Antidepressants and Insomnia

Gary K. Zammit, PhD

ABSTRACT

Mood disorders and insomnia are often comorbid conditions, sharing a complex and bi-directional relationship. Complicating the situation, mood stabilizers can disrupt sleep in a variety of different ways depending on a drug’s mechanism of action, dosage level, and timing of administration. The treatment of comorbid depression and insomnia can be achieved through the use of a sedating antidepressant, a combination of two antidepressants, or a combination of an antidepressant in conjunction with a hypnotic. Common practices typically include the concomitant use of an alerting and a sedating antidepressant. However, the empirical evidence supporting this approach is limited, and there are few indicators that sedating antidepressants are efficacious in the treatment of primary insomnia. This article examines the evidence supporting the efficacy and safety of mood stabilizers in the treatment of comorbid and primary insomnia.

INTRODUCTION

Psychiatric disorders and chronic insomnia are often comorbid with each other. The presence of insomnia symptoms in individuals with a current episode of major depressive disorder (MDD) has been shown to approach 80% to 90%. The incidence of comorbid insomnia is higher when anxiety complicates the clinical presentation, affecting approximately

Needs Assessment: The use of trazodone as an adjunctive therapy for insomnia is increasing while clinical evidence of the safety and efficacy of this approach is lacking. Recent studies of a combination of a hypnotic and an antidepressant offer the potential for a safer, more efficacious course of action.

Learning Objectives:
• List three treatment strategies for depression with comorbid insomnia.
• Name the most commonly used adjunctive insomnia therapy for depressed patients treated with an antidepressant.
• Discuss recent research on the efficacy of combining an antidepressant with a hypnotic to treat depression with comorbid insomnia.

Target Audience: Primary care physicians and psychiatrists.

CME Accreditation Statement: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Mount Sinai School of Medicine and MBL Communications, Inc. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: The Mount Sinai School of Medicine designates this educational activity for a maximum of 3 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty Disclosure Policy Statement: It is the policy of the Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices. This information will be available as part of the course material.

This activity has been peer-reviewed and approved by Eric Hollander, MD, chair and professor of psychiatry at the Mount Sinai School of Medicine, and Norman Sussman, MD, editor of Primary Psychiatry and professor of psychiatry at New York University School of Medicine. Review Date: March 27, 2008.

Drs. Hollander and Sussman report no affiliation with or financial interest in any organization that may pose a conflict of interest.

To receive credit for this activity: Read this article and the two CME-designated accompanying articles, reflect on the information presented, and then complete the CME posttest and evaluation found on page 85. To obtain credits, you should score 70% or better. Early submission of this posttest is encouraged: please submit this posttest by May 1, 2010 to be eligible for credit. Release date: May 1, 2008. Termination date: May 31, 2010. The estimated time to complete all three articles and the posttest is 3 hours.

Dr. Zammit is president and CEO of Clinilabs, director of the Sleep Disorders Institute, and clinical associate professor at the Columbia University College of Physicians and Surgeons in New York City.

Disclosure: Dr. Zammit is a consultant to Boehringer-Ingelheim, sanofi-aventis, Sepracor, and Takeda; receives research support from Forest, GlaxoSmithKline, Pfizer, sanofi-aventis, Sepracor, Takeda Pharmaceuticals North America, Transcept, and Wyeth; and receives honoraria from Takeda.

Acknowledgments: The author would like to thank Ms. Bridget Banas for her assistance in the preparation of this manuscript.

Please direct all correspondence to: Gary Zammit, PhD, Clinilabs, Inc, 423 W. 55th St, 4th Floor, New York, NY 10019; Tel: 212-994-4560; Fax: 212-523-1704; E-mail: gzammit@clinilabs.com; Website: www.clinilabs.com.
90% with a concurrent anxiety disorder. Furthermore, mood disorder symptoms are typically more pronounced in people with insomnia symptoms.

Insomnia is often a precursor to depression. Several longitudinal studies have examined the incidence of psychiatric disorders over periods ranging from 1–40 years following the initial diagnosis of insomnia. In every study completed to date, insomnia has been found to be a significant risk factor for the subsequent onset of depression, with a greater incidence of affective disorder found in people with insomnia. These findings do not suggest that insomnia is merely part of a prodrome that occurs in close temporal association with affective disorders, as depression may first appear several years after the initial diagnosis of insomnia. In addition to these findings, it has been shown that insomnia is a precursor to the recurrence of depression in patients in remission, and that persistent sleep disturbance is associated with non-response to antidepressant therapy.

While insomnia often precedes the onset of affective illness, symptoms of depression and insomnia may be concurrent. Complicating this picture is the fact that many antidepressants used to treat depression disturb sleep, potentially exacerbating the relationship between the two disorders. The type of sleep disturbance produced by depression pharmacotherapy varies based on the compound’s mechanism of action and the dosage employed. Effects may include decrements in rapid eye movement (REM) sleep, a lengthening of the time to sleep onset, and an increase in nocturnal arousals (Table 1). This article reviews the effectiveness and safety of several treatment options for comorbid depression and insomnia.

**PRESCRIBING PATTERNS**

Between 1987 and 1996, the pharmacologic treatment of insomnia decreased markedly. A recent review covering this period found that drug mentions (ie, patient contact that resulted in drug therapy or a mention of drug therapy) fell by >50% for hypnotics, and were down approximately 25% for all forms of insomnia pharmacotherapy combined. Antidepressants used for the treatment of insomnia were the only drug category showing signs of growth—tripling in drug mentions over this period.

In 1996, the two drugs mentioned most frequently for the treatment of insomnia were trazodone, a sedating tricyclic antidepressant (TCA), and zolpidem, a non-benzodiazepine hypnotic. Trazodone is indicated for the treatment of depression, but not specifically labeled for use as a hypnotic. Over the 10-year period examined, the total number of trazodone mentions was steady. However, mentions associated with antidepressant action fell from >70% of all occurrences in 1987 to only 31% in 1996. In contrast, the number of mentions associated with insomnia rose from only 6.5% to almost 42% over the same period.

The conclusion that the use of sedating antidepressants for the treatment of insomnia rose between 1987 and 1996 was based on reported medication doses. The therapeutic daily dosage of trazodone for depression therapy is 150–600 mg/day. Doses below this level may provide sedative effects but are not expected to combat the symptoms of depression. By 1996, two-thirds of all trazodone mentions were associated with a daily dose of ≤100 mg—strongly suggesting that antidepressant effects were not the intended results. Furthermore, almost 40% of treatment mentions in 1996 were concomitant with the mention of another antidepressant. This analysis is consistent with a more recent survey of psychiatrists’ prescribing practices. The survey was conducted at a psychopharmacology review course to investigate the management of antidepressant-induced side effects. Almost 80% of the survey respondents indicated that they would prescribe trazodone to address selective serotonin reuptake inhibitor (SSRI)-induced insomnia.

**TREATMENT OPTIONS**

In light of the common use of trazodone as adjunctive insomnia therapy in depressed patients, it is important to remember that several treatment approaches are available. Insomnia comorbid with depression may be treated using a single hypnotic, a single antidepressant, a combination of two antidepressants, and a combination of one antidepressant and one hypnotic.

**Option 1: A Single Hypnotic**

There is no evidence to support the treatment of patients with MDD and comorbid insomnia with a hypnotic medication alone. Even though these medications are highly efficacious in ameliorating sleep disturbances in a wide range of patient populations, neither the older benzodiazepine nor the newer non-benzodiazepine hypnotics have been shown to be effective therapy for MDD.

**Option 2: A Single Antidepressant**

A single, sedating antidepressant can be employed as a treatment for both insomnia and depression. Candidates for this therapeutic approach include the TCAs and several atypical antidepressants. Most of these TCAs inhibit the reuptake of noradrenaline and serotonin and block histamine (H) receptors and α1-adrenergic receptors. Amitriptyline and trimipramine, both particularly associated with sedation, also block serotonin (5-HT) action. Trazodone is an antagonist at the α1-adrenoceptors, 5-HT, and 5-HT receptors. Nefazodone has strong 5-HT antagonist properties and mild serotonin
reuptake-blocking effects. Finally, mirtazapine blocks 5-HT₂ receptors, H₁ receptors, and α₂-adrenoceptors.

Some practitioners use a single, sedating antidepressant to treat comorbid depression and insomnia. When administered at therapeutic doses for depression, these medications are known to produce sedative side-effects that may be exploited in an effort to treat insomnia and to provide relief from depression. This approach has intuitive appeal, as the use of one medication to

| TABLE 1 | SLEEP EFFECTS OF ANTIDEPRESSANTS*24,86-88 |
|---|---|---|---|---|---|---|
| **TCA** | **Daily Dosage (mg)** | **Lat** | **TST** | **SWS** | **REM** | **NAW** | **Effects in Non-Depressed Patients** |
| **Amitriptyline** | T: 100–300, S: 25–150 | ↓ | ↑ | ↓ | ↓ | Daytime sedation ↑ |
| **Clomipramine** | T: 100–250 | ↓ | | | | REM ↓, NAW ↑ |
| **Desipramine** | T: 75–200 | ↓ | ↑ | ↓ | | |
| **Doxepin** | T: 100–300, S: 25–150 | ↓ | ↓ | ↓ | ↓ | Lat ↓, TST ↑ |
| **Imipramine** | T: 100–300 | ↓ | ↓ | ↓ | ↓ | TST ↓, NAW ↑ |
| **Nortriptyline** | T: 50–150 | ↓ | ↓ | ↓ | ↓ | TST ↑, daytime sedation ↑ |
| **Trimipramine** | T: 100–300, S: 25–150 | ↓ | ↑ | ↑ | ↑ | TST ↑ |
| **SSRI** | **Daily Dosage (mg)** | **Lat** | **TST** | **SWS** | **REM** | **NAW** | **Effects in Non-Depressed Patients** |
| **Citalopram** | T: 20–60 | ↓ | | | | |
| **Fluoxetine** | T: 20–60 | ↑ | ↓ | ↓ | ↓ | REM ↓ |
| **Fluvoxamine** | T: 100–300 | ↓ | ↓ | ↓ | | TST ↓, REM ↓ |
| **Paroxetine** | T: 20–60 | ↓ | ↓ | ↓ | | Lat ↑, REM ↓ |
| **Sertraline** | T: 50–200 | ↑ | ↓ | | | Insomnia symptoms ↑ |
| **MAO** | **Daily Dosage (mg)** | **Lat** | **TST** | **SWS** | **REM** | **NAW** | **Effects in Non-Depressed Patients** |
| **Moclobemide** | T: 150–600 | ↓ | | | | No effect |
| **Phenelzine** | T: 45–90 | ↑ | ↓ | | | |
| **Tranylcypromine** | T: 30–60 | ↑ | | | | |
| **Atypical Antidepressants** | **Daily Dosage (mg)** | **Lat** | **TST** | **SWS** | **REM** | **NAW** | **Effects in Non-Depressed Patients** |
| **Bupropion** | T: 100–450 | ↑ | | | | TST ↓ |
| **Mianserin** | T: 30–90 | ↑ | ↓ | | | |
| **Mirtazapine** | T: 15–45, S: 15–30 | ↓ | ↑ | ↑ | ↓ | NAW ↓ |
| **Nefazodone** | T: 150–450, S: 50–150 | ↓ | ↑ | ↑ | ↑ | ↑ | TST ↓, NAW ↑ |
| **Trazodone** | T: 150–600, S: 25–150 | ↓ | ↑ | ↑ | ↓ | REM ↓, NAW ↓ |
| **Venlafaxine** | T: 75–375 | ↓ | | | ↓ | ↑ |

* Blank spaces indicate no established effect.

Lat=sleep latency; TST=total sleep time; SWS=slow wave sleep; REM=rapid eye movement sleep; NAW=number of awakenings; TCAs=tricyclic antidepressants; T=therapeutic; S=sedating; ↓ decrease; ↑ increase; SSRIs=selective serotonin reuptake inhibitors; MAOIs=monoamine oxidase inhibitors.

treat multiple disorders has the advantage of minimizing the risks associated with drug-drug interactions and may make patient compliance easier. However, the utility of this approach may be limited by current treatment guidelines and safety concerns.

Option 3: A Combination of Two Antidepressants

This approach typically involves employing a therapeutic dose of a non-sedating antidepressant (e.g., SSRIs, monoamine oxidase inhibitors [MAOIs]) to treat depression, and a lower, non-therapeutic dose of a sedating antidepressant to treat insomnia. While this strategy has been used with some popularity, there are relatively few data demonstrating the safety and efficacy of this approach.23-25,26

Option 4: A Combination of One Antidepressant and One Hypnotic

This treatment approach enables clinicians to decouple the treatment for depression from the treatment of insomnia. This approach represents an important treatment option because it is often necessary to experiment with different antidepressants, titrate dosage levels, and modify dose timing to find the most appropriate therapy for an individual with MDD. Employing a hypnotic as an adjunctive treatment enables the clinician to directly and immediately address a patient’s insomnia symptoms while still making necessary adjustments to the pharmacotherapeutic used to treat depression. When present, antidepressant-induced insomnia typically occurs during the first 3–4 weeks of treatment.27 Therefore, addressing sleep complaints early may provide rapid relief to the patient and may also contribute to compliance with depression therapy.

EVIDENCE SUPPORTING THE USE OF A SINGLE ANTIDEPRESSANT

Efficacy

The SSRIs and MAOIs are generally alerting; these drugs tend to exacerbate existing insomnia symptoms or produce treatment-related insomnia (Table 1). As such, they are not considered appropriate for addressing insomnia symptoms in depressed patients as monotherapy.

In contrast, the TCAs commonly produce sedation as a side effect, even though they also tend to suppress REM sleep like the SSRIs and MAOIs. Three TCAs appear to offer the greatest potential for combining both antidepressant and hypnotic effects,24 namely, amitriptyline,28,29 doxepin,28 and trimipramine. Improvements were seen in depressed patients treated with amitriptyline in measures of early morning awakenings,20 nocturnal waking,20 and sleep latency30 as compared to the results produced by imipramine or fluoxetine. Doxepin has been shown to significantly improve Hamilton Rating Scale for Depression (HAM-D) sleep scores as compared to placebo31 and bupropion.32 Trimipramine has been reported to improve sleep efficiency, increase sleep time, and reduce nocturnal awakenings as compared to both fluoxetine33 and imipramine.34

The atypical antidepressants most often used to treat depression and comorbid insomnia are mirtazapine, nefazodone, and trazodone.24 Mirtazapine has been shown to produce a range of effects on sleep in depressed patients. Rapid improvements on quality of sleep and other subjective sleep assessments have been seen with mirtazapine as compared to citalopram,35 while improvements in sleep efficiency and nocturnal distress have been seen relative to both fluoxetine36 or paroxetine treatment.37 It is of interest that HAM-D sleep item scores have been shown to improve more when patients are treated with mirtazapine than with either venlafaxine38 or paroxetine.39 Nefazodone has also been shown to improve HAM-D sleep scores relative to treatment with placebo.40 It also produces less nocturnal disturbance than either fluoxetine41 or paroxetine.42

Trazodone’s effects on sleep in depressed patients are perhaps better characterized than that of any other sedating antidepressant. Two studies have found that, relative to placebo, trazodone objectively increases total sleep time, sleep efficiency, and slow wave sleep (SWS) with limited next-day sedative effects.43,44 It has also been shown that trazodone 75 mg results in increases in SWS and improvements in HAM-D scores and subjective assessments of daytime alertness.45 Higher doses of trazodone also appear to have effects on depression and sleep. Trazodone (150–400 mg) produces significant improvement in symptoms of depression and changes in objective measures of sleep architecture.46 Specifically, sleep latency declined, and total sleep time, SWS, and sleep efficiency increased following active treatment. Doses of 400–600 mg produce significant improvements in Montgomery-Asberg Depression Rating Scale (MADRS) scores (>60% reduction), reduce sleep latency, and increase total sleep time and SWS.47

Safety

Employing a sedating antidepressant to treat both depression and comorbid insomnia is appealing because of the reduced opportunity for drug-drug interactions and the potential increase in patient compliance due to a less complex treatment regimen. However, the available literature suggests caution should be exercised when considering this approach. A recent conference that reviewed the evidence supporting the use of both TCAs and SSRIs resulted in a published statement suggesting that TCAs are no longer justified as first-line...
antidepressant therapy in most situations. This position reflects concerns about the differential efficacy and safety profiles of the TCAs relative to newer therapies.

Two of the three sedating atypical antidepressants reviewed here are also of questionable value as first-line treatment. First, mirtazapine is indicated for the treatment of depression but often is used as an alternative or augmentation therapy for depression rather than a first-line monotherapy. Second, sales of nefazodone have been discontinued in several countries including the United States (branded version) due to concerns of liver toxicity.

The process of elimination leaves trazodone as the most likely candidate for monotherapy in depression with comorbid insomnia. However, while trazodone is considered to be safer than the TCAs, it remains associated with a series of significant side effects. The most common adverse events seen with trazodone at doses of ≥75 mg/day include drowsiness, dizziness, dry mouth, nausea, vomiting, constipation, headache, hypotension, and blurred vision. A review of published data from controlled trials in depressed patients found that 25% to 30% of patients experienced some treatment-emergent adverse event attributed to trazodone. Reported discontinuation rates from clinical trials were relatively high (25% to 60%), with 25% to 50% specifically attributable to adverse events. Most importantly, a recent literature review identified a sizable number of reports of treatment-emergent cardiac events. Adverse events noted in clinical studies and case reports include hypotension, ventricular arrhythmias, cardiac conduction disturbances, and exacerbation of ischemic attacks. Torsades de pointes, a prolongation of the QTc interval, and other cardiac arrhythmias, have been observed in patients treated with trazodone. Finally, a review of psychotropics and priapism found that almost 80% of cases reviewed were associated with trazodone, while the balance was associated with antipsychotics.

**EVIDENCE SUPPORTING THE USE OF A COMBINATION OF TWO ANTIDEPRESSANTS**

**Efficacy**

*Trazodone*

Trazodone is the most widely used sedating antidepressant used as adjunctive therapy to other antidepressants. Given the frequency with which this treatment course is pursued, it is remarkable that the combination of trazodone and other antidepressants has not been ardently investigated. Of the studies that have been conducted, almost all have employed small samples and, therefore, may be of limited applicability to the general population of patients with depression.

In one study, trazodone 100 mg or placebo was given to patients (N=12) stable on different SSRIs for a period of 7 days. At the end of this period, trazodone co-therapy significantly increased total sleep time and SWS, and reduced the number of awakenings seen on polysomnography. Another study examined the impact of prescribing trazodone for patients (N=17) with an incomplete response to fluoxetine or bupropion. In this evaluation, trazodone produced significantly more improvement than placebo in several subjective measures of sleep.

Trazodone has been added to fluoxetine in one study of a group of depressed patients (N=8) for the purposes of either improving sleep or as a possible antidepressant potentiator. Three of the eight patients experienced improvements in both sleep and depression symptoms. A second group of patients on fluoxetine (N=16) was given adjunctive trazodone for complaints of insomnia. All patients had a positive hypnotic response, but five discontinued trazodone due to excessive sedation.

Trazodone was compared to placebo in depressed patients (N=7) who developed insomnia while treated with the MAOI brofaromine. Trazodone increased SWS and was associated with subjective reports of better and deeper sleep. A review of MAOI-induced insomnia treated with trazodone found 13 case-studies. Twelve reported an initial positive response to co-therapy while only nine were able to continue treatment without intolerable side effects.

Depressed patients (N=50) participated in a 4-week study of the atypical antidepressant venlafaxine with adjunctive trazodone, as needed, for the development of comorbid insomnia. The timing and dosage of trazodone was left to the discretion of the clinicians to simulate a naturalistic setting. Patients who received adjunctive trazodone had a lower response to venlafaxine monotherapy on MADRS measures of insomnia and inner tension. Once trazodone was introduced, these patients showed improvements in insomnia symptoms but not in other measures of depression.

**Other Antidepressants**

Aside from trazodone, very little information is available about the impact on sleep parameters of sedating antidepressants used as adjunctive therapy to any of the alerting SSRIs or MAOIs.

**Safety**

*Trazodone*

In one study of trazodone as adjunctive therapy for fluoxetine, five of eight patients were unaffected by the addition of trazodone to fluoxetine or had intolerable adverse drug
reactions. In a second study of trazodone-fluoxetine co-therapy, all patients reported marked daytime sedation with five of 16 discontinuing trazodone as a consequence. The implications of these case reports suggest that the utility of the combination of fluoxetine and trazodone may be limited by adverse effects.

Co-administration of trazodone and brofaromine produced few adverse events and was well tolerated by study participants. A review of several case studies of trazodone-MAOI co-therapy found that one of 13 patients was unable to tolerate the combination initially and another three discontinued this course of treatment due to side effects over a longer period of time. Serotonin syndrome has been described when trazodone was prescribed in combination with nefazodone. Serotonin syndrome has also been reported following the use of venlafaxine and fluoxetine.

Other Sedating Antidepressants
Co-administration of the atypical antidepressant venlafaxine and the TCAs clomipramine or imipramine has been well tolerated. Venlafaxine has been used as adjunctive therapy when patients have realized only partial response to the TCA. However, no effects on sleep parameters were reviewed.

Adjunctive paroxetine has been employed to increase the effectiveness of TCAs (amitriptyline and imipramine) in patients who had not sufficiently responded after 3 weeks of monotherapy. This combination increased TCA serum levels as intended and was well tolerated. Effects on sleep were not reviewed.

When used in combination, the SSRI fluoxetine was shown to increase TCA plasma levels for several members of this class of antidepressants. This increase was highest with clomipramine and imipramine and less notable with amitriptyline. These pharmacokinetic changes did not induce side effects in the patients evaluated. The effects on sleep were not reviewed.

EVIDENCE SUPPORTING THE USE OF A COMBINATION OF ONE ANTIDEPRESSANT AND ONE HYPNOTIC

Efficacy
Although numerous drug-drug interaction studies have been conducted to evaluate the interaction between hypnotics and antidepressants, efforts to evaluate the effectiveness of co-administration of these treatments on comorbid depression and insomnia are still in the early stages. The use of zolpidem was examined in SSRI-treated patients with persistent comorbid insomnia. Patients who participated in this study were diagnosed with depression, treated stably with the SSRIs fluoxetine, sertraline, or paroxetine, and complained of sleep onset difficulty or too-short sleep time at least 3 nights a week and associated with daytime impairment. Over a 4-week period, treatment with zolpidem 10 mg lengthened sleep time, improved sleep quality, reduced the number of awakenings, and improved multiple measures of daytime functioning as compared to placebo.

A recent study evaluated the co-administration of eszopiclone 3 mg with the SSRI fluoxetine in patients with MDD over an 8-week period. Compared to fluoxetine alone, the fluoxetine-eszopiclone group demonstrated statistically significant improvements in all sleep parameters evaluated at all time points. Measures included sleep latency, wake time after sleep onset, total sleep time, sleep quality, and depth of sleep. Importantly, eszopiclone also resulted in a greater treatment response to fluoxetine as measured by improvements on the 17-item HAM-D, Clinical Global Impression (CGI) Improvement scale, and CGI Severity scale. Furthermore, a significantly greater percentage of individuals in the co-therapy group were classified as responders (59% versus 48%) and remitters (42% versus 33%) at the end of the study.

Safety
In the zolpidem-SSRI-induced insomnia study, adverse events were similar between the placebo and zolpidem groups. There was no evidence of dependence or withdrawal from zolpidem during the placebo substitution period at the conclusion of the study.

Zolpidem drug-drug interaction studies have been conducted with two TCAs and two SSRIs. Co-administration of zolpidem and imipramine produced a 20% decrease in peak levels of imipramine and an additive effect of decreased alertness. Chlorpromazine in combination with zolpidem produced no pharmacokinetic interactions; however, decreases in alertness and psychomotor performance were potentiated. Both of these studies evaluated single-dose interactions in healthy volunteers. Thus, the results may not be predictive for chronic administration in depressed patients.

Zolpidem-fluoxetine interactions were examined in both single-dose and multiple-dose studies. A single-dose study in male volunteers with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels did not find any clinically significant pharmacokinetic or pharmacodynamic interactions. Healthy females participated in a multiple-dose study of zolpidem and fluoxetine at steady-state concentrations. The only significant change in this evaluation was a 17% increase in the half-life of zolpidem. No changes in psychomotor performance were seen.
Healthy female volunteers were dosed with sertraline 50 mg for 17 days. Once steady-state levels were reached, subjects were dosed for 5 consecutive nights with zolpidem 10 mg. The pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem, but zolpidem C\textsubscript{max} was significantly higher (43%) and T\textsubscript{max} was significantly decreased (53%).

Adverse events and dropout rates were similar between the placebo and eszopiclone groups in the 8-week eszopiclone-fluoxetine MDD study.\textsuperscript{72} The frequency of adverse events continued to be similar between both groups during the placebo washout period at the conclusion of study.\textsuperscript{73} No evidence of withdrawal effects, rebound insomnia, or rebound depression was observed. A single-dose study of co-administration of eszopiclone 3 mg with paroxetine 20 mg (7 days) found no pharmacokinetic or pharmacodynamic interactions.\textsuperscript{73}

Zaleplon was evaluated in three single-dose antidepressant drug interaction studies.\textsuperscript{75} Zaleplon 20 mg co-administered with the TCA imipramine 75 mg potentiated decrements in next-day alertness and psychomotor performance as compared to either compound administered alone. There was no alteration of the pharmacokinetics of either drug. In two separate studies, neither co-administration of zaleplon with the SSRI paroxetine 20 mg (7 days) or with the atypical antidepressant venlafaxine 150 mg resulted in any pharmacokinetic or pharmacodynamic changes to either zaleplon or the antidepressant.

Ramelteon is the newest hypnotic approved for the treatment of insomnia in the US. It has been evaluated for use in conjunction with two SSRIs. A single-dose of ramelteon 16 mg was co-administered with fluvoxamine 100 mg (3 days).\textsuperscript{76} This combination increased the area under the curve (AUC)\textsubscript{0-\infty} of ramelteon by approximately 190-fold, and the C\textsubscript{max} by approximately 70-fold. This effect appeared to be specific to fluvoxamine and cytochrome P450 1A2 inhibitors rather than being a class effect which could be expected to occur with other SSRIs.

A multiple dose study of co-administration of ramelteon and sertraline was conducted.\textsuperscript{76} Ramelteon had no effect on the systemic availability of sertraline. Decreases in ramelteon AUC and C\textsubscript{max} (23% and 43%, respectively) were deemed clinically irrelevant due to ramelteon’s highly variable inter-subject pharmacokinetic profile.

### TABLE 2

**HYPNOTICS**

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Sleep Initiation</th>
<th>Sleep Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone</td>
<td>1–3 mg</td>
<td>+</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>8 mg</td>
<td>+</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>5–20 mg</td>
<td>-</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5–10 mg (CR formulation: 6.26–12.5 mg)</td>
<td>+ (CR formulation)</td>
</tr>
</tbody>
</table>

+=improvement; -=no consistent effect; CR=controlled release.


### ANTIDEPRESSANTS AND NON-DEPRESSED PATIENTS

A small number of studies have evaluated the efficacy of antidepressants in non-depressed, primary insomnia patients. The extremely limited nature of this evidence and the small scale of most of these studies strongly argues against the use of antidepressants as hypnotics in non-depressed patients.

The largest study (N=306) reported to date has been the only placebo-controlled study of trazodone in insomnia patients.\textsuperscript{77} Over a 2-week period, trazodone improved sleep latency and total sleep time relative to placebo during the first week of treatment only. The loss of efficacy during the second week suggests that trazodone is not an appropriate insomnia treatment choice for non-depressed patients. No other trazodone studies have been reported in primary insomnia patients.

A low-dose formulation of doxepin is currently in development as a hypnotic. Three published studies have examined doxepin’s effects in primary insomnia patients. A placebo-controlled, 4-week study of doxepin 25–50 mg (N=47) found that active treatment improved sleep efficiency and sleep quality over the entire treatment period.\textsuperscript{78} Notably, more rebound insomnia was observed in the doxepin treatment group during the placebo run-out period. Adverse effects were comparable between the two groups, but two doxepin patients discontinued due to adverse effects. In the second study, patients (N=10) were treated with placebo for 1 night and doxepin 25 mg for 3 weeks.\textsuperscript{79} Relative to placebo, sleep was improved after one dose of doxepin during the double-blind phase of the trial. At the end of 3 weeks of open-label treatment, doxepin also improved sleep relative to baseline values. Adverse events and rebound insomnia remained a concern in some patients. Finally, a 2-night cross-over study\textsuperscript{80} (N=67) was employed to evaluate doxepin 1–6 mg. All three doses improved wake time during sleep, total sleep time, and sleep efficiency relative to placebo. The safety profile of doxepin was similar to that of placebo with no evidence of anticholinergic effects, memory impairment, or significant hangover/next-day residual effects.

Two studies evaluated paroxetine in primary insomnia patients. Fifteen insomnia patients were treated for 6 weeks with a flexible dose of paroxetine (median dose=20 mg).\textsuperscript{31} At the end of the treatment period, 11 patients had improved

---

**Primary Psychiatry** © MBL Communications 2008

May 2008
and seven no longer met the diagnostic criteria for insomnia. Subjective measures of sleep quality and daytime function were significantly improved, but neither objective nor subjective measures of sleep quantity were consistently changed with treatment. One participant dropped out due to adverse side effects. A double-blind comparison of paroxetine and placebo in older adults (N=27) found improvements in subjective sleep quality and several measures of daytime function. Sleep efficiency, sleep latency, and wake time appeared to be unaffected by active treatment. Both evaluations suggest that paroxetine is ineffective for treating primary insomnia.

Trimipramine was studied in two groups of primary insomnia patients. It was shown to produce significant improvements in sleep efficiency, total sleep time, wake time after sleep onset, sleep quality, and next-day well-being in 19 primary insomnia patients (mean dose=166 mg). Side effects included dry mouth and the anticholinergic properties of the drug. No rebound insomnia was observed at either 4 or 14 days following drug discontinuation. A 4-week study of trimipramine (mean dose=100 mg) in 55 insomnia patients found significant improvements in sleep efficiency but no impact on total sleep time. Adverse effects were deemed minimal and no rebound insomnia was observed.

One open label study of nefazodone in primary insomnia has been reported. Patients (N=32) were treated with 100 mg nefazodone at bedtime. Over the 4-week period evaluated, this dose could be titrated up to 400 mg depending on treatment response. At the end of the treatment period sleep latency was prolonged and there was less SWS relative to baseline values. The duration of REM sleep was greater on treatment response. At the end of the treatment period subjective sleep quality and several measures of daytime function. Sleep efficiency, sleep latency, and wake time appeared to be unaffected by active treatment. Both evaluations suggest that paroxetine is ineffective for treating primary insomnia.

**REFERENCES**


**CONCLUSION**

Mood disorders are frequently comorbid with insomnia. Treatment options to address both conditions simultaneously include the use of a sedating antidepressant, two antidepressants (one sedating), or an antidepressant in conjunction with a hypnotic. Although the simultaneous use of two antidepressants is perhaps the most common course of action, it has not been well studied and is associated with significant safety concerns. Recent studies suggest that combining an antidepressant with a hypnotic may be a more promising, efficacious, and safe strategy for the treatment of comorbid mood disorders and insomnia. PP