

# Clinical evaluation of zaleplon in the treatment of insomnia

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**Abstract:** Zaleplon is a pyrazolopyrimidine hypnotic used for the treatment of insomnia. Zaleplon binds preferentially at the  $\alpha 1\beta 2\gamma 2$  subunit of gamma aminobutyric acid type A ( $GABA_A$ ) receptors in the central nervous system, and has a half-life of about one hour. Efficacy studies show that zaleplon is a suitable hypnotic for sleep initiation purposes. However, because of its short half-life, zaleplon is less effective in sleep maintenance when compared with other hypnotics. Nevertheless, zaleplon does increase total sleep time. No rebound effects are observed after treatment discontinuation. The use of zaleplon is relatively safe. Adverse effects are mild and of short duration. No important interactions have been reported, and there is no evidence of abuse potential. Relative to benzodiazepine hypnotics, the biggest advantage of zaleplon is that current evidence suggests it does not produce residual next-day effects. As early as four hours after intake of zaleplon, no effects on cognitive, memory, psychomotor performance, and the ability to drive a car have been reported. Future studies should confirm these findings, and comparisons with new nonbenzodiazepine hypnotics should determine the importance of zaleplon in the future treatment of insomnia.

**Keywords:** zaleplon, zolpidem, hypnotics, efficacy, safety, residual effects

## Introduction

People with insomnia have problems initiating and/or maintaining sleep. As a result, they do not wake up refreshed in the morning, and often experience daytime sleepiness that, in turn, may affect daily activities, such as driving a car or on-the-job performance. Insomnia is experienced by about 15%–30% of the population during their lifetime, is comorbid with many diseases and psychiatric illnesses and may significantly reduce quality of life.<sup>1</sup> Therefore, insomnia is a common disease with significant socioeconomic consequences.

The treatment of insomnia comprises both pharmacologic and behavioral approaches.<sup>2</sup> In many instances, improvement of sleep hygiene may relieve problems initiating sleep.<sup>3</sup> Cognitive behavioral therapy can be helpful to improve sleep hygiene. For many decades, pharmacologic treatment of insomnia was dominated by the use of benzodiazepine hypnotics. Although these drugs proved to be effective for the treatment of short-term insomnia, next-day residual effects, such as reduced alertness and sleepiness, could significantly affect daily activities. Development of tolerance, dependence, withdrawal effects, and abuse potential led to the development of new hypnotic drugs. These nonbenzodiazepine hypnotics, collectively called the Z-drugs, include zopiclone, zolpidem, and zaleplon. During the past decade, variants

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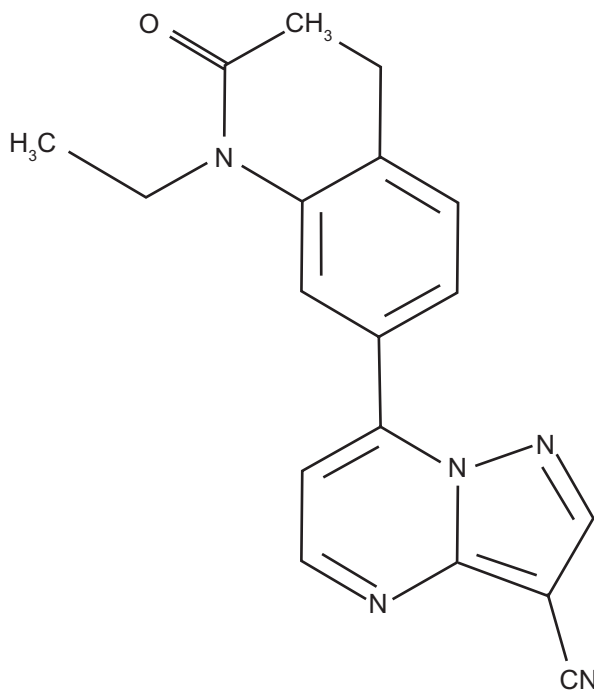
of these drugs, such as eszopiclone, have been marketed as well. The primary purpose of developing these new hypnotics was to provide an improved adverse effect profile, but with at least similar efficacy when compared with benzodiazepine hypnotics. This review focuses on zaleplon, the newest among the Z-drugs.

In the past, four articles have reviewed the clinical efficacy of zaleplon.<sup>4-7</sup> An excellent review of the preclinical development of zaleplon can be read elsewhere.<sup>8</sup> The current review updates previous ones by including more recent studies that have been performed with zaleplon. In addition, when compared with previous reviews, the current review has a stronger focus on potential residual effects on daytime functioning.

For this review, the PubMed and Embase databases and the Cochrane Library were systematically searched, using the search term “zaleplon”. This yielded 954 articles. Articles including experimental data were used for this review. After reading the articles, 886 articles were excluded, because they were general articles on insomnia or reviews (517), included no relevant data (129), were animal studies (21), general guidelines on insomnia treatment (76), written in languages other than English (62), discussed drug synthesis and analysis (40), or were cost-benefit analyses and letters to the editor (43). The remaining 66 articles are discussed in this review.

## Pharmacology

Zaleplon is a pyrazolopyrimidine hypnotic drug indicated for the short-term (ie, 1–2 week) management of insomnia. Its chemical structure is shown in Figure 1. Like benzodiazepine hypnotics, zaleplon acts on gamma aminobutyric acid type A (GABA<sub>A</sub>) receptors in the central nervous system (CNS). GABA<sub>A</sub> receptors are organized through the membrane as pentameric proteins surrounding a central pore that forms the Cl<sup>-</sup> ion channel. Most GABA<sub>A</sub> receptors consist of two  $\alpha$  subunits, two  $\beta$  subunits and a  $\gamma$ ,  $\delta$ , or other subunit. In humans, six different  $\alpha$  subunits, three  $\beta$  subunits, three  $\gamma$  subunits, a  $\delta$ , an  $\epsilon$ , a  $\pi$ , and a  $\theta$  subunit are identified. Approximately 75%–80% of the GABA<sub>A</sub> receptors contain a  $\gamma$ 2 subunit. The most common GABA<sub>A</sub> receptor consists of two  $\alpha$ 1 subunits, two  $\beta$ 2 subunits and a  $\gamma$ 2 subunit.<sup>9</sup> The classic benzodiazepines bind to GABA<sub>A</sub> receptors at the interface of an  $\alpha$  and  $\gamma$  subunit. Benzodiazepines are active at sites where a  $\gamma$ 2 subunit is coupled with one of the subunits,  $\alpha$ 1, 2, 3, or 5.<sup>9</sup> The anxiolytic effect and myorelaxant actions of benzodiazepines are thought to be mediated by the  $\alpha$ 2-containing receptors, whereas the sedative-hypnotic action appears to be mediated through the  $\alpha$ 1 receptors.<sup>10</sup>



**Figure 1** Chemical structure of zaleplon (N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide).

Benzodiazepine hypnotics bind nonselectively to the benzodiazepine recognition site of the GABA<sub>A</sub> receptor complex.<sup>11,12</sup> Whereas most benzodiazepine hypnotics bind to all GABA<sub>A</sub> receptors with similar affinity, zaleplon and zolpidem have a more selective affinity for some of its subunits. Zaleplon and zolpidem prefer the  $\alpha$ 1 $\beta$ 2 $\gamma$ 2 subunit combination, which represents the combination that is most abundantly present in the brain. In addition, zaleplon (but not zolpidem) recognizes  $\alpha$ 2 and  $\alpha$ 3 receptors.

## Pharmacokinetics

Typical pharmacokinetic data for zaleplon and zolpidem are summarized in Table 1. Zaleplon is rapidly absorbed. The time to maximum plasma concentration ( $T_{max}$ ) and elimination half-life ( $t_{1/2}$ ) are approximately one hour, with a narrow range of individual variation.<sup>13-16</sup> The absolute bioavailability of zaleplon is 30% in both men and women. Zaleplon exhibits dose-proportional kinetics, both in peak plasma concentration ( $C_{max}$ ) and area under the concentration-time curve. More than 99% of zaleplon is metabolized by the liver, and less than 1% is eliminated unchanged via the urine. Zaleplon is metabolized by aldehyde oxidase to 5-oxo-zaleplon or by CYP3A4 to desethylzaleplon which is converted to 5-oxodesethylzaleplon by aldehyde oxidase. These metabolites are further metabolized by conjugation and are eliminated in urine.<sup>17</sup> The metabolites of zaleplon are pharmacologically inactive.<sup>18</sup>

**Table 1** Comparative pharmacokinetic data for zaleplon and zolpidem

Pharmacokinetics	Zaleplon 10 mg	Zaleplon 20 mg	Zolpidem 10 mg	Zolpidem 20 mg
C <sub>max</sub> (ng/mL)	26.0 ± 4.4	49.0 ± 5.7	125 ± 15	232 ± 17
T <sub>max</sub> (hours)	1.1 ± 0.17	1.1 ± 0.21	1.7 ± 0.3	2.0 ± 0.3
T <sub>1/2</sub> (hours)	1.01 ± 0.05	0.98 ± 0.03	2.0 ± 0.15	2.2 ± 0.26
AUC (ng/mL/hour)	42.1 ± 5.5	93.2 ± 15	408 ± 48	889 ± 110
Clearance* (mL/min)	4436 ± 457	4299 ± 537	378 ± 52	341 ± 38

**Notes:** Mean (± SE) values from 10 healthy male volunteers. \*Apparent oral clearance.

**Abbreviations:** C<sub>max</sub>, peak plasma concentration; T<sub>max</sub>, time at which C<sub>max</sub> occurs; AUC, area under the plasma concentration versus time curve; T<sub>1/2</sub>, elimination half-life. Data adapted from Greenblatt et al.<sup>15</sup>

## Efficacy

Studies examining the efficacy of short-term and long-term use of zaleplon have focused on the drug's ability to initiate and maintain sleep. The most common endpoints in these clinical trials were latency to falling asleep, number of nightly awakenings, and total sleep time. Additionally, polysomnographic data were examined to determine if zaleplon alters sleep architecture.

### Short-term use (<2 weeks)

A small three-night study in nine insomniacs and two neurotic patients with insomnia revealed that zaleplon 5 mg and 10 mg was effective in shortening sleep latency and slow-wave sleep latency.<sup>19</sup> The treatment nights were followed by two withdrawal nights that showed no signs of rebound insomnia. A much larger study by Ancoli-Israel et al examined sleep in 549 elderly outpatients after two weeks of double-blind treatment with zaleplon 5 mg or 10 mg, zolpidem 5 mg, or placebo.<sup>20</sup> Zaleplon and zolpidem significantly reduced sleep latency and increased total sleep time. Relative to placebo, zaleplon reduced sleep latency by 15–20 minutes and increased total sleep time by about 40 minutes. Drake et al showed that zaleplon 10–60 mg produced significant dose-dependent decreases in latency to persistent sleep in chronic insomniacs.<sup>21</sup> However, only the 60 mg dose of zaleplon produced significant increases in total sleep time when compared with placebo. All doses of zaleplon tended to increase the proportion of stages 3 and 4 sleep.

A double-blind, crossover study using a VAS scale to assess treatment satisfaction in 53 patients after administration of a single dose of zolpidem 10 mg or zaleplon 10 mg reported that 62% of patients preferred zolpidem.<sup>22</sup>

In another study, 47 patients with insomnia received either zaleplon 10 mg or 20 mg or zolpidem 10 mg or 20 mg for two weeks and completed a subjective sleep dysfunction rating scale assessment.<sup>23</sup> Scores were significantly improved in both groups and no significant differences were reported between the treatments. Walsh et al examined the efficacy

of zaleplon 5 mg and 10 mg, triazolam, versus placebo in 132 patients with primary insomnia.<sup>24</sup> Patients received one of these treatments for 14 days. Polysomnographic data showed that zaleplon significantly shortened latency to persistent sleep during the first nights, but not thereafter. In contrast with triazolam, zaleplon did not significantly increase total sleep time, nor did it reduce the number of nightly awakenings. These findings indicate that zaleplon is effective to some extent in initiating sleep and increasing total sleep time.

### Long term use (>2 weeks)

Three studies examined the efficacy of zaleplon when using the drug for more than two weeks. In the first study, 615 adult insomniac patients received zaleplon 5, 10, or 20 mg, zolpidem 10 mg, or placebo for 28 nights. Zaleplon 10 mg and 20 mg significantly decreased sleep latency during all four weeks of treatment.<sup>25</sup> For zaleplon 5 mg, this effect was significant during the first three weeks of treatment. The highest dose of zaleplon also significantly increased total sleep time. Zolpidem 10 mg significantly decreased sleep latency, increased total sleep time, and improved sleep quality. Similar findings were reported by the second study.<sup>26</sup>

In a double-blind study, 113 adult patients with primary insomnia were treated for 35 days with either zaleplon 10 mg or placebo.<sup>27</sup> Zaleplon significantly shortened sleep latency. No consistent effect was found on total sleep time and zaleplon did not affect sleep architecture. These studies suggest that the improvements of sleep quality and duration produced by zaleplon persist during long-term treatment.

## Elderly

Insomnia is common among the elderly, and as a result they are overrepresented among patients using hypnotic drugs. Drug dosages are often adapted to half the recommended adult dose. In the case of zaleplon, 5 mg is commonly prescribed instead of 10 mg. A placebo-controlled study evaluated the

efficacy and safety of zaleplon 5 mg and 10 mg in 422 elderly outpatients with insomnia.<sup>28</sup> Sleep latency, sleep duration, number of awakenings, and sleep quality were recorded for two weeks by using questionnaires. Both dosages of zaleplon significantly reduced subjective sleep latency by 10 to 20 minutes. Relative to placebo, zaleplon 10 mg also significantly improved sleep quality. Walsh et al treated 48 elderly patients (aged 60–80 years) suffering from chronic insomnia with zaleplon 2, 5, and 10 mg or placebo.<sup>29</sup> Polysomnographic measurements showed that latency to persistent sleep was shortened significantly with all three zaleplon doses. Subjective sleep latency was reduced significantly, and total sleep time was significantly increased with zaleplon 5 mg and 10 mg. In an open-label study, 15 psychiatric inpatients were treated with the sedative antidepressant drug trazodone 50–100 mg or zaleplon 10–20 mg, using the medication on an as-needed basis.<sup>30</sup> Whereas trazodone was more successful in promoting and sustaining sleep, residual daytime effects were much less often reported by patients using zaleplon.

One study followed a group of elderly patients (65–95 years) who used zaleplon 5 mg or 10 mg for up to one year. Initial treatment improvement persisted in terms of significantly reduced sleep onset time, increased duration of sleep, and reduced number of nocturnal awakenings (Figure 2).<sup>31</sup>

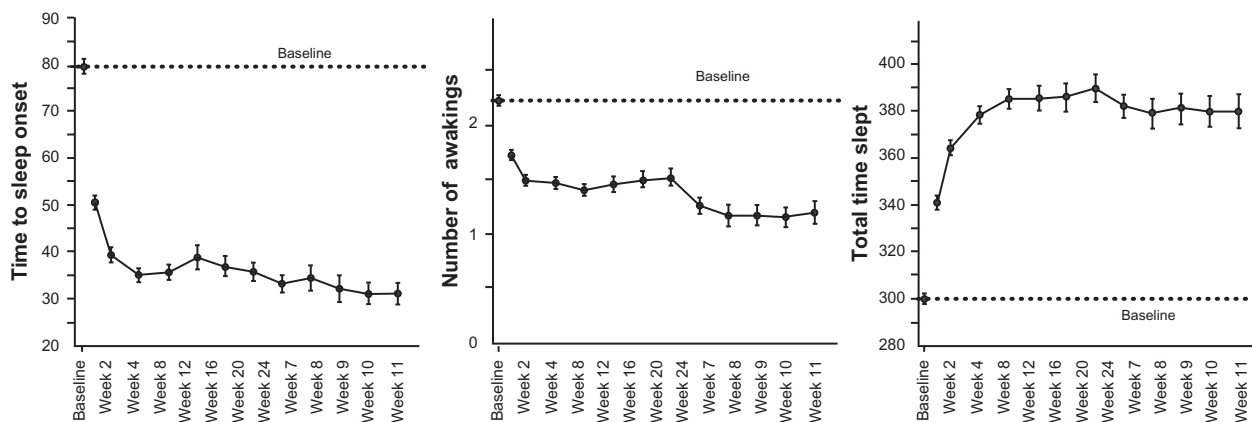
## Daytime sleep and shift work

Zaleplon 10 mg improved daytime sleep in 12 rested healthy subjects.<sup>32</sup> When woken after 3.5 hours, no impairment was found on cognitive, memory, and psychomotor performance. The effect of zaleplon 10 mg and temazepam 20 mg on afternoon sleep (5.30–10.00 p.m.) and effects on performance and

alertness during a subsequent night shift were examined in 11 subjects.<sup>33</sup> Improvement of sleep quality was significantly more pronounced after taking temazepam. Zaleplon did not differ from placebo for any sleep parameter. Temazepam and zaleplon did not affect performance on tests done after waking up (vigilance/tracking and a complex information processing task). Although these studies had relatively small sample sizes, the results indicate that zaleplon is effective in promoting daytime sleep, without residual effects after awaking.

## Efficacy of zaleplon at high altitude

Few studies have tested the effects of zaleplon at high altitude. Mountain climbers can experience respiratory problems and sleep disturbances when at altitude.<sup>34</sup> Poor sleep may affect cognitive and psychomotor functioning and reduce daytime alertness which are essential for safe mountain climbing. Beaumont et al tested 12 healthy men who slept for a night in a decompression chamber at a simulated altitude of 4000 m.<sup>35</sup> In this double-blind, crossover study, zolpidem 10 mg, zaleplon 10 mg, or placebo were administered at bedtime. Polysomnographic and respiratory measures showed that both zaleplon and zolpidem improved slow-wave sleep at high altitude, without negatively affecting respiratory functions. Cognitive and physical performance, examined the next morning at sea level conditions, was not affected by zaleplon or zolpidem. The authors then tested the efficacy of the drugs at a comparable altitude on a mountain (3613 m).<sup>36</sup> Sleep and respiratory functions were significantly disturbed at high altitude on placebo, whereas zaleplon and zolpidem significantly improved sleep quality and respiratory



**Figure 2** Mean (standard deviation) time to sleep onset (left panel), mean (standard deviation) number of awakenings (middle panel), and mean total time slept (right panel) in elderly patients using zaleplon nightly for 6–12 months.

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functioning. Daytime cognitive functioning, examined by the digit symbol substitution test (DSST) showed that, relative to the baseline level (800 m), performance at high altitude was significantly worse after all treatments, including placebo. However, the authors found no impairment after administration of zaleplon or zolpidem.<sup>36</sup>

In a double-blind, crossover design, 12 nonacclimatized male soldiers spent four nights at high altitude (3613 m).<sup>37</sup> Subjects exercised for three days at altitude, followed by a treatment night (zaleplon, zolpidem, or placebo). Arterial oxygen saturation, heart rate variability, and mountain sickness were recorded. Both zolpidem and zaleplon improved sleep and physical fitness at altitude.

## Rebound effects

After discontinuation of hypnotic drugs, rebound effects may occur. Commonly reported rebound effects are prolonged sleep latency, reduced total sleep time, and increased number of awakenings. Often these rebound effects are subjectively reported by patients completing sleep diaries. In contrast with zolpidem, clinical trials that discontinued the use of zaleplon 5 mg and 10 mg reported no significant rebound symptoms.<sup>20,25–27</sup> In the elderly, a weak indication of rebound insomnia was found after discontinuation of treatment with zaleplon 10 mg, but not zaleplon 5 mg.<sup>28</sup> In elderly outpatients discontinuing zaleplon 5 or 10 mg after 6–12 months, no rebound insomnia was observed.<sup>31</sup>

## Safety and tolerability

Adverse effects from zaleplon are of relative short duration, milder, and resolve more quickly when compared with those of benzodiazepine hypnotics. In 1998–2004, Texas poison control centers recorded adverse effects reported by patients using zolpidem or zaleplon. The most frequently reported adverse effects for zaleplon and zolpidem were drowsiness, slurred speech, hallucinations, ataxia, tachycardia, dizziness, confusion, and vomiting.<sup>38</sup>

In a parallel-group design, oral doses of 1, 5, 15, 30, or 60 mg of zaleplon were tested in five healthy male volunteers. Zaleplon was well tolerated and produced no significant changes in vital signs, the electroencephalogram, the electrocardiogram, or hematologic and clinical chemistry parameters.<sup>13</sup> Dose-dependent presence and severity of adverse events were reported. In this small study, impaired concentration, difficulty focusing, and impaired coordination were most frequently reported.

Studies performed at stimulated high altitude<sup>35</sup> and actual high altitude<sup>36</sup> showed that zaleplon did not alter respiratory measures.<sup>35,36</sup> Zaleplon 10 mg administered to 15 patients with obstructive sleep apnea while on continuous positive airway pressure treatment was shown to be safe. Zaleplon did not significantly alter the apnea-hypopnea index or affect respiratory parameters.<sup>39</sup>

In 10 patients on maintenance hemodialysis and suffering from insomnia, Pittsburgh questionnaire scores indicated that zaleplon 5 mg and 10 mg significantly improved overall sleep quality, reduced sleep latency, but did not prolong total sleep time.<sup>40</sup> Zaleplon did not affect any dialysis parameters.

An open-label study in five lactating mothers showed that zaleplon 10 mg taken by a nursing mother is transferred through breast milk to her infant. However, this occurs in very small quantities (0.013%–0.017% of the maternal dose) that are unlikely to be clinically important.<sup>41</sup>

## Adverse reactions after overdose

Few case studies have been published that describe the effects of zaleplon overdose.<sup>42–45</sup> Liskow described a 14-year-old boy who took three tablets instead of one 10 mg tablet zaleplon, three weeks after treatment initiation.<sup>42</sup> The boy was found sleepwalking and his parents took him to hospital. Bhatia et al 2001 described a case of a healthy woman who experienced zaleplon-induced illusions and visual hallucinations, and a feeling of depersonalization within three minutes of ingesting zaleplon 10 mg at bedtime.<sup>43</sup> The duration of events was limited to 15 minutes, but lightheadedness and fatigue persisted until the next day. An overdose of zaleplon in combination with alcohol was described by Hojer et al.<sup>44</sup> A 55-year-old man with bluish-green urine had taken an unknown amount of zaleplon in combination with whiskey. The patient was sedated and had only weak responses. Initial intravenous administration of flumazenil 1 mg immediately woke the patient, but three hours thereafter the patient went into a coma. An additional dose of flumazenil was needed to wake this patient. No arousing effect was observed after administering flumazenil 0.5 mg to a 68-year-old woman who had an overdose of zaleplon and trimipramine. This woman also had bluish-green urine. After two days the patient was fully awake.

Another case described a 24-year-old woman who took about 28 zaleplon tablets. She had bluish-green discoloration of lips, urine, and emesis, was confused and sleepy, and experienced visual hallucinations. The following day the

patient was alert and recovered.<sup>45</sup> Bluish-green urine is an indicator of zaleplon abuse, and is probably due to the indigo carmine used in zaleplon capsules.<sup>45</sup>

## Interactions

In contrast with benzodiazepine hypnotics, few clinically important interactions have been reported for zaleplon. This may reflect the fact that zaleplon is a relatively new hypnotic drug, and only a few studies have been done to investigate interactions.<sup>46</sup> However, few interactions have been studied. There is no significant interaction between zaleplon and ibuprofen<sup>47</sup> or digoxin.<sup>48</sup> Also, coadministration of zaleplon 20 mg and thioridazine 50 mg in 12 healthy subjects did not change the pharmacokinetic profile of either drug. Pharmacodynamic interactions were investigated, with only a significant difference in reaction time found between thioridazine and zaleplon versus thioridazine alone at one hour after administration. This indicates that there is an additive effect of zaleplon and thioridazine when these agents are coadministered. A supra-additive interaction was found for the DSST. However, due to the short half-life of zaleplon, the duration of maximal effect is four hours. The conclusion of the researchers therefore was that thioridazine 50 mg and a nighttime dose of zaleplon 10 mg can safely be administered together.<sup>49</sup>

Other potential, as yet undiscovered, interactions include those with CYP3A4 inhibitors or inducers because this is the main elimination route for zaleplon. As outlined in the summary of product characteristics, the interaction between erythromycin (a strong CYP3A4 inhibitor) caused a 34% higher plasma concentration of zaleplon. Dose reduction is not indicated, but it is advised to inform patients of the larger sedating effect. Also, cimetidine causes a 85% increase in plasma zaleplon concentration because it inhibits both the primary (aldehyde oxidase) and secondary (CYP3A4) elimination route of zaleplon. The combination of zaleplon and cimetidine is therefore not recommended. Combination of zaleplon with other hypnotic sedative drugs or alcohol can produce an additional sedative effect.

## Abuse potential

A dose-ranging study by Beer et al did not report increased drug-liking scores when administering zaleplon dosages up to 60 mg to healthy volunteers.<sup>13</sup> In 14 healthy volunteers with a history of drug abuse, Rush et al tested the abuse potential of zaleplon 25 mg, 50 mg, and 75 mg, triazolam 0.25 mg, 0.5 mg, and 0.75 mg, and placebo.<sup>50</sup> A number of drug effect questionnaires were administered. In addition, a memory and

psychomotor test battery were performed at fixed intervals up to 24 hours after intake. Although the duration of effects was shorter for zaleplon, both zaleplon and triazolam produced comparable dose- and time-related effects on the drug-liking questionnaires and psychometric tests. Subjective ratings of drug-liking suggest that, at higher dosages, zaleplon and triazolam have comparable abuse potential.

## Residual effects and daytime functioning

Because the purpose of hypnotic drugs is to initiate or maintain sleep, there is a risk of sedative effects persisting after waking up and affecting cognitive functioning. Reduced daytime alertness and residual cognitive, memory, and psychomotor impairment have been reported for most hypnotic drugs. The following section summarizes results from studies that have examined the residual effects of zaleplon. The most commonly used psychometric tests are described in Table 2.

## Immediate effects

A couple of studies examined the effects of zaleplon immediately after ingestion. These studies were performed during the daytime and no sleep was allowed. Subjects were tested for several hours after intake of zaleplon, and regular blood samples were taken to establish the pharmacokinetic profile of zaleplon.

In one of the early studies in healthy volunteers, Allen et al showed that whereas impairment by lorazepam 2 mg persisted for 3–5 hours after intake, the effects on psychomotor performance and memory functioning with zaleplon 20 mg were much less pronounced and lasted only one hour.<sup>51</sup>

Greenblatt et al examined the effects of zaleplon 10 mg and 20 mg and zolpidem 10 mg and 20 mg on self-reported sedation, DSST performance, and brain activity up to eight hours after intake in 10 healthy male volunteers.<sup>15</sup> Dose-dependent performance impairment was found for both drugs, which was significantly correlated with plasma concentrations. Memory functioning, measured 1.5 hours after intake, was also impaired for zolpidem, but not for zaleplon. Impairment after zolpidem was much more pronounced when compared with zaleplon.

Another study in 10 healthy volunteers examined the pharmacokinetic and pharmacodynamic profiles of zaleplon 10 mg and 20 mg and zolpidem 10 mg and 20 mg.<sup>14</sup> Blood samples were taken and subjects performed the DSST at fixed intervals. A word learning test was performed 1.5 hours after intake (immediate recall) and after eight

**Table 2** Description of commonly used performance tests

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**Digit symbol substitution test:** Symbols are matched to numbers (0–9). Subjects are instructed to copy as many symbols to a list of numbers as possible within a given time. Parameters of the test are number of correct symbols and percentage of errors.

**Reaction time test:** Subjects are instructed to push a button as soon as possible in response to a stimulus. The response can be either simple or complex. Parameters of the test are reaction speed and percentage of errors.

**Tracking test:** In this eye-hand coordination test subjects have to keep a moving bar at a steady position on the computer screen. Parameter is the tracking error.

**Sternberg memory scanning test:** In this working memory test, subjects have to recall a number of sets of 1–5 digits. After memorizing a set, a digit appears on the computer screen. Subjects have to indicate by button press if the digit was part of the learned set. Parameters are reaction time and percentage of errors.

**Divided attention test:** Two or more tests are performed simultaneously. Often divided attention test is a combination of a tracking test with the Sternberg memory scanning test or a reaction time test.

**Word learning test:** A list of words is learned. Recall is tested directly after learning (immediate recall) and one or more hours thereafter (delayed recall). Often, recognition tests are included in which the learned list is shown mixed with words that were not learned. Parameter is the number of correct words.

**Logical reasoning:** A statement is followed by several possible conclusions that can be drawn from the statement. Only one can be drawn by logical reasoning. Parameter is the number of correct answers.

**Serial subtraction:** Subjects have to subtract a number from a previous one (eg, count backwards from 100 in sevens). Parameter is the number of errors.

**Paired associate learning:** Subjects are shown a set of word pairs that should be learned. Subjects are then shown a list of words. They have to write down the correct other word of each pair. Parameter measured is the number of errors.

**Digit span:** A test to measure memory span. A digit is shown on the computer screen. When it disappears, the subject has to enter the digit. Then two digits appear (the first one and a new one) and the subject has to retype those. This procedure continues until the subject makes a mistake. Parameter is the number of correct digits.

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hours (delayed recall). When compared with placebo, DSST was impaired for up to 6 hours after both zaleplon and zolpidem intake. Impairment after zolpidem was much more pronounced when compared with zaleplon. In contrast with zaleplon, zolpidem also significantly impaired word learning and recall. In line with these findings, subjective sedation scores were of a greater magnitude and longer duration after intake of zolpidem.

Paul et al examined psychomotor performance in 23 healthy volunteers, 1–7 hours after intake of zaleplon 10 mg, zopiclone 7.5 mg, temazepam 15 mg, melatonin 6 mg, and placebo.<sup>52</sup> All treatments except melatonin impaired performance on tests measuring serial reaction time, logical reasoning, serial subtraction, and multitasking. Figure 3 shows the impairment

over time on the serial reaction time test. Impairment for zaleplon was significant up to 3.25 hours after intake, but much shorter when compared with zopiclone and temazepam (up to 6.25 and 5.25 hours after intake, respectively).

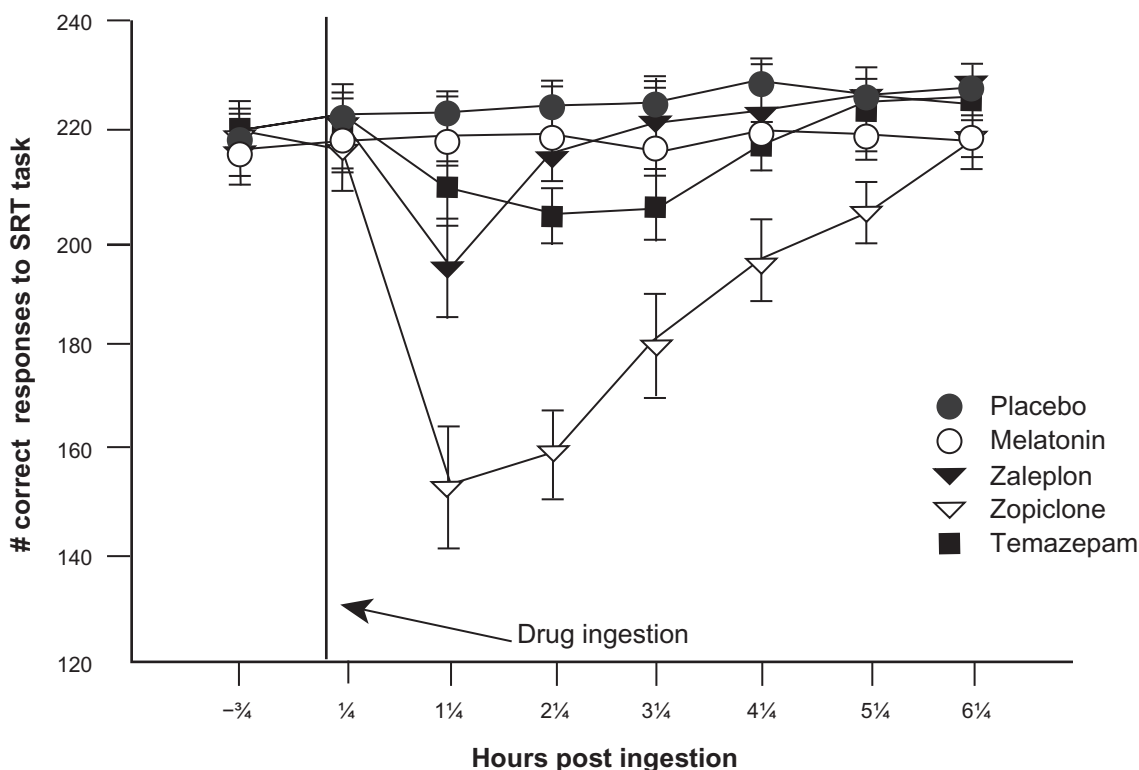
Polysomnographic measurement of total sleep and sleep latency during four minute periods with eyes closed immediately after performing the psychomotor test battery revealed that all treatments produced more sleep, shorter sleep latency, and more drowsiness.<sup>53</sup>

Postural instability is common when using benzodiazepine hypnotics and zopiclone.<sup>54</sup> Balance problems are often the cause of falls and hip fractures.<sup>55</sup> Postural instability is dose- and time-dependent, and most profound at peak plasma concentration (ie, during the night). The latter may be particularly risky for patients who wake up during the night. In a daytime study in 16 health volunteers allowed one hour of sleep, body balance was examined up to seven hours after treatment with zaleplon 10 mg or placebo.<sup>56</sup> Subjects also performed several cognitive and performance tests. Zaleplon 10 mg significantly impaired body balance and performance on most of the tests up to two hours after intake. Symptoms related to drowsiness were reported significantly more often during the first three hours after intake, but not thereafter. Memory was impaired for up to four hours after intake of zaleplon.

To determine a possible interaction with alcohol, the effects of triazolam 0.25 mg, zaleplon 10 mg, and placebo were examined, alone and in combination with alcohol 0.75 g/kg.<sup>57</sup> Eighteen healthy volunteers performed psychomotor tests up to six hours after treatment administration. Blood alcohol concentrations (BAC) at 0.5, 2.0, 4.5, and 6.0 hours after intake were 0.052%, 0.037%, 0.009%, and 0.001%, respectively. Alcohol impaired most measures up to 4.5 hours after intake. Triazolam with and without ethanol impaired performance on the DSST, symbol copying, reaction time tests, and divided attention test. Zaleplon alone produced no impairment, except at two hours after intake for the DSST and tracking in the divided attention test. Combined with alcohol, the impairment of zaleplon was extended up to 4.5 hours after intake. The effect of coadministration of these agents was additive.

## Next-day cognitive, memory and psychomotor functioning

Benzodiazepine hypnotics have shown residual effects that impair daytime functioning, especially during the morning hours after awakening. Several studies have tested the residual effects of zaleplon. In these studies, zaleplon was administered at bedtime, and performance on a variety of



**Figure 3** Number of correct responses in a serial reaction time task after ingestion of placebo, time-released melatonin 6 mg, zaleplon 10 mg, zopiclone 7.5 mg, and temazepam 15 mg. Higher number of responses represents better performance. Data are mean values ( $\pm$  standard error of mean) of 23 subjects. Copyright © 2003. World Association of Sleep Medicine. All rights reserved. Adapted with permission from Paul MA, Gray G, Kenny G, Pigeau RA. Impact of melatonin, zaleplon, zopiclone, and temazepam on psychomotor performance. *Aviat Space Environ Med.* 2003;74(12):1263–70.

cognitive, memory and psychomotor test was examined the following day.

Beer et al<sup>13</sup> examined memory and psychomotor performance in healthy volunteers after administration of oral doses of 1, 5, 15, 30, or 60 mg of zaleplon or placebo. Drowsiness and performance on psychomotor tests was impaired in a dose-dependent manner. Memory functioning was not affected. In a double-blind, crossover study, 24 healthy subjects received zaleplon 10 mg and 20 mg, zolpidem 10 mg and 20 mg, triazolam 0.25 mg, or placebo at bedtime.<sup>58</sup> Tests included word learning, digit span, DSST, paired-associates learning, and divided attention tests, performed after being woken during the night (1.25 hours after intake) and the following morning (8.25 hours after intake). At 1.25 hours after intake, zaleplon 10 mg did not produce any significant changes when compared with placebo, whereas zaleplon 20 mg, zolpidem 10 mg and 20 mg, and triazolam 0.25 mg caused significant psychomotor impairment. Zaleplon 10 mg and 20 mg and zolpidem 10 mg did not affect performance 8.25 hours after intake. Triazolam 0.25 mg and zolpidem 20 mg showed significant impairment on the DSST.

Walsh et al performed several studies in patients with insomnia. In patients who received zaleplon 5 mg or 10 mg

for 14 days, no significant residual effects were found the next morning for performance of simple and complex reaction time tasks, digit span, word learning, and the DSST.<sup>24</sup> In 48 elderly patients with chronic insomnia, zaleplon 2 mg, 5 mg, or 10 mg also did not affect psychomotor performance the next morning.<sup>29</sup> Administering higher dosages, Drake et al also found that zaleplon 10–60 mg produced no significant next-morning impairment on the DSST and digit span test in chronic insomniacs.<sup>21</sup> Although the number of studies is limited, they consistently show absence of performance impairment.

### Residual effects after middle-of-the-night administration

In a double-blind, crossover study, zaleplon 10 mg, zolpidem 10 mg, or placebo was administered at bedtime to 36 healthy subjects.<sup>59</sup> Subjects received their treatment 2, 3, 4, or 5 hours before waking. After waking, a psychometric test battery was performed. Zaleplon did not affect performance at any time. In contrast, zolpidem significantly impaired performance on various memory and psychomotor tests for up to 4–5 hours after administration of the drug.



Hindmarch et al examined the residual effects of zaleplon after middle-of-the-night administration in 40 healthy volunteers.<sup>60</sup> Zaleplon 10 mg or 20 mg, zolpidem 10 mg, or placebo was administered at 5 hours, 3 hours, or 1 hour before morning awakening. Critical flicker fusion, choice reaction time, DSST, Sternberg memory scanning, and a word learning test were conducted after morning awakening. Zaleplon 10 mg did not affect performance, except for a significant decrease in DSST scores 1 hour after intake. Zaleplon 20 mg produced a significant increase in choice reaction time, and a decrease in critical flicker fusion threshold, DSST scores, and immediate- and delayed-recall in the word learning test. These effects were significant only when tested 1 hour after intake. In contrast, zolpidem 10 mg produced significant impairment of choice reaction time, memory functioning, DSST, and the critical flicker fusion test up to 5 hours after intake.

In 30 healthy volunteers, the effects of zaleplon 10 mg and 20 mg, zolpidem 10 mg and 20 mg, and placebo on cognitive, memory, and psychomotor performance were tested four hours after middle-of-the-night administration.<sup>61</sup> Results were compared with those observed after administration of alcohol (BAC 0.05%). Zaleplon 10 mg and 20 mg, and zolpidem 10 mg did not affect performance on the psychometric tests. In contrast, zolpidem 20 mg and alcohol significantly impaired performance on all psychomotor and memory tests.

Thirteen healthy volunteers participated in a double-blind study to examine the residual effects of zaleplon 10 mg or 20 mg, zopiclone 7.5 mg, and placebo, 4 hours after a middle-of-the-night administration.<sup>62</sup> After 5 hours of uninterrupted sleep, subjects were woken to receive treatment, and returned to sleep for another 4 hours. During the second part of the night, subjects were exposed to background noise. In contrast with zopiclone, both dosages of zaleplon did not affect performance on any cognitive tests performed after waking. Zopiclone and zaleplon significantly reduced sleep latency onset when compared with placebo.

Residual effects of zaleplon have also been tested in patients with sleep maintenance insomnia. In a double-blind, crossover design, 22 patients received zaleplon 10 mg, flurazepam 30 mg, or placebo in the middle of the night (3.5 hours after bedtime) for two consecutive nights.<sup>63</sup> The following morning (5 to 6.5 hours after treatment administration), flurazepam, but not zaleplon, significantly impaired performance on DSST and symbol copying. When receiving flurazepam, patients reported significantly increased daytime sleepiness.

In 37 adults with sleep-maintenance insomnia, zaleplon 10 mg, zolpidem 10 mg, or placebo were administered during experimental awakening four hours after bedtime.<sup>64</sup> Latency to persistent sleep, total sleep time before and after awakening, performance on the DSST, and self-reported alertness and concentration were recorded hourly for 4–7 hours after treatment administration. Both zaleplon and zolpidem significantly reduced latency to persistent sleep and increased total sleep time. Residual effects were significant up to seven hours after administration of zolpidem and four hours after administration of zaleplon.

Taken together, these studies show that the impairment effects of zaleplon are limited to 4 hours after dosing, and in most studies were significant only after administering twice the recommended dose (20 mg).

## Effects on driving ability

Most patients using zaleplon are ambulatory and likely to drive a car. Because driving a car is a common but also potentially dangerous daily activity, several studies have examined the effects of hypnotic drugs on driving ability.<sup>65,66</sup> These studies showed that benzodiazepine hypnotics significantly impair the ability to drive, and a significantly increased risk of road traffic accidents has been reported for patients using benzodiazepine hypnotics. Several studies have investigated zaleplon in this regard.

In an early study, 28 healthy volunteers received zaleplon at bedtime and were woken after 5 hours to receive placebo, or *vice versa*.<sup>67</sup> Driving performance was assessed 10 hours after bedtime administration or 5 hours after middle-of-the-night administration of zaleplon 10 mg or 20 mg, zopiclone 7.5 mg, or placebo. Driving ability was measured by a 100 km road driving test. The test is performed on a public highway in normal traffic. Subjects were instructed to maintain a steady lateral position and constant speed. Standard deviation of lateral position, ie, weaving of the car, was the primary parameter measured in the test. Zaleplon 10 mg and 20 mg did not affect driving performance. In contrast, zopiclone significantly impaired driving after bedtime and middle-of-the-night administration.

A second study in 30 healthy volunteers also examined road driving performance 10 hours after bedtime administration of zaleplon 10 mg, zopiclone 7.5 mg, and placebo.<sup>68</sup> In addition to driving, subjects performed a word learning test, tracking test, and divided attention test. Results were compared with those after administration of alcohol (BAC 0.03%). Whereas zopiclone and alcohol significantly impaired driving, memory, and divided attention, zaleplon had no residual effects on driving and the

psychometric tests. The magnitude of driving impairment after zopiclone was twice that observed after alcohol.

A third study tested driving ability in 30 healthy volunteers four hours after middle-of-the-night administration of zaleplon 10 mg and 20 mg, zolpidem 10 mg and 20 mg, and placebo.<sup>61</sup> Zaleplon 10 mg and 20 mg did not significantly impair driving. In contrast, both dosages of zolpidem and alcohol produced significant driving impairment. Whereas an increasing number of sleep-driving events have been reported for zolpidem,<sup>69</sup> sleep-driving events after using zaleplon are rare. Southworth et al<sup>70</sup> described sleep-driving cases for people taking zaleplon, zolpidem, and eszopiclone. Fourteen cases were described, of which 13 involved zolpidem. Only one case involved zaleplon 10 mg, but it was used in combination with alcohol and hydrocodone. Another case study described an impaired driver who had used zaleplon.<sup>71</sup> The concentration of zaleplon determined in the driver's blood was much higher than what would be expected after using the recommended dose of zaleplon. The driver's movements and reactions were slowed, and he showed poor coordination and balance problems.

In conclusion, experimental studies show that, when used as recommended, zaleplon does not appear to impair driving. Currently, no epidemiologic data on road traffic accident risk are available for zaleplon.

## Conclusions

Over the past 20 years, zaleplon has earned its place in insomnia therapy. Efficacy studies show that zaleplon is a suitable hypnotic for sleep initiation purposes. However, because of its short half-life, zaleplon is less effective in sleep maintenance.

The use of zaleplon is relatively safe. Adverse effects are mild and of short duration. Critical interactions have not been reported, and there is no evidence of high abuse potential for zaleplon. Relative to the benzodiazepine hypnotics, the biggest advantage of zaleplon is that there is ample evidence of residual next-day effects. For example, current evidence suggests that as early as four hours after intake, zaleplon does not affect cognitive, memory, and psychomotor performance, or the ability to drive a car in everyday traffic. One should, however, take into account that, when compared with benzodiazepine hypnotics, much less scientific research has been done with zaleplon. Also, many studies with zaleplon have had relatively small sample sizes. Nevertheless, their results were generally consistent with those found in larger studies.

Several topics need to be addressed by future studies or examined in more detail. For example, the efficacy and behavioral effects of long-term zaleplon use have not been examined thoroughly. Most studies are limited to a maximum of 2–4 weeks. Although this is understandable when taking into account the prescription guidelines (the recommended maximal duration of use for zaleplon is two weeks), in reality, a great number of people with insomnia use hypnotics for months or years. In the case of driving, no epidemiologic evidence is available on road traffic accident risk in patients using zaleplon. In addition, there are few data available on interactions of other drugs with zaleplon.

Finally, comparisons with new hypnotics that do not bind to the GABA<sub>A</sub> receptor, such as the melatonin receptor agonist, ramelteon, are important to be able to determine the future role of zaleplon in the treatment of insomnia.

## Disclosure

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