] The relapse rates for patients experiencing residual symptoms are 3 to 6 times higher than for those who achieve full remission.[17] Therefore, it is important that the goal of antidepressant treatment be full, symptom-free remission. An incomplete remission with residual symptoms may suggest that an augmentation medication may be needed to relieve the residual symptoms. Clinicians who are vigilant in identifying and treating residual sleep disturbances during the treatment of depression may help their patients avoid a recurrence of the disorder.

INSOMNIA AS A SIDE EFFECT OF ANTIDEPRESSANT TREATMENT

Sleep disturbances can be short-term or long-term side effects of antidepressant medication. Increased REM sleep is one of the more objectively identified characteristics of clinical depression, and a deprivation of REM sleep time has often been associated with an improvement in depressive conditions.[22,23] According to these findings, it seems likely that effective antidepressant treatments will affect sleep in some way. Many antidepressants suppress REM sleep, bringing about a prolonged REM latency and a reduction in REM sleep.[24] REM phasic activity is often reduced at the beginning of treatment, but the sleep cycles of most patients adapt within the first few weeks. Although their total REM time remains reduced, the density of REM periods is increased. Due to this connection between REM sleep and depression, the REM-suppressive activity of antidepressants was once thought to be a vital mechanism in their effectiveness[23]; however, the effectiveness of newer antidepressants that increase REM sleep makes this supposition uncertain.

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) decrease REM sleep; they also tend to disrupt sleep maintenance by prolonging sleep onset latency, reducing sleep efficiency, and increasing wake time after sleep onset. Insomnia, nervousness, or anxiety were reported[25] by 12% to 16% of fluoxetine-treated patients in placebo-controlled clinical trials for major depressive disorder. In another study,[26] insomnia was reported as both an early-onset side effect and a late-onset side effect of the SSRI fluoxetine. Many patients treated with SSRIs are treated concomitantly with hypnotics. In a study[27] of the Texas Medicare database, almost one third of SSRI-treated patients were

also taking anxiolytic hypnotics and an additional 15% to 18% were taking pure (non-anxiolytic) hypnotics. This high usage of sleep aids by a substantial proportion of patients indicates a high incidence of sleep disturbances among SSRI-treated patients, either as a residual symptom (through an inability of these antidepressants to fully address the depression) or as a side effect of these antidepressants. Serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, are similar to SSRIs in their effects on sleep, showing higher rates of insomnia than placebo.[28,29]

Bupropion

Bupropion, an aminoketone antidepressant with norepinephrine and dopamine reuptake inhibiting properties, is comparable to SSRIs in the sleep maintenance disturbances it causes, but it differs from SSRIs in that it shortens REM latency and increases REM sleep time.[30] The reason for this lengthening of REM sleep is uncertain, as this effect is not clearly attributable to bupropion's noradrenergic and dopaminergic effects. Nonetheless, bupropion is acknowledged to be a nonsedating or mildly alerting antidepressant associated with decreased sleep continuity[31]; 5% more patients treated with bupropion report treatment-emergent insomnia compared with control patients taking placebo.[32]

Nefazodone

Nefazodone, a serotonin 5-HT_2 receptor antagonist with weak serotonin and norepinephrine reuptake inhibiting properties, is similar to bupropion in that it lengthens REM sleep instead of decreasing it; however, unlike bupropion, nefazodone tends to improve sleep continuity and maintenance.[33] In a study[34] comparing nefazodone and fluoxetine, subjects treated with nefazodone showed significantly better sleep efficiency and fewer awakenings compared with fluoxetine-treated subjects. While patients taking fluoxetine showed poorer sleep efficiency and more awakenings than they did at baseline, nefazodone-treated patients showed improvement on these measures from baseline. However, although nefazodone proves to be effective in treating the sleep disturbances associated with depression and its side effects do not include poorer sleep quality, other side effects including headache, dizziness, and a possible sedating effect at higher dosages, along with its association with rare cases of liver failure, must be considered when exploring pharmacologic options for treating depression with insomnia.

Mirtazapine

Mirtazapine, a tetracyclic, atypical antidepressant with presynaptic norepinephrine and serotonin releasing properties and serotonin 5-HT_2 and 5-HT_3 receptor antagonism, has a propensity to shorten sleep onset latency, improve sleep efficiency, and increase total sleep time, partly because of its strong antagonism of histamine H_1 receptors. A clinical trial[35] of mirtazapine showed significant improvements on objective sleep measures—sleep latency, sleep efficiency, and wake time after sleep onset—after only 2 weeks of treatment; however, as a relatively sedating drug, mirtazapine may be an inappropriate choice for some patients.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) differ in their effect on sleep. Secondary amine tricyclics, like desipramine and protriptyline, tend to reduce sleep efficiency and increase wake time after sleep onset. In a trial[36] of healthy subjects, sleep continuity was significantly reduced for subjects treated with desipramine compared with placebo. Conversely, tertiary amine tricyclics such as amitriptyline or trimipramine have a tendency to improve sleep continuity, partly because of their strong antagonism of histamine H_1 receptors. Amitriptyline has been shown[37] to improve insomnia after 2 weeks of treatment. It has been likened[38] to mirtazapine in its effectiveness as an antidepressant and its improvement of related symptoms, including sleep disturbances.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) show a propensity to reduce sleep efficiency and increase sleep onset latency. These agents also drastically suppress REM sleep,[39] sometimes eliminating it altogether during the first stages of treatment. The antidepressant effect of MAOIs has often been attributed to this suppression of REM sleep. Dramatic rebounds of REM sleep time, up to 250% above baseline,[40] occur upon withdrawal from most MAOIs. Reversible MAOIs tend to have the opposite effect, increasing REM sleep during treatment, while maintaining their antidepressant activity.

TREATING DAYTIME SLEEPINESS AND INSOMNIA ASSOCIATED WITH DEPRESSION

Whether daytime sleepiness and nighttime wakefulness associated with depression are symptoms or side effects, they deserve adequate clinical attention. There are several potential treatment options, and the best treatment choice may be different for every patient.

Antidepressant Monotherapy

The most common treatment approach for a patient who presents with major depressive disorder and accompanying nighttime wakefulness and daytime sleepiness is monotherapy with an antidepressant. This treatment is prescribed in the anticipation that, as the depression improves, the accompanying insomnia and resultant daytime drowsiness will improve in parallel fashion. Clinicians may opt for sedating antidepressants, such as mirtazapine

or tertiary amine tricyclics. This approach could theoretically give an advantage for the first few weeks, but the overall, long-term improvements in insomnia and daytime sleepiness with these medications may not be greater than those found in patients treated with nonsedating antidepressants. For most patients, subjective sleep measures show significant improvement during antidepressant treatment, even when treated with alerting antidepressants such as SSRIs.[41] Nevertheless, further options may need to be explored in treating those patients whose sleep does not improve with antidepressant monotherapy.

Antidepressant Augmentation

Augmentation of antidepressant therapy with hypnotics, anticonvulsants, antihistamines, or sedating antidepressants (such as mirtazapine, trazodone, or low-dose tertiary amine tricyclics) is another option for treating insomnia associated with depression. This approach may treat the insomnia more rapidly than antidepressants alone and offer long-term efficacy for sleep maintenance.

Insomnia and accompanying daytime sleepiness, existing as a residual symptom or a side effect of an SSRI, bupropion, TCA, MAOI, or other antidepressant therapy, are commonly treated with an augmentation of trazodone. When clinicians were surveyed[42] about their treatment preferences for side effects of antidepressant therapy, 78% chose to treat SSRI-induced insomnia with an augmentation of trazodone. An analysis[43] of 3 years of Iowa City's Department of Veteran's Affairs prescription records revealed that 27.7% of patients receiving antidepressant medications were receiving adjunctive trazodone. Augmentation with trazodone was most commonly taken by SSRI-treated patients (27%), but 23% of those taking bupropion were also receiving trazodone. TCA-treated patients least often received trazodone augmentation (13%), but the need for a sleep aid was clearly substantial in all treatment groups. The efficacy of concomitant trazodone usage is revealed by its popularity among clinicians, but it has also been proven effective in clinical trials.[44,45]

Other hypnotics have shown efficacy as antidepressant augmentation therapies. In a clinical trial[46] of zolpidem augmentation, SSRI-treated patients suffering from insomnia showed improvement in sleep time and quality and reported feeling refreshed, more able to concentrate, and less sleepy. By improving sleep, hypnotics such as zolpidem also improve daytime functioning and reduce daytime sleepiness.

More recently, the novel agent modafinil has been used successfully in conjunction with antidepressants to treat daytime sleepiness associated with depression. Originally marketed to treat daytime sleepiness associated with narcolepsy, modafinil helps to eliminate residual daytime sleepiness and fatigue experienced by patients treated with antidepressants, especially SSRIs.[47–49] Modafinil shows promise as an adjunctive medication with standard antidepressants in treating daytime sleepiness, which may be both a cause and an effect of major depressive disorder.

CONCLUSION

Insomnia and the accompanying daytime sleepiness are prominent conditions associated with depression that deserve clinical attention, whether they originate before, during, or after depression onset and antidepressant therapy. The relationships between sleep disturbances and depression are varied and intertwined. While these exact relationships may not always be clearly defined, the importance of addressing them is clear. Comprehensive treatment of the daytime sleepiness and nighttime wakefulness that may co-occur with depression can help to bring about complete remission, improve the patient's quality of life, and prevent relapse.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), desipramine (Norpramin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), mirtazapine (Remeron and others), modafinil (Provigil), protriptyline (Vivactil), trazodone (Desyrel and others), trimipramine (Surmontil), venlafaxine (Effexor), zolpidem (Ambien).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, amitriptyline, mirtazapine, trazodone, and trimipramine are not approved by the U.S. Food and Drug Administration for the treatment of insomnia; modafinil is not approved for the treatment of daytime sleepiness associated with major depressive disorder; and bupropion and protriptyline are not approved for the treatment of daytime sleepiness.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Coleman RM, Roffwarg HP, Kennedy SJ, et al. Sleep-wake disorders based on a polysomnographic diagnosis. JAMA 1982;247:997–1003
3. Buysse DJ, Reynolds CF III, Hauri PJ, et al. Diagnostic concordance for DSM-IV sleep disorders: a report from the APA/NIMH DSM-IV field trial. Am J Psychiatry 1994;151:1351–1360
4. Johnson EO, Chilcoat HD, Breslau N. Trouble sleeping and anxiety/depression in childhood. Psychiatry Res 2000;94:93–102
5. Armitage R. The effects of antidepressants on sleep in patients with depression. Can J Psychiatry 2000;45:803–809
6. Perlis ML, Giles DE, Buysse DJ, et al. Which depressive symptoms are related to which sleep electroencephalographic variables? Biol Psychiatry 1997;42:904–913
7. Dahl RE, Ryan ND, Birmaher B, et al. Electroencephalographic sleep measures in prepubertal depression. Psychiatry Res 1991;38:201–214
8. Emslie GJ, Rush AJ, Weinberg WA, et al. Children with major depression show reduced rapid eye movement latencies. Arch Gen Psychiatry 1990; 47:119–124
9. Khan AU, Todd S. Polysomnographic findings in adolescents with major depression. Psychiatry Res 1990;33:313–320
10. Goetz RR, Puig-Antich J, Dahl RE, et al. EEG sleep of young adults with major depression: a controlled study. J Affect Disord 1991;22:91–100
11. Breslau N, Roth T, Rosenthal L, et al. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–418
12. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989;262: 1479–1484
13. Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop

depression? J Affect Disord 2003;76:255–259
14. 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
15. Emslie GJ, Armitage R, Weinberg WA, et al. Sleep polysomnography as a predictor of recurrence in children and adolescents with major depressive disorder. Int J Neuropsychopharmacol 2001;4:159–168
16. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. Am J Psychiatry 1995;152:967–972
17. Tranter R, O'Donovan C, Chandarana P, et al. Prevalence and outcome of partial remission in depression. J Psychiatry Neurosci 2002;27:241–247
18. Fava GA, Fabbri S, Sonino N. Residual symptoms in depression: an emerging therapeutic target. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:1019–1027
19. Menza M, Marin H, Opper RS. Residual symptoms in depression: can treatment be symptom-specific? J Clin Psychiatry 2003;64:516–523
20. 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
21. Reynolds CF III, Frank E, Houck FE, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? Am J Psychiatry 1997;154:958–962
22. Vogel GW, Buffenstein A, Minter K, et al. Drug effects on REM sleep and endogenous depression. Neurosci Biobehav Rev 1990;14:49–63
23. Sharpley AL, Cowen PJ. Effect of pharmacologic treatments on the sleep of depressed patients. Biol Psychiatry 1995;37:85–98
24. Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999;60(suppl 17):28–31
25. Prozac (fluoxetine). Physicians' Desk Reference. 58th ed. Montvale, NJ: Thompson PDR; 2004
26. Zajecka J, Amsterdam JD, Quitkin FM, et al. Changes in adverse events reported by patients during 6 months of fluoxetine therapy. J Clin Psychiatry 1999;60:389–394
27. Rascati K. Drug utilization review of concomitant use of specific serotonin reuptake inhibitors or clomipramine with antianxiety/sleep medications. Clin Ther 1995;17:786–790
28. Effexor XR [package insert]. Philadelphia, Pa: Wyeth Laboratories; 2003. Available at: http://www.effexor.com. Accessed Feb 26, 2003
29. Cymbalta (duloxetine). Indianapolis, Ind: Eli Lilly and Company; 2004. Available at: http://pi.lilly.com/us/cymbalta-pi.pdf. Accessed Sept 23, 2004
30. Nofzinger EA, Reynolds CF III, Thase ME, et al. REM sleep enhancement by bupropion in depressed men. Am J Psychiatry 1995;152:274–276
31. DeVane CL. Differential pharmacology of newer antidepressants. J Clin Psychiatry 1998;59(suppl 20):85–93
32. Wellbutrin SR [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2002. Available at: http://us.gsk.com/products/assets/us_wellbutrinSR.pdf. Accessed Feb 26, 2003
33. Manber R, Rush AJ, Thase MW, et al. The effects of psychotherapy, nefazodone, and their combination on subjective assessment of disturbed sleep in chronic depression. Sleep 2003;26:130–136
34. Armitage R, Yonkers K, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17:161–168
35. Winokur A, DeMartinis NA III, McNally DP, et al. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. J Clin Psychiatry 2003;64:1224–1229
36. Chalon S, Pereira A, Lainey E, et al. Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. Psychopharmacology (Berl) 2004 July 28 [Epub ahead of print]
37. Casper RC, Katz MM, Bowden CL, et al. The pattern of physical symptom changes in major depressive disorder following treatment with amitriptyline or imipramine. J Affect Disord 1994;31:151–164
38. Kasper S, Zivkov M, Roes KC, et al. Pharmacological treatment of severely depressed patients: a meta-analysis comparing efficacy of mirtazapine and amitriptyline. Eur Neuropsychopharmacol 1997;7:115–124
39. Landolt HP, de Boer LP. Effect of chronic phenelzine treatment on REM sleep: a report of three patients. Neuropsychopharmacology 2001;24: S63–S67
40. Monti JM. Effect of a reversible monoamine oxidase-A inhibitor (moclobemide) on sleep of depressed patients. Br J Psychiatry Suppl 1989;6: 61–65
41. Simon GE, Heiligenstein JH, Grothaus L, et al. Should anxiety and insomnia influence antidepressant selection: a randomized comparison of fluoxetine and imipramine. J Clin Psychiatry 1998;59:49–55
42. Dording CM, Mischoulon D, Petersen TJ, et al. The pharmacologic management of SSRI-induced side effects: a survey of psychiatrists. Ann Clin Psychiatry 2002;14:143–147
43. Clark NA, Alexander B. Increased rate of trazodone prescribing with bupropion and selective serotonin-reuptake inhibitors versus tricyclic antidepressants. Ann Pharmacother 2000;34:1007–1012
44. Kaynak H, Kaynak D, Gozukirmizi E, et al. The effects of trazodone on sleep in patients treated with stimulant antidepressants. Sleep Med 2004; 5:15–20
45. Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994;151:1069–1072
46. Asnis GM, Chakraburtty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999;60: 668–676
47. DeBattista C, Lambke A, Solvason HB, et al. A prospective trial of modafinil as an adjunctive treatment of major depression. J Clin Psychopharmacol 2004;24:87–90
48. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000;61: 378–381
49. Ninan PT, Hassman HA, Glass SJ, et al. Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. J Clin Psychiatry 2004;65:414–420