Residual Effects on Memory and Psychomotor Performance of Zaleplon and Other Hypnotic Drugs

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Long-acting benzodiazepine hypnotics are known to cause cognitive and psychomotor impairment throughout the day after a nocturnal dose. Patients using these drugs are overrepresented in injurious falls and traffic accidents. Recognition of this problem has led to the development of compounds that are eliminated rapidly and bind selectively to only 1 of the 3 known benzodiazepine receptors. Zaleplon, the newest in this class, is the most rapidly eliminated of the hypnotics. Some clinicians speculate that zaleplon may be taken in the approved 10-mg dosage for inducing sleep either at normal bedtime or after a nocturnal awakening without risk of residual sedation affecting safety. Extensive research has been devoted to measuring the effects of zaleplon, 10 and 20 mg, on memory, psychomotor performance, and driving at various times after ingestion. The effects of zaleplon have been compared with those of other short-acting hypnotics, notably the nonbenzodiazepines zolpidem and zopiclone. These comparisons have shown that only zaleplon, 10 mg, can be taken to initiate or resume sleep 4 or more hours before final awakening with little risk of the psychomotor impairment that could compromise patient safety. The effect of zaleplon on mnemonic functions, at the same time, is uncertain. If zaleplon affects memory, the extent is not only limited but is also less than that of comparator hypnotics.
(Primary Care Companion J Clin Psychiatry 2002;4[suppl 1]:38–44)

Zaleplon is a novel pyrazolopyrimidine sedative-hypnotic that binds selectively as an agonist at the omega-1 benzodiazepine receptor subtype. This agent is absorbed rapidly (t_{max}, 0.9 to 1.5 hours), forms no active metabolites, and is eliminated with a monoexponential half-life of only 0.9 to 1.1 hours.[1] The unique combination of receptor-binding selectivity and rapid absorption and elimination of zaleplon has suggested that this hypnotic can be taken safely, when symptoms occur, to cope with either long latency-to-sleep or sleep-maintenance problems. According to Stahl,[2] patients whose disturbance delays the onset of sleep might take zaleplon at normal bedtime after attempting to fall asleep, whereas those who fall asleep easily but awaken within several hours might take the drug to resume sleep, without either group suffering from residual sedation after morning awakening. Adequate data are available to critically examine whether zaleplon is safe to take just a few hours before engaging in activities that demand unimpaired cognitive and psychomotor skills.

RESIDUAL EFFECTS OF HYPNOTIC DRUGS OTHER THAN ZALEPLON

The earliest benzodiazepine hypnotics were eliminated so slowly that the concentration in cerebrospinal fluid made them always pharmacologically active during regular nightly use. Flurazepam, perhaps the most illustrative example, was given nightly for 2 weeks in both the usual 30-mg dose and the "geriatric" 15-mg dose.[3] Results showed that relative to placebo, flurazepam consistently impaired patients' explicit memory and psychomotor performance. Mounting empirical and epidemiologic evidence easily dispels any doubt about the clinical relevance of deficits in psychomotor performance shown by patients in relatively simple tests. Standardized driving tests conducted on a highway in normal traffic consistently revealed that the residual effects of flurazepam, 15 and 30 mg, lasted more than 17 hours after a single dose or ongoing nightly doses.[4–6] The effects of the larger dose on outpatient performance 10 to 11 hours and again 16 to 17 hours after ingestion were greater than those measured in another study of social drinkers operating with blood alcohol concentrations (BACs) of 0.10 and 0.08 g/dL, respec-

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Presented at the symposium "Current Considerations for the Clinical Management of Insomnia," which was held April 15, 2000, in Athens, Greece, and supported by an unrestricted educational grant from Wyeth-Ayerst Pharmaceuticals.

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tively.[7] More compelling are the results of surveys showing that flurazepam users are 2 to 5 times more likely to experience injurious falls and traffic accidents than matched controls.[8–10]

No comparable body of evidence exists to show that more recently developed benzodiazepine and benzodiazepine-like hypnotics cause similar problems. Most are eliminated much more rapidly than the active *N*-desalkyl metabolite of flurazepam (mean elimination half-life = 74 hours),[11] and one might suppose that the risks described above are avoided with their use. However, some data suggest otherwise. Although every benzodiazepine appears to interfere with the ability to transfer information from working to long-term memory as well as the ability to explicitly recall events that occur while the drugs are active in the brain,[12] some of the shortest-acting benzodiazepines seem particularly amnestic. In case studies cited by Woods et al.,[13] midazolam and triazolam, having similar average half-lives of approximately 2.5 hours,[14] were implicated in anterograde amnesia that totally blocked the recall of events transpiring for up to 24 hours after the drugs were taken in ordinary oral doses. Zopiclone is a cyclopyrrolone hypnotic that also acts as an allosteric γ-aminobutyric acid agonist but possibly through a different conformational change in the receptor complex.[15] Although the half-life of zopiclone is only about 5 hours,[16] drivers' use of this agent at night was associated with a 4-fold increase in risk of first-time traffic accidents the next day.[17] Clearly, problems persist with these agents despite their short half-lives.

Besides zaleplon, the imidazopyridine zolpidem is the only hypnotic possessing both the pharmacodynamic and pharmacokinetic profile that would conceivably render the drug free of residual effects within a few hours after ingestion. Zolpidem also binds selectively at the omega-1 benzodiazepine receptor, produces peak plasma levels within 1 hour, and has an elimination half-life of about 2 hours.[18] Numerous studies have shown that the standard 10-mg dose of zolpidem lacks residual effects after normal 7- to 9-hour sleeping periods.[19] However, the proposition that zolpidem would be similarly safe after shorter periods was not seriously considered until recently.

RESIDUAL EFFECTS OF ZALEPLON

Effects of Zaleplon on Memory

The effects of zaleplon on memory acquisition and explicit recall have been assessed in 7 double-blind, placebo-controlled, and active drug–controlled studies using variations of a standard test.[20–26] This test traditionally involves the presentation of 15 to 20 unrelated, monosyllabic nouns. The method of presentation varied between studies, but the objective was always the same: to measure the number of words the subject was able to recall immediately after a single presentation or several presentations, and again after a delay of 0.5 to 7 hours. The former is immediate recall (IR) score, and the latter is delayed recall (DR) score. Occasionally, relative DR (rDR) has been calculated as a percentage of IR to adjust for initial learning. As a further embellishment, some investigators have added new words to the original word set and shown this new set to subjects. The subjects had to respond as quickly as possible, and investigators recorded the number of correct recognitions (CR) and average reaction time (RT).

Allen et al.[20] were the first independent investigators to measure the effects of zaleplon on cognitive functions. The dose they administered to 12 volunteers was higher than that eventually approved for use, but the study is still relevant. It remains the most comprehensive assessment of the effects of zaleplon on mnemonic functions other than the acquisition and explicit recall of verbal information. Also measured were working memory, the speed of confirming the veracity of blatantly true and false statements from information stored in long-term memory, and the accuracy of recalling prose passages from a story. Memory was tested before and 1, 3, and 5 hours after administration of zaleplon, 20 mg; lorazepam, 1 mg; and placebo in a crossover study design. The overall effects of lorazepam were significantly worse than those of placebo in practically every test and significantly worse than those of zaleplon in most tests. However, zaleplon also impaired working memory, IR, DR, and prose recall over the entire testing period. Naturally, these effects were greatest at 1 hour after ingestion, but some persisted at 3 hours and 1 (prose recall) persisted at 5 hours.

Studies of zaleplon in the standard 10-mg dose concentrated on residual effects in men and women, in approximately equal proportions, after various sleeping periods. On separate occasions, Vermeeren et al.[22] treated 28 volunteers with zaleplon, 10 and 20 mg; zopiclone, 7.5 mg; and placebo in the evening before sleep and in the middle of the night after being awakened from sleep. The effects on memory were tested at the same time in the morning, 8.75 and 3.75 hours after administration of the respective doses. Evening zaleplon doses had no significant effects on any memory parameter, whereas zopiclone impaired DR. The middle-of-the-night zopiclone doses greatly impaired IR, DR, rDR, CR, and RT. Both middle-of-the-night zaleplon doses significantly impaired DR, though less than zopiclone. Zaleplon, 20 mg, also reduced rDR and CR, but these effects dropped below the level of significance after adjustment for multiple testing.

Danjou et al.[23] followed a similar procedure of briefly interrupting volunteers' sleep to give them zaleplon, 10 mg; zolpidem, 10 mg; and placebo at 5, 4, 3, and 2 hours before final awakening and testing. Treatments were administered according to an incomplete-block design so that each of the 36 participants was tested in 6 of the 12 possible drug/time conditions, and 18 participated in each condition. Zaleplon had no significant effects on memory in the standard test or in the Sternberg Memory

Scanning Task, even when taken 2 hours beforehand. In contrast, zolpidem consistently impaired IR and DR up to 5 hours and memory scanning up to 4 hours after dose administration.

Troy et al.[21] compared 10 and 20 mg of both zaleplon and zolpidem with triazolam, 0.25 mg, and placebo at times after ingestion and sleep, when the plasma concentrations of the drugs should have been near maximum (+1.25 hours) and very low (+8.25 hours). The 24 volunteers' mnemonic functions were tested at both times after each treatment in the standard test, the Digit Span Test, and the Paired Associates Learning Test. After 1.25 hours, zaleplon, 10 mg, had no significant negative effects, whereas every other treatment impaired memory in all or nearly all tests. The differences between equal doses of zaleplon and zolpidem were all significant in favor of zaleplon. Only the standard test revealed residual effects after 8 hours; every treatment impaired DR of words presented 7 hours earlier. Unlike other treatments, zaleplon, 10 mg, did not impair rDR relative to placebo, indicating to the investigators that "the therapeutic dose of zaleplon does not impair memory."[21(p332)] However, if not the result of chance, a significant effect on DR but not rDR may indicate some deficit in initial acquisition. The fact that IR at 1.25 hours was not significantly different between zaleplon, 10 mg, and placebo in this study does not preclude the possibility of such a deficit. In any case, the effects of zaleplon at 8 hours on DR and rDR were significantly less than those of zolpidem in both 10- and 20-mg doses.

Findings from 2 recent studies of the effects of zaleplon on memory have been reported in conference proceedings. Stone et al.[26] administered zaleplon, 10 and 20 mg; zopiclone, 7.5 mg; and placebo on separate occasions to 13 volunteers after they had slept 5 hours and before they attempted to resume sleep in the presence of noise. The standard test was applied 4 hours after dosing and showed a significant effect of zopiclone on DR, but no effect of zaleplon, either 10 or 20 mg. Hindmarch et al.[24] studied 40 volunteers using an incomplete-block design in which subjects were tested after each combination of 4 treatments (zaleplon, 10 and 20 mg; zolpidem, 10 mg; and placebo) and at 3 times after administration (5, 3, and 1 hour before awakening). Zaleplon, 10 mg, had no significant deleterious effects. The 20-mg dose impaired IR and DR, but only when given 1 hour before awakening. In contrast, zolpidem impaired DR when administered for up to 5 hours before awakening and memory scanning (Sternberg) for up to 3 hours before awakening.

Effects of Zaleplon on Simple Psychomotor Performance

The studies described in the preceding section also included laboratory assessments of functions that mediate information processing between exteroceptive or proprioceptive sensory input and an adaptive motor reaction, i.e., psychomotor functions.[21–26] The number and diversity of functions vary widely between these tests. The simplest measure is a single function such as proprioceptive motor control while maintaining an erect posture. More complex measures are sensitive to intervening factors, such as sustained or divided attention, decision making, and working memory. A few of the oldest, most sensitive, and widely used tests, e.g., the Digit Symbol Substitution Test (DSST), are sensitive to so many factors that it is difficult to say exactly what it measures other than some combination of the above, yet all measure the speed of the information flow through relatively invariant channels in the brain. Drugs that retard the flow increase latency and diminish accuracy in response to discrete events. Similarly, these tests expand error variability during closed-loop situations because of delayed response to dynamic changes in the environment.[27]

Table 1. Psychomotor Tests Showing Significant (*italicized*) and Nonsignificant Effects of Zaleplon and Reference Hypnotics, Relative to Placebo, at Different Times After Administration[a]

	Time After Administration (h)				
Drug	1.0–2.25	2.25–3.25	3.25–4.25	4.25–5.25	5.25–8.25
Zaleplon, 10 mg	CFF[23,24] CRT[23,24] DIV[21] DSST[21,23] *DSST*[24]	CFF[23,24] CRT[23,24] DSST[23,24]	CFF[23,26] CRT[23,26] DSST[23,26] PS[22]	CFF[23,24] CRT[23,24] DSST[23,24]	CTT[25] DIV[21,25] DSST[21,25] PS[22]
Zaleplon, 20 mg	*CFF*[24] *CRT*[24] *DIV*[21] *DSST*[21,24]	CFF[24] CRT[24] DSST[24]	CFF[26] CRT[26] DSST[26] PS[22]	CFF[24] CRT[24] DSST[24]	CTT[25] DIV[21,25] DSST[21,25] PS[22]
Zolpidem, 10 mg	CFF[23] *CFF*[24] *CRT*[23,24] *DIV*[21] *DSST*[21,23,24]	CFF[24] *CFF*[23] *CRT*[23,24] *DSST*[23,24]	*CFF*[23] *CRT*[23] DSST[23]	CFF[23,24] CRT[23] *CRT*[24] *DSST*[23,24]	CTT[25] DIV[21,25] DSST[21,25]
Zolpidem, 20 mg	*DIV*[21] *DSST*[21]				*CTT*[25] DIV[21] *DIV*[25] *DSST*[21,25]
Zopiclone, 7.5 mg			CFF[26] *CRT*[26] *DSST*[26] *PS*[22]		PS[22]
Triazolam, 0.25 mg	DIV[21] *DSST*[21]				DIV[21] *DSST*[21]

[a]Data from Troy et al.,[21] Vermeeren et al.,[22] Danjou et al.,[23] Hindmarch et al.,[24] Volkerts et al.,[25] and Stone et al.[26] Abbreviations: CFF = Critical Flicker Fusion (measures visual discrimination), CRT = Choice Reaction Time (measures recognition speed and motor speed), CTT = Critical Instability Tracking (measures motor control), DIV = Divided Attention (measures visuomotor coordination, motor speed, and concentration), DSST = Digit Symbol Substitution Test (measures cognitive performance and motor speed), PS = Postural Stability (measures postural sway).

The results of psychomotor testing from the aforementioned studies[21–26] are given in Table 1. They show that zaleplon, 10 mg, was practically devoid of significant residual effects even 1 to 2 hours after administration. Zaleplon, 20 mg, significantly impaired performance at the time its plasma concentration must have been near maxi-

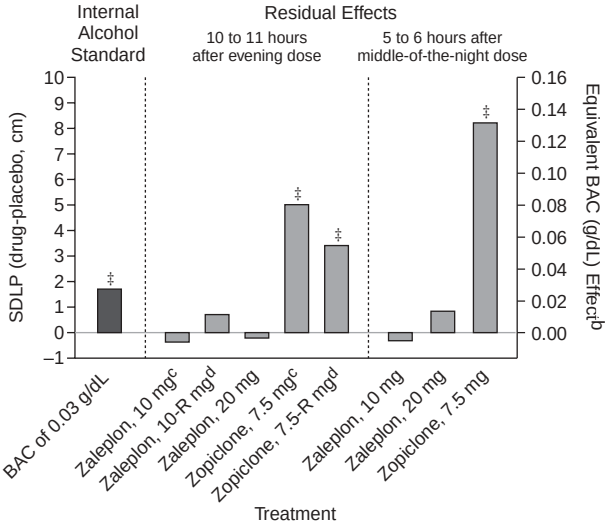
mum (1 to 2 hours), but never thereafter. In contrast, zolpidem, 10 mg, generally impaired performance in all tests for up to 5 hours after administration.

Results of another study[28] differed from those cited in Table 1 in several respects, the most important being the subjects—22 patients with sleep maintenance insomnia who spent 2 consecutive nights at a sleep laboratory. They retired without medication, to be awakened 3.5 hours later for respective treatments with zaleplon, 10 mg; flurazepam, 30 mg; and placebo. Residual sedation was assessed using the DSST both 5 and 6.5 hours after treatment. Flurazepam had the expected impairing effect. However, mean performance with zaleplon was slightly better than with placebo, although the difference was not significant.

Effects of Zaleplon on Actual Driving Performance

However useful short and artificial psychomotor tests may be for the initial assessment of the residual effects of a hypnotic, they cannot provide unequivocal evidence that impairments will not emerge in more complex real-life activities that extend over hours. This fact was recognized by the European Medicines Evaluation Agency (EMEA), the pan-European equivalent to the U.S. Food and Drug Administration, in guidelines for the development of hypnotic drugs.[29] EMEA strongly recommended the application of more realistic tests lasting a minimum of 1 hour. A standardized actual driving test was one of several that could meet this need. One test developed by O'Hanlon[4] in the early 1980s has been applied in more than 50 major studies.[30] The subject, accompanied by a licensed instructor who has access to redundant controls, begins by assuming control of a specially instrumented vehicle at the entrance to a 100-km (61-mile) primary highway circuit. The subject attempts to drive at a constant speed and steady lateral position between the boundaries of the slower traffic lane. Speed and lateral position relative to lane-line delineation are continuously recorded by apparatus aboard the vehicle. After the subject completes the circuit in about 1 hour, the data are reduced to yield the mean and standard deviation of speed and lateral position by successive 10-km segments. The pooled lateral position variance is calculated, and its square root, the mean-adjusted standard deviation of lateral position (SDLP), is taken as the primary outcome variable.[4] It is an integrated measure of road-tracking error. SDLP, which is also an extremely reliable (test-retest r = 0.70 to 0.90) parameter during normal driving under all but extreme traffic and weather conditions, is very sensitive to all types of sedating drugs. In an early study[7] of 24 "social drinkers," the correlation between mean BAC (range, 0.03–0.15 g/dL) and SDLP was so strong (r = 0.98) that the mathematical equation describing the relationship has been used ever since for calibrating every other drug's effect in terms of a BAC equivalent. The standard driving test has been applied for measuring the residual effects of most approved hypnotics. Three of the most recent applications have studied zaleplon with zopiclone as the comparator in 2 and zolpidem in the third. The results are shown in Figures 1[7,22,31] and 2.[7,25]

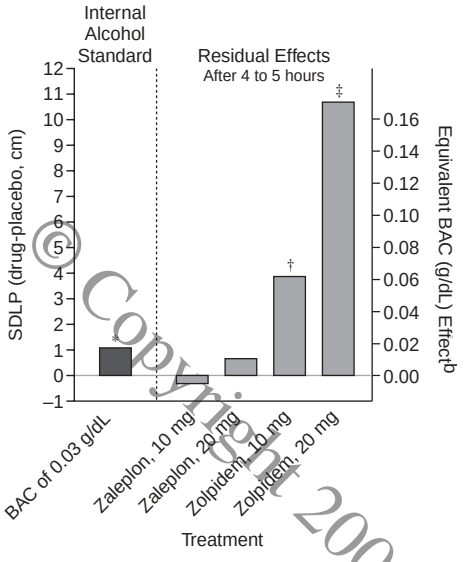
Figure 1. Mean Change in SDLP From Placebo After Treatments With Alcohol, Zaleplon, and Zopiclone[a]



[a]Based on data from Louwerens et al.,[7] Vermeeren et al.,[22] and Vermeeren et al.[31] Abbreviations: BAC = blood alcohol concentration, R = "repeat" test, SDLP = standard deviation of lateral position.
[b]From the equation by Louwerens et al.[7]
[c]From Vermeeren et al.[22]
[d]From Vermeeren et al.[31]
‡p < .001.

In the first zaleplon study by Vermeeren et al.,[22] 24 volunteers drove, on separate occasions, 10 to 11 and 5 to 6 hours after evening and middle-of-the-night doses, respectively, of zaleplon, 10 and 20 mg; zopiclone, 7.5 mg; and placebo. Zaleplon did not affect SDLP regardless of dose and time of administration before driving. However, zopiclone given in the evening significantly increased SDLP (compared with placebo) to the equivalent of an approximate BAC of 0.09 g/dL (approximately equal to the legal limit for intoxication in the United States). Zopiclone given in the middle of the night produced an even greater increase in SDLP to the equivalent of an approximate BAC of 0.13 g/dL. At this time, 5 subjects (18%) had to stop prematurely after driving with SDLPs higher than the normal limit (35 cm). Astonishment at the stark contrast between effects of the drugs led the investigators to attempt a partial replication in a second study.[31] A new group of 30 volunteers were given zaleplon, 10 mg; zopiclone, 7.5 mg; and placebo at bedtime, 10 to 11 hours before taking the driving test. Again, zaleplon did not affect mean SDLP, while zopiclone significantly increased SDLP compared with placebo. This time the investigators chose not to rely on historical data for describing the effects of zopiclone relative to those of alcohol. Instead, they separately tested the subjects' driving performance after drinking alcohol,

Figure 2. Mean Changes in SDLP From Placebo After Treatments With Alcohol, Zaleplon, and Zolpidem[a]



[a]Based on data from Louwerens et al.[7] and Volkerts et al.[25]
Abbreviations: BAC = blood alcohol concentration, SDLP = standard deviation of lateral position.
[b]From the equation by Louwerens et al.[7]
*p < .05.
†p < .01.
‡p < .001.

sufficient for achieving a mean BAC of 0.03 g/dL, and an alcohol placebo. The effect of alcohol on SDLP was almost the same as predicted by the calibration equation. Moreover, the effect of alcohol on mean SDLP of these subjects was only half that of zopiclone. Thus, the residual effect of zopiclone on driving in the standard test 10 to 11 hours after its administration is about the same as that of BACs between 0.06 and 0.09 g/dL.

Volkerts et al.[25] combined elements of the former studies for comparing the effects of zaleplon and zolpidem in both 10- and 20-mg doses versus those of placebo and alcohol controls. Again, the investigation was designed in 2 parts—a 2-way crossover between alcohol and alcohol placebo and a 5-way crossover between the hypnotics and placebo—involving the same 30 volunteers. The mean BAC of the subjects in the first part was 0.03 to 0.64 g/dL, and its significant effect on SDLP was about the same as in the earlier experiment. In the second part, subjects retired without medication but were aroused for treatment 5 hours later. Subjects were allowed to resume sleeping for 3 hours, and after final awakening, their driving performance was tested within 4 to 5 hours after treatment. Neither zaleplon dose affected SDLP. Zolpidem, however, increased SDLP in a dose-dependent manner, with 10 and 20 mg producing mean elevations that were respectively 4 and 11 times greater than those of alcohol in the same subjects.

DISCUSSION

The hypnotic effects of zaleplon, 10 mg, extend for several hours after ingestion. If used at normal bedtime, the initial pharmacologic effect may give way to normal sleeping lasting the night. Given the rapid rate of elimination of zaleplon, one would not expect, and indeed no investigator has shown, any residual effects after normal 7- to 9-hour sleeping periods, but the same can be said for other widely used hypnotics, such as zolpidem. However, zaleplon can be taken closer to the time of final awakening with the same lack of residual effects. Results from Volkerts et al.[25] are perhaps the most definitive. No significant effects of zaleplon, either 10 or 20 mg, on actual driving performance were observed 4 to 5 hours after ingestion. In contrast, the effects of zolpidem were marked after the recommended 10-mg dose and would have been dangerous in normal driving after a 20-mg dose. Similar results were obtained by Vermeeren et al.[22] At 5 to 6 hours after ingestion, zaleplon, 10 and 20 mg, did not affect driving, whereas the normal 7.5-mg zopiclone dose produced strong impairments. These results support the entirely consistent nature of zaleplon, 10 mg, not to affect psychomotor performance in laboratory tests at all times from 2 hours after ingestion. One could argue that those tests were selected or approved by the manufacturer of the drug and therefore might not be the most sensitive available. Certainly, they were not comprehensive in the sense of measuring every brain function that determines the efficiency of psychomotor performance in real life. However, the same argument cannot be leveled at the driving test. In the applications reported here, the driving test, which is the most realistic test commonly used for drug screening, was sensitive to the deleterious effects of alcohol in the lowest blood concentrations known to affect any type of performance. Although not absolutely conclusive, the evidence supporting the safety of driving or performing any other psychomotor task 4 hours after ingesting zaleplon, 10 mg, is about the strongest evidence presently possible to obtain in an experimental situation.

It is not as easy to argue that the effects of zaleplon, 10 mg, on mnemonic functions are totally gone at the same time that psychomotor functions return to normal. The specific amnestic effect of benzodiazepine-receptor agonists is thought to be somewhat independent of the general central nervous system depression responsible for both hypnotic potency and psychomotor impairment[32–36] and that the former outlasts the latter.[37,38] Moreover, some drugs that induce sleep and impair psychomotor performance by other mechanisms of action (e.g., H_1 receptor antagonism) do not cause anterograde amnesia.[39] Unique among those who have studied the effects of zaleplon on memory, Vermeeren et al.[22] found small but significant effects 4 hours after ingestion of both 10- and 20-mg doses on DR in the word learning test. Nevertheless, they failed to

observe the effects of the drug on postural stability at approximately the same time or driving 1 hour thereafter. It would appear from their data that Allen et al.[20] measured a similar disparity between the effects of zaleplon, 20 mg, on memory 3 hours and perhaps 5 hours after ingestion. However, the slight residual impairment to memory acquisition and/or explicit recall sometimes observed 4 hours after taking zaleplon, 10 mg, is probably of little clinical significance. Such changes have never been associated with severe memory disturbance, much less anything related to safety. On the other hand, postural instability leads to falling accidents, and because of the inability to control the trajectory of a vehicle during high-speed travel, postural instability leads to traffic accidents. Finally, the effects of zaleplon on memory were always less, and sometimes much less, than those of the comparator hypnotics in equivalent doses.

CONCLUSION

Zaleplon can be taken in the standard 10-mg dose to initiate or resume sleep for up to 4 hours before final awakening with little risk of subsequent psychomotor impairment that reduces safety. In this respect, zaleplon, 10 mg, is superior to zolpidem, 10 mg; zopiclone, 7.5 mg; and, by inference, all more slowly eliminated benzodiazepine hypnotics in comparable doses. Although zaleplon, 10 mg, may not be completely devoid of amnestic properties, if any occur, they are less severe and persistent than those of comparators, including zolpidem, 10 mg, and zopiclone, 7.5 mg.

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

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