The Importance of Residual Effects When Choosing a Hypnotic: The Unique Profile of Zaleplon

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Background: Insomnia is a prevalent medical disorder that has significant effects on occupational performance, health, and quality of life. Insomnia places an enormous burden on society through increased visits to physicians, loss of productivity in the workplace, and an increased rate of accidents. An estimated sum of $100 million is spent each year on direct treatment of unresolved insomnia. Physicians need to initiate early effective treatment to prevent development of chronic insomnia and its associated morbidity. Institution of good sleep hygiene practices may be useful in some patients but may not be adequate for resolution of all sleep problems. Behavioral treatments, while effective and durable, are time consuming and not widely utilized in clinical practice. Pharmacotherapy includes benzodiazepine hypnotics, but concerns regarding adverse effects (e.g., residual sedation) prompted the search for safer options.

Data Sources: Published and presented studies containing clinical data on zaleplon, a new nonbenzodiazepine sleep medication, were identified via MEDLINE, Current Contents (ISI database), bibliographic reviews, and consultation with sleep specialists.

Results: Zaleplon effectively shortens sleep onset time and improves the quality of sleep in patients with insomnia. Whether administered at bedtime or later at night, zaleplon is devoid of residual sedative effects that impair next-day functioning. Follow-up studies evaluating the long-term efficacy and safety of zaleplon showed that decreased time to sleep onset was maintained during therapy lasting up to 52 weeks, without a withdrawal syndrome after discontinuation.

Conclusion: Insomnia is recurrent and unpredictable in nature. Despite the long-term morbidity of this sleep disorder, research evidence and practice guidelines have not explored long-term use of hypnotics. Many patients could benefit from long-term drug therapy with a sleep medication that is devoid of residual effects and can be taken at bedtime or later as symptoms occur, rather than nightly in anticipation of a sleep problem.

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Insomnia is an important public health problem, affecting 30% to 40% of adult Americans annually and becoming severe or chronic in 10% to 15% of these individuals.[1–3] This disorder is defined by an inability to initiate or maintain sleep or by a deficiency of restorative sleep that negatively impacts next-day functioning. Insomnia results in significant consequences influencing daily life, such as fatigue, irritability, impaired concentration and daytime productivity, and reduced social interactions.[4] Epidemiologic studies indicate that the incidence of sleep disturbances is elevated in persons of advanced age, women, and those who are shift workers, unemployed, or without a life partner.[1–3,5,6] Individuals with insomnia are more likely to exhibit signs and symptoms of cardiovascular disease, obstructive airway disease, and arthritis than those who experience quality sleep.[3,7,8] Sleep difficulties have also been strongly linked with a higher incidence of major depression, anxiety disorders, increased alcohol consumption,[1,5,7] and death.[9,10]

Decreases in mental alertness and daytime productivity related to untreated insomnia produce far-reaching economic effects on society. In the workplace, insomnia is associated with increased absenteeism, reduced job performance, and work-related accidents.[2,8] In the general population, traffic or other serious accidents and injuries are significantly increased in and frequently caused by sleep-deprived individuals.[11,12] Insomnia also causes greater utilization of health care resources,[13] as evidenced by increased hospitalization rates among workers with chronic insomnia,[8] increased primary care consultations in adults with underlying sleep disorders,[14] and earlier nursing home placement in elderly men with insomnia.[10] Moreover, a recent study shows that total health care costs over a 3-month period were 60% higher in adult health maintenance organization (HMO) enrollees with insomnia, compared with patients experiencing quality sleep.[15] Total direct and indirect costs related to the treatment of insomnia

and its associated morbidities are estimated at $100 million annually.[16]

Although many individuals experience transient sleep alterations in response to acute life stressors or travel, the association of insomnia with several chronic medical and psychiatric disorders is consistent with its characteristically persistent and recurrent nature. This is supported by the results of a large longitudinal study by Klink et al. in which patients with complaints of difficulty initiating or maintaining sleep 10 years prior to assessment were 3.5 times more likely to present similar symptoms of insomnia in a health examination survey.[3] Despite these findings, patients with chronic insomnia may be reluctant to seek medical attention specifically for sleep complaints,[1,6] possibly because of the irregular pattern of sleep complaints. In the most recent National Sleep Foundation survey, 80% of patients polled believed their sleep complaints were not serious enough to prompt a physician visit, and 16% believed a physician could not effectively treat their insomnia.[6] As a result, patients may resort to self-medication with nonprescription sleep aids, natural remedies, or alcohol to promote sleep.[6] The risks for developing either chronic insomnia or adverse events related to inappropriate medication use support both the need for routine medical evaluation of sleep patterns in the primary care setting[17] and the need for data on long-term use of sleep medications. Early recognition and effective treatment may be instrumental in lowering the morbidity, mortality, and economic burden associated with chronic insomnia.

OVERVIEW OF INSOMNIA TREATMENT

The ongoing evaluation of an insomnia complaint should consider multiple potential causes, including medical illness (e.g., arthritis, asthma), sleep disorders (e.g., restless legs), psychiatric conditions (e.g., depression, bipolar disorder), environmental issues (e.g., noise, light), alcohol or substance abuse, and adverse effects of medications. If the assessment identifies a primary problem as the basis of the sleep difficulty, primary treatment is indicated. However, an underlying condition may not be initially recognized, may not rapidly respond to treatment, or may not exist. Still, the patient will benefit from direct treatment of insomnia, which may respond to a variety of therapeutic modalities.

Regardless of the treatment method selected, all patients should be educated regarding general sleep hygiene measures to promote restoration of quality sleep (Table 1).[18] However, this approach will not provide positive results in all patients, and sole reliance on these methods is likely to be insufficient for adequate resolution of insomnia.[19] A sleep diary may be very useful in identifying patient-specific issues and assessing the benefit of a 7-day trial of selected hygiene strategies.[18]

Table 1. Recommendations for Improving Sleep Hygiene[a]

Maintain a comfortable sleep environment; keep room dark and quiet
Initiate pre-bedtime rituals, e.g., warm bath, music, stretching exercises
Stick to a regular sleep/wake schedule
Eliminate the alarm clock to reduce anxiety about falling asleep
Avoid excessive time in bed; restrict the bedroom to sleep and sex
Avoid daytime naps
Exercise regularly
Avoid alcohol, nicotine, and caffeine
Avoid large meals late in the evening; eat a light bedtime snack

[a]Based on Hauri.[18]

Behavioral methods, including relaxation therapy, sleep restriction therapy, stimulus control, and cognitive therapy, are considered effective first-line treatments for insomnia unrelated to an underlying medical or psychiatric condition and are described in greater detail elsewhere.[18,20] A recent meta-analysis of the efficacy of various behavioral approaches administered for 5 weeks to patients with chronic insomnia indicated a significant reduction in sleep-onset latency and time awake following sleep onset when compared with pretreatment values and control patients.[19] Total sleep time and number of nocturnal awakenings were also statistically significantly improved compared with pretreatment assessments. In addition, follow-up evaluation at 6 months demonstrated persistence of clinical benefits. However, despite the documented efficacy and durability of their effects, behavioral interventions are not widely used, possibly due to costs of repeat office visits and the time and expertise required to administer treatments.[19]

In clinical practice, pharmacotherapy is often provided prior to the introduction of behavioral approaches. Studies have documented the efficacy of sedative-hypnotics and indicate that they offer resolution of the symptoms of insomnia.[21] Benzodiazepine hypnotic agents, antidepressants, and zolpidem have been frequently prescribed for the short-term management of insomnia.[22,23] Nonprescription sleep aids containing antihistamines are widely available, but the lack of objective efficacy data and reports of residual drowsiness limit their usefulness.[24] A recent study evaluating physician prescribing trends in the treatment of insomnia reflects ongoing resistance to the use of hypnotic medications because of associated daytime sedation, residual effects at the time of awakening, and the risk of tolerance and dependence. Between 1987 and 1996, prescriptions for hypnotic agents (i.e., benzodiazepines and zolpidem) declined by 54%, while the use of antidepressants rose by 146%.[23] Although use of antidepressants in the treatment of depressed patients may result in the indirect resolution of secondary sleep disturbances, clinical support for use of antidepressants in treating insomnia unrelated to a depressive disorder is minimal, and the risk for multiple adverse effects in these patients should be considered.[24,25] The recent approval of zaleplon, a new nonbenzodiazepine hypnotic agent,

provides an alternative to conventional hypnotic medications because of its unique pharmacokinetic profile and selective receptor-binding properties.[26,27] To examine the current knowledge base on the agent, we identified published and presented studies containing clinical data on zaleplon by using MEDLINE, Current Contents (Institute for Scientific Information database), and bibliographic reviews and consulting with sleep specialists. The efficacy and safety characteristics of zaleplon will be highlighted throughout the remainder of this article, with an emphasis on the unique absence of residual sedative effects associated with its use.

SELECTION OF A SEDATIVE-HYPNOTIC AGENT

When selecting an appropriate hypnotic agent, the clinician must consider several patient-related factors in conjunction with a critical evaluation of the efficacy, safety, and pharmacodynamic profiles of the currently available agents. Clearly, identifying the presence of an underlying medical or psychiatric condition is foremost; treatment should be directed toward resolution of the primary disorder, and hypnotic therapy may be contraindicated. When there is no contraindication, however, the clinician may consider the use of a hypnotic agent to address the symptoms of insomnia while awaiting resolution of the underlying problem. Patient age is an important consideration, because elderly patients are generally at greater risk for the development of hypnotic-related adverse effects due to decreased drug clearance and other age-related physiologic changes.[28,29] A clear description of sleep habits and the specific sleep complaint (e.g., inability to initiate sleep or maintain sleep) may facilitate not only the identification of sleep hygiene issues requiring adjustment, but also the selection of the best medication for the patient. It has been traditionally thought that patients unable to initiate sleep would likely benefit more from a hypnotic medication with rapid absorption and elimination properties, whereas those unable to maintain sleep might require a longer acting agent[30] given prophylactically at the beginning of the night before retiring. The availability of zaleplon allows for use of a sleep medication not merely on the night when the difficulty with falling asleep occurs, but also at the specific time the problem occurs—whether at bedtime or later at night. By comparison, other prescription agents, as well as nonprescription products, require the patient to spend 7 to 8 hours in bed before resumption of activity.[31,32] Rapid drug elimination facilitates the progression of natural sleep processes while also preventing impairment of memory, psychomotor, and cognitive performance upon awakening.

Efficacy

The efficacy of a hypnotic medication relates to its ability to induce and maintain sleep of sufficient quantity and quality such that the individual functions in an energetic and alert state the following day.[33] In clinical trials, these outcomes are often assessed subjectively by determining the perceived time to sleep onset, duration of total sleep, number of awakenings, and morning energy level via patient interview, questionnaire, or sleep diary. A positive therapeutic outcome is based on patient reports of falling asleep more quickly, remaining asleep with fewer nocturnal awakenings, and feeling rested and alert upon awakening. Given the large variability in subjective responses, an objective assessment of these parameters using polysomnography (PSG) can be useful in documenting drug efficacy. However, a meta-analysis by Nowell et al. showed PSG was infrequently used in comparative drug evaluations.[22]

The clinical effects of zaleplon as observed in several studies (Table 2)[34–38] are consistent with published data regarding its pharmacodynamic and pharmacokinetic profiles. Preclinical studies demonstrated that zaleplon preferentially binds to benzodiazepine type 1 receptors located on the γ-aminobutyric acid type A ($GABA_A$) receptor complex, resulting in sedative effects similar to those produced by benzodiazepines[27] and zolpidem.[39] In humans, patient- and observer-rated sedative effects associated with zaleplon, 10 mg, were consistent with benzodiazepine agonist effects, but less intense than those experienced with zolpidem, 10 mg,[26] which is consistent with reports of the less vigorous binding affinity of zaleplon for the receptor site.[40] Pharmacokinetic studies indicate that zaleplon is rapidly absorbed, achieving peak plasma concentrations at an average of 1 hour after oral administration.[26] Subsequently, zaleplon undergoes extensive hepatic metabolism to produce pharmacologically inactive metabolites,[41] with an elimination half-life of approximately 1 hour.[26] These kinetic properties are reflected in the therapeutic outcome observed with administration of zaleplon, 10 mg: an increase in total sleep time over baseline and a significantly shortened latency of sleep onset as compared with placebo, but without the withdrawal or rebound effects seen with zolpidem, 10 mg.[35] Importantly, the pharmacokinetic profile is virtually the same in elderly patients up to 85 years of age.[42]

Effects During the Sleep Period: Sleep Architecture, Memory, and Psychomotor Performance

Normal human sleep is composed of alternating periods of rapid eye movement (REM) and non-REM sleep. Non-REM sleep is further divided into 4 stages corresponding to the depth of sleep experienced. Deepest sleep occurs in Stages 3 and 4, collectively referred to as "slow-wave sleep" or "delta sleep."[43] The distribution of sleep stages may be influenced by many factors, but it is unknown whether these alterations significantly affect physical or mental well-being.

Advancing age is associated with changes in sleep architecture. Typically, reductions in slow-wave sleep and

Table 2. Clinical Efficacy Endpoint Results of Zaleplon Treatment for Insomnia

Reference	Design	Drugs	Efficacy	Outcomes
			Latency to persistent sleep[a]	Total sleep time[a]
Walsh et al[34]	Randomized, multicenter, double-blind, placebo-controlled, parallel-group N = 132, 14 days	Zaleplon, 5 mg	–20.13	25.0
		Zaleplon, 10 mg	–20.50	7.0
		Triazolam, 0.25 mg	–16.50	29.70
		Placebo	–17.13	27.50
			Subjective sleep latency[b]	Subjective total sleep time[b]
Elie et al[35]	Randomized, multicenter, double-blind, placebo-controlled, parallel-group N = 574, 28 days	Zaleplon, 5 mg	31	372
		Zaleplon, 10 mg	28*	384
		Zaleplon, 20 mg	27†	385*
		Zolpidem, 10 mg	36	400†
		Placebo	36	377
			Latency to persistent sleep[a]	Total sleep time[a]
Dietrich and Farr[36]	Randomized, multicenter, double-blind, placebo-controlled N = 137, 5 days	Zaleplon, 5 mg	17.45*	18.06
		Zaleplon, 10 mg	–22.75*	23.51
		Zaleplon, 20 mg	–34.55*	41.91*
		Placebo	–3.93	8.53
			Latency to persistent sleep[b]	Total sleep time[b]
Erwin et al[37]	Randomized, multicenter, double-blind, placebo-controlled N = 54 (elderly), 2 nights	Zaleplon, 5 mg	26.0*	363.0*
		Zaleplon, 10 mg	21.8*	362.0
		Placebo	47.7	351.2
			Subjective sleep latency[b]	Subjective total sleep time[b]
Walsh et al[38]	Randomized, multicenter, double-blind, parallel-group N = 549 (elderly), 2 weeks	Zaleplon, 5 mg	38.75‡	325.73
		Zaleplon, 10 mg	31.00‡,§	350.00
		Zolpidem, 5 mg	42.19†	360.36†
		Placebo	55.71	326.25

[a]Changes from baseline (min).
[b]Actual values at the end of treatment (min).
*$p \leq .05$ vs. placebo.
†$p \leq .01$ vs. placebo.
‡$p < .001$ vs. placebo.
§$p < .001$ vs. all other treatments.

REM sleep lead to more frequent nocturnal awakenings and reduced total sleep time.[30] PSG studies indicate that the administration of or withdrawal from drug therapies with central nervous system effects (e.g., tricyclic antidepressants, barbiturates, benzodiazepines, and chloral hydrate) may produce alterations in sleep states and stages.[44] Discontinuance of these agents, particularly tricyclic antidepressants and short-acting benzodiazepines, can result in REM rebound and an associated increase in nightmare occurrence and nocturnal awakenings.[44,45] Clinical studies involving insomniacs aged 18 to 80 years have not demonstrated any alterations in sleep architecture associated with short-term zaleplon administration.[34,37] This may suggest that the rapid elimination of zaleplon permits the resumption of natural sleep processes.

Memory impairment occurring during the night in association with an abrupt awakening can be a frightening and potentially dangerous experience, particularly in the elderly. Hypnotic medications, including benzodiazepines, have been shown to adversely affect both immediate and delayed recall (anterograde amnesia) of information presented after drug administration.[46,47] Memory impairment is maximal at the time of peak serum concentration and is greatest with high doses and high-potency agents.[47] Studies examining the safety of zaleplon in healthy subjects indicate minimal effects on short-term memory.[48,49] A randomized, double-blind, placebo-controlled trial of single-dose zaleplon (1, 5, 15, 30, or 60 mg) failed to demonstrate any difference between treatment groups in word recall testing at 24 hours.[48] Similarly, at 1.25 hours after drug administration, Troy and colleagues did not observe impairment of immediate or delayed recall in association with zaleplon, 10 mg, unlike zaleplon, 20 mg, zolpidem, 10 mg, zolpidem, 20 mg, and triazolam, 0.25 mg.[49]

Psychomotor performance testing shortly after hypnotic administration may be clinically relevant in defining potential drug utility in individuals required to be immediately alert and awake in emergency situations (e.g., paramedics and volunteer firefighters). Significant impairment has been previously demonstrated to occur in healthy subjects 1.5 hours after single doses of zolpidem (10 mg) and triazolam (0.25 mg); this impairment persisted for up to 4 to 6 hours after drug administration.[46] A placebo-controlled study comparing the effects of zaleplon (20 mg) and lorazepam (2 mg) showed a significantly smaller effect on psychomotor performance with zaleplon.[50] In 3 of 5 tests administered, no impairment was evident with zaleplon at 1 hour, and effects were not significantly different from placebo. On the remaining 2 tests, zaleplon became no different from placebo within 3 hours of administration.[50] However, in all assessments, lorazepam was consistently associated with psychomotor

impairment significantly greater than that seen with placebo and zaleplon. In a study by Troy et al., psychomotor function associated with zaleplon, 10 mg, was not significantly different from placebo at 1.25 hours, whereas some impairment was evident for comparative drugs in the following order: zolpidem, 20 mg > zolpidem, 10 mg > zaleplon, 20 mg > triazolam, 0.25 mg.[49]

RESIDUAL SEDATIVE EFFECTS

Continuous hypnotic use generally has not been recommended in chronic insomnia. The development of residual sedation, or the persistence of sleepiness related to hypnotic medication use occurring past the usual sleep period, may offset benefits by producing impaired daytime function.[51] Dose administration should be followed quickly by quality sleep without negative effects on daytime functioning to putatively reduce insomnia-related morbidity.

In clinical studies, the presence of daytime sleepiness is often determined by psychomotor testing performed at various times throughout the 24-hour period after drug ingestion.[52] It has been suggested that hypnotic-related effects be examined using polysomnographical Multiple Sleep Latency Testing (MSLT), as patients may be subjectively unaware of decreased performance in the presence of objectively documented impairment.[33,53] MSLT specifically assesses daytime sleepiness by measuring the time required to initiate sleep at several times throughout the day. Results can be interpreted by comparing this value with the typical latency time of 10 to 20 minutes in normal individuals. Because of its sensitivity, MSLT can be a useful tool in identifying the presence of daytime sleepiness due to residual hypnotic effects.[53]

Several factors influence the degree to which residual sedation is observed. In a meta-analysis of 52 placebo-controlled studies of hypnotic drugs (benzodiazepines, barbiturates, and others) administered to subjects with and without insomnia, dose had the strongest influence on next-day performance impairment.[52] Accordingly, higher doses of all hypnotics studied were associated with impairment of next-day functioning, which was persistently decreased throughout the day as assessed by psychomotor testing. In addition, benzodiazepines with long half-lives or active metabolites were more likely to produce psychomotor impairment and to do so throughout the 7- to 22.5-hour period of observation following medication administration.[52] A double-blind, crossover study by Bliwise et al. showed that a 7-day course of flurazepam, 30 mg, but not triazolam, 0.5 mg, produced significant daytime sleepiness as assessed by MSLT measurements.[54]

Daytime sleepiness related to hypnotic therapy may substantially influence the development of adverse health outcomes. In a retrospective review of elderly inpatients, flurazepam administration was significantly more common in those who experienced a fall during their hospital stay as compared with those who did not (70% vs. 19%, $p < .01$).[55] Use of moderate to high doses of any benzodiazepine or zolpidem has been found to increase the risk of hip fractures in elderly patients.[56] Ray and colleagues also observed an 80% increase in risk for hip fractures related to falls in patients 65 years of age or older without dementia who were taking benzodiazepine hypnotics with an elimination half-life longer than 24 hours.[57]

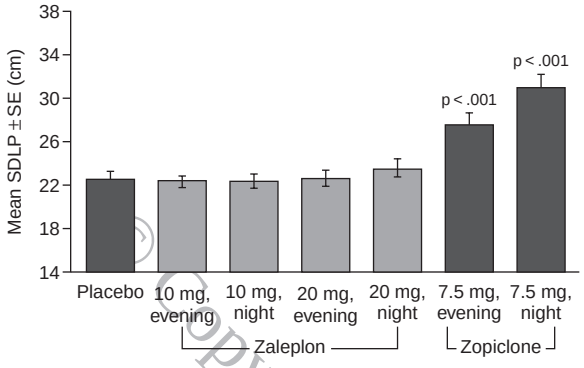
Benzodiazepine hypnotics, particularly those with long half-lives, have also been associated with a significantly increased risk of traffic accidents and injuries requiring hospital admission, leading to recommendations advising against the operation of a motor vehicle while using these medications.[58,59] Behavioral tolerance to the residual effects of hypnotics, determined by increases in MSLT scores, may occur with repeated administration,[53] and residual sedation may lessen. Nevertheless, the use of short-acting hypnotics may be preferable to longer acting agents in reducing the risk of daytime impairment related to residual drug effects, particularly in elderly patients. When the individuality of insomnia experiences is considered, the adaptability of a sleep medication to each patient's need can be significant, particularly when the opportunity to avoid nightly use in patients with chronic insomnia is combined with the ability to take medication specifically when symptoms occur.

Lack of Residual Sedation With Zaleplon

Residual daytime sedation resulting in impaired psychomotor function or cognitive ability has not been observed with zaleplon administration.[34,48,60–64] As described previously, lack of residual sedation with zaleplon is likely related to the pharmacokinetic properties of the medication, which include rapid elimination, lack of active metabolites, and a selective but relatively low affinity for the benzodiazepine type 1 receptor subtype—a significant improvement in therapeutic profile.

Bedtime administration of zaleplon, 10 mg, in healthy subjects was associated with MSLT values and psychomotor test scores not significantly different from those following administration of placebo; however, flurazepam, 30 mg, produced significantly shorter MSLT scores and worsened psychomotor function, which indicate greater daytime sleepiness.[64] In another study, 22 otherwise healthy patients with sleep maintenance insomnia were given zaleplon, 10 mg, flurazepam, 30 mg, or placebo following an experimental nocturnal awakening. No evidence of residual sedation 5 and 6.5 hours after administration of zaleplon was observed as assessed by MSLT, psychomotor testing, and visual analog scale.[63] Measures of sleepiness following flurazepam administration were all significantly different from those following placebo and zaleplon.

Figure 1. Mean Standard Deviation of Lateral Position (SDLP) by Treatment[a]



[a]Adapted from Vermeeren et al.[62] with permission.

In a randomized, double-blind, placebo-controlled, crossover study, Vermeeren and colleagues compared the next-day effects of zaleplon (10 or 20 mg) and zopiclone (7.5 mg) on mood, memory, and automobile driving performance.[62] Twenty-eight healthy volunteers received study drug at bedtime or in the middle of the night, 10 hours or 5 hours, respectively, prior to a driving test. Memory testing and subjective assessments of alertness were completed approximately 1 hour before driving tests commenced. The standard deviation of lateral position (SDLP), an indicator of the amount of weaving that occurs during driving, is presented for each study treatment in Figure 1.[62] Administration of zopiclone at either bedtime or nighttime resulted in significant increases in SDLP, while the effects of zaleplon at either dose and dosing time were no different from those with placebo. In addition, zaleplon-treated patients were considered by their driving instructors to be more alert, exhibiting driving skills equivalent to those associated with placebo but significantly better than those of subjects receiving zopiclone.

Benefits Related to Lack of Residual Sedation

Most clinicians agree that successful treatment of insomnia enhances daytime functioning. The absence of hypnotic-related residual sedative effects persisting into a patient's waking hours should provide numerous benefits for the patient, the prescribing practitioner, and society. Most obviously, increased daytime alertness should improve patient mood and overall quality of life by enhancing energy levels and the ability to enjoy social interactions and recreational activities. Job performance and productivity should also be positively affected as absenteeism and work-related accidents decrease. Similarly, the lack of associated psychomotor dysfunction related to hypnotic hangover should correlate with lower motor vehicle accident rates, as well as a reduced incidence of falls and hip fractures in the elderly.

Given the numerous comorbidities linked with untreated insomnia, safe and effective hypnotic therapy should successfully reduce medical and psychiatric morbidity and mortality and the direct and indirect health care costs associated with these complications. To accomplish this, physicians must incorporate sleep-related discussions into every encounter with patients and develop the skills required to effectively diagnose and treat insomnia before it becomes a chronic disorder. This practice may enhance patients' understanding of the serious consequences of untreated insomnia, enable them to recognize the need for medical assistance, and encourage them to report symptoms earlier.

The combined safety characteristics and pharmacokinetic profile of zaleplon allow increased treatment adaptability for patients' specific insomnia experiences. Medication can be taken when symptoms occur rather than as prophylactic treatment. Zaleplon is the first agent approved by the U.S. Food and Drug Administration for use in such a manner.

As mentioned previously, other medications require patients to be in bed for 7 to 8 hours before becoming active[31,32]; by comparison, zaleplon may be safely given to patients with sleep maintenance difficulties during nocturnal awakening or within 4 hours of normal awakening, without causing daytime sedation.[65] Clinical studies have shown no carryover sedation affecting daytime activities such as driving performance as early as 2 hours after administration.[60,62,66,67] Although long-term, double-blind outcome studies related to zaleplon administration are not yet available, the documented lack of residual sedation associated with zaleplon use suggests a potentially significant improvement in the treatment of insomnia. Evidence from open-label studies in which zaleplon was administered for up to 12 months of continuous use indicates that tolerance to the pharmacologic effect is not likely to be of concern in adult or elderly patients who require ongoing treatment.[68,69] In addition, these open-label trials have indicated that no rebound insomnia[68] or withdrawal[69] occurs following abrupt discontinuation of zaleplon after long-term nightly use.

CONCLUSION

Consideration of the residual effect profile is a critical factor in the choice of sleep medication for the treatment of insomnia. Zaleplon is a nonbenzodiazepine sleep medication with documented efficacy and safety in treating adult and elderly patients with insomnia who have difficulties initiating or maintaining quality sleep at any time of night. Clinical studies indicate that the rapid absorption and elimination characteristics of zaleplon are important determinants of the ability of the medication to significantly decrease sleep onset latency without residual effects upon awakening. Residual sedation affecting

psychomotor function, cognitive skills, and memory has not been reported with up to 5 weeks of use of zaleplon. However, insomnia is generally persistent and relapsing in nature, and chronic drug therapy may be beneficial to many patients. Current recommendations for sleep medication therapy limit administration to 4 to 6 weeks due to the paucity of information regarding long-term safety. Results of future clinical trials evaluating the long-term effects of zaleplon on sleep-related morbidity are eagerly awaited.

Drug names: lorazepam (Ativan and others), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

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