

Pharmacologic Approaches for the Treatment of Chronic Insomnia

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Insomnia is a common problem that for many sufferers persists chronically and may result from a wide range of causes. Specific treatments address particular underlying medical disorders. General therapeutic approaches, including pharmacologic and behavioral strategies, may have broad applicability to insomnia patients. Many different medications and substances have been used in an attempt to improve sleep. This article reviews the advantages and disadvantages of medications and other substances employed to promote improved sleep. Special emphasis is given to the use of the newer-generation benzodiazepine receptor agonist hypnotics. Clinical Cornerstone Vol. 5, No. 3. Copyright © 2003 Excerpta Medica, Inc.

Insomnia is a distressing condition that affects not only the ability to sleep adequately at night, but also to function effectively during one's desired waking time (1). Throughout history people have tried a remarkable range of substances in an attempt to sleep better. These substances have varied widely in safety and efficacy, and in many cases no substantial evidence has supported their use. Alcohol, assorted folk remedies, herbal and other so-called "natural" preparations, dietary supplements, over-the-counter (OTC) antihistamines promoted as sleep aids, and various classes of prescription pharmacologic medications have all been used in an attempt to treat insomnia.

EVALUATION OF INSOMNIA AND TREATMENT STRATEGIES

Insomnia may result from many different and sometimes simultaneous causes. In chronic insomnia, major influences causing sleep disturbance may change over time (2). For example, work conflicts or physical discomfort from a medical problem may initiate an insomnia episode. Insomnia may be perpetuated by factors such as daytime nap-

KEY POINT

The comprehensive evaluation of an insomnia patient should first focus on any specific underlying processes and disorders that may be present.

ping, alcohol use, psychologic conditioning, and major depression. Effective treatment may require a combination of therapies; therefore, in reviewing insomnia treatment approaches, it is useful to consider both specific and general strategies.

Specific insomnia treatment strategies address primarily any identified underlying medical or other disorders. Major depression may be treated with an antidepressant; sleep apnea with continuous positive airway pressure; and pain with analgesics. Clearly, the management of these contributing conditions must be optimized to improve the sleep disturbance.

The simultaneous use of 1 or more general treatment strategies may be beneficial in a broad spectrum of patients suffering from insomnia. These approaches include behavioral, schedule, and environmental changes conducive to improved sleep. Valuable recommendations are based on well-established principles regarding the regulation of the sleep-wake cycle. Psychotherapeutic approaches and most formalized behavioral sleep medicine therapies, which often are combined in a cognitive-behavioral approach, also have broad applicability with insomnia patients. The use of hypnotic medications can be seen as a general approach with value in the treatment of patients with insomnia from varied causes.

Evidence-based guidelines for the pharmacologic treatment of insomnia are rather limited, in part because insomnia is not a specific disease but rather a diffuse condition with a wide range of severity and duration. However, short-term pharmacologic studies and extensive long-term clinical experience have demonstrated that certain medications show safety, tolerability, and efficacy in the treatment of insomnia in both acute and chronic cases.

The ideal medication intended primarily for insomnia will have a rapid sedating effect that does not persist into the desired waking time; will not promote the development of tolerance and dependence; will have specific pharmacodynamic activity that avoids adverse effects from undesired receptor activity; and will have low toxicity if an excessive dose is ingested. In improving the duration and quality of nighttime sleep, the use of the insomnia medication should result in improved daytime symptoms, such as greater alertness and concentration.

Many factors influence the choice of medications and other substances taken for insomnia. Patients may view OTC, herbal, and dietary supplement preparations as safer and more “natural,” whereas some may worry about dependence on “sleeping pills.” Others desire a medication to put them to sleep. Recommendations made by health care providers are determined by their own sleep medicine knowledge and their attitudes about treating insomnia. The result may be an appropriate

treatment plan, but in the community as well as in clinical practice, remedies used for insomnia are sometimes much less rationally determined.

The comprehensive evaluation of an insomnia patient should first focus on any specific underlying processes and disorders that can be directly addressed (3). General pharmacologic and behavioral approaches can then be considered. Any patient history should review what the patient has done to improve sleep and daytime functioning. In addition to past treatment trials (successes and failures), the history should include all current OTC and prescription medications to assess the potential for pharmacokinetic and pharmacodynamic interactions.

The pharmacologic management of insomnia, especially with chronic insomnia patients, should be in the context of a strong therapeutic relationship. Education about sleep and patient support during the treatment process are important components. The use of medication for sleep should be integrated with good sleep hygiene and other appropriate behavioral changes. Although the pharmacologic approach to insomnia is beneficial for many patients, it is rarely the sole solution. In fact, a medication that might otherwise help some patients fall asleep more quickly could be undermined by their intense anxiety and fear that they will never again sleep well and function normally. Ultimately, the resolution of insomnia lies at the nexus of psychologic and physiologic processes.

Insomnia and Major Depression

Insomnia is one of the most common symptoms of a major depressive episode (4,5). About 90% of depressed patients will report difficulty initiating or maintaining sleep. Often insomnia is the first symptom heralding a relapse (6). Several pharmacologic treatment strategies are available. One choice is a sedating antidepressant, which may improve sleep while treating the depression. The single medication approach is appealing and may benefit compliance; however, this strategy limits the range of antidepressant selections and exposes the patient to a medication that may cause undesired daytime sedation. An alternative treatment plan

would be to combine an antidepressant with a hypnotic, which allows for a broader range of antidepressant choices and offers greater reliability in helping with nighttime sleep while minimizing daytime sedation. This combined approach may be particularly advantageous with selective serotonin reuptake inhibitor (SSRI) antidepressants as the hypnotic can offer immediate relief from the insomnia and also help minimize the sleep disturbance that could result from the antidepressant. A placebo-controlled study performed with zolpidem in combination with several different SSRI antidepressants demonstrated hypnotic efficacy, improvement in daytime functioning, and no worsening of depression scores (7). Studies of zolpidem combined with fluoxetine or sertraline found no clinically significant pharmacokinetic and pharmacodynamic interactions in healthy individuals (8,9).

Insomnia and Bipolar Disorder

It is often said that when bipolar disorder patients are experiencing manic or hypomanic episodes, they do not complain of insomnia but simply need less sleep and keep themselves busy with other activities. Although this does seem true for some patients, many suffer considerably with insomnia during these episodes. In fact, sleep loss from any cause can precipitate or exacerbate a manic or hypomanic episode (10). Therefore, it is important for bipolar disorder patients to avoid situations leading to sleep loss. Education about the need for adequate sleep is crucial, and sedating medications, including hypnotics, may play a pivotal role in preventing or minimizing exacerbations.

Alcohol

Alcohol deserves special attention because of the popular notion that it can be used medicinally to enable sleep. Prior to seeking professional help for insomnia, some people will try drinking wine or experiment with some other kind of alcoholic “nightcap.” Those who do not drink alcoholic beverages regularly may attempt this remedy out of desperation. Alcohol may be sedating initially, but over a period of a few hours as the blood alcohol level decreases, there may be a hyperarousal effect that causes more sleep disruption and awak-

enings (11). For some patients, the effective treatment of their insomnia will require the avoidance of alcohol, particularly within a few hours before bedtime.

Dietary Supplements and Herbal and Homeopathic Preparations

A confusing collection of compounds marketed as sleep aids can be found on pharmacy and supermarket shelves. Many do not have active ingredients with sedating properties or any other actions related to sleep-wake cycle regulation. Few studies have evaluated the safety and efficacy of these products as many are not subject to Food and Drug Administration (FDA) control (12). In some cases there may be a placebo benefit. In others, such as valerian preparations, there may be a degree of sedating action, but questions remain about the duration of action, appropriate dosage, potential interactions, and preparation purity. In recent years kava preparations have been banned in some countries because of reports of liver failure associated with its use. In the United States, the FDA has issued a warning regarding this potential problem. Evidence is equivocal regarding the use of *melatonin** as a sleep-inducing agent—most studies have not demonstrated subjective or objective improvement in sleep, but there is some evidence

KEY POINT

Special attention should be given to the potential anticholinergic effects of antihistamines in elderly patients and patients taking concomitant medications with anticholinergic effects such as antidepressants, antipsychotics, and bladder control agents.

that it may be useful for selected patients in modulating the intrinsic circadian system. A major problem with these OTC sleep aids is that in experimenting with them, persons may delay seeking

*Not FDA approved for the management of insomnia.

medical attention and receiving effective treatment for their insomnia.

Antihistamines

A major class of the OTC products marketed as sleep aids contains antihistamines (primarily diphenhydramine), although these medications may be available by prescription at higher doses for various indications, including allergic reactions.

These H₁ antihistamines may be mildly to moderately sedating for some individuals. The elimination half-life tends to be relatively long (about 8 hours); therefore, residual next-morning “hang-over” effects may be present after bedtime use. Some degree of tolerance to the sedating effects of these medications also may occur. In addition to the postsynaptic H₁ antagonism, muscarinic antagonism must also be considered. Accordingly, attention should be paid to the potential anticholinergic effects of antihistamines, especially in elderly patients or patients taking concomitant medications with anticholinergic effects, such as antidepressants, antipsychotics, and bladder control agents. Excessive anticholinergic activity may lead to blurred vision, constipation, urinary retention, confusion, and delirium, all of which have been associated with diphenhydramine alone or in combination with other medications (13). It should be noted that diphenhydramine may inhibit CYP2D6-mediated hepatic metabolism.

Another concern about OTC antihistamine use is the popular combination with analgesics, especially acetaminophen. While this may be a useful combination in certain circumstances, such as when pain interrupts sleep, often these preparations are taken in the absence of any pain symptoms. Chronic use and high doses of analgesics unnecessarily expose patients to the risks associated with analgesics, especially hepatic and renal effects.

Antidepressants

Antidepressants play a vital role in treating major depression and other psychiatric disorders. Some sedating antidepressants may have an immediate effect in improving sleep; however, the role of antidepressants employed as sleep-inducing agents in

KEY POINT

The role of antidepressants employed as sleep-inducing agents in the absence of depression remains debatable.

the absence of depression remains debatable. In the past, amitriptyline commonly had been prescribed, and in recent years trazodone has been used in this manner. The potential adverse effects of the tricyclic antidepressants are well known, and they also have various possible pharmacokinetic and pharmacodynamic drug interactions. A common undesired consequence of using tricyclic antidepressants primarily for insomnia is the residual daytime sedation resulting from the relatively long elimination half-lives of these agents. These daytime symptoms also may result from some nontricyclic antidepressants, such as mirtazapine and trazodone.

The SSRI antidepressants warrant particular attention because they are widely prescribed for several different indications. Some practitioners will recommend these medications for insomnia, although in the absence of a depressive disorder, they tend not to be beneficial for sleep. In fact, SSRIs may result in excessive stimulation and insomnia as side effects. Most classes of antidepressants, including the SSRIs and tricyclics, may be associated with the development or exacerbation of periodic limb movements during sleep, which can result in awakenings or a decrease in sleep quality.

Trazodone is often prescribed for insomnia. Trazodone is typically prescribed in doses of 50 to 150 mg. It may be mildly to moderately sedating and beneficial for selected patients; however, there has been little research regarding either its efficacy or safety when used for insomnia at these doses and there is no body of data supporting its safety or efficacy at lower doses. There are several concerns regarding its use. The most frequent problem encountered is residual morning sedation or difficulty in concentrating following bedtime use. The elimination half-life is ~8 hours. Although some patients may feel that they fall asleep better, they do

not necessarily wake up better. The postsynaptic alpha antagonism may promote orthostatic hypotension, which may be clinically significant in elderly patients or patients taking antihypertensives. Priapism and painful clitoral engorgement are rare adverse reactions. More important is the development of the serotonin syndrome, which has been reported with trazodone coadministered with other serotonergic medications (eg, fluoxetine, paroxetine, monoamine oxidase inhibitor antidepressants). Symptoms and consequences of the serotonin syndrome may include agitation, restlessness, confusion, hyperreflexia, autonomic instability, fever, coma, and death (14). In addition trazodone is a substrate of CYP3A4, and it is metabolized to meta-chlorophenylpiperazine (mCPP), which also is pharmacologically active; therefore, drug interactions are possible with other 3A4 substrates, inhibitors, and inducers. For instance, fluoxetine, a 3A4 inhibitor, may increase the concentration of trazodone and mCPP.

Hypnotics

Bromides, barbiturates, paraldehyde, and methaqualone are among the medications that have been employed as hypnotics. While they have marked sedating properties, they also have significant toxicity and no current role in the treatment of insomnia (12). The use of chloral hydrate for insomnia is limited by toxicity and tolerance. Current medications available in the United States that are indicated for use in treating insomnia include 5 traditional benzodiazepines and 2 newer nonbenzodiazepine

KEY POINT

The short-term safety and efficacy of the newer-generation BZRA hypnotics are well established.

medications (zaleplon and zolpidem) that also function as benzodiazepine receptor agonists (BZRAs) (Table). BZRAs enhance the normal inhibitory activity of the GABA(A) receptor complex. The traditional and newer-generation BZRAs can be dif-

ferentiated by their specificity for the benzodiazepine receptor subtypes, of which at least 5 have now been identified (15). Generally, the traditional benzodiazepine hypnotics are agonists for all of the identified subtypes, whereas the newer-generation BZRAs preferentially bind to the type-1 receptor. It is speculated that this pharmacologic property explains some of the clinical advantages of the newer hypnotics. For example, zaleplon and zolpidem generally are not associated with tolerance, withdrawal, and dependence difficulties and therefore have minimal abuse potential.

Traditional benzodiazepines have been available for use as hypnotics since the 1960s. Aside from the 5 traditional benzodiazepine hypnotics, several other benzodiazepines (eg, alprazolam, lorazepam, clonazepam) are prescribed for insomnia. The traditional benzodiazepines vary widely in their elimination half-lives and subsequent durations of action, which is a concern regarding adverse effects. The half-lives range from a few hours (eg, triazolam) to a few days (eg, flurazepam). The longer half-life hypnotics may be associated with residual daytime effects after a single dose. Repeated nightly doses may lead to a blood-concentration accumulation and a steady-state level with an increased potential for daytime impairment, and may be associated with a greater risk of falls, accidents, and cognitive effects. Only rarely are daytime effects from a bedtime hypnotic desirable; therefore, shorter-acting medications almost always are recommended.

The pharmacologic specificity noted earlier and the short elimination half-lives contribute to the benefits of the newer nonbenzodiazepine BZRAs zaleplon and zolpidem. Zolpidem first became available in 1988 in Europe and was marketed in the United States in 1993. Zaleplon became available in 1999. These 2 medications function similarly in helping people fall asleep. The onset of action may be rapid, so patients should take the medication just before they get into bed and not earlier in anticipation of falling asleep instantly when they go to bed. The duration of action is influenced by the elimination half-life, which for zolpidem is about 2.5 hours and for zaleplon about 1 hour; therefore, there is little risk of morn-

TABLE. BENZODIAZEPINE RECEPTOR AGONIST HYPNOTICS

<i>Generic Name</i>	<i>Brand Name</i>	<i>Elimination Half-Life (h) (including active metabolites)</i>
Benzodiazepine		
Estazolam	ProSom [®]	10–24
Flurazepam	Dalmane [®]	40–250
Quazepam	Doral [®]	40–250
Temazepam	Restoril [®]	3.5–18
Triazolam	Halcion [®]	1.5–5.5
Nonbenzodiazepine		
Zaleplon	Sonata [®]	1
Zolpidem	Ambien [®]	2.5

ing sedation or other cognitive impairment following bedtime use. When taken at bedtime, zolpidem is more likely to promote improved sleep throughout the night. The ultrashort zaleplon half-life should minimize any residual effects 4 hours after its use; therefore, it could be taken (1 dose only) during the night (16). Zaleplon and zolpidem typically are well tolerated. There are no contraindications to their use, although they are not recommended during pregnancy. Both medications are available in 5-mg and 10-mg strengths; 10 mg is the standard recommended dose for adults and 5 mg is suggested for initial use in the elderly and for patients with hepatic or renal impairment. Serious adverse reactions are infrequent; however, based on controlled clinical trials, the more common reactions are headache, dizziness, drowsiness, and nausea.

The short-term safety and efficacy of these newer-generation BZRAs are well established (17–21) although long-term, double-blind, placebo-controlled studies of their safety and efficacy have not been performed. Nonetheless, clinical experience does exist that supports the continued effectiveness and safety of the BZRAs when they are prescribed for long-term nightly use, episodic use over a period from months to years, and long-term frequent intermittent use (a few nights per week). Dose escalation is rare. Discontinuation effects (eg, worsened insomnia relative to baseline sleep quality) are minimal and transient, and usually can be prevented with a gradual decrease in the dose.

Hypnotics and Abuse Potential

The potential abuse of hypnotic medications remains a concern for some physicians that may lead them to avoid or limit the use of this pharmacologic approach in treating their insomnia patients. There likely is some residual apprehension due to the earlier generation of hypnotics that had significant safety, dependence, and abuse problems. Some physicians are reluctant to prescribe hypnotics, not because they fear they will be ineffective or unsafe, but because they worry that patients will sleep much better and be reluctant to discontinue the medication. In actuality, most patients take hypnotics for a relatively short period (days to weeks), and of those who do use them, only about 10% to 15% do so chronically. This long-term use may be entirely appropriate from a clinical perspective. The class labeling for all hypnotics specifies a class IV scheduling and an indication for short-term use, but it does not restrict long-term use. For some providers, it is the regulatory concerns more than any clinical issues that influence their prescribing practices.

Abuse of the BZRA hypnotics is rare among insomnia patients. Abuse might be indicated by excessive nonprescribed doses, recreational daytime non-sleep-related use, and the acquisition of multiple prescriptions from different clinicians. While insomnia patients rarely do so, substance abusers will sometimes abuse the traditional benzodiazepines; however, they rarely abuse the newer-

generation nonbenzodiazepine hypnotics (22). It is good clinical practice to monitor prescriptions and regularly assess the patient's medication use.

An important issue in the treatment of insomnia is the management of sleep complaints of patients with a history of substance abuse (23). Many clinicians restrict or limit the use of any hypnotic for this population. One key question: Is the risk of abusing a hypnotic the same for a person with a very recent history of substance abuse as it is for a person who last abused substances 10 years ago? It is a concern because insomnia may increase the risk for substance-abuse relapse as the patient attempts "self-medication." Further research is necessary to determine the risks and benefits of using low-abuse-potential hypnotics to help maintain abstinence for these patients.

Hypnotic Prescribing Guidelines

The use of a hypnotic medication may be key in the overall treatment plan for a patient suffering with insomnia. Whenever possible, the physician should identify and address specific behaviors, circumstances, and underlying disorders that might be contributing to the insomnia. General treatment strategies can then be employed. A pharmacologic approach is most likely to help if it is part of an integrated plan that incorporates behavioral changes and monitors progress in alleviating insomnia symptoms. Having the patient maintain a sleep log may aid this process. It is useful to establish partic-

KEY POINT

A pharmacologic approach is most likely to succeed if it is part of an integrated plan that incorporates behavioral changes and monitors progress in alleviating insomnia symptoms.

ular therapeutic goals in relation to the patient's chief complaints, such as lengthy nighttime awakenings or poor daytime concentration.

In selecting a medication for insomnia, the safety, tolerability, and efficacy of the newer-

generation BZRA hypnotics make them first-line choices. They should be prescribed at the recommended doses to maximize the therapeutic benefit, and should be taken when the patient is attempting to fall asleep. The frequency and duration of use should be customized to each patient's circumstances. Some patients who experience transient crises may benefit for a few days or weeks and then discontinue the medication when no longer necessary. Others can be supported with a pattern of intermittent use that reflects fluctuations in their symptoms. For selected patients, the best clinical solution may be long-term use of the hypnotic, which may maximize nighttime sleep, daytime functioning and overall quality of life. In some cases, patients using hypnotics on a nightly basis can transition to an intermittent pattern (24,25). When patients who have taken hypnotics nightly for several weeks or longer are to stop using the medication, a gradual decrease in the dose should minimize the potential for recurrence of the insomnia.

CONCLUSION

The pharmacologic treatment of insomnia has developed over the past century from profoundly sedating compounds with significant risk of dependence and fatal overdose to the current generation of safe and effective BZRAs. The pharmacologic management of insomnia over the next several years is likely to build on the current foundation of hypnotic medications and perhaps incorporate innovative modifications that may be appropriate for specific types of insomnia patients. As a more detailed understanding of the physiologic regulation of sleep emerges, new opportunities will arise for exploring pharmacologic strategies to modulate these processes. Further delineation of the interactions of sleep with other bodily systems, such as immune and hormonal functioning, is sure to emphasize the key role of achieving adequate sleep and the necessity of effectively identifying and treating patients with insomnia.

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Dialogue Box

EDITORIAL BOARD

It has been estimated that 5% of the general population may have primary insomnia and that primary insomnia is responsible for 20% of patients presenting clinically with insomnia. Do you agree with these figures?

NEUBAUER

Those are fairly reasonable estimates although it's really difficult to attach percentages for any given etiology. If you survey the general adult population, 10% to 15% of subjects will report they have a persistent or serious problem with insomnia. Trying to break that down further into etiologic categories is really a challenge. Although conceptually it is helpful to categorize insomnia into primary or secondary, clinically the border between the two can be quite blurred. For many patients with insomnia, a number of possible causative factors may be present and which of them is responsible for the insomnia may change over time. And so, 1 week into the insomnia there may be one constellation of factors responsible and 3 months later they may be entirely different. Whatever originally may have caused the sleeplessness may be gone yet the insomnia may persist due to maladaptive sleep behaviors (such as napping in the afternoon) that subsequently evolved. This in turn might lead the patient to turn to alcohol as a remedy, which in turn will cause the sleep to deteriorate even more. At some point the insomnia might assume the characteristics of what is called "psychophysiological" insomnia, which is a learned, conditioned hyperarousal state that can be indistinguishable from primary insomnia. Thus, in the same individual, depending on what point in time you look for a specific etiology, you might come up with one of 4 or 5 different causes.

EDITORIAL BOARD

What OTC medications are important causes of insomnia?

NEUBAUER

Cold and allergy medications containing pseudoephedrine are particularly common. And paradoxically, antihistamines, although sedating for most people, can cause a paradoxical response that results in nervousness and agitation. This is particularly a problem at the higher dosages, which some of the more desperate insomnia patients sometimes take.

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What about caffeine?

NEUBAUER

There is no question that people run into trouble with caffeine. Most people with insomnia do not need to eliminate caffeine entirely but should restrict it to a fairly moderate amount in the morning. My usual guideline for an insomnia patient is to cut off all caffeine after lunchtime since its effect can linger for quite a while.

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A number of people rely on antihistamine products containing diphenhydramine for sleep. If a patient with insomnia is using such a product successfully, is there any reason to change that or would you leave well enough alone?

NEUBAUER

If a younger patient tells me that it is helping him or her to sleep, is functioning well and is not experiencing side effects, and if there is no potential for drug interactions, then I would probably allow the patient to continue its use. On the other hand, if the patient is older and is taking additional medications that run the risk of causing a drug interaction, such as a psychotropic medication or a urinary incontinence medication that possesses anticholinergic activity, then I'd definitely discourage its use. In the elderly, why would you choose an agent with the potential for causing anticholinergic side

Dialogue Box

effects, which can have a negative impact on memory or cause confusion? Even in patients who initially deny any side effects, it is not uncommon to elicit a history of grogginess in the morning on further questioning.

EDITORIAL BOARD

What about the use of psychotropic agents such as amitriptyline, doxepin, or trazodone for sleep?

NEUBAUER

Once again it comes down to the individual patient. If it's a young healthy patient and it's the only medication used and the patient is happy with it, then that's fine. If it's an older patient using trazodone or doxepin, I'd be more troubled by concerns related to alpha-blockade potentially causing hypotension or the potential for drug interaction with other medications the patient may be taking. Let me tell you about a man I recently saw, an 80-year-old patient whose primary care doctor had him taking amitriptyline for sleep for 25 years without mishap. A week prior to seeing me something happened to his sleep that prompted him to go to the drug store and buy Benadryl®. The next morning he ended up in the emergency room for acute urinary retention. In the vast majority of patients, I think using tricyclic antidepressants indefinitely is not a good idea. If I'm going to prescribe a pill for sleep, I would be much more comfortable prescribing one of the newer-generation short-acting hypnotics since I have a good sense of what that medication is doing. These agents are relatively clean in terms of being a BZRA, and unlike the other agents discussed, I can be certain they're not affecting other receptors in the brain or elsewhere in the body. Furthermore, they are short-acting so I also know they get out of the body's system relatively quickly and will not cause side effects.

EDITORIAL BOARD

Why do you think there is such a medical and social stigma surrounding the issue of sleeping pills?

NEUBAUER

I think there are many contributing factors. In our culture, insomnia tends to be viewed as a form of moral weakness as opposed to a true medical concern, such as heart disease, and thus not worthy of attention or drug treatment. Much of the reluctance stems from the old days when the sleeping pills available were in fact dangerous. Although those agents are no longer used, nevertheless things change slowly, particularly in light of the fact that even the traditional benzodiazepine hypnotics that followed have been problematic. Such concerns have only been reinforced with current FDA labeling, which approves these agents for no more than short-term use. In talking with a lot of other doctors about their attitudes concerning sleeping medications, what emerges has nothing to do with safety or efficacy issues, but rather a regulatory concern. Their reluctance stems from a concern that someone might be looking over their shoulder—that the package insert says 2 weeks and not to prescribe them for more than 30 days at a time.

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In some ways the current situation with insomnia and the use of the new hypnotic agents seems to parallel issues in the past related to pain management and the use of medications such as benzodiazepines for treating chronic anxiety. It wasn't until these disorders were somehow "legitimized" as real medical problems that physicians grew more comfortable treating these patients and prescribing medications as required to relieve the patient's symptoms.

NEUBAUER

I would agree. Although the sleep medicine community has done a good job in getting the knowledge out regarding primary sleep disorders such as sleep apnea, restless legs syndrome (RLS), and to some degree, narcolepsy, we still have a way to go with regard to "legitimizing" insomnia as a real problem warranting greater

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attention and appropriate treatment. Although the number of patients being treated for insomnia has been on the rise, unfortunately there are many patients who remain unidentified and who are in need of appropriate treatment.

EDITORIAL BOARD

A major concern of physicians with regard to prescribing a hypnotic agent revolves around the potential for addiction. How real a concern is this for the BZRA agents, zolpidem and zaleplon?

NEUBAUER

Based on my experience, not at all. Obviously there are substance abusers who like benzodiazepines and perhaps the benzodiazepine hypnotics, but you just don't see recreational use of these newer-generation drugs. Not only is it unlikely they will be abused, patients treated for insomnia generally don't become dependent on the use of these hypnotics. The other issue to look at would be if there is any development of tolerance or a definite withdrawal syndrome—from that point of view, the answer is no. If a patient is taking one of the newer-generation hypnotics every single night for a while and then suddenly stops, a withdrawal reaction will probably not occur.

EDITORIAL BOARD

So in the studies with the BZRA agents, you don't see an escalation of dose and you don't see a withdrawal syndrome.

NEUBAUER

That is right. In the clinical trials that have been done with this class of medication, you won't find dose escalation. In addition, when the hypnotic is stopped, patients may not sleep as well the following night or two, but there is no real withdrawal syndrome. Their insomnia is certainly not worse than it was at baseline.

EDITORIAL BOARD

What do you recommend for treating insomnia arising from the use of one of the SSRIs?

NEUBAUER

Although a number of agents have been used, including trazodone, olanzapine, and most recently quetiapine, my choice would be to add one of the short-acting hypnotics, specifically a BZRA agent such as zolpidem.

EDITORIAL BOARD

If the patient were to require the hypnotic agent throughout the course of SSRI treatment, once the SSRI is stopped, will the need for the hypnotic agent stop as well?

NEUBAUER

Yes, I think for most patients it will. However, if the patient has been taking fluoxetine then I'd be inclined to continue the hypnotic a little while longer because of the long half-life of this particular antidepressant.

EDITORIAL BOARD

For the patient with chronic insomnia in whom primary sleep disorders (such as sleep apnea and RLS) as well as reversible medical or psychiatric disorders have been excluded, and in whom bad lifestyle issues and causative medications have been excluded, what percentage will require nightly hypnotic use? What percentage will respond to cognitive behavioral therapy (CBT) alone or with intermittent use of a hypnotic?

NEUBAUER

Those are difficult questions since so many variables play a role. Based on my experience, roughly 10% to 15% with truly chronic insomnia will end up requiring the nightly use of a hypnotic agent and 20% or so will respond to CBT alone. Thus, 65% to 70% would likely require CBT plus the use of an intermittent hypnotic regimen.

Dialogue Box

EDITORIAL BOARD

For patients with chronic insomnia, regardless of cause, describe how you have them use a hypnotic intermittently.

NEUBAUER

Well I think it is very individualized. Probably the most common scenario is a patient coming to see me very distressed about not sleeping and after evaluating the patient coming to the conclusion that this is someone who will benefit from a hypnotic, I usually will begin by telling the patient to take the BZRA hypnotic nightly for the first 2 to 3 weeks. The nightly use of these agents early goes a long way toward helping to alleviate the huge distress and worry such patients carry to bed each night—concerns related to their lack of confidence in their ability to sleep and thoughts that they are never going to be right or function well again. By giving them a short-acting hypnotic that helps them at night they feel better during the day and they come to realize that their problem is not going to go on forever. Following this phase, I then work with them on their sleep hygiene and behavior and transition them to intermittent use of a hypnotic. I tell them not to routinely take the hypnotic each night but assure them that it is there if they need it. Just that knowledge ends up being therapeutic for the patient.

EDITORIAL BOARD

How often do you tell patients they can use the hypnotic?

NEUBAUER

I don't set any limits—I tell them to use it whenever they feel they need it. Thus, depending on what's hap-

pening in their lives, the frequency of use might be once a week or once a month. Other months they may need the medication 5 or 6 times, and then there may be a time when they need to take it every night for a week. In this way, I strive to establish a partnership with my patients that empowers them to exert control over when or whether they use the hypnotic.

EDITORIAL BOARD

Is there any problem with leaving the use of the hypnotic agent open-ended? Is it okay to tell patients that as long as they practice good sleep hygiene and behavior, if they need a hypnotic 7 days a week, to go ahead and take the medication?

NEUBAUER

Yes, that's a reasonable approach. Remember, you are not going to send patients off with a hypnotic agent to use forever. You're going to follow those patients long term and receive ongoing feedback as to how often they are requiring the medication. Over time, the patients are going to let you know what their requirement is, based on need. Although 10% may end up requiring the hypnotic nightly, the majority will find their intermittent use to be effective, with some requiring the hypnotic occasionally, others requiring it rarely, and some not requiring it at all. The appropriate number of times that a patient uses the hypnotic agent is dictated not by any predetermined number but by whatever number is required to improve the patient's sleep and optimize the quality of daytime life.

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