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The safety and tolerability of zolpidem — an update

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Zolpidem belongs to a new class of hypnotic agents, chemically distinct from the pre-existing ones, and has a unique neuropharmacological profile. It induces sedative/hypnotic effects in rodents at doses much lower than those for anticonvulsant and myorelaxant activities. Clinically, zolpidem is indicated for the short term treatment of insomnia. It has a short half-life (2.4 h), with no active metabolite, and does not accumulate during repeated administration. The pharmacokinetic profile associated with the absence of active metabolites is consistent with the short duration of action and absence of residual effects that have been observed. Polysomnographic experience indicates that zolpidem induces a sleep pattern which is similar to that of physiological sleep, and which produces either no or only minimal effects on sleep architecture after abrupt discontinuation. Aspects of the general safety of zolpidem have been studied in data obtained from healthy volunteers and patients, both adult and elderly, during its clinical development and in post-marketing experience. Zolpidem appears to be well-tolerated in adults and in the elderly, when administered in accordance with prescribing instructions. The available data indicate that, in these circumstances, the risk of abuse or dependence is minimal.

Key words: benzodiazepines; hypnotic; insomnia; imidazopyridines; zolpidem

Introduction

The most important pharmacological agents available for the treatment of insomnia can be approximately divided chronologically into three classes: barbiturates were the first generation, but were rapidly replaced by the benzodiazepines (BZD), which represented the most widely prescribed group of drugs for three decades. However, self-medication with various sedatives, including antihistamine drugs, remains widely used in some countries (e.g. USA and Germany). The main unwanted effects of BZD are represented by alteration of sleep architecture, carry-over effects, synergism with alcohol, alteration of cognitive functions and performance, and a non-negligible risk of dependence and abuse (Lader, 1994). A third generation of non-benzodiazepine hypnotics (non-BZD) has emerged during the last decade, including cyclopyrrolone and imidazopyridine compounds, which can be considered a valuable alternative to BZDs for the short-term treatment of insomnia.

Zolpidem is a new hypnotic drug with a novel, imidazopyridine chemical structure (Fig. 1), chemically distinct from the BZDs and cyclopyrrolones, and has a unique neuropharmacological profile (Langer and Arbilla, 1988; Zivkovic and Sanger, 1994; Benavides *et al*., 1995; Frey *et al*., 1996). Similar to BZD and cyclopyrrolones, zolpidem potentiates the activity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) by binding to BZD receptors (also known as BZ or ω receptors) which are modulatory sites of the $GABA_A$ receptor complex. However, in contrast to these other drugs, zolpidem shows selectivity for BZ_1 (ω_1) receptor subtype which corresponds to $GABA_A$ receptors containing the α_1 subunit (Pritchett *et al*., 1989). Thus, zolpidem has high affinity for $GABA_A$ receptors containing α_1 subunits, lower affinity for $GABA_A$ receptors containing α_2 or α_3 subunits and no significant affinity for $GABA_A$ receptors containing the α_5 subunit (Faure-Halley *et al*., 1993). This receptor selectivity coupled with high intrinsic activity (Itier *et al*., 1996) probably explains why the sedative activity of zolpidem in rodents occurs at doses which produce very low levels of receptor occupation in the brain (Sanger and Zivkovic, 1992). A recent positron emission tomography study using ^{11}C-flumazenil in human volunteers produced comparable results (Abadie *et al*., 1994; Benavides *et al*., 1995). It has been suggested that its receptor selectivity and high intrinsic activity may be responsible for the low propensity of zolpidem to produce pharmacological tolerance or physiological dependence in animal models (Perrault *et al*., 1992; Sanger *et al*., 1994).

Clinically, zolpidem is indicated for the short-term treatment of insomnia. It has a short half-life (2.4 h), with no active metabolite, and does not accumulate during repeated administration. The drug is extensively metabolized and rapidly removed both from the central compartment and from the site of action. It is oxidized and hydroxylated by the liver to inactive metabolites that are eliminated primarily by renal excretion. Limited data indicate that zolpidem and, to a lesser extent, its metabolites do cross the placenta and are excreted in the milk (Pons *et al*., 1989). As a matter of caution therefore zolpidem should not be used during pregnancy or by nursing

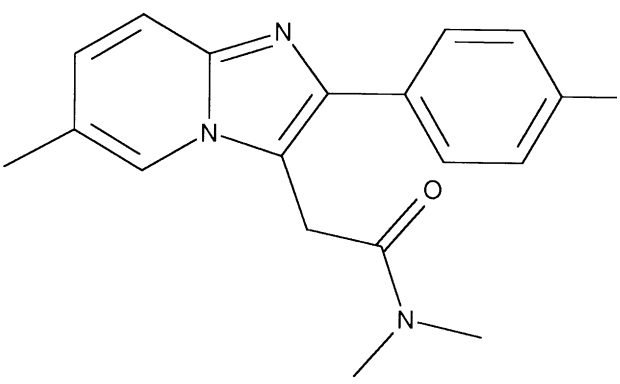

Figure 1 Zolpidem chemical structure

mothers. In addition, it has a moderate first pass metabolism, which may contribute to its approximately 70% oral bioavailability (Fraisse *et al*., 1996) (Table 1).

Oxidative metabolism of zolpidem by liver cytochrome P450s (CYP) has recently been investigated (Pichard *et al*., 1995): the formation of alcohol derivatives of zolpidem is rate-limiting and principally mediated by CYP3A4. Whilst CYP1A2 and CYP2D6 participate in alcohol formation, because of their low relative level of expression in the human liver, their contribution is likely to be minor. However, in addition to the clear involvement of CYP3A4, it appears that CYP1A2 could also contribute to the biotransformation of zolpidem in humans. As a consequence, it can be hypothesized that the risk for zolpidem to cause adverse drug reactions (ADRs) should be less than with compounds where a single isoform is responsible for the principal metabolic pathway or compounds with a high first-pass effect and low-to-moderate bioavailability such as some BZD hypnotics (midazolam and triazolam). Thus, the pharmacokinetic profile associated with the absence of active metabolites is consistent with the short duration of action and absence of residual effects that have been observed in several studies (Unden and Schechter, 1996).

Zolpidem's hypnotic activity is such that it maintains or preserves the integrity of sleep architecture both in adults and the elderly, while it does not significantly alter the modulation of hormonal secretion during nocturnal sleep (Copinschi *et al*., 1995). Extensive polysomnographic experience indicates that zolpidem induces a sleep pattern which is similar to

Table 1 Pharmacokinetics profile of zolpidem

	Zolpidem
Physicochemical characteristics	
Molecular formula	$C_{18}H_{21}N_3O$, $1/2C_4H_6O_6$
Molecular weight (salt)	392.4
Lipophilic activity	Moderate
Absorption and bioavailability in man	
Absorption	Very rapid
T_{max} (min)	30–60
F%	70%
Food	T_{max} prolonged
pK_A	6.16
Log P^a*	2.42
Metabolism	
Three routes of biotransformation	Main route: methyl oxidation on the phenyl moiety
(seven major pharmacologically inactive metabolite)	Different pathways of biotransformation suggest minimal risk of interaction
principally mediated by CYP3A4. CYP1A2 and CYP2D6 also participate	
Distribution	Homogeneously in the various tissues
Plasma protein	92.5%
	66.0% to albumin, 56.6% to α_1-AGP
Free fraction in normal subjects	8%
V_d(L/K^{-1}):man (volume of distribution)	0.54
	Quite low; no redistribution effect
Brain Uptake Index (BUI): rat	0.67
Excretion	Cross the placenta
Unchanged compounds	Trace
Urinary elimination	48–67%
Faeces elimination	29–42%
Pharmacokinetic parameters	
Single administration in healthy volunteers	
Plasma elimination half-life	0.8–3.2 h (mean value 1.7 ± 0.1 h)
Systemic clearance	0.15–0.68 (mean v 0.26 ± 0.3 l/h/kg)
Chronic administration in healthy volunteers	Lack of accumulation
Effect of age (20 mg)	Slightly prolonged in elderly
	Shorter in children (4–13 years)
Hepatic insufficiency	Terminal half-life: 9.9 ± 2.9 h
Renal impairment	Terminal half-life: 3.0 ± 0.7 h

*Octanol/water partition coefficient at pH = 7.4 (determined by high-performance liquid chromatography). Adapted with permission from Fraisse (1996).

Table 2 Profile of zolpidem

Mechanism of action	Specific agonist at ω_1 sites of $GABA_A$ receptor complex (in-vivo and in-vitro studies)
Induction of sleep	Rapid, usually within 30 min
Mean half-life	2.4 h (2.9 in elderly)
Sleep physiology	Stages 3 and 4 preserved
Next-day residual effects	Not significant
Memory impairment	Not significant
Rebound in insomnia	No objective evidence in studies of up to 35 days
Tolerance	Not seen in studies of up to 35 days
Withdrawal syndrome	Not noted at dose and treatment duration recommended
Abuse potential	Limited
Drug interactions	Additive effect possible with central nervous system depressants
Interaction with alcohol	Additive effects
Most commonly observed adverse events seen at statistically significant differences from placebo[a]	Short-term drowsiness 2% dizziness 1% diarrhoea 1% Long-term dizziness 5% drugged feelings 3%

[a]US labelling.

physiological sleep, and which produces either no or only minimal effects on sleep architecture after abrupt discontinuation (Parrino and Terzano, 1996).

Aspects of the general safety of zolpidem have been studied in data obtained from healthy volunteers and patients, both adult and elderly, during its clinical development and in post-marketing experience (Allain and Monti, 1997). The available data indicate that the risk of abuse or dependence is minimal, when zolpidem is prescribed according to duration and dose recommendations (Table 2).

Adverse events and surveillance issues

When a new drug is made available for clinical use, detailed studies of its action will have been made up to then in carefully selected and precisely monitored patients. However, it is generally considered that during the early general use of such a drug, some questions will still remain to be answered: more accurate evaluation of the incidence of ADRs and their relationship to dosage and duration of therapy, the definition of the optimum dose for the majority of patients, identification of particular patients/situations at risk, and rare ADRs.

Chaumet-Riffaud *et al.* (1992) reported an analysis of spontaneously reported adverse events connected with zolpidem during the first 3 years after its launch in Europe. A total of 822 spontaneous reports of these events in France were reviewed, 505 of which contained sufficient information for analysis. During this period, it was estimated that zolpidem prescriptions represented about 122 million nights of treatment; comparable adverse event profiles were observed in other European countries (Belgium, Italy and Denmark). Two-thirds of the cases reported were central nervous system (CNS)-related events. Approximately half occurred between intake of zolpidem and onset of sleep, when the patients were maintaining their routine activities. Over two-thirds of the adverse events were recorded during the first week of therapy, and particularly during the first 2 days. At the time of this communication, there were no marked differences in spontaneous reports concerning adults or elderly patients, respectively. However, since 14% of these cases occurred in the early treatment phase, after BZD discontinuation, withdrawal manifestations in relation to discontinuation of previous BZD treatment could not be excluded.

Both the low incidence of reported adverse events during the first 3 years of clinical use of zolpidem and the large body of data obtained from surveillance studies have corroborated the results of the earlier clinical investigations. To date, 13 post-marketing surveillance surveys (PMS), including more than 59 000 patients suffering from various types of insomnia, have been carried out and published (Allain and Monti, 1997). The primary concern of such a study is safety in accordance with the approved indications. Therefore, cohort studies under normal prescribing conditions are necessary to define more precisely the safety profile under routine conditions of use in the usual patient population, as well as for the detection of rare, unexpected, or serious adverse events.

The most common side-effects reported during zolpidem administration have been CNS-related, including infrequent reports of confusion, anterograde amnesia, and somnambulism, sometimes associated with inappropriate behaviour. Reports of short-lasting psycho-sensory disturbances (e.g. perceptual distortions, visual illusions, hallucinations), often occurring 30–60 min after intake of the drug, are also infrequent and most of these phenomena may be indistinguishable from those usually described as hypnagogic hallucinations (Ansseau *et al.*, 1992; Iruela *et al.*, 1993). There have also been sporadic reports of zolpidem abuse/misuse in former drug abusers and/or patients with chronic psychiatric disorders (Gericke and Ludolph, 1994; Wesson *et al.*, 1994; Buzo Sanchez *et al.*, 1996).

After 8 years of clinical use under routine conditions, no major significant source of concern regarding hepatic, cardiovascular, or renal function has been raised. No non-sporadic congenital abnormalities or complications during pregnancy or delivery have been reported, and no previously unrecognized

Table 3 Zolpidem: safety in overdose

Study	Country	Design	Number of cases
Auzepy (1991)	France	Case report	91
Garnier (1994)	France	Anti-Poisoning Centre Survey[a]	344
Jonville (1991)	France	Case report	18
Lheureux (1990)	Belgium	Case report	1
Tracqui (1993)	France	Case report	1
Mercurio (1994)	USA	Pilot survey	35
Meeker (1995)	USA	Case report	1
Augsburger (1994)	Switzerland	Case report	1
Carbajal (1996)	France	Case report	2
Wyss (1996)	Switzerland	Comparative Survey (STIC)	Zolpidem, 91 Midazolam, 53
Winek (1996)	USA	Case report	1
Kurta (1996)	USA	Case series, paediatrics	12

[a]Anti-Poisoning Centre: cases collected by anti-poisoning centre. STIC, Swiss Toxicological Information Centre.

risk factors have emerged in relation to the risk of zolpidem abuse, which appears to be minimal.

Comparative studies versus other sedatives and hypnotics

The hypnotic efficacy, safety, residual effects, and performance of zolpidem have been reviewed by analysing more than 50 international clinical trials published since 1988 (Roth, 1996). Zolpidem's hypnotic activity has been explored in different types of populations including normal subjects, general practice outpatients, and psychiatric out- or inpatients with various kinds of transient or chronic sleep disorders (as well as preoperative administration).

Various assessment methods have been used, including objective or subjective measures of hypnotic efficiency, for different lengths of treatment time. The comparative efficacy, safety, residual effects, and performance of zolpidem for the induction and maintenance of sleep have been established both in healthy volunteers and in geriatric, psychiatric, and general practice patients with insomnia (Unden and Schechter, 1996). It was confirmed that 10 mg is superior to placebo and as efficacious as a reference hypnotic BZD with, in contrast to most BZD hypnotics, no or minimal impact on sleep architecture in polysomnographic recordings. Indeed, zolpidem acted favourably in most trials on sleep parameters such as sleep onset latency, nocturnal awakenings, and total sleep time. In contrast to many BZDs, the duration and latency of rapid eye movement (REM) sleep were usually unmodified, while slow wave (profound) sleep was unchanged or enhanced (Monti *et al*., 1995; Walsh *et al*., 1996).

The comparative efficacy, safety, residual effects and performance of zolpidem have been established for: bretazenil (Gieschke *et al*., 1994), diazepam (Maillard *et al*., 1992), doxylamine (Gengo *et al*., 1995; Schadeck *et al*., 1996), flunitrazepam (Emeriau *et al*., 1988; Maggioni and Frattola, 1988; Guieu *et al*., 1991; Vermeeren *et al*., 1991; Guazzelli *et al*., 1993; Murciano *et al*., 1993; Genton *et al*., 1994), flurazepam (Cirignotta *et al*., 1988; Scharf *et al*., 1992; Fleming *et al*., 1995; Mendelson *et al*., 1995a), lorazepam (Lebrault *et al*., 1989) lormetazepam (Lund *et al*., 1988; Cluydts *et al*., 1995), midazolam (Praplan Pahud *et al*., 1990) nitrazepam (Uchiumi *et al*., 1994), oxazepam (Coupez *et al*., 1988), RO 41–3696 (Dingemanse *et al*., 1995), temazepam (Ochs *et al*., 1992; Gremion *et al*., 1992; Erman *et al*., 1995; Gengo *et al*., 1995; Rush and Griffiths, 1996), trazodone (Walsh *et al*., 1995), triazolam (Louvel *et al*., 1988; Nagakome *et al*., 1991; Takasawa *et al*., 1991; Balkin *et al*., 1992; Ochs *et al*., 1992; Ferrillo *et al*., 1992; Berlin *et al*., 1993; Kanno *et al*., 1993; Pagot *et al*., 1993; Roger *et al*., 1993; Steens *et al*., 1993; Monti *et al*., 1994; Uchiumi *et al*., 1994; Greenblatt *et al*., 1996; Rush and Giffiths, 1996; Wesensten *et al*., 1996; Silvestri *et al*., 1996; Morgan *et al*., 1997), zopiclone (Guieu *et al*., 1994; Walters *et al*., 1994; Allain *et al*., 1995; Lemoine *et al*., 1995).

Comparison of zolpidem with reference BZD sedatives, an antidepressant (trazodone), and an over-the-counter remedy (doxylamine) in controlled studies showed that zolpidem had at least similar or even superior efficacy in terms of sleep onset in chronic insomniac patients and poor sleepers. Herrmann *et al*. (1991) have suggested that zolpidem actually consolidates slow wave sleep into the first period, rather than increasing it overall.

Acute overdose with zolpidem

Several recent publications have dealt with the question of acute overdose with zolpidem (Table 3). Garnier *et al*. (1994) retrospectively analysed 344 cases of intentional overdose that had been reported to a French poison control centre. The patients were predominantly female (70%), most of them in their third or fourth decade. The estimated ingested dose ranged up to 1400 mg, but in 80% of the cases, it was limited to 200 mg or less. In 48%, other substances, most frequently psychotropic drugs or alcohol, were co-ingested with zolpidem. Signs of poisoning were reported in two-thirds of the cases, but could only be attributed to zolpidem in 105 out of 224 cases. Most often, the clinical symptomatology was limited to drowsiness (84 cases) for doses below 1200 mg. Only five cases of coma or respiratory depression were reported for doses of 140–400 mg. No electrocardiographic (recorded in 51

patients) or biological abnormalities (94 laboratory assessments) could be specifically attributed to zolpidem. In 167 out of the 184 specified cases with CNS-related symptomatology, the clinical course was rapidly favourable, without sequelae. Among the 17 remaining patients, five of the patients recovered without sequelae, despite complications with intensive care; one recovered with nerve compression and a fatal outcome occurred in 11 cases.

However, at the time of follow-up, none of these negative outcomes could be clearly related to zolpidem. In addition to supportive measures and gastric evacuation, flumazenil was administered to 16 of the patients: it led to complete or partial reversal of the symptoms in 10 cases.

Another death has been reported following an overdose which involved zolpidem and acepromazine (Tracqui *et al.*, 1993). Augsburger *et al.* (1994) also reported a case of death involving zolpidem overdose and hypothermia. Recently, Winek *et al.* (1996) reported a fatal overdose of zolpidem in combination with meprobamate and carisoprodol in a 68-year-old woman. Additional data on acute zolpidem poisoning were reported by Jonville *et al.* (1991), who identified eight cases of drowsiness and one case of coma in 18 subjects. More recently in the USA (Mercurio *et al.*, 1994; Kurta *et al*, 1996), and in Switzerland (Wyss *et al.*, 1996), studies of a limited number of subjects, including a paediatric case series, have confirmed that zolpidem has a satisfactory therapeutic index.

As with all sedatives, intoxication produced by drug combinations could result in more severe symptoms, and patients then need to be monitored and treated by appropriate medical intervention. However, zolpidem alone appears not to show a significant degree of toxicity in overdose.

Dependence and abuse liability

Drug addiction or dependence is acknowledged to be a serious health problem, but besides the major drugs of concern (opioids, CNS stimulants, alcohol) sedatives also have to be taken into account. Thus, reducing the extent of drug dependence constitutes one of the major objectives to be achieved in the development of hypnotics (Costa E Silva *et al.*, 1996).

The generally accepted definition of insomnia includes persistent difficulties in initiating or maintaining sleep, or having non-restorative sleep. However, the term is somewhat vague and ambiguous, referring to any and all gradations of sleep loss (ICSD, 1990). It is associated with several daytime consequences, including increased morbidity and mortality (Balter and Uhlenhuth, 1992). On a long-term basis, insomnia constitutes the commonest sleep disorder, affecting up to 10% of adults (Roth *et al.*, 1994; Ohayon, 1996).

Since 1988, evaluation of the abuse potential of zolpidem has been documented in several studies, carried out in both Europe and the USA, and this proceeded through pre-clinical to clinical investigations. It is also recognized that the testing of abuse and dependence liabilities requires a multidimensional approach in order to assess tolerance, withdrawal, and self-administration potential, so as to maximize the predictability of the relative risk under naturalistic conditions of use. Even though the processes underlying dependence and abuse are still poorly understood, there are pre-clinical, biochemical and pharmacological data which establish firm differences between zolpidem, zopiclone and BZD in this respect. In contrast to BZD and cyclopyrrolones, zolpidem facilitates GABAergic neurotransmission through its selective affinity for BZ_1 (ω_1) modulatory sites.

In contrast to BZD, pre-clinical studies have shown that zolpidem is preferentially active as a sedative (Sanger and Zivkovic, 1992). Zolpidem produces sedative effects at doses which are lower than those needed for the antagonism of convulsions or for myorelaxant effects, whereas zopiclone, like BZD, is more active in tests predictive of anticonvulsant activity than in tests predictive of sedation. In rodents, several studies (Depoortere *et al.*, 1986; Sanger and Zivkovic, 1986) have also indicated that discriminative stimulus effects of zolpidem are different from those of BZD and zopiclone. In mice, zolpidem is devoid of any disinhibitory activity, measured by food consumption in a novel environment, whereas zopiclone behaves like a BZD (Perrault *et al.*, 1990). Studies involving repeated administration of zolpidem which assessed sedative and/or anticonvulsant effects failed to detect either tolerance to the sedative effect or withdrawal manifestations (Perrault *et al.*, 1992; Sanger and Zivkovic, 1992; Schoch *et al.*, 1993). This is in contrast to BZD and zopiclone.

These animal data suggest that during clinical administration of zolpidem, it may not produce BZD-like physical dependence. In the baboon study by Griffiths *et al.* (1992), zolpidem produced discriminative stimulus effects that were similar to BZD and showed reinforcing effects more like barbiturates than BZD. These differences led these authors to suggest that there may be meaningful species differences between baboons and rodents. The relevance of any of this information to human abuse of zolpidem remains questionable and it is generally recognized that pre-clinical assessment of abuse liability can only partially predict the risk of drug abuse; the real-life situation is more complex, and any new psychotropic agent is likely to be tested by chronic drug abusers (Balster, 1991).

In specific studies carried out in former drug abuser volunteers, it has been demonstrated that high doses (15, 30 and 45 mg) of zolpidem produced increases in some positive subjective measures and in drug-liking scores, indicating that it may have some abuse potential (Evans *et al.*, 1990). However, there was no significant effect on the Morphine–Benzedrine Group Scale (De Wit and Griffiths, 1991) of the Addiction Research Centre Inventory (ARCI) (Jasinski, 1977), which is used as an indication of euphoria. In addition, zolpidem produced an increased score on the dysphoria score of the ARCI and the authors of this report suggested that such negative effects of high doses might limit the abuse potential of the drug. On specific questionnaires, the effects of doses of 40 mg of zolpidem (four times the recommended dose) were described as similar but not identical to the effects of 20 mg of diazepam (Jasinski *et al.*, 1989). Since 1988, anecdotal reports of abuse in chronic psychiatric patients have been reported in the literature (Cavallaro *et al.*, 1993; Wesson *et al.*, 1994; Gericke and Ludolph, 1994; Thome *et al.*, 1995), but there is no evidence to date that the drug possesses any significant 'street value' for drug abusers.

The potential abuse liability of a substance may also be partially influenced by the need to increase the doses to obtain the same effects during long-term treatment (tolerance phenomenon) (Nutt, 1996). Tolerance to the effects of a drug can be of two types: metabolic and functional. Enzyme induction is well demonstrated by the barbiturates: continued administration stimulates production of liver enzymes that metabolize it more rapidly, and so a higher dose is needed for the same effect. Though there is no good evidence that BZD are associated with metabolic tolerance, indications exist that cross-tolerance between BZD, barbiturates, and alcohol does occur (Owen and Tyrer, 1983).

Although such durations of administration are not recommended in the therapeutic use of hypnotic agents, some researchers studied the efficacy of zolpidem for up to 360 days during its clinical development. In studies with a total of 340 patients (Sauvanet *et al*., 1988; Schlich *et al*., 1991; Maarek *et al*., 1992; Pagot *et al*., 1993), improvement in subjective parameters of sleep were maintained throughout the whole treatment period, in most cases with doses of 10 mg/day. In contrast, objective assessments during polysomnographic recordings by Monti *et al*. (1994) have shown that partial tolerance to the sleep-inducing and maintaining effects of triazolam developed during medium-term treatment (28 days) in 18 chronic insomniac patients with polysomnographic recordings.

In the USA, according to the Controlled Substance Act Classification of Drugs (1970) to regulate the manufacture, distribution, and dispensing of controlled substances, zolpidem was classified as a Schedule IV controlled substance, which means that it should not be considered as risk-free. However, cumulative experience with zolpidem since 1988 does not suggest that this drug produces a significant risk of abuse/misuse and dependence. Nevertheless, precautions should be exercised with patients who have current or prior dependence on sedative hypnotics (or alcohol), and those with chronic psychiatric disorders (including chronic dysphoria, dysthymia, and personality disorders). Such patients should be under close medical supervision when receiving zolpidem or any other sedatives.

Rebound insomnia

There is no clear agreement on the definition of rebound insomnia (Mendelson *et al*., 1995b). Some authors define it as an increase of 40% or greater of total wake time, as compared to baseline (Kales *et al*., 1979, 1983). In most cases, though, rebound is conceptualized as a significant worsening of some clinically significant sleep parameters (sleep onset, number of awakenings, and total sleep time) during discontinuation nights compared with the baseline condition (Angst *et al*., 1995).

Several studies (e.g. Vogel and Poirrier, 1996) have been carried out in both healthy volunteers and patients (adults and elderly) to assess the potential of zolpidem to provoke rebound insomnia. In these studies, discontinuation was abrupt — a condition that is known to increase the risk of rebound with hypnotic agents. Both the objective and subjective data indicate that following discontinuation, patients do not experience the change as being a significant problem when using zolpidem according dose and duration recommended (Roehrs *et al*., 1992). To date, the literature concerning the occurrence of rebound insomnia with zolpidem, using objective polysomnographic measurements (PSG), primarily a recording of brain wave activity, as well as subjective doctor- and patient-reported analyses (questionnaires), in different populations and with different treatment durations, provides evidence that abrupt discontinuation of zolpidem is easy to manage in most patients.

Safety in elderly patients

The incidence of complaints of insomnia increases dramatically with age; the sleep of elderly people tends to be fragmented and disrupted by awakenings, and as many as 35% have been found to suffer from recurrent or chronic sleep disorders (Fairweather *et al*., 1992). The elderly population is particularly exposed to hypnotic use (Foley *et al*., 1995) and may be especially sensitive to the effects of sedatives. These patients tend to clear drugs more slowly and are more likely to develop cognitive and motor impairment. Ataxia, risk of falls, and memory deficits may not occur until several weeks after beginning treatment. Respiratory disturbances whilst asleep, including sleep apnoea, may also be exacerbated with sedatives. Thus, such adverse drug effects must be specifically explored in this population at risk (Consensus Conference, 1984; Morgan *et al*., 1994). Because these patients use a large proportion of issued prescriptions and are more susceptible to develop undesirable manifestations, including substance abuse, it is particularly important to explore specifically the safety of hypnotic agents in elderly populations (Morgan *et al*., 1994; Asscher *et al*., 1995; Foley *et al*., 1995; Mendelson and Jain, 1995b; Naranjo, 1995).

Thirteen zolpidem studies, carried out in this population, have been published (Table 4). These involved more than 1000 subjects aged 60 years and over. With zolpidem, there was no significant effect on the normal sleep stages throughout the night, as measured by PSG (Scharf *et al*., 1991a). The lowest dose that produced a statistically significant improvement in sleep efficiency and wake time during sleep, compared to placebo, was 5 mg. On this basis, it was suggested that 5 mg is the lowest dose of zolpidem with optimal efficacy for treating insomnia in the elderly.

Guerault *et al*. (1992) summarized the adverse events of 21 European studies, involving a total of 464 elderly patients treated with zolpidem 5 or 10 mg. Approximately half of this sample was aged 80 years or older, and more than 90% received zolpidem for periods of not more than 4 weeks. At the dose of 5 mg ($n = 127$), only mild CNS events with comparable rates in the placebo group, not requiring discontinuation of the drug were observed: daytime drowsiness (3.1%), headache (1.6%), nightmares (1.6%), dizziness (0.8%) and agitation (0.8%). Higher rates of other types of adverse events were noted with a starting dose of 10 mg ($n = 271$): falls (2.4%), confusion (1.7%) and memory disorders (1.4%). These events were generally associated with recognized risk factors: in-patients, aged 80 years or older, presence of gait and balance disorders, dementia, and concomitant drugs. The incidence of

Table 4 Zolpidem studies in the elderly population

Study	Patients/subjects	Design	*n*	Doses	Duration (days)
Kurtz (1991)	Elderly healthy volunteers	SB/CO/Pla	12	Zol 10 mg	7
Scharf (1991b)	Elderly chronic insomnia	DB/CO/Pla Dose Response	24	Zol 1.25, 2.5, 5, 10 mg	2
Scharf (1991a)	Elderly healthy volunteers	DB/CO/Pla	33	Zol 5–20 mg	2
Roger (1988)	Elderly chronic insomnia	DB/PG/Pla	111	Zol 10–30 mg/Tria 0.25 mg	1
Rhodes (1990)	Elderly healthy volunteers	DB/PG/Pla	21	Zol 10 mg	1
Fairweather (1992)	Elderly healthy volunteers	DB/CO/Pla	24	Zol 5, 10 mg	7
Roger (1993)	Elderly chronic insomnia	DB/PG/Tria	221	Zol 5, 10 mg/Tria 0.25 mg	21
Shaw (1992)	Chronic insomnia	DB/PG	119	Zol 10, 20 mg	21
Ochs (1992a)	Chronic insomnia	DB/PG/Pla	335	Zol 5 mg/Tria 0.125 mg/Tema 15 mg	28
Benoit (1994)	Elderly healthy volunteers	DB/CO/Pla	11	Zol 10 mg	21
Emeriau (1988)	Elderly chronic insomnia	DB/PG	84	Zol 10, 20 mg/Fluni 1 mg	28
Cohn (1994)	Elderly chronic insomnia	DB/PG/Pla	335	Zol 5, 10 mg/Tria 0.125 mg Tema 15 mg	28
Kummer (1993)	Elderly chronic insomnia	SB	14	Zol 20 mg	180
Sauvanet (1988)	Elderly chronic insomnia	Open	42	Zol 10, 20, 30 mg	60–360

DB, Double blind; PG, parallel groups; SB, single blind; CO, crossover; Zol, zolpidem; Tema, temazepam; Tria, triazolam; Fluni, flunitrazepam. Adapted with permission from Allain (1997).

any CNS effects was: 14.9% at 10 mg, 9.4% at 5 mg and 6% with placebo.

Chaumet-Riffaud *et al.* (1992) reviewed the spontaneous adverse event reports for elderly patients (25% of the cases) for the first 3 years after zolpidem became available for clinical use in Europe. No increased rates of CNS-related adverse drug experiences (falls, confusion, memory disorders, or vertigo/dizziness) were found in these patients. Adverse events in the elderly generally occurred at a starting dose of 10 mg, rather than at the recommended dose of 5 mg/day. Based on several clinical and pharmacokinetic studies, an initial 5 mg dose was recommended in the elderly, who may be especially sensitive to the effects of zolpidem.

In addition, because hypnotic drugs may be potentially harmful in respiratory disorders and these disorders increase with age, many authors have specifically explored effects of zolpidem on respiratory function (Table 5). In healthy volunteers, zolpidem 10 or 20 mg/day did not significantly alter respiratory parameters (Davenne *et al.*, 1991; Maillard *et al.*, 1992). Using a double-blind design comparing zolpidem 10 mg and placebo, in 21 postoperative elderly females without lung disease over a 4-night period, Rhodes *et al.* (1990) did not find any significant increase in the frequency or severity of sleep-related breathing disorders, such as modification in respiratory rhythms and oxygen saturation. However, the author notes that sleep-related respiratory disturbances are more common in men and that further study of zolpidem should be carried out in a male population.

In patients with insomnia, several studies (Armangaud *et al.*, 1990; Aubier *et al.*, 1991; Murciano *et al.*, 1992; Quera-Salva *et al.*, 1992) have found only minimal effects of zolpidem, administered up to 60 days, on respiratory parameters and arterial blood gases in a small group of snorers or in patients with chronic obstructive pulmonary disease (COPD). Steens *et al.* (1993) reported on 23 patients with chronic insomnia and mild COPD who received placebo, triazolam 0.25 mg, zolpidem 5 mg and zolpidem 10 mg in a double-blind, randomized, single-dose, crossover trial. None of the drugs significantly affected arterial O_2 saturation (SaO_2), the apnoea–hypopnoea index, or heart rate. However, in some patients, there were

Table 5 Zolpidem: effects on respiratory drive

Study	Patients/subjects	Design	*n*	Doses	Duration (days)
Murciano (1993)	COPD	DB/CO/Pla	12	Zol 10 mg/Tria 0.125 mg	1
Cirrignotta (1988)	Sleep apnoea syndrome (moderate)	DB/CO/Pla	12	Zol 20 mg/Flur 30 mg	1
Davenne (1991)	Healthy volunteers	DB/CO/Pla	8	Zol 10 mg	1
McCann (1991)	Snorers	DB?CO/Pla	20	Zol 10 mg	1
Mougin (1992)	Healthy volunteers	DB/CO/Pla	8	Zol 10 mg	1
Quera-Salva (1992)	Snorers	DB/CO/Pla	10	Zol 10 mg	1
Rhodes (1990)	Elderly healthy volunteers	DB/CO/Pla	21	Zol 10 mg	1
Murciano (1992)	COPD	Open	12	Zol 10 mg	60
Maillard (1992)	Healthy volunteers	DB/CO/Pla	16	Zol 10, 20 mg/Dia 10 mg	1
Steens (1993)	COPD	DB/CO/Pla	24	Zol 5, 10, 20 mg/Tria 0.25 mg	1
Cohn (1993)	Healthy volunteers	DB/CO/Pla	12	Zol 10, 20 mg/codeine 60 mg	1
Henderson (1996)	Obstructive sleep apnoea syndrome	Open	8	Zol 10 mg	1
Beaumont (1996)	Healthy volunteers (simulated altitude)	DB/CO/Pla	8	Zol 10 mg	

COPD, chronic obstructive pulmonary disease; DB, double blind; CO, crossover; Zol, zolpidem; Tria, triazolam; Flur, flurazepam; Dia, diazepam; Pla, placebo.

Table 6 Studies on daytime drowsiness induced by zolpidem and other hypnotics measured with the multiple sleep latency test (MSLT)

Study	Patients/subjects	Duration (days)	Doses	Results (MSLT)
Scharf (1991b)	30 elderly healthy volunteers	2	Zol 5, 10, 15, 20 mg	Zol = Pla
Kurtz (1991)	10 poor sleepers	14	Zol 10 mg	Zol = Pla
Poirrier (1994)	11 psychophysiological insomnia	28	Zol 10 mg	Reduction of daytime sleepiness
Lund (1988)	10 healthy volunteers	1	Zol 10, 20 mg Tria 0.5 mg Lorm 2 mg	Zol = Tria = Pla > Lorm
Bensimon (1990)	12 healthy volunteers	1	Zol 20 mg Fluni 2 mg	Zol = Pla > Fluni
Fleming (1995)	144 chronic insomnia	3	Zol 10, 20 mg Flura 30 mg	Zol = Pla > Flura

Zol, zolpidem; Pla, placebo; Tria, triazolam; Lorm, lormetazepam; Fluni, flunitrazepam; Flura, flurazepam.

some adverse respiratory events involving SaO_2 and the apnoea–hypopnoea index. Therefore, the authors concluded that these low-to-moderate dosages of zolpidem are generally safe and effective in patients with insomnia and mild to moderate COPD, but that extra caution is still advisable when using hypnotics in the individual patient, particularly with repeated use or in the presence of severe COPD.

Impact on memory and performance

The impact that insomnia has on daytime alertness, memory, and performance, as well as the effects of hypnotic medication, have been emphasized in various surveys. In a telephone survey (Balter and Uhlenhuth, 1992), some form of memory impairment was also commonly reported in respondents with untreated insomnia. Transitory disturbances of memory have been also reported with hypnotic agents (Morris and Estes, 1987; Woods *et al*., 1987; Rakel, 1993). The amnesia is anterograde in nature, so that next-day recall of events that occur after the drug is taken (e.g. late-night phone conversations) can be impaired (World Psychiatric Association, 1993). Moreover, there is some evidence that sleep onset per se could be associated with both anterograde and retrograde amnesia (Wyatt *et al*., 1994).

The potential effects of zolpidem on cognitive and psychomotor functions have been explored in more than 30 placebo-controlled studies, in which many cases of zolpidem were compared with BZD reference hypnotics (flunitrazepam, nitrazepam, triazolam, flurazepam). Various kinds of subjects were included in these studies: young adults, the elderly, healthy volunteers, and insomniac patients; there were also different durations of treatment, ranked between one single dose and 15 daily doses, being tested. Scharf *et al*. (1992) used the Digit–Symbol Substitution Test (DSST) to compare residual effects of zolpidem and BZD.

In several studies with zolpidem, involving both elderly and non-elderly subjects and patients, there was no evidence of residual next-day effects, based on standard measures of daytime sleepiness, psychomotor performance, and attention (Borbély *et al*., 1988; Lund *et al*., 1988; Merlotti *et al*., 1989; Vogel *et al*., 1989; Bensimon *et al*., 1990; DeJong *et al*., 1991; Kryger *et al*., 1991; Bergougnan *et al*., 1992; Mougin *et al*., 1992; Richens *et al*., 1993; Sicard *et al*., 1993; Guieu *et al*., 1994). Standard procedures used to evaluate the residual effects of zolpidem were the Multiple Sleep Latency Test, as well as the DSST, and the Symbol Copying Test, which measure alertness/attention and psychomotor performance (Unden and Schechter, 1996) (Table 6).

The daytime impact of drug administration on alertness has been studied with the multiple sleep latency test, and unlike BZD, no significant impairment was found after zolpidem 5–10 mg (Scharf *et al*., 1991a). Exploration of attention and psychomotor skills through the critical flicker fusion threshold, substitution or copying tests, choice reaction times, or driving tests have also shown that at recommended doses, zolpidem has no residual effect on vigilance, concentration, or coordination performance on the morning after intake (Unden and Schechter, 1996).

On memory function, the effect of zolpidem is limited to the first hours after administration; no differences have been observed between zolpidem 5–10 mg and placebo, 6 h after intake, though memory impairment of longer duration has been found with flunitrazepam or triazolam (Bensimon *et al*., 1990; Balkin *et al*., 1992; Berlin *et al*., 1993; Fairweather and Hindmarch, 1995; Wesensten *et al*., 1995; Rush and Giffiths, 1996). However, in some studies using objective measures, rare memory deficits have been reported following the administration of zolpidem, predominantly at doses above 10 mg (Vaucher *et al*., 1988; Bensimon *et al*., 1990; Wesensten *et al*., 1991; Roehrs *et al*., 1994; Wesensten *et al*., 1995; Greenblatt *et al*., 1996). Since 1988, under routine conditions of use, episodic spontaneous post-marketing surveillance reports of anterograde amnesia have been collected and published (Chaumet-Riffaud *et al*., 1992). In most cases, impairment of memory is significant, at doses above those clinically recommended, near the time of peak plasma concentration, but not significant on the morning after administration.

Thus, based on more than 30 international clinical trials involving more than 2600 subjects (Unden and Schechter, 1996), there is strong evidence in favour of a remarkably safe profile of zolpidem 5–10 mg on cognitive functions compared with other hypnotics. With single or repeated doses, in either healthy subjects or insomniac patients, zolpidem appears to induce minimal next-day residual effects. However, next-day residual impairment has been reported in some studies with

doses above the therapeutic range, which do not in fact result in substantially higher efficacy (Fleming *et al.*, 1995).

Discussion

The literature reviewed in this report indicates that at the recommended doses, with single or repeated use, in either healthy subjects or insomniac patients, there appear to be minimal significant next-day residual effects after the predominantly short-term administration of zolpidem. Effects of doses exceeding the therapeutic range indicate a dose–effect relationship for some residual impairment, and such doses do not provide substantially greater efficacy (Scharf *et al.*, 1994; Fleming *et al.*, 1995).

The most frequent adverse effects reported during administration of zolpidem are CNS-related. They can be greatly limited by strict adherence to the prescribing recommendations: limited treatment duration, prescription of 10 mg in adults, 5 mg starting dose in elderly and debilitated patients, and intake of the drug just before going to bed. However, like all other hypnotics, zolpidem cannot be considered risk-free, even at therapeutic dosage. Extra caution is advised in elderly patients with chronic obstructive pulmonary disease, particularly in men.

In the reported cases of overdose with zolpidem alone, no repeated severe clinical or biological consequences have been identified up to now, and a full recovery was generally obtained. However, more severe complications, including fatal outcome, have been observed when zolpidem was taken in combination with other drugs (e.g. alcohol) or in particular pathological conditions.

Comparison of zolpidem with reference BZD hypnotics, a sedative antidepressant (trazodone), and an over-the-counter remedy (doxylamine) in controlled studies showed that zolpidem had at least similar or even superior efficacy in terms of sleep onset in insomniac patients. Sleep electroencephalogram records in insomniac patients, as well as in healthy volunteers, found that in comparison to BZD, zolpidem had a very limited impact on sleep structure (especially on REM sleep stages) and on cognitive functioning. Furthermore, in contrast to BZD, zolpidem preserved or tended to prolong the more restorative sleep stages 3 and 4 (facilitation of slow wave sleep). Bedtime administration of zolpidem to normal women does not alter endocrine markers of circadian rhythmicity and does not affect growth hormone secretion; this may improve the adaptation of sleep patterns to abrupt shifts (e.g. jet-lag, shift-work).

In contrast to most BZD hypnotics, the abrupt discontinuation of treatment is readily possible in the great majority of patients, and withdrawal from treatment does not induce marked rebound insomnia within the interval of 4 weeks of recommended prescription. Since tolerance to the hypnotic effect seems unlikely to appear, the dependence potential should be very low in patients who are not at risk for that problem.

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