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Zolpidem

An Update of its Pharmacology, Therapeutic Efficacy and Tolerability in the Treatment of Insomnia

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Data Selection

Sources: Medical literature published in any language since 1966 on zolpidem, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'zolpidem' or 'SL-80-0750-23N'. Medline search terms were 'zolpidem'. Searches were last updated 21 February 2000.

Selection: Studies in patients with insomnia who received zolpidem. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: zolpidem, insomnia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Zolpidem is an imidazopyridine agent that is indicated for the short term (≤4 weeks) treatment of insomnia (recommended dosage 10 mg/day in adults and 5 or 10 mg/day in the elderly or patients with hepatic impairment).

Data have shown that the hypnotic efficacy of zolpidem is generally comparable to that of the benzodiazepines flunitrazepam, flurazepam, nitrazepam, temazepam and triazolam as well as nonbenzodiazepine hypnotic agents such as zopiclone and trazodone in the treatment of elderly and adult patients with insomnia. The comparative efficacy of a recently available nonbenzodiazepine hypnotic zaleplon and zolpidem has yet to be established. There was no evidence of tolerance developing to the hypnotic effects of zolpidem in a number of studies of up to 6 months' duration. However, tolerance has been described in a few patients taking the drug at high dosages for periods of up to several years.

Zolpidem is well tolerated in patients with insomnia and the most common adverse events are generally nausea, dizziness and drowsiness. Although zolpidem produced some psychomotor and memory impairment over the first few hours after administration, it had few next-day effects (including effects on daytime well-being and morning coordination). In this respect, it was comparable or superior to flunitrazepam and flurazepam and comparable to other benzodiazepines in patients with insomnia. Zolpidem appears to have a low potential for abuse.

Conclusions: Zolpidem is effective and well tolerated in patients with insomnia, including the elderly. Studies have shown that zolpidem generally has similar efficacy to other hypnotics including benzodiazepines and zopiclone. Zolpidem appears to have minimal next-day effects on cognition and psychomotor performance when administered at bedtime. In addition, there is little evidence of tolerance to the hypnotic effects of zolpidem, or rebound insomnia or withdrawal symptoms after discontinuation of the drug when it is given as recommended (10 mg/day for <1 month) or over longer periods.

Pharmacodynamic Profile

Zolpidem is an imidazopyridine agent that is an agonist at the benzodiazepine receptor component of the γ-aminobutyric acid $(GABA)_A$-receptor complex. Zolpidem has shown weaker anxiolytic, anticonvulsant and myorelaxant effects than benzodiazepines in animal models, and the sedative effects of zolpidem predominate.

The hypnotic effects of zolpidem, in addition to the lack of effects of the drug

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on sleep architecture, have been demonstrated in a large number of studies in healthy volunteers and patients with insomnia.

In patients with chronic insomnia, zolpidem 10 mg/day had psychomotor effects comparable to or less than those of flunitrazepam or flurazepam the morning after drug administration. Some psychomotor and memory impairment was observed with zolpidem in healthy volunteers during the first few hours after administration, but these effects were generally not observed from 6 hours after administration (a more relevant assessment time for 'before bed' use). The psychomotor and cognitive profile of zolpidem was comparable to that of temazepam and comparable to or better than that of other benzodiazepines including flunitrazepam and triazolam and the nonbenzodiazepine hypnotic zopiclone in healthy volunteers. Zolpidem produced greater psychomotor and memory impairment than another nonbenzodiazepine hypnotic, zaleplon, generally for a period of up to 5 hours after drug administration in volunteers; however, comparative data are not yet available in patients with insomnia.

Zolpidem has no significant effects on respiration in most patients other than negative effects in those with sleep apnoea.

Overview of Pharmacokinetic Properties

Zolpidem is rapidly absorbed: a mean maximum plasma concentration of 121 μg/L is reached 1.6 hours after a 10mg dose. The drug does not accumulate after multiple doses. Zolpidem is extensively metabolised by a range of cytochrome P450 isoenzymes, predominantly CYP3A4 (≈60%), to 3 inactive metabolites. Zolpidem has a short elimination half-life ($t_{1/2}$) in healthy volunteers (2.5 hours after a 10mg dose).

Mean maximum plasma concentrations of zolpidem are increased and elimination is reduced in the elderly and in patients with hepatic impairment or chronic renal insufficiency altering dosage recommendations in the 2 former groups of patients (Dosage and Administration section).

Therapeutic Efficacy

The hypnotic efficacy of zolpidem is generally equivalent to that of the benzodiazepines flunitrazepam, flurazepam, nitrazepam and triazolam. In addition, zolpidem demonstrated better effects on sleep parameters than temazepam and similar efficacy to doxylamine, trazodone and zopiclone in single trials. The efficacy of a recently available nonbenzodiazepine hypnotic zaleplon relative to that of zolpidem has yet to be established: 2 large studies have been conducted but they predominantly compared results for active treatments against placebo and not each other.

Studies in elderly patients with insomnia suggested that zolpidem has equivalent efficacy to flunitrazepam, temazepam and triazolam in this group.

There was no evidence of tolerance developing to the hypnotic effects of zolpidem in a number of clinical studies of 3 to 6 months' duration that generally considered patients' self assessments. However, case reports have described tolerance to the hypnotic effects of zolpidem in patients, usually with psychiatric disorders, taking the drug at high dosages for periods of up to several years.

Discontinuous or 'as needed' use of zolpidem 10 mg/day over 2 to 8 weeks was found to be effective for the treatment of chronic insomnia based on subjective ratings in 3 randomised, double-blind, parallel studies, 1 of which has been published in full.

Tolerability

Zolpidem is well tolerated in patients with insomnia, including the elderly. The most common adverse events generally include nausea, dizziness and drowsiness.

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In patients with insomnia, the next-day effects and adverse events profile of zolpidem were generally comparable to those of benzodiazepine and non-benzodiazepine hypnotics. Findings were similar in elderly patients.

There was no evidence of rebound insomnia after sudden withdrawal of zolpidem 10 mg/day after up to 6 months' treatment in all but a few clinical trials. In addition, zolpidem appears to have a low potential for abuse.

Drowsiness or somnolence was the most common symptom of zolpidem overdose. Fatalities have been reported in patients taking an overdose of zolpidem: where full details are available there was usually a concomitant overdose of other drugs.

Drug Interactions

No pharmacokinetic interactions have been observed between zolpidem and cimetidine, ranitidine, haloperidol or imipramine. However, cimetidine, chlorpromazine and imipramine increased the sedative effects of zolpidem. Rifampicin reduced the plasma concentration and pharmacodynamic effects of zolpidem.

Ketoconazole and itraconazole increased the area under the plasma concentration-time curve of zolpidem. Ketoconazole also increased the $t_{1/2}$ of zolpidem and enhanced zolpidem-related impairment of psychomotor function, whereas itraconazole had no such effect. Fluconazole did not affect the pharmacokinetics of zolpidem.

No clinically significant drug interactions were observed between zolpidem and the SSRIs fluoxetine and sertraline in studies in healthy volunteers.

Dosage and Administration

It is recommended that zolpidem is given orally immediately before bedtime for the treatment of insomnia. The maximum recommended dosage of zolpidem is currently 10 mg/day in adults. Each course of zolpidem should not exceed 4 weeks.

In patients with hepatic impairment and the elderly, zolpidem should be initiated at a dosage of 5 mg/day and these patients should be closely monitored. The maximum recommended dosage of zolpidem in the elderly is 10 mg/day (5 mg/day in the UK). No dosage reduction is required in patients with renal impairment, although this group should also be closely monitored. It may be necessary for lower than recommended dosages of zolpidem to be given when the drug is coadministered with drugs having depressant effects on the CNS, because of potential additive effects. Zolpidem is contraindicated in patients with severe hepatic impairment, obstructive sleep apnoea, acute pulmonary impairment or respiratory depression. The use of zolpidem during pregnancy and in women who are breast feeding is not recommended.

The pharmacodynamic and pharmacokinetic properties and therapeutic potential of zolpidem were previously reviewed in *Drugs* in 1990.[1] This review re-examines the role of zolpidem in the treatment of insomnia in light of the considerable amount of new data that has become available since the last review. Data relating to zolpidem dosages other than those recommended (10 mg/day in adults and 5 or 10 mg/day in the elderly or patients with hepatic impairment; section 6) have not been included unless contributory.

1. Pharmacodynamic Profile

1.1 Mechanism of Action

Zolpidem is an imidazopyridine agent that is an agonist at the benzodiazepine receptor component of the γ-aminobutyric acid $(GABA)_A$-receptor

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complex.[2,3] It seems likely that zolpidem, like other agonists at this complex, enhances the inhibitory effects of GABA on neuronal excitation.[4]

Zolpidem has shown weaker anxiolytic, anticonvulsant and myorelaxant effects than benzodiazepines in animal models, and the sedative effects of zolpidem predominate, as reviewed previously.[3,5,6] This profile has been proposed to be a result of high affinity of the drug for central benzodiazepine ω_1 (type 1) receptors, which correspond to $GABA_A$ receptors containing α_1 subunits; these receptors may be particularly important in mediating hypnotic effects.[1,3] This is in contrast with the nonselective affinity of benzodiazepines (including flunitrazepam and diazepam) for $GABA_A$ receptors containing the α_1, α_2, α_3 or α_5 subunits.[1,3,5] However, oral zolpidem 20mg did not show regional selectivity in the human brain.[2]

1.2 Sedative-Hypnotic Effects

Zolpidem, administered at a dosage of 10 mg/day (the recommended dosage; section 6), had been shown to reduce time to onset and prolong the duration of sleep in healthy volunteers at the time of the earlier review.[1] Similar effects were generally found with zolpidem 10mg in later studies in healthy adult volunteers[7-13] and in patients with insomnia (section 3). In addition, zolpidem (at dosages from 5 mg/day) improved sleep parameters in elderly volunteers[14] or patients (section 3.2). Zolpidem also had beneficial effects on sleep in volunteers at a simulated altitude of 4000 metres (n = 8),[15] in heavy snorers (n = 10),[16] in hospitalised patients the night before surgery (n = 357)[17] and in individuals who took the drug for the first 2 nights after eastward transatlantic travel (n = 130).[18] However, it should be noted that zolpidem (and other available hypnotics) are not currently indicated for the treatment of jetlag.

Sleep architecture has generally not been affected with zolpidem given as 10mg doses nightly in healthy volunteers, as reviewed previously[1] and in subsequent studies in adults[11,19-25] and the elderly.[14] In patients with insomnia including the elderly, zolpidem 10mg was usually associated with no changes in sleep structure apart from an increase in slow wave sleep (stages 3 and 4) in some studies.[19,26-33] The effects of zolpidem contrast with those of benzodiazepines which usually adversely affect sleep structure by reducing slow wave sleep.[24,25,27,34-36]

Zolpidem increased slow wave sleep to a greater extent than zopiclone in 2 studies, each in 10 volunteers, although between-group differences were not significant.[32,37] Zolpidem was also more effective than zopiclone at improving sleep microstructure [reducing the cyclic alternating pattern (CAP) rate of non-REM sleep and the number of arousal events] assessed by polysomnography in patients with situational insomnia (n = 6)[38] or primary insomnia (n = 20).[32] There is evidence that the CAP rate significantly correlates with the subjective appreciation of sleep quality.[34]

1.3 Effects on Psychomotor Function

1.3.1 In Patients with Insomnia

Zolpidem 10 mg/day had effects on psychomotor function that were comparable to or less than those of flurazepam or flunitrazepam the morning after drug administration in patients with chronic insomnia.[27,36,39]

In a study in 141 patients, flurazepam (30 mg/day for 3 days) recipients had a significantly greater decrease from baseline in the number of correct responses for the Symbol Copying Test and the Digit Symbol Substitution Test (DSST) than zolpidem recipients each day and placebo recipients on days 2 and 3 ($p < 0.05$).[39] In contrast, zolpidem recipients did not have significantly different DSST scores than patients receiving placebo. No significant differences were detected between zolpidem and flurazepam in other measures of performance including Choice Reaction Time, Auditory Vigilance, Divided Attention Task and Simple Reaction Time.[39]

Compared with placebo, a measure of driving performance was not significantly different after zolpidem or flunitrazepam 2 mg/day (a higher than usual dosage) in patients with insomnia (n = 17),

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although 1 flunitrazepam recipient was too drowsy to complete the driving test.[27] Data on daytime sleepiness and activation (analysed from subgroups of 10 and 15 patients, respectively) showed that flunitrazepam recipients were significantly more drowsy and less active than placebo recipients ($p = 0.034$), whereas patients receiving zolpidem had similar scores to placebo recipients.[27] Next-day cognitive effects of zolpidem and flunitrazepam 1 mg/day (assessed using the sign-crossing test) were equivalent in a small study in 12 patients with insomnia.[36]

Clinical residual effects that are reported by patients or are evident from post-sleep efficacy assessments are discussed in section 4.2.

1.3.2 In Volunteers

Impairment of psychomotor tests was observed in volunteers receiving zolpidem in some studies in the first few hours after daytime[40,41] or nighttime[42,43] administration. However, from 6 hours after administration (a more relevant assessment time for normal 'before bed' hypnotic use), zolpidem generally had similar psychomotor and cognitive effects to placebo (table I).

Studies have shown that zolpidem 10mg has similar effects on psychomotor function to that of the benzodiazepine temazepam and equivalent to or better than that of the benzodiazepines triazolam and flunitrazepam as well as the nonbenzodiazepine hypnotic zopiclone (table I). However, zolpidem 10mg produced greater psychomotor impairment than the same dosage of another nonbenzodiazepine hypnotic zaleplon at 1.25[43] and 3[51] hours after drug administration and similar effects to zaleplon 20mg to 8.25 hours after administration[50] in 2 studies ($n = 24$[43,50] or 36[51]) [specific data were not presented for 1 trial].[43,50] Zolpidem 10 and 20mg and zaleplon 20mg impaired performance on the Digit Symbol Substitution Test in another study: there were significant differences among active treatments and placebo.[49] The usual daily dose of zaleplon is 10 mg/day (maximum 10 mg/day in Europe[56] and 20 mg/day in the US[57]).

In elderly volunteers with sleep latency ≥30 minutes ($n = 24$), zolpidem 5 or 10mg had no significant effects on psychomotor or cognitive function when tests were performed the following day (10 to 18 hours after the dose).[58]

The effects of concurrent administration of alcohol and zolpidem 10 or 15mg on psychomotor performance have been assessed over a 5-hour postdose period in 24 healthy volunteers.[59] Results suggest that the combination has no more than additive effects.[59]

1.4 Effects on Memory

Recent studies confirm earlier findings[1] that zolpidem generally does not produce next-day memory impairment (6 to 10 hours after the dose) in patients with insomnia,[27,36] in healthy volunteers,[40-42,60] or in elderly volunteers with delayed sleep onset.[58] However, some impairment of memory was found in the first few hours after drug administration[40-42] and when using a higher dose than is currently recommended (15mg/70kg bodyweight).[61]

In comparative studies, zolpidem 10mg had effects on memory similar to or less than those of triazolam for up to 8 hours after a daytime dose.[41,42,45,62] Next-day memory effects of zolpidem were also similar to those of zopiclone in healthy volunteers[40] and similar to or less than those of flunitrazepam in healthy volunteers (table I) or patients with insomnia.[27,36] In contrast, volunteers receiving a single dose of zolpidem 10mg had significantly impaired memory (word recall) compared with recipients of zaleplon 10mg for up to 5 hours in a fully reported study.[51] In a study in 10 healthy volunteers, zolpidem 10 and 20mg were associated with significantly impaired free recall versus placebo at 24 hours ($p < 0.05$); differences among treatment groups (zolpidem and zaleplon 10 or 20mg and placebo) were significant ($p < 0.001$).[49] Zolpidem 10mg produced similar memory impairment to zaleplon 20mg when data from 11 studies were combined, according to a Committee for Proprietary Medicinal Products European Public Assessment Report.[56]

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Table I. Psychomotor effects of zolpidem (ZOL) in healthy volunteers: summary of data from comparative single dose crossover studies

Reference	No. of volunteers	Drugs (dosage) [mg]	Tests	Results
Comparison with flunitrazepam (FLU)				
Sicard et al.[44]	24	ZOL 10 FLU 1 PL	Tracking test (in 12 airforce ground personnel); simulated standardised flight test (in 12 experienced pilots)	ZOL ≡ FLU ≡ PL at 7 to 10.5h
Comparison with lormetazepam (LTZ)				
Cluydts et al.[13]	12	ZOL 10 LTZ 2 PL	Four Choice Reaction Test, Digit Span Memory Test, Symbol Digit Modalities Test	ZOL ≡ PL > LTZ for Four Choice Reaction Test at 9h ZOL ≡ LTZ ≡ PL for other tests at 9h
Comparisons with temazepam (TEM) or doxylamine (DOX)				
Erman et al.[11]ab	634	ZOL 10 TEM 15 PL	DSST, Symbol Copying Time	TEM ≡ PL > ZOL for DSST at 8h ZOL ≡ TEM ≡ PL for Symbol Copying Time at 8h
Gengo et al.[10]b	66	ZOL 10 DOX 25 TEM 30 PL	CRT, DSST	ZOL ≡ PL > TEM > DOX at 7h ZOL ≡ PL > TEM ≡ DOX at 9.5h
Comparisons with triazolam (TRZ) or TEM				
Berlin et al.[42]	18	ZOL 10 TRZ 0.25 PL	CFF, CRT, DSST, paired words associate test, pictures test, postural sway	PL > ZOL & TRZ at 1.5h ZOL & PL > TRZ for some memory and performance tests at 4h ZOL ≡ TRZ ≡ PL at 6 to 8h
Greenblatt et al.[45]	18	ZOL 10 TRZ 0.25	DSST	ZOL ≡ TRZ at 1h
Mintzer et al.[46]	11	ZOL 5-20 TRZ 0.125-0.5[c]	DSST, circular lights, balance, computerised trail-making	ZOL ≡ TRZ. Effects on psychomotor performance peaked at 1-1.5h for ZOL and 1.5-2h for TRZ
Rush et al.[47]	11	ZOL 5-20 TRZ 0.125-0.5 TEM 15-60[c]	Digit entry and recall, repeated acquisition, DSST and circular lights task	ZOL 5 & 10, TRZ 0.125 & 0.25, TEM 15 & 30 ≡ PL to 6h PL > ZOL 20, TRZ 0.5, TEM 60 to 6h
Wesensten et al.[48]ad	70	ZOL 5-15 TRZ 0.125-0.5	Logical reasoning, column addition, repeated acquisition	ZOL 15 & TRZ 0.5 impaired performance at 1.5h but not 6h after dose
Comparisons with zaleplon (ZAL) or TRZ				
Greenblatt et al.[49]	10	ZOL 10 & 20 ZAL 10 & 20 PL	DSST, free recall	PL > ZOL 20 for DSST at 4h PL > ZOL 10 & 20 for free recall at 24h ZAL 10 & 20 ≡ PL for DSST and free recall
Troy & Darwish[43,50]	24	ZOL 10 ZAL 10 TRZ 0.25 PL	Word recall, paired associates test, Digit Span Test, DSST, Divided Attention Test	ZAL ≡ PL > ZOL & TRZ for most tests at 1.25h and for delayed word recall test at 8.25h
Danjou et al.[51]	36	ZOL 10 ZAL 10	DSST, CRT, CFF, Sternberg Memory Scanning Test	ZAL > ZOL for some tests at 2 to 5h
Comparisons with zopiclone (ZOP), loprazolam (LOP) or FLU				
Allain et al.[40]	16	ZOL 10 ZOP 7.5 FLU 1 PL	CFF, clinical stabilometric platform, memory tests	PL > ZOL, ZOP & FLU from 1 to 7 or 10h ZOL & FLU > ZOP for postural sway at 4 to 7h ZOL ≡ ZOP > FLU for word recall at 1.25h
Bocca et al.[52]	16	ZOL 10 ZOP 7.5 FLU 1 PL	Driving performance, occular saccade	At 10h: PL > ZOP & FLU and ZOL ≡ PL for driving performance; PL > ZOP, PL ≥ FLU and PL ≡ ZOL for saccadic eye movements latency At 12h: ZOL ≡ ZOP ≡ FLU ≡ PL

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Hergueta et al.[53]b	16	ZOL 10 ZOP 7.5 LOP 1 PL	CFF, CRT, paired word associate test, Iconic memory test	PL > ZOL ≡ ZOP ≡ LOP at 1.5h CRT impaired with LOP & ZOP (not ZOL) *vs* baseline at 8h
Uchiumi et al.[54,55]	12	ZOL 10 ZOP 7.5	Tapping test, CFF, Letter Cancellation Task	ZOL > ZOP for tapping test ZOL ≡ ZOP for CFF and Letter Cancellation Task

a Parallel group design.

b Study reported as an abstract or poster.

c Drug dosages were based on a 70kg individual.

d Volunteers slept in a non-sleep conducive chamber to simulate military troop transport.

CFF = Critical Flicker Fusion test; **CRT** = Choice Reaction Time; **DSST** = Digit Symbol Substitution Test; **PL** = placebo; **>** indicates a significantly ($p \leq 0.05$) better psychomotor profile (i.e. less impairment) than comparator; ≡ indicates similar effects.

1.5 Abuse and Dependence Liability

Physical dependence has developed in nonhuman primates given zolpidem[63-65] (reviewed by Rush[66] and Stephens & Sanger[67]). However, zolpidem appears to be associated with a low abuse and dependence potential in humans (relevant studies in patients are discussed in section 4.3.2).

Results of studies in healthy volunteers investigating the relative potential for abuse with zolpidem and triazolam have been inconsistent. In healthy volunteers, the discriminative stimulus effects of zolpidem (which may be relevant to the potential for abuse of the drug) were similar to those of triazolam in 2 studies that used the 2-response discriminative procedure.[47,68] Zolpidem (5 to 20 mg/70kg[47] or 2.5 to 20mg[68]) and triazolam (0.125 to 0.5 mg/70kg[47] or 0.0625 to 0.5mg[68]) were given to 4[68] or 11[47] volunteers in these trials. In contrast, the results of a study using a 3-response drug discrimination procedure (considered by the study authors to be more sensitive than a 2-response procedure to between-drug differences) in 17 healthy volunteers demonstrated that zolpidem 20 mg/70kg has different discriminative stimulus effects from those of triazolam 0.5 mg/70kg.[69]

In 10[70] or 15[71] volunteers with histories of alcohol and drug abuse, zolpidem 15 to 45mg was thought to have similar abuse potential to triazolam 0.25 to 0.75mg based on individuals' ratings of drug liking.[70] Zolpidem 10 or 15mg appeared to have modest abuse potential and this was not appreciably increased by the concomitant administration of alcohol in 41 individuals who reported previous social use of alcohol and psychoactive drugs.[72]

The abuse liability of a drug may also be influenced by the development of tolerance (a decrease in drug efficacy or potency). Tolerance to zolpidem did not develop in mice, in contrast with the effects of classical benzodiazepines,[1,73-76] but was apparent in baboons to a similar extent as with midazolam.[65] Tolerance was not reported in clinical trials of long term zolpidem treatment for up to 6 months, although there have been case reports of tolerance to zolpidem when high doses of the drug were taken for long periods (section 3.3).

1.6 Other Effects

Zolpidem has no clinically significant effects on respiration in most volunteers[1,15,77,78] or in patients with chronic obstructive pulmonary disease.[26,79-81] There is evidence, however, that zolpidem increases apnoea in patients prone to this condition,[16,82] and the drug is contraindicated in patients with obstructive sleep apnoea (section 6).

Administration of a 10mg dose of zolpidem did not affect the nocturnal profile of growth hormone, thyrotropin or luteinising hormone in healthy male[83,84] or female[85] volunteers. Modestly increased prolactin levels, within the physiological range, were observed in female volunteers.[85] Moreover, zolpidem did not affect nocturnal

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growth hormone levels in children (mean age 11 years).[84]

2. Overview of Pharmacokinetic Properties

The pharmacokinetics of zolpidem have been reviewed previously[1,86] and are summarised in table II.

Zolpidem is rapidly absorbed, has a bioavailability of approximately 70% after oral administration, and does not accumulate after multiple doses. The drug is highly protein bound. Zolpidem is extensively metabolised to 3 inactive metabolites by a range of cytochrome P450 isoenzymes, predominantly CYP3A4. The majority of a dose is excreted as metabolites in the bile, urine and faeces and only minute amounts of unchanged zolpidem have been detected in excreta (table II). The mean elimination half-life ($t_{1/2}$) of zolpidem was 2.6 hours for a 5mg dose and 2.5 hours for a 10mg dose.[89]

Plasma concentrations of zolpidem are increased and elimination is reduced in the elderly and in patients with hepatic impairment or chronic renal insufficiency (table II). Lower initial dosages of zolpidem are recommended in the treatment of the 2 former patient groups (see section 6). Patients' ethnicity does not appear to affect the pharmacokinetics of zolpidem.

3. Therapeutic Efficacy

The efficacy of zolpidem 10 mg/day has been confirmed in large noncomparative trials of 3 to 4 weeks' duration in general practice patients,[90,91] hospitalised patients[92] and elderly patients[93] and in well-designed placebo comparisons (dosage 10 to 20 mg/day for ≤35 days) in patients with acute and chronic insomnia,[28,29,94-98] including those receiving concomitant treatment with selective serotonin reuptake inhibitors (SSRIs).[98] This section concentrates on comparisons with other hypnotics in adult populations (section 3.1) and studies specifically in elderly patients (section 3.2).

Patients generally had 2 or more of the following symptoms:

- sleep onset latency >30 minutes

Table II. Summary of the pharmacokinetic properties of zolpidem[1,86-89]

Absorption and distribution
• Absolute bioavailability ≈70% after oral doses of 0.5 to 20mg
• C_{max} of 59 or 121 μg/L reached 1.6h after a 5 or 10mg dose, respectively, with similar values reached after long term administration
• Pharmacokinetics linear over 5 to 20mg dose range
• Highly bound to plasma proteins (≈92% in healthy volunteers)
• Small amounts (0.004 to 0.019%) of a 20mg dose secreted into breast milk within 3h
• Vd 0.54 L/kg after an 8mg intravenous dose
Metabolism and elimination
• Metabolised by cytochrome P450 (CYP) isoenzymes CYP3A4 (≈60%), CYP2C9 (≈22%), CYP1A2 (≈14%), CYP2D6 and CYP2C19 (both ≈3%) into 3 metabolites (all pharmacologically inactive)
• 79 to 96% of a dose excreted as metabolites in bile, urine and faeces (<1% of dose excreted unchanged in urine)
• $t_{1/2}$ 2.6 or 2.5h, respectively, after administration of 5 or 10mg dose in healthy volunteers
• CL 0.26 L/h/kg after an 8mg intravenous dose
Pharmacokinetics in specific patient groups
• Increased AUC, C_{max}, $t_{1/2}$ and t_{max} in elderly volunteers (>70 years) *vs* adults (19 to 45 years)
• Increased $t_{1/2}$, C_{max}, AUC and unbound fraction in plasma (11%) in pts with cirrhosis *vs* healthy volunteers
• Increased Vd, AUC and $t_{1/2}$ in pts with chronic renal insufficiency not on dialysis *vs* healthy volunteers
• Pharmacokinetics similar (AUC increased by 20% in 1 study) in pts with end-stage renal failure undergoing dialysis *vs* healthy volunteers
• Ethnicity does not affect zolpidem pharmacokinetics

AUC = area under the plasma concentration-time curve; **CL** = systemic clearance; **C_{max}** = mean maximum plasma concentration; **pts** = patients; **$t_{1/2}$** = plasma elimination half-life; **t_{max}** = time to reach C_{max}; **Vd** = volume of distribution.

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- total sleep time <6 hours
- >3 nocturnal awakenings
- daytime complaints, including fatigue, associated with disturbed sleep.

Some trials considered the efficacy of zolpidem in patients with chronic insomnia (symptoms of insomnia present for >1 month).

Oral zolpidem and comparators were taken once daily before bedtime for ≤4 weeks in clinical trials. The dosage of zolpidem was 10 mg/day in adults and 5 mg/day in the elderly unless stated otherwise. In most trials, active treatment was preceded by a 2- or 3-day placebo run-in period. Clinical trials of zolpidem generally excluded patients with psychiatric disorders but a number of studies, discussed in sections 3.1 and 3.2, specifically assessed the efficacy of the drug in this patient group.

Efficacy was usually determined subjectively by patients' responses to questionnaires including assessments of sleep onset latency, sleep duration and quality, number of nocturnal awakenings, dreams and morning condition or patients' visual analogue scale (VAS) scores for particular variables. In some trials, nurses or physicians assessed the efficacy of treatments or objective data were obtained with polysomnography.

3.1 Comparisons with Other Hypnosedatives

In the following subsections, benzodiazepines have been classified as long acting ($t_{1/2}$ ≥18 hours), intermediate acting ($t_{1/2}$ ≈6 to 17 hours) or short acting ($t_{1/2}$ <6 hours). Clinical residual effects are tabulated along with efficacy results to give a balanced view of the clinical profile.

3.1.1 Long-Acting Benzodiazepines

Zolpidem 10 or 20 mg/day has hypnotic efficacy generally equivalent to that of flunitrazepam, nitrazepam and flurazepam; differences noted in clinical trials were few and inconsistent.

Zolpidem in a single 10mg dose did not differ from flunitrazepam 2mg (a higher than usual dose) in a small study in women with chronic insomnia.[27] Zolpidem and flunitrazepam significantly improved sleep latency and the number of awakenings versus placebo, and flunitrazepam also improved the duration of sleep and sleep quality versus placebo (table III).

At a dosage of 10 mg/day, zolpidem was as effective as nitrazepam 5 mg/day in psychiatric patients in the larger of two 14-day trials comparing these 2 drugs (table III). In the other trial, which excluded psychiatric patients, significantly more zolpidem than nitrazepam patients rated their treatment as 'useful' or better based on their improvement in sleep and the tolerability of the drug (62.5 *vs* 43.3%, $p \leq 0.05$).[100]

Zolpidem 10 or 20 mg/day and flurazepam 30 mg/day were both effective hypnotics over 3 days in a well controlled trial in patients with insomnia (table III).[39] Flurazepam recipients reported significantly better sleep quality than patients receiving zolpidem 10 or 20 mg/day ($p < 0.001$), although next-day performance (the primary efficacy parameter assessed with the Symbol Copying Test and DSST) was better with zolpidem than flurazepam, as discussed in section 1.3.1. In addition, zolpidem recipients had a significantly greater improvement from baseline versus placebo and flurazepam in subjectively assessed sleep latency on all treatment nights and in objectively assessed sleep latency on nights 1 and 3 ($p \leq 0.05$).[39]

3.1.2 Intermediate- and Short-Acting Benzodiazepines

The efficacy of zolpidem 10 mg/day was equivalent to that of the short-acting benzodiazepine triazolam 0.25 mg/day for sleep variables in three 14-day trials, according to patients' assessments[101-103] or polysomnographic data[102] (table IV). However, the change in sleep duration with zolpidem tended to be longer than with triazolam 0.5 mg/day when measured objectively in a 27-day comparison (113 *vs* 41 minutes), but the difference was not statistically significant in this small trial.[30]

A small 10-day trial reported as an abstract showed that, compared with temazepam, zolpidem significantly improved time to sleep onset and sleep quality (both $p \leq 0.05$) and tended to improve objectively assessed wake time after sleep onset (10.2 *vs* 6.6 minutes).[104]

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Table III. Summary of double-blind trials comparing the hypnotic efficacy of zolpidem (ZOL) with long-acting benzodiazepines in patients with insomnia

Reference	Study design (duration) [pt type]	No. of evaluable pts	Drugs and dosages (mg/day)	Results[a]				
				sleep latency	no. of awakenings	duration of sleep	sleep quality	clinical residual effects
Comparison with flunitrazepam (FLU)								
Vermeeren et al.[27]	co (1 day) [women with chronic insomnia]	17 17 17	ZOL 10 FLU 2 PL	ZOL ≡ FLU > PL[b]	ZOL ≡ FLU > PL	FLU > PL ZOL ≡ PLb	FLU > PL ZOL ≡ PL	PL > FLU & ZOL ≡ PL for daytime sleepiness and activation
Comparison with flurazepam (FLR)								
Fleming et al.[39]	mc, r, pll (3 days) [chronic insomnia]	35 35 36 35	ZOL 10 ZOL 20 FLR 30 PL	ZOL 10 ≡ ZOL 20 > FLR ≡ PL[b]		ZOL 10 ≡ ZOL 20 ≡ FLR > PLc	FLR > ZOL 10 ≡ ZOL 20 ≡ PL	
Comparisons with nitrazepam (NTR)								
Kazamatsuri et al.[99]	mc, r, pll (14 days) [pts with schizophrenia or manic depression]	73 74	ZOL 10 NTR 5	ZOL ≡ NTR	ZOL ≡ NTR	ZOL ≡ NTR	ZOL ≡ NTR	ZOL > PL, NTR ≡ PL &, ZOL ≡ NTR for physical condition upon awakening and during day
Kudo et al.[100]	mc, r, pll (14 days) [in- or outpts]	64 67	ZOL 10 NTR 5		ZOL ≡ NTR		ZOL ≡ NTR	ZOL ≡ NTR for physical condition upon awakening and during day

a All values subjectively assessed by patients unless otherwise noted.

b Values assessed using polysomnography.

c Data not shown.

co = crossover; **inpts** = inpatients; **mc** = multicentre; **outpts** = outpatients; **pll** = parallel; **PL** = placebo; **PL-R** = placebo run-in period; **pts** = patients; **r** = randomised; ≡ indicates efficacy similar to that of comparator; **>** indicates significantly greater efficacy ($p \leq 0.05$) than comparator.

3.1.3 Nonbenzodiazepine Hypnosedatives

Zolpidem had equivalent hypnotic efficacy to the antihistamine doxylamine 15 mg/day according to Spiegel's questionnaire scores after 15 days' treatment in a large trial (n = 338) [table IV].[107] Both drugs also had similar global efficacy.

Similarly, zolpidem and the antidepressant trazodone 50 mg/day had equivalent effects on a range of sleep variables, including patient global impression of therapy effect, in a placebo-controlled study in 278 patients who did not have depression.[109] The only statistically significant difference observed between active treatment groups was shorter sleep latency with zolpidem than trazodone at week 1 of the 2-week treatment period (48.2 *vs* 57.7 minutes, $p < 0.037$).

A large placebo-controlled 4-week study compared zolpidem 10 mg/day with zaleplon 5 to 20 mg/day but did not evaluate whether differences between these active treatments were statistically significant (table IV).[105] Zolpidem and zaleplon 20 mg/day were generally significantly more effective than placebo for sleep latency, sleep duration and quality of sleep throughout the study; however, the usual dosage of zaleplon (10 mg/day) significantly improved only sleep latency versus placebo.

Compared with placebo, sleep duration was increased with zolpidem during all 4 weeks of treatment ($p \leq 0.001$) and with zaleplon 20 mg/day for all weeks apart from week 3 ($p \leq 0.05$) [see fig. 1]. The proportion of patients reporting improved sleep quality from baseline was significantly greater with zolpidem than placebo at weeks 1 (61.4 *vs* 45.7%, $p = 0.017$) and 4 (66.7 *vs* 52.4%, $p = 0.038$). Furthermore, mean scores for sleep

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Table IV. Summary of double-blind, parallel trials comparing the hypnotic efficacy of zolpidem (ZOL) with short-acting benzodiazepines and nonbenzodiazepine hypnosedatives in patients with insomnia

Reference	Study design (duration of active treatment)	No. of evaluable pts	Drugs and dosages (mg/day)	Results[a]				
				sleep latency	no. of awakenings	duration of sleep	sleep quality	clinical residual effects
Comparison with temazepam (TEM)								
Kerkhof et al.[104]b	r (10 days)	17 13	ZOL 10 TEM 20	ZOL > TEM			ZOL > TEM	
Comparisons with triazolam (TRZ)								
Monti et al.[30]	r (27 days)	8 8 8	ZOL 10 TRZ 0.5 PL	ZOL ≡ TRZ ≡ PL[c]		ZOL ≥ TRZ ≥ PL[c]		
Rosenberg et al.[101]	mc, r (14 days)	71 68	ZOL 10 TRZ 0.25		ZOL ≡ TRZ	ZOL ≡ TRZ	ZOL ≡ TRZ	ZOL ≡ TRZ for morning feeling, daytime alertness and subjective day feeling
Silvestri et al.[102]	mc, r (14 days)	10 10	ZOL 10 TRZ 0.25	ZOL ≡ TRZ[c]	ZOL ≡ TRZ[c]	ZOL ≡ TRZ[c]	ZOL ≡ TRZ	
Tsutsui et al.[103]	mc (14 days)	63 68	ZOL 10 TRZ 0.25		ZOL ≡ TRZ	ZOL ≡ TRZ		ZOL ≡ TRZ for physical state during following day
Comparisons with nonbenzodiazepine hypnosedatives								
Elie et al.[105]d	mc, r (28 days)	115 113 112 116 118	ZOL 10 ZAL 5 ZAL 10 ZAL 20 PL	ZOL > PL ZAL 5, 10 & 20 > PL	ZOL ≡ PL ZAL ≡ PL	ZOL > PL ZAL 20 > PL ZAL 5 & 10 ≡ PL	ZOL > PL ZAL 10 & 20 ≥ PL ZAL 5 ≡ PL	
Fry et al.[106]bd	mc, r (28 days)	598	ZOL 10 ZAL 5 ZAL 10 ZAL 20 PL	ZAL 20 > ZOL 10	ZAL 20 > PL ZAL 5 & 10 ≡ PL	ZAL 20 > PL ZAL 5 & 10 ≡ PL	ZAL 20 > PL ZAL 5 & 10 ≡ PL	
Schadeck et al.[107]	mc, r (15 days)	118 111 109	ZOL 10 DOX 15 PL	ZOL ≡ DOX > PL	ZOL ≡ DOX > PL	ZOL ≡ DOX > PL	ZOL ≡ DOX > PL	ZOL ≡ DOX > PL for morning condition
Tsutsui et al.[108]e	mc, r (14 days)	209 219	ZOL 10 ZOP 7.5	ZOL > ZOP	ZOL ≡ ZOP	ZOL ≡ ZOP	ZOL ≡ ZOP	
Walsh et al.[109]	mc, r (14 days)	91 90 97	ZOL 10 TRZ 50 PL	ZOL ≥ TRZ ZOL > PL TRZ ≥ PL	ZOL ≡ TRZ > PL	ZOL ≡ TRZ ZOL > PL TRZ ≥ PL	ZOL ≡ TRZ > PL	ZOL ≡ TRZ for morning sleepiness

a All values subjectively assessed by patients unless otherwise noted.
b Reported as an abstract.
c Values assessed using polysomnography.
d Comparisons not made between zolpidem and zaleplon for most efficacy parameters unless otherwise indicated.
e Unpublished data.

DOX = doxylamine; **mc** = multicentre; **PL** = placebo; **pts** = patients; **r** = randomised; **TRZ** = trazodone; **ZAL** = zaleplon; **ZOP** = zopiclone; ≡ indicates efficacy similar to that of comparator; **>** indicates significantly greater efficacy ($p \leq 0.05$) than that of comparator; ≥ indicates tendency for better effect than comparator.

quality were significantly better with zolpidem 10 mg/day than with placebo during weeks 1 to 4 ($p < 0.05$). Apart from improved mean scores at week 1, zaleplon recipients reported no significant differences in sleep quality versus placebo.[105] Both zaleplon and zolpidem improved sleep latency and significant differences versus placebo were observed for zolpidem and zaleplon 5 mg/day at

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weeks 1 to 3 and for zaleplon 10 and 20 mg/day at weeks 1 to 4 ($p \leq 0.05$) [results were presented graphically].

In another large 4-week study that has yet to be published in full, zaleplon 20 mg/day was significantly more effective than zolpidem at improving sleep latency (table IV).[106] However, comparisons between zolpidem and zaleplon 5 to 20 mg/day or zolpidem and placebo were not reported for other efficacy parameters, and only the largest dosage of zaleplon was associated with significant improvements in sleep duration, number of awakenings and sleep quality versus placebo.[106]

Zolpidem 10 mg/day had equivalent efficacy to zopiclone 7.5 mg/day for the treatment of insomnia in a large unpublished double-blind, randomised study (n = 479) [table IV]. The only significant between-group difference was that a greater proportion of zolpidem than zopiclone recipients experienced improvement in sleep latency (85.8 *vs* 77.5% of patients, $p = 0.041$).[108] A similar proportion of zolpidem and zopiclone recipients rated their sleep disorder as being 'markedly improved' (18.7 *vs* 16.4%) or 'moderately improved' (67.9 *vs* 61.6%).[108]

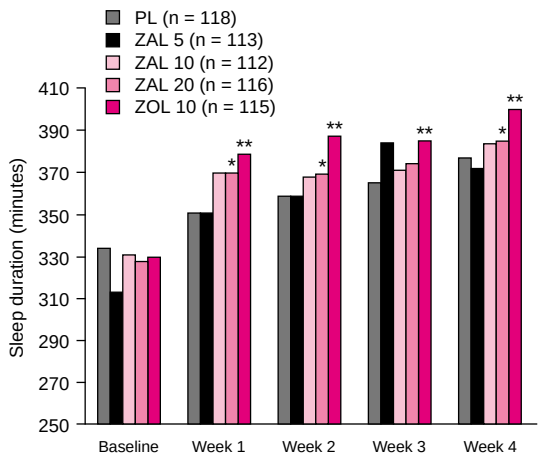

Fig. 1. Efficacy of placebo (PL), zaleplon (ZAL) 5 to 20 mg/day and zolpidem (ZOL) 10 mg/day in patients with insomnia [the usual dosage of zaleplon is 10 mg/day (maximum recommended dosage 10 mg/day in Europe[56] and 20 mg/day in the US[57])].[105] Median sleep duration at baseline and during 4 weeks' once daily treatment, assessed by patients using sleep questionnaires, in a double-blind, randomised, multicentre study. * $p \leq 0.05$, ** $p \leq 0.001$ *vs* placebo.

3.2 Efficacy in the Elderly

At the time of the previous review,[1] the efficacy of zolpidem had been assessed in few studies in elderly patients, although results were promising. Comparative efficacy data are now available from well controlled trials of 3 to 4 weeks' duration in 80 to 335 patients (table V). All studies assessed outcome variables subjectively from patient questionnaires.[110-112]

No dose-response relationship is apparent for zolpidem in the dose range of 5 to 20mg (table V); indeed, zolpidem 10mg provided better quality sleep than the 20mg dose in elderly patients with psychiatric disorders.[113] Zolpidem 5 mg/day appears to be the lowest effective dose for most sleep parameters[33] and it is recommended that this dosage is used in the treatment of elderly patients with insomnia (section 6). In comparative trials of zolpidem, the 5mg dose significantly improved sleep parameters including sleep duration and latency (table V) and sleep quality (no data presented) versus placebo.[111]

Zolpidem 5, 10 or 20 mg/day produced comparable improvements in sleep variables from baseline to flunitrazepam 1 mg/day, triazolam 0.125 or 0.25 mg/day and temazepam 15 mg/day in elderly patients with insomnia in 3- to 4-week trials (table V). In the largest comparison (n = 335), the only difference between active treatment groups was significantly shorter sleep latency in the zolpidem (5mg) and temazepam groups than the triazolam group at weeks 1 and 3 (44.7 and 43.1 *vs* 60.8 minutes and 43.5 and 39.1 *vs* 56.6 minutes, respectively; p values not given).[111] Results for improvements from baseline in sleep latency and duration at week 4 are shown in figure 2.

3.3 Tolerance

Long term efficacy data are useful for determining whether tolerance develops to zolpidem, although it should be noted that long term daily use

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Table V. Summary of double-blind, randomised, parallel, multicentre trials comparing the efficacy of zolpidem (ZOL) with the benzodiazepines flunitrazepam (FLU), triazolam (TRZ) and temazepam (TEM) in elderly patients (aged ≥58 years) with insomnia

Reference	Duration	No. of evaluable pts (type of pts)	Drugs and dosages (mg/day)	Results[a]				
				sleep latency	no. of awakenings	duration of sleep	sleep quality	clinical residual effects
Emeriau et al.[110]	4wk	80 (inpatients)	ZOL 10 ZOL 20 FLU 1	ZOL 10 ≡ ZOL 20 ≡ FLU	ZOL 10 ≡ ZOL 20 ≡ FLU	ZOL 10 ≡ ZOL 20 ≡ FLU	ZOL 10 ≡ ZOL 20 ≡ FLU	ZOL 10 ≡ ZOL 20 ≡ FLU for subjective state on awakening
Leppik et al.[111]	4wk	335 (pts with chronic insomnia)	ZOL 5 TRZ 0.125 TEM 15 PL	ZOL ≡ TEM ≡ TRZ[b]	ZOL ≡ TEM ≡ TRZ ≡ PL TRZ > PL	ZOL ≡ TEM ≡ TRZ ≡ PL	ZOL ≡ TEM ≡ TRZ[b]	ZOL ≡ TEM ≡ TRZ for morning sleepiness and ability to concentrate
Roger et al.[112]	3wk	205 (inpatients)	ZOL 5 ZOL 10 TRZ 0.25	ZOL 10 ≡ ZOL 5 ≡ TRZ	ZOL 10 ≡ ZOL 5 ≡ TRZ	ZOL 10 ≡ ZOL 5 ≡ TRZ	ZOL 10 ≡ ZOL 5 ≡ TRZ	ZOL 10 ≡ ZOL 5 ≡ TRZ for next-day freshness and alertness

a All values subjectively assessed by patients.

b Difference between active treatments and PL not reported.

PL = placebo; **pts** = patients; ≡ indicates efficacy similar to that of comparator; **>** indicates significantly greater efficacy ($p < 0.05$) than that of comparator.

of the drug is not recommended and the duration of treatment with zolpidem should not exceed 4 weeks (section 6).

There was no evidence of tolerance developing to zolpidem 20 mg/day in 2 double-blind, randomised trials of 3 months' duration in patients with insomnia who also had psychiatric disorders or were general practice patients at the time of the previous review in *Drugs*.[1] Data confirming previous results have become available from a number of additional 3- to 6-month trials that, apart from a double-blind, randomised study[114] and 2 single-blind studies,[115,116] were noncomparative and nonblind in design.[117-119] However, case reports have described tolerance to the hypnotic effects of zolpidem in patients taking the drug at high dosages for periods of 2 months to several years.[120-124] Patients steadily increased their zolpidem dosage to between 70 and 400 mg/day. Apart from 1 patient, all had depressive or personality disorders.

3.4 Discontinuous or 'As Needed' Use

Zolpidem 10 mg/day for 2 to 8 weeks (taken 'as needed' or for the first 5 days of each week) was found to be effective for the treatment of chronic insomnia based on patients' ratings in 3 randomised, double-blind, parallel studies[125-127] (1 trial has been published in full[127]).

'As needed' zolpidem for 4[125] or 8[126] weeks (n = 245[125] or 156,[126] respectively) was associated with significant improvements versus placebo in a number of parameters including sleep quality, Clinical Global Impression (CGI) scale scores,[125,126] number of awakenings and refreshed feeling in the morning.[126] In a pilot study in 154 patients, a discontinuous regimen of zolpidem (5 nights' treatment followed by 2 nights' placebo each week) for 2 weeks had similar hypnotic efficacy to a continuous regimen of zolpidem.[127] Sleep duration was improved from approximately 6 hours at baseline to 7 hours during treatment in both groups and sleep quality and CGI scores were improved equally with both regimens.[127]

4. Tolerability

4.1 General Profile

A number of studies have shown that zolpidem is well tolerated in patients with insomnia, including the elderly (section 4.1.1). Postmarketing studies of zolpidem have included a total of >76 000 patients, as reviewed by Allain et al.[128] or discussed in separate publications.[90,129-131] The most common adverse events are generally CNS-related, including nausea, dizziness and drowsiness.[128-131] The incidence of adverse events with

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zolpidem appears to be dose-related, particularly for CNS and gastrointestinal events in elderly patients.[132,133]

The 2 largest postmarketing studies to date showed a low rate of adverse events with zolpidem: 182 of 16 944 patients (1.1%) experienced 268 events[129] and 629 of 30 043 patients (2.1%) reported 1174 events.[90] The most common events with zolpidem were nausea, dizziness, malaise, nightmares, agitation and headache (each in 0.1 to 0.2% of patients)[129] or dizziness, hypotension, headache and nausea (reported by 0.3 to 0.5% of patients).[90] Other events including vomiting, somnolence and confusion occurred less frequently in 1 trial.[129] The only serious adverse event reported was paranoid symptoms in a 48-year-old woman.[129] Approximately 0.7%[129] and 1.2%[90] of patients withdrew from treatment because of adverse events. Events resulting in withdrawal included mainly CNS or gastrointestinal events[90] or, where specific details were given, the most common reasons for withdrawal were nausea, dizziness, nightmares and agitation.[129]

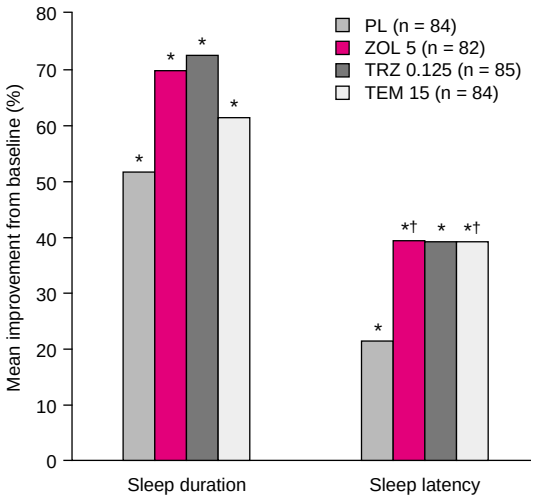

Fig. 2. Comparative efficacy of placebo (PL), zolpidem (ZOL) 5 mg/day, triazolam (TRZ) 0.125 mg/day and temazepam (TEM) 15 mg/day in elderly patients (59 to 85 years) with insomnia.[111] Mean improvement from baseline in sleep duration and latency after 28 days' treatment, assessed by patients using sleep questionnaires, in a double-blind, randomised, multicentre study. * $p < 0.001$ *vs* baseline; † $p < 0.05$ *vs* placebo.

Zolpidem 10 mg/day taken 'as needed' for 4[125] or 8[126] weeks was well tolerated and was associated with a similar incidence of adverse events to placebo in 2 well designed trials.

In comparative trials, the incidence and types of adverse events reported with zolpidem 10 mg/day were similar to those reported with triazolam 0.25 or 0.5 mg/day,[30,101-103] flurazepam 30 mg/day,[39] trazodone 50 mg/day,[109] zaleplon 5 to 20 mg/day,[105] doxylamine 15 mg/day[107] and nitrazepam 5 mg/day.[99,100] The incidence of adverse events was significantly higher with zopiclone than zolpidem in patients with insomnia in an unpublished study (45.3 *vs* 31.3%, $p < 0.01$).[108] The most common adverse events with zolpidem and active comparators were generally somnolence/drowsiness and headache. Withdrawal rates were similarly low for all active treatment groups.[30,39,99-103,105,107-109]

Amnesia, an adverse event associated with benzodiazepines,[134] was reported by 0.02% of 16 944 patients given zolpidem in one of the postmarketing surveillance studies discussed above.[129] However, there have been spontaneous reports of next-day anterograde amnesia in 4 patients with insomnia after taking zolpidem 10mg: 2 patients had taken 1 or 2 glasses of wine before taking zolpidem and another patient was taking fluvoxamine concomitantly.[135,136] The effects of zolpidem on memory, as assessed in pharmacodynamic studies, are discussed in section 1.4.

There have been instances of psychotic symptoms (hallucinations) in patients taking zolpidem.[136-141] Macropsia (in a woman with anorexia nervosa and low bodyweight)[140] and acute hepatitis (in conjunction with chronic alcohol intake in 1 patient)[142,143] have been reported rarely with zolpidem, although there was no relationship between zolpidem and 51 hepatic adverse events reported during a pharmacovigilance survey (≈930 treatment days).[144]

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4.1.1 In Elderly Patients

Zolpidem 5 mg/day was well tolerated in studies including only elderly patients with insomnia that were also discussed in section 3.2.[111,112] In addition, zolpidem 5 mg/day (n = 127) was associated with only mild neurological adverse events, including drowsiness (3.1% of patients), headache (1.6%), nightmares (1.6%), dizziness (0.8%) and agitation (0.8%), in pooled data from 21 studies in elderly patients (reported as an abstract).[145] Zolpidem 10 mg/day (n = 271) was associated with a higher incidence of adverse events and with events not reported with the lower dosage including falls (2.4%), confusional episodes (1.7%) and memory disorders (1.4%).[145]

In a trial in 335 elderly patients (mean age 69 years) with chronic insomnia, the incidence of adverse events was 63.4% with zolpidem 5 mg/day, a similar rate to that reported with triazolam 0.125mg (63.5%), temazepam 15mg (66.7%) and placebo (56%).[111] The most common adverse events with zolpidem were headache (18.3%), myalgia (9.8%), nausea (7.3%) and upper respiratory tract infection (7.3%), and there were no significant between-group differences for the incidence of events.[111] The overall frequency of adverse events was lower in a trial in elderly patients with a mean age of 81 years and was similar for zolpidem 5mg (16%), zolpidem 10mg (11%) and triazolam 0.25mg (21%).[112] Nightmares were the most common adverse event and were reported by 2 patients each in the zolpidem 5mg and triazolam groups and in 3 recipients of zolpidem 10mg.[112] Three zolpidem recipients from either trial withdrew because of adverse events: heart palpitations, drugged feeling[111] and pulmonary embolism[112] (the latter event was not thought to be treatment-related).

4.2 Clinical Residual Effects

The undesirable clinical effects of zolpidem during the morning and daytime after treatment compared with those of benzodiazepine and non-benzodiazepine hypnotics, are discussed below. Details of these studies and an overview of the comparative clinical residual effects are presented in tables III to V; it should be noted that studies were not primarily designed to assess this effect. Residual effects detected by psychomotor tests are discussed in section 1.3.

Zolpidem had similar next-day effects (including daytime well-being and morning coordination) to nitrazepam,[99,100] triazolam,[101,103] doxylamine,[107] and trazodone[109] in patients with insomnia. Similarly, in trials in elderly patients with insomnia, there were no statistically significant differences between zolpidem and triazolam or temazepam for morning sleepiness[111,112] and ability to concentrate.[111] Zolpidem and flunitrazepam had similar effects on morning condition in a trial in elderly patients.[110] However, one of 2 smaller studies in patients with chronic insomnia reported residual effects on daytime sleepiness and activation, as assessed by psychomotor tests, with flunitrazepam but not with zolpidem (section 1.3.1).[27]

A review (by Undén and Schechter[146]) of 34 trials involving 2511 patients with insomnia or healthy volunteers concluded that zolpidem had minimal next-day effects when given at recommended dosages.

4.3 Withdrawal Effects

4.3.1 Potential for Rebound Insomnia

There was no evidence of rebound insomnia (worsening from baseline values of insomnia symptoms) after sudden withdrawal of treatment with zolpidem 10mg daily for up to 6 months in previous studies[1] or in most,[28-30,96,97,102,105,107,111,112,115,117,147-149] but not all,[98,100,105,106] subsequent trials. In addition, sudden discontinuation of zolpidem 10 mg/day taken 'as needed' for 8 weeks was not associated with rebound insomnia.[126] In 2 comparisons, triazolam but not zolpidem was associated with rebound insomnia.[30,102] These results have been confirmed in a recent meta-analysis of data from 668 healthy volunteers or patients with insomnia taking zolpidem: the drug was not associated with rebound insomnia, on the basis of mean values, for the first 3 withdrawal nights and only mild first night re-

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bound insomnia (a significant increase in sleep latency only).[150] In contrast, triazolam was associated with significant rebound insomnia (n = 381).[150]

4.3.2 Withdrawal Reactions and Dependence Potential

There have been spontaneous reports of zolpidem dependency,[120-124,151-153] some of which involved patients with histories of substance abuse.[124,151] Patients had generally been taking zolpidem for several months or years. However, zolpidem was not included in a list of the 83 most commonly abused drugs in recent data from the US Substance Abuse and Mental Health Services Administration Drug Abuse Warning Network.[154]

Sudden discontinuation of zolpidem after 2 to 4 weeks' treatment was not associated with withdrawal symptoms in a number of double-blind randomised studies of continuous[28,30,96,98,107] or discontinuous or 'as needed'[125,127] administration or in a postmarketing surveillance study (n = 16 944).[129] However, the incidence of withdrawal effects was significantly greater with zolpidem than placebo on the first night, but not the second or third, after treatment discontinuation in a randomised, double-blind, placebo-controlled study.[105] In this study, a withdrawal effect was considered to have occurred if patients experienced ≥3 new symptoms on the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ).[155] Withdrawal of zaleplon 5 to 20 mg/day was not associated with any such effects in the above study; however, active treatments were not compared.[105]

The effects of gradual withdrawal of zolpidem 10 mg/day or zopiclone 7.5 mg/day after 3 months' treatment (longer than the recommended duration of treatment; section 6) have been assessed in 2 separate double-blind randomised studies.[156] Patients were randomised to continue receiving treatment for 3 weeks or to gradually have their treatment withdrawn (1 week at the same dosage, 1 week at half the previous dosage and 1 week with placebo). Possible withdrawal syndromes (defined as the occurrence of an adverse event between days 7 and 21, premature treatment discontinuation or an increase of ≥3 on the BWSQ) occurred in 38% of patients who withdrew from either zolpidem or zopiclone, a significantly greater proportion than in those who continued with treatment (24 and 20%, respectively, both $p < 0.05$ *vs* continuation group). However, it appeared that withdrawal symptoms may have been a relapse of patients' initial sleep problems.[156]

4.4 Overdosage

Garnier et al.[157] have reviewed the details of 344 cases of overdose, where the highest dose taken was 1400mg (the mean dose was approximately 190mg). Around half of the patients took other drugs concomitantly (predominantly neuropsychotherapeutics and alcohol). Drowsiness was the most common symptom and was reported in 89 patients. Vomiting occurred in 7 patients and coma in 4 patients (the latter event occurred with doses of 140 to 400mg); other events were rarely reported. Of the 185 patients for whom information on outcome were available, there was a fatal outcome for 10 patients, although few details were available for these patients. Most of the remaining patients recovered without sequelae. Zolpidem overdose was treated with the benzodiazepine antagonist flumazenil, gastric lavage or activated charcoal.[157] In an additional report discussed previously (n = 20)[1] and a case series (n = 10),[158] all patients recovered after taking an overdosage of zolpidem (70 to 390mg): somnolence was the most common symptom.

There have been other spontaneous reports of fatalities in patients taking zolpidem.[159-162] In 1 patient, the estimated dose of zolpidem was 600mg; however, the cause of death was determined to be drowning.[159] In other fatalities, patients took overdoses of multiple drugs in addition to zolpidem (hydrocodone and morphine,[160] meprobamate and carisoprodol[161] or acepromazine[162]).

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5. Drug Interactions

Possible interactions between oral zolpidem (generally given at 10 mg/day) and coadministered drugs have been studied in healthy volunteers.

The coadministration of zolpidem and cimetidine, ranitidine,[163] haloperidol or imipramine[164] did not affect the pharmacokinetics of either drug. In addition, zolpidem did not affect antipyrine clearance and would therefore not be expected to induce or inhibit hepatic enzymes.[165]

Despite this apparent lack of pharmacokinetic interaction, cimetidine, chlorpromazine and imipramine increased the sedative effects of zolpidem,[163,164,166] whereas caffeine had no effects on zolpidem-induced sedation.[167] Five of 8 volunteers who received zolpidem plus imipramine developed anterograde amnesia.[164]

Rifampicin reduced the plasma concentration and pharmacodynamic effects of zolpidem.[168]

Ketoconazole increased the $t_{1/2}$ and AUC of zolpidem and decreased the apparent oral clearance of the drug.[169] Itraconazole also increased the AUC of zolpidem when the drugs were coadministered.[170] However, ketoconazole, but not itraconazole, enhanced zolpidem-related impairment of psychomotor function.[169,170] Fluconazole did not affect the pharmacokinetics of zolpidem.[169]

No clinically significant drug interactions were observed between zolpidem and the SSRIs fluoxetine and sertraline in studies in healthy volunteers. When zolpidem and fluoxetine were coadministered, zolpidem t_{max} and fluoxetine AUC and C_{max} increased in male volunteers[171] and zolpidem $t_{1/2}$ increased in female volunteers.[172] None of these pharmacokinetic changes were considered to be clinically significant and there were no changes in pharmacodynamic parameters.[171,172] Zolpidem t_{max} was reduced (by 53%) and C_{max} was increased (by 43%) when zolpidem and sertraline were given together for 5 days in female volunteers; however, there were no significant pharmacodynamic interactions between the drugs.[173]

Concomitant administration of triazolam and ritonavir resulted in a significant reduction in triazolam clearance and potentiation of the psychomotor effects of the drug, whereas there were no clinically relevant changes in the pharmacodynamics or pharmacokinetics of zolpidem when that drug and ritonavir were given together (n = 6).[174] The authors of this unpublished abstract concluded that these differences are accounted for by the contribution of a number of CYP isoenzymes to the metabolism of zolpidem (table II) versus the dependence of triazolam clearance on CYP3A.[174]

Case reports in patients with insomnia have described possible drug interactions between zolpidem and sertraline, desipramine, fluoxetine, bupropion or venlafaxine (hallucinations)[175,176] and warfarin (increased prothrombin levels).[177]

6. Dosage and Administration

It is recommended that zolpidem is given orally immediately before bedtime for the treatment of insomnia. The maximum recommended dosage of zolpidem is currently 10 mg/day in adults.[132,178] Each course of zolpidem should not exceed 4 weeks.[132]

In patients with hepatic impairment and the elderly, zolpidem should be initiated at a dosage of 5 mg/day and these patients should be closely monitored.[132,178] The maximum recommended dosage of zolpidem in the elderly is 10 mg/day (5 mg/day in the UK[132]). No dosage reduction is required in patients with renal impairment, although this group should also be closely monitored.[178] It may be necessary for lower than recommended dosages of zolpidem to be given when the drug is coadministered with drugs having depressant effects on the CNS, because of potential additive effects.[132,178] Zolpidem is contraindicated in patients with severe hepatic impairment, obstructive sleep apnoea, acute pulmonary impairment or respiratory depression,[132] and the drug should be given with caution to patients with depression.[132,178] The use of zolpidem during pregnancy is not recommended because the effects of the drug in this patient group have not been established.[132,178] Small amounts of zolpidem are excreted in the breast milk (table II) and therefore the

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drug should not be used in women who are breast feeding.[132,178]

7. Place of Zolpidem in the Management of Insomnia

Insomnia, a disturbance of the usual sleep pattern including the inability to fall asleep or maintain sleep, or sleep that is nonrefreshing or nonrestorative, is thought to affect approximately one-third of the population.[179-181] Of these patients, approximately 17% consider that their symptoms seriously affect their lives.[180] Symptoms of insomnia are most frequent in elderly individuals. Indeed, it has been estimated that 40% of the elderly population experiences intermittent or moderate insomnia.[182]

Insomnia is recognised as being a symptom of a number of different disorders. Apart from intrinsic sleep disorders (including psychophysiological insomnia and restless legs syndrome), insomnia may be a result of extrinsic factors (such as inadequate sleep hygiene or altitude insomnia), circadian rhythm problems or mental disorders.[183] Insomnia can also be classified according to the duration of symptoms. Transient (2 to 3 days' duration) and short term (<3 weeks' duration) insomnia are usually clearly related to stressors, whereas the cause of chronic insomnia (duration >3 weeks) is often difficult to determine.[134,180]

Insomnia is thought to be associated with substantial costs. For example, in the US, it was estimated that the direct costs of insomnia, including costs arising from healthcare services and drug therapy, were $US13.9 billion in 1995.[184]

Despite the high prevalence of insomnia, fewer than half of those with frequent sleep problems seek professional help. Behavioural and educational interventions, including relaxation techniques, sleep hygiene and cognitive therapy, play an important part in the management of short term or chronic insomnia.[183,185,186]

Pharmacological intervention may be used in conjunction with behavioural treatment when nonpharmacological methods do not sufficiently manage symptoms of insomnia. Benzodiazepine hypnotics have been widely used for the treatment of insomnia since the 1970s.[187] Although these drugs are effective hypnotic agents, there has been some concern regarding the potential for withdrawal reactions, rebound insomnia and dependency with benzodiazepines. Recently, there has been a trend for the use of short-acting nonbenzodiazepine hypnotic agents including zolpidem and the cyclopyrrolone agent zopiclone which have partly superseded the benzodiazepines for the treatment of insomnia.[188] There is also increasing use of antidepressants for the treatment of insomnia, although there is little controlled evidence for the efficacy of this class of drugs in patients with chronic insomnia who do not have depression.[189]

Since the previous review of zolpidem in *Drugs*,[1] a considerable amount of new data has become available confirming the efficacy of once daily oral zolpidem for the treatment of insomnia. Data from short term trials in adults have shown that zolpidem has generally equivalent hypnotic efficacy to the benzodiazepines flunitrazepam, flurazepam, nitrazepam and triazolam as well as nonbenzodiazepine hypnotic agents such as zopiclone and trazodone, and better efficacy than the benzodiazepine temazepam. The efficacy of a recently available nonbenzodiazepine hypnotic zaleplon relative to that of zolpidem remains unclear: although 2 large studies have been conducted, they predominantly compared results for active treatments (zolpidem and zaleplon) against placebo but not each other. More rigorous comparative data and clinical experience with zaleplon are needed to address this issue. Studies performed to date have shown that zaleplon reduces sleep latency, but that it is not effective for increasing sleep duration or reducing the number of awakenings.[56,57]

The efficacy of zolpidem in elderly patients is now confirmed, with the drug showing similar efficacy to flunitrazepam, temazepam and triazolam.

Zolpidem was associated with a low incidence of adverse events in clinical trials in patients with insomnia, including the elderly. Nausea, dizziness

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and drowsiness were generally the most frequent adverse events with the drug. Respiration is not significantly affected with zolpidem in most patients, apart from those with sleep apnoea in whom the drug is contraindicated.

Zolpidem produced some impairment of psychomotor function and memory the first few hours after administration; however, as expected from its short $t_{1/2}$, the drug had few next-day effects, which is important in the context of 'before bed' hypnotic use. In patients with insomnia, the next-day effects of zolpidem were in the main similar to those of benzodiazepines and nonbenzodiazepine hypnotics. Zaleplon produced less psychomotor and memory impairment than zolpidem in healthy volunteers, particularly in the first few hours after drug administration. However, comparative data on the clinical residual effects of zaleplon and zolpidem are not yet available in patients with insomnia.

There have been concerns that shorter acting hypnotic agents may cause greater rebound and withdrawal problems than long-acting drugs.[188] Rebound insomnia was not seen with zolpidem in most of a large number of trials including a withdrawal period. Similarly, withdrawal symptoms were infrequently seen in clinical trials.

There was no evidence of tolerance to the hypnotic effects of zolpidem in a number of clinical trials of up to 6 months' duration. However, there have been spontaneous reports of tolerance and dependence to the drug in patients, usually those with psychiatric disorders, taking high dosages for periods of up to several years. Tolerance is unlikely to develop to zolpidem in the context of use of the drug for the recommended period of 4 weeks. Pharmacological data to date in volunteers are inconsistent as to the comparative abuse potential of zolpidem and triazolam, although clinical experience suggests that the abuse potential of zolpidem is low.

Although little investigated for hypnotics apart from zolpidem,[190] discontinuous or 'as needed' administration may be a feasible strategy for the treatment of chronic insomnia,[190] particularly in view of concern for the possibility of dependence or tolerance with regular long term nightly use of hypnotics.[191] Discontinuous regimens of zolpidem ('as needed' or 5 days per week) have shown promise for the treatment of insomnia and sudden discontinuation of therapy was not associated with rebound insomnia or withdrawal symptoms.

In summary, zolpidem is effective and well tolerated in patients with insomnia, including the elderly. Studies have shown that zolpidem generally has similar efficacy to other hypnotics including benzodiazepines and zopiclone. Zolpidem appears to have minimal next-day effects on cognition and psychomotor performance when administered at bedtime. In addition, there is little evidence of tolerance to the hypnotic effects of zolpidem, or rebound insomnia or withdrawal symptoms after discontinuation of the drug when it is given as recommended (10 mg/day for <1 month) or over longer periods.

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