A Breakthrough in the Pharmacologic Management of Insomnia: Overview of the Clinical Profile of Zaleplon

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Insomnia is associated with an increase in the risk of depression and accidents and in utilization of health care and also a decrease in cognition, productivity, and quality of life. The need is evident for an advanced sleep medication that acts quickly, produces no next-day residual effects, and avoids the development of withdrawal effects. Zaleplon is a novel sleep medication that rapidly induces sleep with minimal residual sedation or impairment of psychomotor and cognitive skills. The unique characteristics of zaleplon are believed to be related to a combination of its low receptor-binding affinity and its rapid elimination. Accordingly, studies have shown that zaleplon can be safe and effective for sleep induction whether taken at bedtime or during the night, which makes zaleplon a distinctly versatile tool for the pharmacologic management of insomnia.

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Insomnia is a common disorder that prevents the sufferer from falling asleep, staying asleep, or obtaining refreshing sleep and often leads to functional impairment throughout the following day. The sleep difficulty may be either the primary disorder or secondary to another medical problem, such as pain or depression, and is often unpredictable. Regardless of its cause, insomnia is associated with significant morbidity that includes not only an increase in the risk of depression and accidents and in utilization of health care but also a decrease in cognition, productivity, and quality of life.[1–8] Other articles in this supplement discuss the relationships of the various potential causes of insomnia and address numerous approaches to treatment. The need is evident for an advanced sleep medication that acts quickly, produces no next-day residual effects (and minimal impairment even at peak plasma concentration), and avoids the development of withdrawal effects. This article focuses on the properties of zaleplon with respect to the aforementioned characteristics. More extensive reviews of zaleplon are published elsewhere.[9–12]

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STRUCTURE, RECEPTOR BINDING, AND PHARMACOKINETIC PROFILE

Zaleplon, the first pyrazolopyrimidine sleep medication, is structurally unrelated to the benzodiazepines.[13] Benzodiazepines exert their effects by nonpreferentially binding with the benzodiazepine binding site at the γ-aminobutyric acid (GABA)–receptor complex. Similarly, zaleplon binds with benzodiazepine receptors but does so with high specificity for the benzodiazepine subtype 1 receptor.[14] Nonbenzodiazepines zopiclone and zolpidem, which are also benzodiazepine receptor agonists, also favor benzodiazepine subtype 1 receptors.[15] However, zaleplon has much less affinity for benzodiazepine subtype 1 receptors than do other nonbenzodiazepine compounds, and its Hill coefficient, which is significantly greater than 1, demonstrates positive cooperativity at the benzodiazepine subtype 1 receptors.[16] Lower affinity for the benzodiazepine subtype 1 receptor and positive cooperativity are probably aspects of the characteristic ability of zaleplon to induce sleep effectively without the degree of psychomotor or cognitive impairment seen with older hypnotics.

Zaleplon exhibits linear pharmacokinetics, which means that an incremental dose increase causes a predictable increase in the peak plasma concentration.[13] Peak plasma levels of zaleplon usually are achieved within 1 hour, which correlates to its rapid onset of action, and the elimination half-life is also about 1 hour, which limits residual effects after administration.[13,17,18] First-pass elimination is extensive, resulting in oral bioavailability of approximately 30%.[17,18] Significant hepatic metabolism requires a reduction in dose for patients with mild to moderate hepatic impairment.[19] However, patient age, gender,

or renal dysfunction do not significantly alter the pharmacokinetics of zaleplon.[20,21]

EFFICACY

Nineteen clinical trials, conducted in both Europe and North America, have documented the efficacy of zaleplon in inducing sleep in both younger adults and the elderly, and several of these trials have been published.[22–30] Each study evidenced a decrease in latency to persistent sleep (LPS) after administration of the recommended dose of 10 mg of zaleplon in younger adults and 5 mg in elderly individuals. Objective data have been collected through polysomnographic measurement in the sleep laboratory setting, and subjective data have been gathered through patient questionnaires or sleep diaries. Although positive objective results are an important foundation, subjective improvement is necessary to achieve successful treatment outcomes.

The longest double-blind sleep laboratory study, which was conducted during 35 nights in 113 patients, compared the soporific effects of zaleplon, 10 mg, and placebo on LPS.[28] Zaleplon decreased median LPS from 45 minutes to less than 30 minutes, which was statistically significant versus placebo for each of the 5 weeks (week 1, $p = .05$; week 2, $p < .001$; week 3, $p = .027$; week 4, $p = .031$; week 5, $p = .027$). Tolerance to the soporific effect of zaleplon did not develop, as demonstrated by the continued efficacy throughout the study. The time to sleep onset reported on at-home questionnaires was also significantly reduced with zaleplon versus placebo for all 5 study weeks ($p < .05$). Rebound insomnia was not seen after discontinuation of zaleplon. The subjective total time slept with zaleplon was increased above baseline throughout the study. Total time slept was significantly greater with zaleplon than with placebo during weeks 1 and 3 ($p \leq .05$ for each).

Although approved indications for hypnotics require limiting the treatment period to 4 weeks or less, extended use is often necessary to control symptoms. The absence of tolerance to the therapeutic effect of zaleplon has also been shown in open-label trials in which nightly treatment continued for up to 12 months[31,32]; patients in these studies had successfully completed 4-week double-blind trials and elected to enroll in these evaluations.

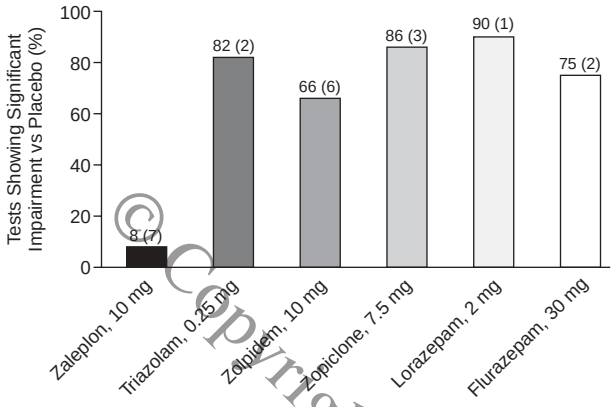
RESIDUAL EFFECTS

Memory and psychomotor function are important measures of the unwanted effects produced by a hypnotic. Numerous trials have evaluated these aspects of zaleplon administration, many versus comparators such as zolpidem, 10 mg, or zopiclone, 7.5 mg.[17,22,23,26,27,30,33–41] As discussed above, the maximal plasma level of zaleplon occurs approximately 1 hour after administration, which would be expected to correlate with the greatest degree of impairment of psychomotor function or memory. These measures were evaluated with zaleplon, 10 mg; zaleplon, 20 mg; zolpidem, 10 mg; zolpidem, 20 mg; triazolam, 0.25 mg; or placebo in a randomized, double-blind, crossover study of 24 healthy adult subjects.[35] At 1.25 hours after dose administration, zaleplon, 10 mg, did not produce any significant changes in cognitive or psychomotor performance compared with placebo. Impairment of memory following administration of zolpidem, 10 mg, was similar to that with triazolam, 0.25 mg, and impairment of psychomotor skills was greater with zolpidem than triazolam. All drug treatments except zaleplon, 10 mg, impaired immediate recall at peak plasma levels.

Two recent reports[38,41] specifically evaluated the residual effects of zaleplon, 10 mg, after administration in the middle of the night, an administration method not approved for use with any hypnotic compound. One double-blind, randomized trial[38] examined psychomotor and memory functioning in 40 healthy volunteers who slept for 8 hours, except for a brief arousal at 1, 3, or 5 hours before morning awakening for administration of zaleplon, 10 or 20 mg, or zolpidem, 10 mg. Zaleplon, 10 mg, was without residual effects, except for a small, significant decrease in a single psychomotor procedure 1 hour after administration. Twice the usual 10-mg zaleplon dose caused significant residual effects on multiple tests 1 hour, but not 3 or 5 hours, after dosing. Conversely, zolpidem, 10 mg, produced significant residual effects on reaction and long-term memory at 5 hours, processing and working memory at 3 hours, and alertness at 1 hour after administration. In patients with sleep maintenance insomnia, middle-of-the-night treatment with zaleplon, 10 mg, or zolpidem, 10 mg, improved sleep in the second half of the night, but zolpidem produced residual sedation for up to 7 hours, while zaleplon was virtually devoid of residual sedative effects within 4 hours of dosing.[41] These studies indicate that zaleplon has minimal potential to cause residual effects that impair functioning.

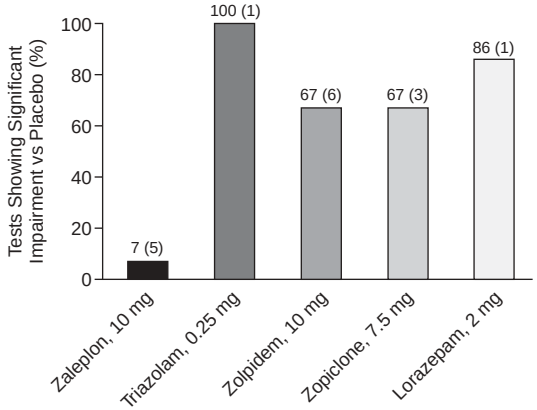
An integrated analysis of 15 randomized, double-blind, placebo-controlled trials was conducted to compare the effects of recommended doses of zaleplon and comparator agents (i.e., flurazepam [psychomotor tests only], lorazepam, triazolam, zolpidem, and zopiclone) on psychomotor and memory function (Figures 1 and 2).[42,43] For zaleplon, performance was assessed at near-peak plasma concentration, approximately 0.5 to 2 hours after dosing; no more than 8% of tests showed significant impairment. Measurement of similar effects of the other agents was not specifically performed at peak concentrations, yet 66% of the tests following administration of another agent showed statistically significant decrements in psychomotor or memory function compared with placebo. This suggests an improved benefit-to-risk profile of zaleplon over older available agents.

Figure 1. Summary of Psychomotor Tests Performed at Approximate Peak Plasma Concentration of Zaleplon During 15 Investigations[a]



[a]Reprinted with permission from Mangano,[43] as adapted from Darwish et al.[42] Numbers above bars indicate percentage of tests indicating statistically significant impairment compared with placebo. The numbers of trials are given in parentheses.

Figure 2. Summary of Memory Tests Performed at Approximate Peak Plasma Concentration of Zaleplon During 15 Investigations[a]



[a]Reprinted with permission from Mangano,[43] as adapted from Darwish et al.[42] Numbers above bars indicate percentage of tests indicating statistically significant impairment compared with placebo. The numbers of trials are given in parentheses.

EFFECTS OF DISCONTINUATION

Older rapidly eliminated hypnotics have been associated with rebound insomnia, a sleep latency greater than that before treatment, after discontinuation of therapy[44,45]; so this parameter has been closely evaluated with zaleplon, the most rapidly eliminated sleep medication available. The effects of discontinuing nightly treatment with zaleplon have been extensively evaluated in double-blind investigations ranging from 2 to 5 weeks[22,23,25,26,28,29] and in open-label studies lasting up to 12 months.[31,32] Evidence of rebound events associated with zaleplon has not been clearly demonstrated by any of these trials.

Other possible discontinuation effects include a withdrawal syndrome, characterized by the occurrence of 3 or more new symptoms (e.g., depressed mood, muscular pain, peculiar taste, memory loss, olfactory sensitivity) on the Benzodiazepine Withdrawal Symptom Questionnaire,[46] a survey developed to associate such aftereffects of therapy with benzodiazepines. In both double-blind and open-label investigations, no withdrawal syndrome was identified following discontinuation of nightly zaleplon use.[22,23,26,32]

CONCLUSION

Zaleplon, 10 mg, achieves maximal plasma levels within 1 hour after administration, while simultaneously causing significantly less psychomotor and cognitive impairment than usual doses of older hypnotics at their peak plasma levels. Middle-of-the-night dosing studies have proved that zaleplon is effective and safe to take when the individual cannot initiate or resume sleep, whether at bedtime or during the night. This versatility provides clinicians and patients much greater flexibility with sleep medication than does traditional insomnia pharmacotherapy. Additionally, administration of zaleplon in such a manner also permits drug-free nights when the patient falls asleep naturally and without difficulty. The characteristics of zaleplon discussed in this overview demonstrate the unique versatility of this sleep medication. Clinicians now have a new tool to consider for pharmacologic management of insomnia in patients for whom these properties are deemed suitable.

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

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