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New Drugs for Insomnia

Comparative Tolerability of Zopiclone, Zolpidem and Zaleplon

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Contents

Abstract

Insomnia affects 30–35% of people living in developed countries. The impact of insomnia on daytime functioning and its relationship with medical and psychiatric illnesses necessitate early treatment to prevent insomnia becoming persistent and to avoid the development of complications. However, pharmacological strategies must achieve a balance between sedative and adverse effects.

In the last 30 years, benzodiazepines have been the preferred drugs for the treatment of insomnia. Benzodiazepines act nonselectively at two central receptor sites, named ω_1 and ω_2, which are located in different areas of the CNS. The sedative action of benzodiazepines is related to ω_1 receptors, whereas ω_2 receptors are responsible for their effects on memory and cognitive functioning. According to their pharmacokinetic profile, benzodiazepines can be classified into three groups: short half-life (<3 hours), medium half-life (8–24 hours) and long half-life (>24 hours).

The newer non-benzodiazepine agents zopiclone, zolpidem and zaleplon have a hypnosedative action comparable with that of benzodiazepines, but they display specific pharmacokinetic and pharmacodynamic properties. These three 'Z' agents all share a short plasma half-life and limited duration of action. In addition, these agents are selective compounds that interact preferentially with ω_1 receptors (sedative effect), whereas benzodiazepines also interact with ω_2 receptors (adverse effects on cognitive performance and memory). Zaleplon is characterised by an ultrashort half-life (approximately 1 hour). Zolpidem and zopiclone have longer half-lives (approximately 2.4 and 5 hours, respectively). These properties, together with the low risk of residual effect, may explain the limited negative influences of these agents on daytime performance. Psychomotor tasks and memory capacities appear to be better preserved by non-benzodiazepine agents than by benzodiazepines. When present, cognitive deficits almost exclusively coincide with the peak plasma concentration. In particular, impairment can emerge in the first hours after drug administration, whereas psychomotor and memory tests carried out 7–8 hours later (i.e. in the morning) generally show no relevant alterations.

As with benzodiazepines, the three 'Z' non-benzodiazepine agents should be used for a limited period, even in chronic relapsing conditions. Further evaluation is needed of the safety of hypnosedative medications in the long-term management of insomnia.

Insomnia is characterised by poor sleep quality or inadequate quantity of sleep. Research has focused on the relevance of insomnia as a public health problem.[1] It is the most prevalent sleep disorder: approximately 30–35% of adults report experiencing insomnia at least once a year.[2] The risk for developing disturbed sleep is higher in patients with chronic or psychiatric disorders,[3] individuals of lower socioeconomic status, and women.[4] Daytime functioning and performance are often seriously affected by insomnia, which is responsible for irritability, tiredness, anxiety, poor concentration, memory impairment and reduced efficiency in performing difficult tasks,[5] impairments in quality of life, increased healthcare costs[6] and manifold clinical and neurophysiological aspects.

1. International Classification of Sleep Disorders

According to the International Classification of Sleep Disorders (ICSD), most insomnias are included in the category of dyssomnias, which are divided into intrinsic, extrinsic and circadian rhythm disorders. Intrinsic dyssomnias include psychophysiological insomnia, sleep state misperception, idiopathic insomnia, narcolepsy, restless legs syndrome, periodic limb movements and sleep apnoea. Extrinsic dyssomnias include inadequate sleep hygiene, environmental noise or other disturbing conditions such as altitude, alerting substances, alcohol and drugs. Circadian rhythm sleep disorders include jet-lag syndrome, shift-work syndrome, irregular sleep-wake pattern, and delayed and advanced sleep phase. Moreover, insomnia can be an important symptom of neurological, psychiatric and medical disorders.[7]

2. Nocturnal Profile and Evolution

Insomnia can be due to difficulty in falling asleep (initial insomnia), to multiple or prolonged awakenings in the middle of the night (sleep maintenance) or to an early final awakening in the early morning (final or terminal insomnia). In clinical practice it can be useful to classify insomnia according to the duration of the symptoms:

- transient insomnia, in which sleep disturbance lasts for a few days, is usually precipitated by an abrupt change in life and sleep schedule (acute stress, transcontinental travel, shift-work);[8]
- short-term insomnia, in which the disturbance lasts up to 3–4 weeks;[8]
- chronic insomnia, in which the sleep disturbance lasts for several weeks, months or years.[9]

3. Treatment Strategies

When the underlying cause of poor sleep can be identified, it should be removed before considering any pharmacological or nonpharmacological treatment.[6] Whatever the aetiology, good sleep hygiene and proper sleep habits should always be encouraged. This can dramatically improve the clinical picture in all forms of insomnia. Transient insomnia generally subsides upon resolution of the acute stressing cause. Short-term pharmacological therapy (2–3 days) is recommended for brief periods[10] and could be particularly useful when periods of poor sleep occur in a predictable manner (jet-lag, shift-work). In any case, clinical surveillance is fundamental to prevent insomnia becoming persistent. Chronic insomnia is often a consequence of medical conditions, psychiatric disorders or chronic use/abuse of several substances. If underlying causes can be ruled out, behavioural and cognitive approaches should be attempted first.[11] If this is insufficient to solve the patient's problem, the nonpharmacological procedures should be supplemented with drug therapy.

4. Hypnosedative Drugs

Over the last 30 years, benzodiazepines have been the cornerstone drugs for the treatment of insomnia, a use supported by extensive evaluation and by their relative safety in short-term use. Benzodiazepines act nonselectively at two central receptor binding sites, named ω_1 and ω_2, which are both located on the $GABA_A$ receptor complex but in different areas of the CNS. The hypnosedative action of benzodiazepines is related to ω_1 receptors, whereas ω_2 receptors are responsible for their effects on memory and cognitive functioning. According to their pharmacokinetic profile, benzodiazepines can be classified into three groups: short half-life (<3 hours), intermediate half-life (8–24 hours) and long half-life (>24 hours).

The use of benzodiazepines can result in a variety of problems, such as alteration of sleep structure, tolerance to the hypnosedative effect, pharmacological dependence, rebound insomnia and withdrawal reactions at discontinuation, anterograde amnesia, cognitive and psychomotor impairment, abuse potential and respiratory depression. Newer, more selective non-benzodiazepine compounds have been developed in an attempt to overcome some of the adverse effects of benzodiazepines. The scope of this study is a systematic

Table I. Glossary of terms

Term	Definition
Tolerance	Reduction in response to the drug after repeated administration
Dependence	Condition generally determined by long-term use of a hypnosedative drug and characterised by the occurrence of a withdrawal syndrome after abrupt discontinuation
Withdrawal syndrome	A complex of clinical manifestations (insomnia, convulsive episodes, irritability, anxiety) that occur when drug administration in a physically dependent person is abruptly discontinued
Rebound insomnia	Transient sleep disturbance (worse than before medication) that occurs after abrupt discontinuation of hypnosedative drugs
Abuse potential	Tendency of a drug to induce improper use

review of the tolerability of the non-benzodiazepine hypnosedatives zopiclone, zolpidem and zaleplon, which represent new tools in the pharmacological treatment of insomnia.

5. Data Sources and Evaluation Method

A Medline search was performed to identify clinical studies, case reports and abstracts with no restriction on year and type of data analysis. Keywords included zopiclone, zolpidem, zaleplon, CL 284,846 and insomnia. Additional references were obtained from the lists of articles and textbooks. Data concerning the safety and tolerability of the three hypnosedatives reviewed were extracted from all available sources; nevertheless, studies with the highest methodological quality were favoured.

Table I provides a glossary of terms used in the following sections, and table II outlines the most frequently used psychomotor and memory tests used in research on hypnosedative drugs.

6. Zopiclone

6.1 Chemical Structure and Pharmacology

Zopiclone is a hypnosedative drug belonging to the family of cyclopyrrolones. It binds to specific benzodiazepine receptor subtypes, with greater affinity for ω_1 than ω_2 receptors.[12] The degree of receptor selectivity of zopiclone is midway between the low level of benzodiazepines and the high level of zolpidem and zaleplon. Zopiclone can induce hypnotic, tranquillising, anticonvulsive and sedative effects. It has to be taken orally and is rapidly adsorbed, with peak blood concentrations about 105 minutes after ingestion. The pharmacology of zopiclone is characterised by a short half-life (4–5 hours) and high bioavailability (approximately 80%). It is extensively metabolised, resulting in various products. In particular, the *N*-dimethyl metabolite is inactive, whereas the *N*-oxide metabolites show some activity but are less active than the parent compound.[12] A considerable amount of these metabolites is finally excreted in the urine, and about 50% of an oral dose of zopiclone is decarboxylated and excreted via the lungs.[12]

The recommended dose of zopiclone is 7.5mg in adults, which should be decreased to 3.75mg in elderly patients and those with chronic respiratory failure or impaired renal or liver function.

6.2 Effects on Memory

There is some evidence that prolonged (3 weeks) nightly treatment with zopiclone 7.5mg does not affect memory performance in the early morning.[13] Moreover, Billiard and colleagues[14] found that, in healthy volunteers, zopiclone 3.75 and 7.5mg did not produce any detrimental effect on memory tests performed 1.5, 10 and 14 hours after drug intake. In a meta-analysis carried out on 2672 patients with insomnia comparing zopiclone and a number of benzodiazepines, zopiclone was not found to be superior to benzodiazepines on any of the memory and cognitive measures examined.[15]

In summary, zopiclone at recommended doses generally seems to be free of next-day negative

Table II. Most frequently used psychomotor and memory tests in the literature on hypnosedative drugs

Choice reaction time test: A measure of psychomotor performance; six stimulus lights are individually illuminated in a random sequence and subjects respond by pressing the appropriate key as quickly as possible. The mean latency of responses to 25 stimulus presentations is used as a measure of the test performance
Critical flicker fusion threshold: An indirect measure of information-processing capacity; four light-emitting diodes in foveal fixation at 1m are used to determine the critical flicker fusion threshold by the psychophysiological method of limits for three ascending and three descending scales
Symbol copying: Symbol copying for 2 minutes is a simple test of recognition of symbols and perceptual skills; parallel forms of the test card are provided for each consecutive testing instance
Simulated driving test: There is a computer-generated road on a colour TV screen and the subject has to keep an alignment mark (car) on the road by turning the steering wheel. The test lasts for 5 minutes. Its first half comprises simple tracking; the second requires a response to sound stimuli and 60 lights while tracking. The numbers of tracking errors as well as the error percentages (relative length of the track driven off the road) are recorded for both halves of the track separately. The tracking error severity index is computed to cover the whole track. The number of reaction errors and the cumulative reaction times are recorded for the second half of the track. Two different matched versions of the program are used, alternating in consecutive weeks
Restricted reminding test: Subjects attempt to recall 20 words from a single semantic category. On subsequent trials, subjects are read only the words not recalled during the preceding trial. Five forms of the test are administered in a counterbalanced order across sessions. A sixth form is used for practice on the evening prior to drug administration. Dependent measures include total misses (number of times a word is not remembered: 160 possible per session) and intrusions (number of unique, non-list items, i.e. errors of commission)
Paired associates test: Forms A and B of the Wechsler memory scale associative learning subtest are used. Subjects are asked to attempt to recall the second word of a pair. Three trials of the same ten word pairs are presented for the immediate recall phase, and errors are corrected by the investigator. The delayed recall phase consists of one trial in which errors are not corrected. Order of forms A and B is counterbalanced among subjects. Each trial is scored for number of correctly recalled associates
Digit span test: A series of numbers are read to the subjects, who are asked to repeat the entire series either forward or backward. The digits forward test consists of number lists that increase progressively from five to nine digits. On the digits backward test, the numbers increase progressively from four to eight digits. The score assigned is the longest series of correct numbers that a subject can recall. The digits forward and digits backward tests are scored separately
Digit symbol substitution test: A part of the Wechsler adult intelligence scale. This test involves symbol-encoding skills and is used to assess cognitive performance and motor speed; it is administered on a paper from which rows of numbers from 1 to 9 in random sequence are matched with symbols. Referring to the key that appears at the top of the form, the subject writes the correct symbol in the blank square below each number. A different symbol key is used for each test to control for memorising and learning. Subjects are given 90 seconds to complete as many items as possible. The score assigned is the number of correctly completed items
Immediate and delayed word recall test: This test is used to assess short-term and long-term memory. Each subject is given a list of 20 unrelated nouns to study for a period of 2 minutes; at the end of this period the list is returned to the administrator. Subjects are given 2 minutes to write down as many words as they can remember (immediate recall); 30 minutes later, they are given 2 minutes to rewrite as many words as they can remember from the original list (delayed recall). The number of correct words represents the score
Sternberg's memory test: Subjects are shown a short (one to six items) list of numbers and are asked to memorise them. After memorising them, a probe number is shown. The probe number is either one of the numbers in the list or a new number. The subject has then to respond as quickly as possible as to whether the probe number is in the list or not. The reaction time of the subject should reflect the time spent to determine whether the probe number is part of the list
Free recall test: In free recall, the participant is shown a list of items which must then be recalled in any order. Typically, the participant shows subjective organisation, in which similar items are grouped together in recall. In many cases, the serial position effect is produced in which the person recalls more items from the beginning (primacy) and end (recency) of the list
Divided attention: Measures visumotor coordination, motor response speed, and sustained attention. Subjects track a randomly moving circle on the screen by moving a target controlled by a joystick. Every time a solid circle appears on the screen either in the central or peripheral field of vision the subject has to press a button on the joystick as rapidly as possible. Scores obtained from this test include cumulative tracking score, and number of missed or ignored signals
Column addition: Subjects mentally add a column of five 2-digit numerals appearing on the screen and enter the sum using a numeric keypad; 30 addition problems (30 trials) are administered
Logical reasoning: Subjects determine whether the letter order described in a statement appearing at the top of a computer screen is the same as or different from the order of letters appearing below the statement. They press either the "S" key (statement order is the same as the letter order) or the "D" key (statement order is different from the letter order). Fifty trials are administered

effects on immediate memory and delayed memory. Nevertheless, some evidence suggests that zopiclone can induce significant memory impairment lasting up to the following morning (see comparative study with zaleplon described in in section 8.2[16]). Zopiclone seems to share many pharmacological properties with benzodiazepines, but with less effect on memory functions.

6.3 Cognitive and Psychomotor Function

6.3.1 Healthy Volunteers

A double-blind study in six middle-aged healthy volunteers investigated the psychomotor effects of zopiclone 5, 7.5 and 10mg. The compound was taken before retiring to bed and measurements were made the next morning (9 hours after ingestion). There was no cognitive dysfunction as ascertained by the digit symbol substitution test, symbol copying time or choice reaction time test.[17] Similar results were reported in another study.[13] In a double-blind, crossover study, healthy volunteers were given higher than recommended doses of zopiclone (10mg), taken before retiring to bed; this induced significant next-day variations in the mean scores of the complex reaction time test.[18]

Billiard et al.[14] found a significant alteration in the choice reaction time test performed 1.5 hours after evening intake of zopiclone 7.5mg. Complete recovery was evident the next morning, and no other psychomotor test was altered at any time. In a double-blind study, zopiclone 7.5mg was administered in the evening and psychomotor tests were performed. Two performance tests, the eye-hand coordination and the choice reaction time, were highly impaired 2 hours after administration. Moreover, the eye-hand coordination test was still altered 10 hours after ingestion. A further measurement, performed approximately 14 hours after drug intake, showed a complete recovery of psychomotor function.[19]

6.3.2 Patients with Insomnia

In a randomised, double-blind, multicentre, parallel-group study, patients were given zopiclone 7.5mg or nitrazepam 5mg on a nightly basis for 6 weeks. The symbol copying, digit symbol substitution, and choice reaction tests were performed at the end of weeks 1, 2, 4 and 6 of the study. No objective psychomotor impairment was evident with either zopiclone or nitrazepam at any timepoint.[20]

In many studies, zopiclone appeared to display a lower potential for cognitive impairment compared with benzodiazepines. In particular, there are indications that zopiclone 7.5mg, unlike temazepam 20mg, preserves cognitive and psychomotor performance when administered nightly for 2 weeks to patients with insomnia.[21] Zopiclone seems to be less active than flunitrazepam in producing driving impairment.[22] Another study involving patients with insomnia compared zopiclone 7.5mg and flurazepam 30mg. No negative effects were detected with zopiclone, whereas flurazepam produced residual sedative activity[13] (see also[21]). Moreover, there is evidence that zopiclone, nitrazepam[20] and triazolam[23] preserve psychomotor performance, with no apparent differences between the three compounds.

6.3.3 Overview

In healthy volunteers, therapeutic doses of zopiclone exert no or few negative influences on next-day cognitive functions. Higher than recommended doses of zopiclone can be detrimental to cognitive performance for up to 3 hours after administration. However, in the comparative studies described in section 8.3,[16,24] psychomotor dysfunction with zopiclone appeared to be more marked than with zaleplon and to last for a longer time.

6.4 Tolerance, Dependence, Rebound Insomnia and Withdrawal

The tendency to develop rebound insomnia and pharmacological tolerance to the hypnosedative effect of zopiclone 7.5mg was studied in a double-blind, randomised, parallel-group study. A total of 612 patients with insomnia took zopiclone on a nightly basis for 28 days. No tolerance or rebound phenomena occurred after abrupt discontinuation of the compound.[23] These findings are confirmed

by other studies in the literature.[25] Moreover, no rebound insomnia was evident up to 7 days after discontinuation of 2 weeks of treatment with zopiclone.[26] In a review of 25 studies performed on healthy individuals and patients with insomnia receiving zopiclone, withdrawal effects were observed in only 2.7% of cases.[27] Another study in 13 177 patients reported that the risk of developing dependence or withdrawal effects with therapeutic doses of zopiclone was nearly absent (0.05%).[28] Close study of patients receiving zopiclone 7.5mg for 2 weeks showed that sleep deterioration was maximal on the first night after withdrawal of medication but that sleep patterns had returned to placebo levels within 2–3 days.[26] In a double-blind study in healthy volunteers carried out after 1 week of treatment with either zopiclone 7.5mg or triazolam 0.5mg, there was no rebound insomnia after discontinuation of either drug.[29] In a single-blind study in 12 patients with insomnia, score values of different sleep parameters returned to baseline after 4 weeks of treatment with zopiclone 7.5mg without withdrawal effects. No evidence of tolerance was found throughout the entire treatment period.[21] Using the multiple sleep latency test, zopiclone 7.5mg caused a significant decrease of sleep latency.[30] Dependence on zopiclone has been described only in case reports.[31,32]

6.5 Adverse Effects

Zopiclone appears to be well tolerated. Many studies performed on a self-reporting basis show the absence of serious adverse events. The most commonly reported adverse event is bitter taste, found in 5 out of 49[20] and 9 out of 37[26] patients in various studies. Other disturbances are rare and mild in intensity.[33] In a large postmarketing surveillance study on 20 513 patients, no serious adverse events were reported.[34] The overall percentage of reported events was 9.2%. The most frequent were bitter taste (3.64%), dry mouth (1.6%), difficulty arising in the morning (1.3%) and daytime sleepiness (0.5%). All these effects were judged by patients as being mild in magnitude.

Other studies have also documented mild adverse reactions, such as taste perversion, headache and somnolence.[21] In a study involving 612 patients with insomnia treated with zopiclone 7.5mg and placebo,[23] bitter taste was the most frequently reported adverse reaction (1.7%). Only occasionally was the problem severe enough to interfere with therapy. No respiratory changes have been documented during zopiclone administration in patients with insomnia.[35]

7. Zolpidem

7.1 Chemical Structure and Pharmacology

Zolpidem is an imidazopyridine derivative hypnosedative drug belonging to a chemical class different in structure from benzodiazepines. Zolpidem selectively binds to ω_1 receptors on the $GABA_A$ benzodiazepine receptor complex. Zolpidem has a highly selective effect on sleep induction and, compared with benzodiazepines, has no or fewer anticonvulsive and myorelaxant actions. Zolpidem has high bioavailability (70%), a short elimination half-life (1–2.4 hours) and is rapidly absorbed (20–40 minutes) and distributed (without accumulation). It quickly crosses the blood-brain barrier.[36] Zolpidem is administered orally, and the plasma concentration reaches a peak after about 1.5 hours. In the bloodstream, zolpidem binds to both albumin and α_1 acid glycoprotein. It is metabolised in the liver by cytochrome P450 (CYP; the isoenzyme mainly involved is CYP3A, and CYP1A1 and CYP2D6 play a minor role) to three inactive metabolites and is finally excreted in the urine.[37]

The recommended dose is 10mg in adults, decreased to 5mg in elderly or debilitated patients and in those with liver failure.

7.2 Effects on Memory

7.2.1 Healthy Volunteers

There is some evidence in the literature that zolpidem can exert a benzodiazepine-like effect on memory function.[38] Several studies have ex-

plored the effects on memory throughout the night and after morning awakening.

No significant differences were reported in next-day memory function in healthy male adults after night-time administration of zolpidem 10mg, zopiclone 7.5mg or placebo. In the memory scanning task, zolpidem prolonged the nonspecific component of reaction time in Sternberg's memory test at 1.5 hours after administration, but the effect disappeared after 12.5 hours.[39] In another randomised, double-blind, crossover study, 24 healthy volunteers received zaleplon 10 or 20mg, zolpidem 10 or 20mg, triazolam 0.25mg or placebo and then performed a wide battery of tests including immediate and delayed word recall test, digit span test, paired associates learning test, divided attention test and digit symbol substitution test at 1.25 and 8.25 hours after drug ingestion. Zolpidem 10mg produced memory impairment at the 1.25-hour timepoint, and amnestic dysfunction persisted up to 8.25 hours in individuals who had taken zolpidem 20mg.[40] In a double-blind, randomised, crossover study carried out in 36 healthy volunteers, zolpidem 10mg showed significant negative effects on memory after administration up to 5 hours before normal waking.[41]

The memory effects of zolpidem therapy throughout the night were also assessed in a double-blind study involving 60 healthy volunteers. Twenty received zolpidem 20mg, 20 received triazolam 0.5mg and the remaining 20 received placebo. After 1.5 hours, flumazenil 1mg was injected intravenously in one-half of the participants in each drug group and the rest were given placebo. Memory tests (restricted reminding test, immediate or delayed recall, paired associates test) and cognitive tests were administered at 1.5, 3, 4.5 and 6 hours after treatment. Zolpidem induced memory impairment only at the time near to peak plasma concentration; the effect was rapidly reversed by flumazenil.[42] The same authors reported similar results in another trial, in which only the higher dose of zolpidem (20mg) impaired memory tests at peak blood drug concentration.[43] Similar findings have been reported elsewhere.[44]

When compared with bretazenil, a partial agonist of benzodiazepine receptors,[45] or with the benzodiazepine flunitrazepam,[46] zolpidem seems less active in producing memory impairment. Memory and attentional processes after zolpidem and triazolam intake were assessed by means of a wide battery of tests in a double-blind, placebo-controlled, crossover study. The two compounds produced similar memory impairment effects that typically peaked 1.5 hours after drug administration, with a progressive offset until 2.5–3 hours after drug ingestion. Nevertheless, zolpidem showed fewer negative memory effects than triazolam, with a selective impairment of explicit memory.[47-49] Other authors have found zolpidem equivalent to triazolam in effects on memory loss.[43,50,51]

7.2.2 Patients with Insomnia

No next-day memory impairment was found in several studies in patients with insomnia[52] and normal volunteers. In a double-blind study in 12 patients with insomnia treated with zolpidem 10mg, no significant next-day effects were found on memory performance tests (digit span test, visual recognition test, free recall test) immediately and 2 minutes after final awakening. In contrast, flunitrazepam 1mg significantly affected memory test scores.[46]

7.2.3 Overview

Memory tests in healthy volunteers and patients with insomnia show no significant score reduction at 6–8 hours after drug intake. Recommended doses of zolpidem induce memory impairment only near the time of peak plasma concentration. Memory impairment after therapeutic doses of zolpidem coincides temporally with the sedative effect (5–6 hours), but twice the recommended dose or more may have negative effects for up to 8 hours. As discussed in the comparative studies described in section 8.2,[37,41,53] memory impairment by zolpidem seems to be more marked than that by zaleplon.

7.3 Cognitive and Psychomotor Function

7.3.1 Healthy Volunteers

Zolpidem in healthy individuals does not induce any residual next-morning negative effect on cognitive functions. In 24 healthy male volunteers treated with zolpidem 10mg, no next-day alterations emerged from psychomotor assessments and EEG analysis. It was also observed in healthy individuals disturbed by noise that zolpidem 10mg lacks detrimental effects on performance.[54] In a double-blind, placebo-controlled, crossover study in healthy volunteers, next-day performance was evaluated by means of a five-choice serial reaction test, critical flicker fusion test and saccadic eye movement analysis. No differences were observed between zolpidem 5, 10 or 20mg and placebo.[45]

In a double-blind, randomised, crossover study in 36 healthy volunteers, zolpidem 10mg showed significant negative effects on cognitive functions (choice reaction time, critical flicker fusion test, digit symbol substitution test) after administration between 2 and 5 hours before normal waking.[41] In another double-blind trial, 70 healthy male volunteers were treated with zolpidem 5–15mg or triazolam 0.125–0.5mg. All participants were evaluated by means of response time and correct answer on the logical reasoning and column addition tasks 90 minutes and 6 hours after drug intake. The higher doses of zolpidem and triazolam induced score reduction 1.5 hours after administration, but no effect was detected 6 hours after drug intake.[43] Similar dose-related negative psychomotor effects a few hours after drug administration emerge from some studies in the literature.[44,47] Other studies indicate a lack of any negative effect on psychomotor function from 6 hours after therapeutic doses of zolpidem.[50]

7.3.2 Patients with Insomnia

Zolpidem does not affect cognitive function in patients with insomnia. In a double-blind, crossover study carried out in 16 women complaining of chronic sleep disturbance, next-day driving and memory tests were impaired by flunitrazepam, whereas zolpidem 10mg had no effects on test scores.[52] In a multicentre, double-blind, randomised, placebo-controlled, parallel-group study in patients with chronic insomnia, the residual effects of zolpidem 10–20mg or flurazepam 30mg on cognitive performance were compared with those of placebo, using a choice reaction time test, an auditory vigilance test, divided attention tasks and a simple reaction time test. No significant differences were observed between patients treated with zolpidem and those receiving placebo. In contrast, flurazepam significantly impaired psychomotor functioning.[46,55]

The residual daytime effects of zolpidem 10mg on driving performance and ocular saccades, compared with those of flunitrazepam 1mg and placebo, were investigated in a study with balanced, double-blind, crossover design. Zolpidem had no residual effect, but flunitrazepam impaired driving performance and increased saccadic latency the next morning.[22] Richens et al.[56] found that zolpidem significantly slows saccadic movements, but only at 1.5 hours after drug intake.

Thus, compared with the benzodiazepines, zolpidem preserves daytime cognitive function, resulting in being apparently safer than flunitrazepam[46,52] and flurazepam,[55] whereas it seems similar to triazolam in reducing mean scores in performance tests.[51] In a large postmarketing study involving 16 944 patients with insomnia, minimal next-day impairment of memory, psychomotor performance and cognitive ability was detected after daily use of zolpidem.[57] In a 3-year multicentre postmarketing surveillance study on zolpidem,[58] 1972 patients with insomnia were recruited for detection of adverse events. The average daily dose of zolpidem, taken at bedtime, was nearly 10mg. Adverse events were reported by 8.9% of patients. Among CNS-related adverse events, eight patients reported confusion (0.5%), seven disorientation (0.4%), 11 (0.6%) concentration impairment and 15 (0.8%) amnesia or memory impairment. In another study, no subjective cognitive deterioration was self-reported by patients in an 8-week treatment schedule with zolpidem.[59]

7.3.3 Overview

No significant next-day psychomotor and cognitive impairment occurs with the recommended doses of zolpidem (5 or 10mg). Only higher than recommended doses are able to induce significant psychomotor dysfunction. A negative effect on psychomotor tests has been reported in many studies near the time of estimated plasma peak concentration. Impairment disappears approximately 6 hours after drug administration. Nevertheless, comparative studies (section 8.3) suggest that psychomotor dysfunction with zolpidem appears to be more marked than with zaleplon and lasts for a longer time.[41,60]

7.4 Tolerance, Dependence, Rebound Insomnia and Withdrawal

Despite the widespread use of zolpidem in numerous countries, very few cases of abuse, dependence or tolerance have been reported in the literature.[61-65] Sanchez et al.[66] reported the case of a patient with insomnia who developed rebound insomnia, anxiety, agitation, tremors and seizures after having abruptly discontinued zolpidem 400mg. A 43-year-old woman had an epileptic attack after abrupt interruption of zolpidem 600mg.[67] Some cases may be attributed to other forms of abuse or drug dependence or to the psychiatric condition of the patient. However, zolpidem treatment may carry some degree of risk for developing abuse and discontinuation effects similar to those of other hypnosedative drugs, even in the apparent absence of predisposing factors in the individual.

Development of tolerance and rebound insomnia with zolpidem, zopiclone and benzodiazepine hypnosedatives (brotizolam, midazolam, triazolam) was evaluated in a meta-analysis based on 75 studies involving 1276 individuals (804 patients with insomnia and 472 healthy volunteers).[65] By using a mixed effects regression model, reliable estimation of the effects of the recommended doses of each drug on patients with insomnia was obtained. Tolerance associated with intermediate and long-term use clearly developed with triazolam and was only marginal with midazolam and zolpidem. Because of insufficient data, tolerance could not be estimated for brotizolam and zopiclone. Rebound insomnia on the first night after discontinuation was only mild with zolpidem but intense with triazolam. Data were unavailable for brotizolam and inadequate for midazolam and zopiclone.

In a double-blind, placebo-controlled trial involving 12 patients with chronic primary insomnia, zolpidem 10mg was administered for 27 days, preceded and followed by 2 and 3 nights of placebo, respectively.[68] The hypnosedative effect of zolpidem lasted throughout the whole treatment period with no rebound insomnia or withdrawal reactions after discontinuation. In another study conducted in 11 young patients with psychophysiological insomnia, zolpidem 10mg, administered nightly for 1 month, caused a significant improvement of sleep parameters that lasted the full duration of the treatment.[69] These results have been confirmed in other studies.[70,71]

In a double-blind trial in 21 patients with learned or idiopathic insomnia,[72] patients received placebo for 1 week, active treatment (zolpidem 10mg) or placebo for 2 weeks and placebo again for a further week. In the late withdrawal phase (day 28 of the study), there was a significant difference between groups, in favour of zolpidem, in sleep efficiency, total sleep time and percentage of time spent awake. Thus, the positive effects of the active treatment were still present during the week after abrupt discontinuation, without signs of rebound insomnia or withdrawal phenomena. Similar observations have been reported in a multicentre trial.[73]

A 5-week polysomnography (PSG) study evaluating zolpidem in patients with insomnia was performed to assess the sensitivity of microstructural sleep parameters to prolonged pharmacotherapy.[74] In this study, six adult patients with transient or short-term insomnia took zolpidem 10mg on a regular basis for 28 days. The active treatment period was preceded by a baseline placebo night and followed by a 4-night gradual tapering phase. PSG recordings were performed on baseline night,

on nights 1, 7 and 28 of the active treatment period and on the third night after the end of the tapering phase. At the microstructural level, highly significant variations emerged for cyclic alternating pattern (CAP) parameters. The ratio of CAP time to non-rapid eye movement sleep time (CAP rate) remained significantly lower than baseline even during the tapering phase (43%). These findings indicate that patients retain an improved quality of sleep after withdrawal of zolpidem.

The safety of zolpidem 10 or 15mg has been evaluated in patients with insomnia over a 12-week treatment period, preceded and followed by placebo.[70] By means of subjective measures, no tolerance emerged throughout the 12 weeks and no rebound insomnia occurred in the withdrawal phase in spite of the prolonged use of higher than recommended doses. In a placebo-controlled study, the positive effect of zolpidem on self-rated measures (sleep latency, total sleep time, number of awakenings, quality of sleep) lasted for the whole treatment period. A perception of disturbed sleep characterised the first night after discontinuation of the 15mg dose.[75] In elderly patients with insomnia, the significant improvement of sleep quality (subjectively assessed) was maintained during the week following withdrawal of zolpidem, both 5 and 10mg.[76]

In summary, therefore, although zolpidem should be used for a limited time, some trials have demonstrated that even when used for long-term treatment of insomnia it does not induce tolerance,[77,78] withdrawal symptoms or rebound insomnia either in objective[68-71,79] or subjective[59,70,75,76,80] assessments. Furthermore, some data indicate that after drug withdrawal, patients can retain an improved quality of sleep compared with the pretreatment period.[72,73,81] Nevertheless, cases of tolerance, rebound effects or withdrawal reactions have been reported in the literature,[61-67] and a large multicentre comparative study with zaleplon described in section 8.4[82] showed that after abrupt discontinuation of zolpidem 10mg, the incidence of withdrawal symptoms was significantly greater than with placebo, and significant signs of rebound insomnia were noticed.

7.5 Adverse Effects

Different incidences of adverse events with zolpidem have been reported, ranging between 1%[57] and approximately 30%.[70] Several observations indicate that CNS-associated adverse effects, such as headache[57,70,71] and daytime somnolence/drowsiness,[58,73,83,84] represent an infrequent but real possibility with zolpidem even when administered at recommended doses and for recommended periods. In contrast, non CNS-related adverse effects are rare.

In a multicentre, single-blind study, long-term treatment (3 months) with zolpidem was associated with headache (28.4%), followed by drowsiness (26.2%), fatigue (16.6%) and dizziness (14%). During the discontinuation phase, headache was the most frequent adverse event.[70]

Two large postmarketing surveillance studies showed different rates of adverse events with zolpidem: 182 of 16 944 patients (1.1%) experienced 268 events[57] and 175 of 1972 patients (9.9%) reported 343 events.[58] The different rates of adverse events could be related to the methodological procedures used in the two studies, including different recruitment criteria and different treatment periods. In particular, only the study with the higher amount of adverse events[58] allowed inclusion of patients who used alcohol on a regular daily basis and patients with hepatic insufficiency. In the first study, the most common adverse events were nausea, dizziness, malaise, nightmares, agitation and headache (each in 0.1–0.2% of patients); somnolence, confusion, abnormal gait, hallucination, anxiety and insomnia occurred less frequently. The only serious problem was paranoid symptoms in a 48-year-old woman. In the second survey, CNS-related adverse events were seen in 6.6% of patients, the most common events being residual daytime sedation and lack of efficacy in 3.7 and 1.6% of patients, respectively. Confusion, disorientation, obsessive ideas, delirium and psychosis had an incidence of 1%.

Among non-CNS-related effects, gastrointestinal symptoms (nausea, vomiting, abdominal pain/spasm, diarrhoea), headache and skin reactions were reported by 1.7, 1.1 and 0.5% of patients, respectively. Approximately 0.7[57] and 5.2%[58] of patients withdrew from treatment because of emerging adverse events. Similar adverse events have been reported in other surveillance studies.[73,85]

Coadministration of zolpidem 10mg and other compounds acting on the CNS appears to be relatively free from serious adverse effects.[86-88] In contrast, other data in the literature indicate that zolpidem can induce hallucinations when associated with other drugs.[74] Several cases of delirium and hallucinations related to zolpidem administration have been described.[61,89-91] In particular, it is likely that nightmares can occur independent of the drug concentration (i.e. they are not necessarily precipitated by toxic concentrations) in an idiosyncratic manner,[91] whereas hallucinations and delirium could be manifestations of toxicity and be dose-dependent. Zolpidem toxicity appears to be mediated by several variables including drug dose, the patient's sex and age, protein binding levels (interaction with other compounds) and degree of inhibition of the CYP3A4 isoenzyme.[89,91] Another possibility is that psychiatric or cognitively impaired patients may be at high risk of experiencing CNS-related adverse effects.[90]

Zolpidem 10mg has no effect on respiratory disturbance index, arterial oxygen saturation, systolic blood pressure, heart rate or other vital parameters in healthy individuals and in patients with pulmonary[92] and sleep disorders, even at higher than recommended doses.[93] Other data indicate that zolpidem 20mg induces a significant reduction of respiratory flow in healthy individuals[94] and decreased oxygen saturation in patients with sleep apnoea syndrome.[95]

Rare observations suggest that zolpidem could be responsible for hepatic toxicity[96] and for worsening of hepatic encephalopathy by contributing to the accumulation of benzodiazepine-like substances in the brain.[97]

7.6 Intermittent Use

The persistence of beneficial effects after drug discontinuation, as described for zolpidem in section 7.4, can offer new perspectives in the use of sedative drugs. It is known that many patients with insomnia take sedative drugs on a non-nightly basis, either spontaneously or according to their physician's prescription. In 1996, the WHO identified non-nightly use of hypnosedatives as a possible tool to overcome development of dependence in patients who are in need of long-term pharmacological therapy.[98] Although this practice is widely endorsed and applied, the first data providing scientific validation of the efficacy and safety of this approach in controlled trials have only recently been published. A multicentre, randomised, double-blind, placebo-controlled, parallel-group investigation was performed in 159 drug-free patients with insomnia enrolled by primary-care physicians. It compared continuous nightly treatment with zolpidem with intermittent treatment consisting of 5 consecutive nights of zolpidem followed by 2 nights of placebo per week, for a total of 2 weeks. Comparing a placebo baseline of 3–5 nights with the active treatment period, there was a clear and comparable improvement in total sleep time by day 14 in both treatment groups. Sleep onset latency and quality of life were also similarly improved by continuous and intermittent zolpidem treatment. Safety data showed no adverse effect on patients of abrupt replacement of zolpidem by placebo on 2 nights per week.[80]

In a larger study (n = 789) with the same design, at the end of the 2-week treatment period, 65.2% of the patients receiving zolpidem continuously and 58.6% of those receiving it discontinuously were judged to be 'very much' or 'much' improved.[99] In a 4-week study of 245 patients with chronic insomnia comparing non-nightly zolpidem treatment with non-nightly placebo, the patients were allowed a certain degree of flexibility with respect to weekly tablet intake. The mean tablet intake during the final week of treatment did not differ significantly between the placebo group and the zolpidem group. More patients in the zolpidem

group showed an improvement in quality of life, with a lower discontinuation rate in this group.[100] In a multicentre, double-blind, randomised, placebo-controlled trial in 163 patients with primary insomnia, non-nightly zolpidem treatment was compared with non-nightly placebo treatment for a total of 8 weeks. The results showed a stable pattern of tablet intake, ranging from 7.6 to 7.9 nights per 2-week period, with no difference between the treatment groups at any time. The mean patient global ratings for sleep parameters were all significantly better with zolpidem than with placebo.[59] Treatment of chronic primary insomnia with non-nightly administration of zolpidem appears to be effective even over a 3-month period, without leading to tolerance or rebound insomnia.[101]

A PSG study was conducted in 12 patients with primary insomnia who alternated zolpidem and placebo over a 10-day period. After an adaptation night, all patients slept in the sleep laboratory on the first two and the last four nights. Patients were informed that the blister pack contained 10 tablets – both active and inactive treatment – in a random order. PSG recordings were scored by a 'blind' technician. Sleep latency and total sleep time improved on each night of active treatment, while patients experienced a return to baseline (both objectively and subjectively) on the nights they received placebo. In other words, there was no evidence of rebound insomnia. In addition, the alternating drug-placebo procedure did not appear to affect performance on a morning four-choice reaction time test.[102]

8. Zaleplon

8.1 Chemical Structure and Pharmacology

Zaleplon (CL 284,846) is a pyrazolopyrimidine non-benzodiazepine hypnotic agent. Zaleplon, like zolpidem, binds selectively to the ω_1 receptor located on the GABA receptor complex.[103] It exerts sedative, anxiolytic, muscle relaxant and anticonvulsive effects. In animals, zaleplon induces muscle relaxation, anticonvulsant effects, decreased locomotor activity and motor deficits without next-day hangover effects, amnesia or tolerance.[104]

Zaleplon is almost completely absorbed, and peak plasma concentration is reached after 1 hour. High-fat meals can interfere with absorption: time to peak plasma concentration is delayed and maximum plasma concentration is reduced. Zaleplon undergoes significant first-pass metabolism, which accounts for its relatively low bioavailability (30%). Zaleplon is metabolised by the liver into inactive compounds (the major one being 5-oxo-zaleplon), which are excreted in the urine. The elimination half-life of zaleplon is approximately 1 hour.[104]

The recommended dose of zaleplon is 10mg in adults and 5mg in elderly patients.

8.2 Effects on Memory

Zaleplon does not produce next-day effects on memory when administered at bedtime to healthy individuals[16,37,105] and those with insomnia.[106] Middle-of-the-night administration of recommended doses (5 and 10mg) causes little or no next-morning memory impairment.[16,41,105] Moreover, zaleplon induces little impairment even at the time when peak plasma concentrations are reached.[37,40,53] The effect on short-term memory is dose-related, with more marked impairment at doses of 20mg or higher.[37,53,107] Memory impairment by zolpidem[37,41,53] and zopiclone[16] seems to be more marked than that by zaleplon.

The pharmacodynamic profile of zaleplon has been assessed in healthy volunteers in a double-blind, placebo-controlled design.[105] In this study, male volunteers were randomised to receive either placebo or doses of 1, 5, 15, 30 or 60mg of the active compound. Memory tests were administered 2.5, 9 and 25 hours after drug ingestion. No effects on memory were noted at any dose.

In a multicentre study, 132 patients with primary insomnia were given zaleplon 5 or 10mg at bedtime.[106] The next morning (9 hours later), memory and psychomotor assessment was performed. There were no significant differences be-

tween zaleplon and placebo at any timepoint in any psychomotor or memory measure.

The effects of zaleplon (10 and 20mg) and zopiclone (7.5mg) on memory, learning, reasoning and body sway were studied in a double-blind, placebo- and active-controlled crossover design.[16] Twenty-eight healthy volunteers were given one of the two active compounds in the evening before initiating sleep or in the middle of the night (approximately 5 hours after evening doses; 4 hours before awakening). If the active compound was administered in the evening, it was followed by placebo at night and vice versa. The next morning a battery of memory tests was carried out. Evening doses of zaleplon had no effects on any assessment, whereas middle-of-the-night administration of zaleplon 10 and 20mg produced a small but significant impairment only in the delayed recall test. In contrast, zopiclone exerted significant next-day effects on memory with evening ingestion, and these effects were most pronounced with middle-of-the-night medication.

The residual effects of zaleplon and zolpidem after administration during the night were assessed in a double-blind, placebo-controlled, crossover study.[53] Healthy volunteers went to bed at midnight and were subsequently wakened and given either placebo, zaleplon 10 or 20mg, or zolpidem 10mg at 5, 3 or 1 hours before morning awakening, which was scheduled 8 hours after bedtime. Memory (Sternberg memory scanning, word list) and psychomotor tests were performed on morning awakening. Zaleplon 10mg was free from residual effects regardless of the time of administration, while zaleplon 20mg produced a marked effect in the immediate and delayed recall of words when administered 1 hour before morning awakening. In contrast, zolpidem 10mg induced a significant negative effect on some tests even when administered 5 hours before the assessment. Similar observations have been reported by other authors.[40,41] According to the magnitude of memory impairment potential shown by the two compounds, the residual effects of zolpidem 10mg seem more marked than those of zaleplon 20mg.[53] Such differences could be explained by the ultrashort pharmacokinetic profile of zaleplon.

The effects on memory of zaleplon 10 and 20mg and zolpidem 10 and 20mg were assessed in another double-blind, placebo-controlled, crossover study.[37] Memory tests (word list free recall) were administered to ten healthy male volunteers 1.5 and 24 hours after drug ingestion. Zaleplon 20mg produced an initial learning impairment of the word list at 1.5 hours after administration, whereas zaleplon 10mg had no residual effects. Compared with placebo, zolpidem 10 and 20mg significantly impaired test scores 1.5 and 24 hours after drug ingestion. Benzodiazepine agonist activity was dose- and concentration-dependent but, when administered at the same doses, the effects of zolpidem exceeded those of zaleplon.

8.3 Cognitive and Psychomotor Function

Zaleplon preserves cognitive and psychomotor function, inducing minimal next-day effects.[16,24,106-108] Moreover, psychomotor functioning 1–3 hours after administration is impaired with higher than recommended doses, but recovery is rapid.[40,60,105,107] Therapeutic doses have no negative effects even at the time when peak plasma concentrations are reached, approximately 1 hour after administration.[40] Psychomotor dysfunction with zopiclone[24] and zolpidem[41] appears to be more marked than with zaleplon and lasts for a longer time.[16,60]

8.3.1 Healthy Volunteers

The effects of zaleplon 20mg, lorazepam 2mg and placebo were examined in 12 healthy volunteers in a double-blind, three-way crossover study.[107] Psychomotor tests (tapping rate, focused attention, rapid information processing, digit symbol substitution, symbol copying, critical flicker fusion) were administered before and again 1, 3 and 5 hours after drug intake. Both zaleplon and lorazepam impaired performance at the 1-hour timepoint, although the effect of zaleplon on test scores was less intense than that of lorazepam. Recovery of psychomotor functioning following zaleplon was complete after 3 hours, whereas im-

pairment following lorazepam was still marked 5 hours after drug ingestion.

8.3.2 Patients with Insomnia

Comparable results were seen in a double-blind, crossover study assessing residual sedation after zaleplon 10mg, flurazepam 30mg and placebo, taken 3.5 hours after bedtime in 22 patients with sleep maintenance insomnia.[108] Unlike flurazepam, no residual psychomotor disturbance was noted with zaleplon 10mg at 5 and 6.5 hours after taking the drug.

Residual sedation after zaleplon 5 and 10mg and zopiclone 7.5mg was assessed in a double-blind, placebo-controlled, crossover study carried out on a phase-advance model of transient insomnia.[24] Twenty-eight healthy individuals received active drug or placebo at bedtime 4 hours earlier than usual, thereby simulating time-zone or shift-work conditions. Psychometric examination was performed 8.25, 10.25 and 12.25 hours after drug intake. Zaleplon had no residual effects, whereas zopiclone impaired some test scores even at the 12.25-hour timepoint.

Danjou et al.[41] found that zaleplon 10mg, given 2 hours before morning awakening, produced no significant residual effects on psychomotor performance, as indicated by both subjective and objective assessments (digit symbol substitution, critical flicker fusion, choice reaction time). Significant residual effects were observed with zolpidem 10mg after administration up to 5 hours before awakening.

In a double-blind, crossover study, zaleplon 10mg produced no significant changes on a wide battery of cognitive tests performed 1.25 hours after drug administration.[40] Conversely, zaleplon 20mg negatively affected cognitive skills at the same timepoint, but the effect was not present after 8.25 hours. In another study, zaleplon 30 and 60mg impaired performance 2.5 hours after administration, but only the higher dose altered test scores at both 9 and 25 hours.[105]

In a double-blind, placebo-controlled design, the effects of zaleplon 10 and 20mg and zopiclone 7.5mg on driving performance were assessed.[16] Participants received drug or placebo either at bedtime or 5 hours later after an induced awakening. No individual received more than one dose of active compound on any single night. Using a standardised driving test performed between 5 and 6 hours after the second dose, the participants were asked to maintain a constant speed (95 km/h) and a steady lateral position on the road for 100km. No effects on driving were documented with evening or middle-of-the-night administration of zaleplon 10 and 20mg. In contrast, objective driving performance was significantly affected after both evening and night administration of zopiclone 7.5mg. Similar results have been reported in another double-blind study[60] in which the standard car driving testing method was used to assess the residual effects of zaleplon 10 and 20mg, zolpidem 10 and 20mg and placebo 4 hours after middle-of-the-night drug ingestion. Both doses of zolpidem significantly impaired driving performance. In contrast, no effects were seen after zaleplon 10 and 20mg.

8.4 Tolerance, Rebound Insomnia, Withdrawal Reactions and Abuse Potential

General guidelines for hypnosedative drugs state that drug administration should not exceed 4 weeks. There are some reports that the sedative efficacy of zaleplon is maintained for up to 4–5 weeks[82,106,109] and perhaps for longer periods.[110] No significant evidence of rebound insomnia and serious withdrawal reactions has been documented,[111] and definite data about abuse potential of zaleplon are not currently available.

A large multicentre study evaluated the efficacy and safety of zaleplon and zolpidem in 574 adult patients with a diagnosis of insomnia.[82] The study protocol was composed of four phases: phase 1, an initial washout period (1–3 weeks); phase 2, a single-blind placebo run-in (7 nights); phase 3, a double-blind treatment period (28 nights); phase 4, a single-blind placebo run-out period (3 nights). During the treatment period, patients received either zaleplon 5, 10 or 20mg, zolpidem 10mg or placebo just before bedtime. Subjective sleep data

evaluating sleep latency, sleep duration, number of awakenings and sleep quality were obtained from questionnaires that patients completed each morning. The possible occurrence of rebound insomnia was ascertained from sleep data of the placebo run-out phase. Withdrawal effects were evaluated using the Benzodiazepine Withdrawal Symptom Questionnaire. The favourable effect of zaleplon 10 and 20mg persisted throughout the duration of the study, although efficacy with zaleplon 5mg was lost by week 4. Moreover, zaleplon 20mg increased sleep duration in all but week 3 of the study. There was no evidence of rebound insomnia or withdrawal symptoms after discontinuation. In contrast, after abrupt discontinuation of zolpidem 10mg, the incidence of withdrawal symptoms was significantly greater than with placebo, and significant signs of rebound insomnia were noticed. Other studies confirm that rebound insomnia is not likely to occur after abrupt discontinuation of recommended doses of zaleplon given nightly for 4–5 weeks.[109,112]

It has been suggested that the hypnosedative effectiveness of zaleplon is maintained after 12 months of a regular nightly regimen, without rebound phenomena at discontinuation.[110] Despite these positive indications, further evidence is needed to determine the real risk for developing tolerance over longer treatment periods.

The abuse potential of zaleplon 25, 50 and 75mg and triazolam 0.25, 0.5 and 0.75mg was examined in 14 healthy volunteers with a history of drug abuse.[113] Subject-rated measures of 'drug strength' and 'drug liking' were similar for both zaleplon and triazolam. Most participants described the effects of the two active compounds as being similar to those experienced after a benzodiazepine.

8.5 Adverse Effects

Zaleplon has a favourable safety profile and is well tolerated. According to the manufacturer, the frequency of adverse events is not significantly higher than with placebo.[114] No relevant changes in laboratory values or vital signs have been documented, except for a limited number of patients showing relevant ECG changes during a multicentre clinical trial, although no dose-related trends were observed.[82]

Headache is the most commonly reported adverse event with usual recommended doses (5 and 10mg) of zaleplon (15% and 18%, respectively) and appears to be dose-dependent.[82,106] CNS-related adverse effects such as somnolence, paraesthesia, incoordination, dizziness, hallucinations and ataxia have been reported in a low proportion of patients. There are indications that perceptual disturbances are a rare but real possibility with zaleplon;[107] they have been attributed to the rapid increase in plasma concentration, which, in turn, could induce a hypnotic or dream-like state a few minutes after ingestion.[115] Other 'peripheral' adverse effects (pain, nausea, dyspepsia, rhinitis, pharyngitis, asthenia, unpleasant taste) are infrequent.

9. Discussion

The ideal hypnosedative should rapidly induce sleep, preserve sleep continuity throughout the night and preserve sleep architecture; it should also be free from adverse reactions and next-day effects related to its sedative properties.[116] The newer non-benzodiazepine agents zopiclone, zolpidem and zaleplon have a hypnosedative action comparable with that of benzodiazepines, but owing to their increased receptor-binding specificity and favourable pharmacokinetics (table III) and broader ranges of safety, they provide potentially better alternatives to the older agents (table IV).

The three 'Z' non-benzodiazepine agents all share a short plasma half-life and limited duration of action. In addition, zopiclone, zolpidem and zaleplon are selective compounds that link preferentially to ω_1 receptors (sedative effect), whereas benzodiazepines also interact with ω_2 receptors (adverse effects on cognitive performance and memory). Compared with the drugs previously used in clinical practice for the treatment of insomnia (i.e. benzodiazepines), zolpidem, zopiclone and zaleplon are all characterised by a 'soft' pro-

Table III. General properties of zopiclone, zolpidem and zaleplon; triazolam is included as a benzodiazepine comparator

Property	Zopiclone	Zolpidem	Zaleplon	Triazolam
Structure	Cyclopyrrolone derivative	Imidazopyridine derivative	Pyrazolopyrimidine derivative	Triazol benzodiazepine
Elimination half-life (h)	4–5	1.5–2.4	1–1.5	1.5–5.5
Metabolism	Liver, with weakly active metabolites	Liver, with inactive metabolites	Liver, with inactive metabolites	Liver, with one active metabolite
Receptor selectivity	$\omega_1 > \omega_2$	$\omega_1 >> \omega_2$	$\omega_1 >>> \omega_2$	$\omega_1 = \omega_2$

file. For the three 'Z' agents, headache is the most commonly reported adverse effect, whereas bitter taste is limited to zopiclone. Overall, the potential for withdrawal syndrome is low and tolerance is unlikely to develop. After sudden discontinuation, rebound insomnia is rarely observed. The main differences are related to specific pharmacokinetic properties – the longer the half-life the higher the risk of next-day effects. Because of its ultrashort half-life (approximately 1 hour), zaleplon appears to be the best tolerated of the three compounds in terms of next-day effects and adverse reactions.

Conversely, however, because of this short half-life zaleplon is also the 'Z' agent with the most limited therapeutic application. In particular, zaleplon has dose-related effects in reducing sleep latency and therefore appears appropriate only for patients with insomnia resulting from difficulty in falling asleep.[117] Zolpidem and zopiclone, with relatively longer half-lives (approximately 2.4 and 5 hours, respectively), counteract difficulties in both initiating and maintaining sleep as they curtail not only sleep latency but also the number and duration of nocturnal awakenings.[116] Both zolpidem and zopiclone increase sleep stability, but zolpidem also reduces the number of nocturnal arousals.[118] The beneficial effects of these two agents on sleep (mainly on sleep efficiency and total sleep time) tend to persist even after drug discontinuation.[72,73]

Unlike benzodiazepines, the three 'Z' hypnosedatives provide a natural architecture of sleep.[116] This, together with the low risk of residual effects, may explain their limited negative influence on daytime performance. Psychomotor tasks and memory capacity appear more preserved by non-benzodiazepine agents than by benzodiazepines. When present, cognitive deficits with the 'Z' agents almost exclusively coincide with peak plasma concentration. Thus, these problems are seen in the first hours after drug administration, whereas psychomotor and memory tests carried out 7–8 hours later (in the morning) generally lack relevant alterations. Impairment of psychomotor tasks during the night or shortly after drug intake has limited practical implications; it is more important for a hypnotic agent to guarantee a morning wake-up free of residual consequences. Nevertheless, in some circumstances early drug effects could be a potential danger. Forced awakening of on-call staff could actually coincide with the peak

Table IV. Memory, psychomotor effects, tolerance, withdrawal reactions and adverse effects of zopiclone, zolpidem and zaleplon; triazolam is included as a benzodiazepine comparator

Property	Zopiclone	Zolpidem	Zaleplon	Triazolam
Memory effects	+ +	+ +	+	+ + +
Cognitive effects	+ +	+ +	+	+ +
Tolerance	–	–	–	+ +
Withdrawal effects	+ +	–	–	+ + +
Most frequent adverse effect	Bitter taste	Headache	Headache	Drowsiness

– = absence of effect; + = very mild effect; ++ = mild effect; +++ = moderate effect.

of the hypnosedative action and therefore jeopardise the individual's vigilance and performance.

Taking into account the neurophysiological background on which the drug operates can also help to shed light on the outcome of diurnal tests. The data presented in this review derive from both healthy individuals and patients with insomnia, and functional impairment can differ strongly between the two groups. In normal individuals, the drug is administered to a person with a healthy nervous system used to experiencing nightly a satisfactory quality of sleep. In patients with insomnia, the drug acts on a person who, thanks to the drug, has finally slept throughout the entire night after a more or less prolonged period of poor or insufficient sleep. Moreover, insomnia is often associated with other sleep disorders[119] that may interfere with or even be worsened by the hypnosedative agent. Thus, evaluation of a hypnosedative compound must be integrated with a full sleep history and by a standardised classification of the sleep disorder according to the DSM-IV[9] or the ICSD.[7]

In preparing this review, we found many studies that, although extremely accurate in the exploration of neuropsychological aspects, neglected to provide detailed information on the type of patients with insomnia included in the trial. Nevertheless, the hypnosedative action was in most cases satisfactory and the daytime consequences of drug treatment were limited. Despite the fact that most cases of insomnia seem to have a psychiatric origin, the three 'Z' drugs, although lacking any clear anxiolytic or antidepressant properties, proved to be effective and well tolerated as hypnosedative compounds. This indicates that these drugs, as with all sedative compounds, act on a common neural network that controls and regulates the sleep process, whatever the cause of disturbance (pain, noise, anxiety or depression).[120,121]

Because non-transient factors (particularly mental disorders and organic diseases) can initiate and maintain insomnia, the long-term use of hypnosedative drugs may become a justified practice. However, current guidelines for the use of these agents are very restrictive and indicate that such drugs should not be taken for longer than 2–4 consecutive weeks.[122] These limits derive from concerns about tolerance during long-term use and about abuse. These concerns are perhaps excessively restrictive for 'soft' hypnosedatives. Recent studies with zolpidem have ascertained that administration of the drug on an as-needed basis is as effective and safe as continuous intake.[100] As-needed or intermittent treatment (see section 7.6) represents a highly attractive option, taking into consideration lower costs and the possibility of extending the conventional treatment period of 4 weeks with a lower risk of rebound insomnia, tolerance and withdrawal reactions. The latter effects, however, occur rarely even when the 'Z' drugs are used nightly. Available subjective findings on intermittent or as-needed treatment with zolpidem in patients with insomnia indicate an overall improvement in sleep, but not necessarily good sleep every night. This outcome, initially assessed in a 2-week study,[102] has been confirmed in a recent investigation covering a 3-month period.[101]

10. Conclusion

New tools and new procedures are available for the investigation and treatment of insomnia, a topic that is receiving growing attention. In recent years, a number of surveys have shown the importance of insomnia, not only in terms of reduced productivity and impaired quality of life, but also as a cause of increased absenteeism, accidents, hospitalisation, alcohol consumption, depression, morbidity and mortality.[123-125]

Selecting the keyword 'insomnia' restricted to the human domain over the last 5 years, more than 1500 references can be found on Medline. The present review included published material of different methodological weight. On the one hand, this offered an extensive outline of available data, but on the other hand, accurate comparison of the literature was blunted by the procedural weaknesses that characterised several articles. Moreover, in some cases the doses of investigated drugs (either benzodiazepines or non-benzo-

diazepines) were not equipotent. From the literature, zaleplon seems to be the 'Z' drug with the lowest risk, but it is also the compound with fewest published articles and shortest follow-up. In contrast, the evidence from the literature and postmarketing surveillance for the safety of zolpidem is the most extensive available among these three agents.

Isolated cases of tolerance, rebound insomnia and withdrawal reactions have been reported with all the 'Z' drugs. In spite of the infrequency of these effects, it is always recommended to use a tapering procedure when any kind of hypnosedative medication is discontinued. There is no clear evidence in the literature that tapering is safer than abrupt discontinuation. However, clinical practice suggests that a gradual withdrawal is preferable.

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