Eszopiclone: its use in the treatment of insomnia

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Abstract: Eszopiclone is the S-isomer of racemic zopiclone, a cyclopyrrolone with sedative-hypnotic activity that has been available in Europe, Canada, and Latin America since 1987. Eszopiclone acts by binding to the $GABA_A$ receptor. In contrast to the benzodiazepine (BZD) hypnotics, eszopiclone has more selectivity for certain subunits of the $GABA_A$ receptor. Oral eszopiclone is rapidly absorbed and extensively distributed to body tissues including the brain. Peak plasma concentrations are attained 1.0–1.6 hours after a 3 mg dose, while the mean elimination half-life is 6 hours. The half-life increases with age to about 9.0 hours in patients 65 years or older. Eszopiclone's pharmacokinetic (PK) profile is not substantially modified in patients suffering from renal failure or mild-to-moderate hepatic impairment, although patients with severe hepatic insufficiency should have a reduced dose. The subjective perception of improved sleep following eszopiclone 2 or 3 mg treatment has been demonstrated in randomized, double-blind, placebo-controlled studies of up to 6 months' duration. In these studies the drug significantly reduced sleep onset latency (SOL), the number of awakenings, and wake time after sleep onset (WASO) whereas total sleep time (TST) and quality of sleep were increased in non-elderly and elderly subjects. Sleep laboratory studies of the effects of eszopiclone have confirmed the drug's clinical efficacy in subjects with chronic primary insomnia. Eszopiclone, unlike BZD hypnotics, does not significantly alter values corresponding to slow wave sleep (SWS or stages 3 and 4) and rapid eye movement (REM) sleep. Rebound insomnia following withdrawal of eszopiclone has been examined in only one study. Discontinuation of the active treatment with 2 mg was followed by rebound insomnia in non-elderly subjects. Three-mg doses of eszopiclone administered for a period of up to 12 months was associated with a sustained beneficial effect on sleep induction and maintenance, with no occurrence of tolerance. The most common side-effects were unpleasant or bitter taste, headache, dyspepsia, pain, diarrhea, dry mouth, upper respiratory infection, urinary tract infection, dizziness, and accidental injury. New adverse events (withdrawal symptoms) including anxiety, abnormal dreams, hyperesthesia, nausea, and upset stomach were recorded in one study on the days following eszopiclone 2 or 3 mg discontinuation. Although dependence and abuse potential have not been formally assessed, unpublished data show that eszopiclone at doses of 6 and 12 mg produces euphoria effects similar to those of diazepam 20 mg in BZD drug addicts. In conclusion, available evidence tends to indicate that eszopiclone is effective and safe for the treatment of chronic primary insomnia in non-elderly and elderly subjects. Tolerance did not occur during active drug administration for a 12-month period. Thus eszopiclone can be efficacious not only during short- and intermediate-term administration but also in patients requiring prolonged regular drug usage.

Keywords: eszopiclone, cyclopyrrolone, hypnotic, insomnia, sleep disorders

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Insomnia: diagnostic criteria

Insomnia is a complaint characterized by difficulty falling asleep (sleep latency of more than 30 minutes), insufficient sleep (total sleep time (TST) of less that 5.5–6 hours), numerous nocturnal awakenings, an early morning awakening with inability to resume sleep, or nonrestorative sleep. Common daytime symptoms occurring secondary to the complaint of insomnia include somnolence, fatigue, irritability, and difficulty in concentrating or performing every day tasks. In addition, subjects with a diagnosis of

insomnia are at risk of injury, drowsiness while driving, and illness. The objective measures for insomnia (sleep latency and total sleep time) correlate poorly with the subjective complaint of insomnia. Thus, when considering the results of clinical trials that have used self reports it should be taken into consideration that subjects with insomnia tend to overestimate the degree of their sleep difficulty, ie, they tend to report shorter sleep times and longer times to sleep onset compared with subjects assessed in the sleep laboratory. In addition, the reliability and the interpretation of results can be affected by the subject's estimates of hypnotic drug effects, which are quite variable because of the influence of recent as well as past experiences with other sleep medications.

The International Classification of Sleep Disorders (2005) uses the severity of impairment as a guide to be applied in conjunction with consideration of the patient's clinical status. Mild insomnia refers to an almost nightly complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode. Moderate and severe insomnia refer to the nightly experience of an insufficient amount of sleep or of not feeling rested despite having spent a normal amount of time in bed, accompanied by impairment of social and/or occupational functioning.

The duration of insomnia has been considered an important guide to its evaluation and treatment. Individuals with transient insomnia are normal sleepers who experience an acute stress for a few days (eg, air travel to a new time zone, hospitalization for elective surgery, changing work shifts, or sleeping in an unfamiliar environment) which disrupts their sleep. Short-term insomnia is usually associated with situational stress, often related to work or family life or serious medical illness. This type of insomnia may last up to 3 weeks. However, in some cases short-term insomnia may progress into a chronic condition. Conventionally, long-term or chronic insomnia has been considered to be that which lasts for at least 21–30 nights. Usually, it persists for months or years, and its onset may or may not be associated with an identifiable stressor. Insomnia can be considered also primary or secondary. The diagnosis of primary insomnia (APA 1994) has been considered to be chronic insomnia occurring in patients without sleep, medical, substance abuse, or psychiatric diagnoses causing those symptoms. However, this diagnosis has been defined differently in different studies. In the eszopiclone studies, the patients had long-term insomnia (>3 months), with >45 min time to sleep onset and <6.5 hours per night, stable medical status, no psychiatric diagnoses, and controlled caffeine and nicotine use. The current diagnostic codes included in the International Classification of Sleep Disorders (2005) comprise four primary insomnia diagnoses: adjustment insomnia, psychophysiological insomnia, paradoxical insomnia, and idiopathic insomnia. Secondary insomnia can be precipitated or aggravated by another sleep disorder, a disturbance of circadian rhythm, a neurological or psychiatric disease, a general medical condition, or the direct effects of a medication or a substance of abuse. In sleep disorders centers, about 20% of all insomniacs are diagnosed with primary insomnia and about 44% of cases with secondary insomnia, the most frequent form of insomnia that is predominantly associated with psychiatric disorders (eg, mood disorders) (Buysse et al 1994; Coleman et al 1981).

Insomnia is a multidimensional disorder and may have varied underlying pathology. Any strategy to its effective management should appropriately combine both pharmacological and a non-pharmacological measures and depends on the duration, severity, and complexity of the underlying pathology. In practice, pharmacological treatment of insomnia predominates over psychotherapy and other treatment methods. In patients with chronic insomnia combined with coexisting psychiatric, neurologic, or medical conditions; the underlying disorder needs to be assessed and treated appropriately (Lichstein et al 2006).

Several classes of medication have been prescribed as hypnotics over the years. The benzodiazepine receptor agonists (BzRAs) were introduced in the 1970s, and rapidly increased in popularity because of their efficacy and relative safety compared with the barbiturates, carbamates, chloral derivatives, and methaqualone (Harvey 1980). However, the risk of dependence, the occurrence of rebound insomnia following the withdrawal of short- and intermediate-acting derivatives, and the loss of efficacy after a few weeks of treatment led to a decrease in their use in recent years. The reduction in BZD hypnotics use has coincided with the introduction of a structurally dissimilar group of non-benzodiazepine (non-BZD) derivatives, such as the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem, and the pyrazolopyrimidine compound zaleplon (Monti 2004; Monti and Monti 2006). Such an approach to new drug developments in the central nervous system (CNS) sector unequivocally must demonstrate: (a) a gradually improved efficacy and markedly reduced half-life for the newest drugs; (b) greatly enhanced safety and side-effect profile; and (c) the search for other structurally dissimilar groups (eg, cyclopyrrolones, imidazopyridine, pyrazolopyrimidine, and also melatonin receptor agonists [MelRAs; eg, ramelteon]) possessing varied mechanisms of action with improved clinical outcome (Ebert et al 2006).

Preclinical pharmacology of the cyclopyrrolone derivatives

Zopiclone {[6-(5-chloro-2-pyridyl)-6, 7-dihidro-7-oxo-5H-pyrrolo [3,4-b]pyrazin-5-yl]4-methyl-1-piperazine-carboxylate} was synthesized by Rhône-Poulenc Recherches in the early 1970s (Bardone et al 1978), and its therapeutic activity as an hypnotic was recognized soon after (Duriez et al 1979; Nicholson and Stone 1983).

Eszopiclone, the dextrorotatory enantiomer of racemic zopiclone, has a single chiral center with an S(+)-configuration (Najib 2006).

Preclinical studies have shown zopiclone to exhibit sedative-hypnotic, anticonvulsant, myorelaxant, antiaggressive, and anticonflict activities (Joulou et al 1983, 1985). With regard to the sedative-hypnotic activity, zopiclone decreases locomotor activity, disrupts rotarod performance, reduces waking, and increases SWS in the rat (Joulou et al 1985; Ueki et al 1987; Carlson et al 2001). Spectral analysis of the cortical EEG after zopiclone administration has shown an increase of power density in the 2.0–4.0 Hz (delta), and the 12.0–16.0 Hz (beta) bands in the rat (Depoortere et al 1986). Eszopiclone shares the sedative-hypnotic properties of zopiclone whereas the (R)-enantiomer has no hypnotic activity (Carlson et al 2001).

Mechanism of action of zopiclone and eszopiclone

γ-Amino butyric acid (GABA) is the most important inhibitory neurotransmitter in the mammalian brain and localizes to approximately 30% of CNS synapses. This inhibitory neurotransmitter is of particular interest because most therapeutically useful hypnotic drugs work by selectively affecting GABA receptors.

A number of classes of GABA receptors including the $GABA_A$, $GABA_B$, and $GABA_C$ receptors have been characterized in the CNS of several species, including man (Korpi 2006). The distribution of GABA receptor types varies throughout the CNS. The $GABA_A$ receptor is the site of action of several hypnotic agents including BZDs, cyclopyrrolones (zopiclone, eszopiclone), imidazopyridine (zolpidem), and pyrazolopyrimidine (zaleplon) derivatives. These different classes of hypnotic drugs modulate GABAergic function through different $GABA_A$ receptor subtypes, defined by the subunits that participate in the receptor assembly. Most $GABA_A$ receptors consist of α, β, and γ subunits which contain multiple isoforms or variants: α_1–α_6, β_1–β_3, and γ_1–γ_3. Zolpidem and zaleplon preferentially bind α_1-containing subtypes (Ator and McCann 2005). On the other hand, BZDs, zopiclone, and eszopiclone bind at all $GABA_A$ subtypes. Notwithstanding this, the mechanism of action of the cyclopyrrolone derivatives may not be identical to that of the BZD hypnotics. In this respect it has been proposed that the cyclopyrrolones might have more selectivity for certain subunits of the $GABA_A$ receptor (Double 1999; Drover 2004; Sanger 2004). This could tentatively explain the difference in effects on sleep architecture and the lower incidence of adverse events, including rebound insomnia and withdrawal phenomena, during the administration of zopiclone and eszopiclone to patients with insomnia.

Pharmacokinetics of eszopiclone in healthy adults and in populations at risk

The pharmacokinetics of the (S)-isomer of zopiclone has been investigated in healthy adults and in populations at risk (Table 1). Eszopiclone is rapidly absorbed and extensively distributed to body tissues including the brain. It is weakly bound to plasma protein (52%–59%). Peak plasma concentrations (t_{max}) are attained 1.0–1.6 hours after a single therapeutic dose of 3 mg, and the terminal-phase elimination half-life ($t_{½}$) amounts to approximately 6.0 hours. Eszopiclone is metabolized in the liver to form (S)-N-desmethyl zopiclone and (S)-zopiclone-N-oxide (Fernández et al 1993; Sanger 2004). Racemic zopiclone is also extensively transformed in the liver to the N-oxide (less active) and the N-desmethyl (inactive) derivative; the N-oxide metabolite contributes to the hypnotic effect of zopiclone (Noble et al 1998). Although studies of the clinical effect of the N-oxide derivative of eszopiclone are not complete, the metabolite would be expected to contribute to the sleep-inducing and maintenance effect of the parent drug. In vitro studies have shown that CYP3A4 and CYP2E1 are the major enzymes involved in eszopiclone metabolism. CYP2C8 contributes also to (S)-zopiclone-N-oxide formation (Becquemont et al 1999). After oral administration, eszopiclone is predominantly excreted in the urine, primarily as metabolites. Less than 10% of the compound is excreted in the urine as parent drug.

The metabolic clearance of eszopiclone is reduced in elderly subjects, aged 65 years and older, resulting in increases in C_{max} and $t_{½}$, the latter amounting to approximately 9.0 hours (Sanger 2004). The removal of eszopiclone from the body is also impaired in patients with severe hepatic insufficiency, thus requiring dose reduction. On the other hand, no dose

Table 1 Pharmacokinetic parameters for eszopiclone in healthy adults and populations at risk

Non-elderly subjects[1]
rapidly absorbed (data not available for eszopiclone; racemic zopiclone: 95% of absorption with a bioavailability of 80%).
C_{max}[2]: 87.3 ng/mL
T_{max}[3]: 1.0–1.6 hours
AUC[4]: 691.3 mg/mL
weakly bound to plasma protein (52%–59%)
$t_{½}$[5]: 6.0 hours
Vd[6]: 98.6 L
effect of high-fat meal: reduces C_{max} by 21%, and delays T_{max} by approximately 1 hour; $t_{½}$ remains unchanged.
metabolized by oxidation and demethylation to (S)-zopiclone-N-oxide and (S)-N- desmethyl zopiclone. CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone.
excreted in the urine primarily as metabolites; less than 10% of the orally administered
eszopiclone is excreted as parent drug.

Elderly subjects
the metabolism is reduced resulting in increased AUC (41%) and prolonged $t_{½}$ to approximately 9 hours.

Hepatic impairment
the AUC was increased 2-fold in patients with severe impairment (alcoholic cirrhosis); C_{max} and T_{max} remained unchanged.

Renal impairment
reductions in clearance in patients with mild, moderate, or severe renal impairment were not significant.

Women who are breast-feeding
eszopiclone is secreted into breast milk.

Distribution to salivary glands
the data on eszopiclone distribution to salivary glands are not complete. Following racemic zopiclone administration bitter taste occurs when saliva concentrations exceed 50 μg/L.

From Fernández et al (1993, 1995); Noble et al (1998); Lunesta [Prescribing information] 2005.
[1]Single doses of up to 7.5 mg and once-daily administration of 1.0, 3.0, and 6.0 mg for 7 days.
[2]C_{max}: maximum plasma concentration.
[3]T_{max}: time to peak concentration.
[4]AUC: area under the concentration curve.
[5]$t_{½}$: mean elimination half-life.
[6]V_d: volume of distribution.

adjustment is necessary for patients with mild-to-moderate hepatic impairment. The clearance of eszopiclone is not altered in patients with mild, moderate, or severe renal insufficiency. Thus, no dose adjustment is required in patients with renal failure (Najib 2006).

In summary, based on the available evidence, a reduction in the initial dose of eszopiclone is recommended in elderly subjects and patients with severe hepatic impairment.

Evidence for eszopiclone hypnotic activity

Eszopiclone was approved by the US Food and Drug Administration (FDA) in 2004 for the treatment of insomnia, the first insomnia treatment medication to be approved without the short-term indication associated with all previous hypnotics.

Two principal techniques have been employed to evaluate the effects of eszopiclone on sleep in humans. One of the techniques makes use of subjective evaluation based on questionnaires (clinical approach) whereas the other approach involves the utilization of the sleep laboratory. In some studies, the efficacy has been assessed using both polysomnography (PSG) and subjective self reports (Zammit et al 2004; Rosenberg et al 2005; Roth et al 2005; McCall et al 2006; Soares et al 2006).

The efficacy endpoints included sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), number of awakenings, sleep efficiency (SE), quality of sleep, daytime ability to function, daytime alertness, and sense of physical well-being (Zammit et al 2004; Rosenberg et al 2005).

Various populations were included in the studies that assessed the efficacy and safety of eszopiclone: healthy volunteers, non-elderly, and elderly subjects with chronic primary insomnia, and patients with major depressive disorder (MDD) and comorbid insomnia (Rosenberg et al 2005; Zammit et al 2006). However, as discussed above, to date much of the published information on the effect of

eszopiclone on sleep variables has been gathered from studies that included subjects with chronic primary insomnia.

Taking into consideration that long-term hypnotic medication may be beneficial in patients with chronic insomnia, the efficacy and safety of eszopiclone have been assessed following 6 and 12 months of treatment in adult subjects with chronic primary insomnia.

Transient insomnia

Previous studies have shown that the first night in a sleep laboratory can be used as an effective model of transient insomnia (Koshorek et al 1988; Monti et al 1993). In this respect, Rosenberg et al (2005) assessed the effect of eszopiclone on transient insomnia in healthy adults who slept in an unfamiliar environment (sleep laboratory) for one night (Table 2a). The study included 436 healthy adults with no sleep laboratory experience. The subjects were randomly assigned to one of four treatment groups (placebo, eszopiclone 1, 2, 3, or 3.5 mg), and spent one night in the sleep laboratory. They remained in bed for 8 hours with standard PSG recordings. In the morning the subjects were interviewed about the efficacy and safety of treatment. In addition, the digit symbol substitution test (DSST) was administered to objectively determine residual next-day psychomotor drug effects.

Compared with placebo, stage 2 sleep latency and the number of awakenings were significantly reduced by eszopiclone 2–3.5 mg and 3–3.5 mg, respectively. Moreover, all doses of eszopiclone induced a significant reduction of WASO and an increase of sleep efficiency. Stage 1 sleep and the amount of REM sleep as a percentage of TST showed a significant decrease after the 3.5 mg dose of the cyclopyrrolone derivative. On the other hand, eszopiclone did not alter the percentage of stage 3 and stage 4 sleep.

Eszopiclone significantly improved the self-reported ease of getting to sleep, TST, and quality of sleep. There was also a reduction in the subjects' reports of the number of awakenings and WASO.

There were no significant decrements in the next-morning DSST scores across any treatment groups. Moreover, the experimental subjects were not more or less sleepier than those taking the placebo. Despite reports of side-effects of unpleasant taste, somnolence, headache, and dizziness, eszopiclone was generally well tolerated.

As pointed out by the authors, no studies have been carried out on the effect of eszopiclone in a true transient insomnia population. However, this is not the case with zopiclone. Momose (1982) examined the efficacy of zopiclone on the preoperative night's sleep of patients who were scheduled to undergo a surgical operation. The patients were randomly assigned to one of three treatment groups of 59 patients (placebo, zopiclone 7.5, or 10 mg). The treatment was administered double-blind at 21.00 h the night preceding the day of operation. Subjective efficacy measures were recorded and rated by a physician on the day of operation. Zopiclone 7.5 or 10 mg proved superior to placebo on sleep induction, number of nocturnal awakenings, duration and quality of sleep, and state on awakening the next morning. The cyclopyrrolone derivative was assessed as very useful or useful by 75% of patients. The commonest side-effects were bitter taste, dizziness, and heaviness.

In a study by Moon et al (1990) zopiclone 7.5 mg or placebo was given to 12 healthy young male subjects working 12-hour shifts in radar installations. The subjects received zopiclone 7.5 mg or placebo at bed-time during each of the 4-day shift cycles with a 4-day rest period as a washout phase. Zopiclone significantly improved night-time sleep quality (LSEQ; Leeds Sleep Evaluation Questionnaire) of subjects before the day shifts. Day-time sleep before night shifts showed a non-significant trend in the direction of improvements, which could have been related to the particular work schedule of the volunteers. There were no significant effects on any of the measures of performance (assessed by critical flicker fusion test, choice reaction time, and DSST) or mood (assessed by linear visual analogue scales).

It can be concluded that racemic zopiclone improves sleep in true transient insomnia populations, and that a similar outcome can be expected during eszopiclone administration.

Chronic primary insomnia in non-elderly subjects

Zammit et al (2004) evaluated the effects of 6 weeks of eszopiclone treatment in insomniac subjects with respect to effects on nocturnal sleep, rebound insomnia, and tolerance. The study involved 308 subjects with moderate chronic primary insomnia (mean values = sleep latency: 33.0 min; WASO: 50.0 min; number of awakenings: 6.6; sleep efficiency: 83.5%). Subjects were randomly assigned to one of three treatment groups: placebo (n = 99); eszopiclone 2 mg (n = 104), or eszopiclone 3 mg (n = 105). The period of treatment involved 44 nights, including 4 nights in the sleep laboratory. On the first night a placebo was administered single-blind, and sleep was recorded and quantified so that the extent and nature of the sleep disturbance could be estimated. The second night (first double-blind treatment night) was used for analysis of short-term effectiveness, night

Table 2a Effects of eszopiclone on sleep parameters in normal subjects with transient insomnia, and non-elderly and elderly patients with chronic primary insomnia

	Rosenberg et al (2005)	**Zammit et al (2004)**
Study design	randomized double-blind placebo-controlled multicenter	randomized double-blind placebo-controlled multicenter
Number of patients	436 healthy adults	308 (95% completed the study)
Mean age (years)	33.7 (range: 25–50)	39.8 (range: 21–64)
Diagnostic criteria	transient insomia (first night effect)	DSM-IV criteria for primary insomnia
Number of drug evaluation night(s)	one night	44 nights
Dosage (mg)	placebo (n = 98);eszopiclone 1 mg (n = 47); 2 mg (n = 97); 3 mg (n = 98); 3.5 mg (n = 96)	placebo (n = 99); eszopiclone 2 mg (n = 104); 3 mg (n = 105)
Assessment of sleep	polysomnography self-reports	polysomnography: nights 1, 15 and 29 self-reports: nights 1, 15 29 and 43/44
Objective sleep parameters		
Sleep induction		
NREM sleep latency (min)	decrease (2–3.5 mg)[a]	decrease (2–3 mg)[a,d]
Sleep maintenance		
Number of awakenings	decrease (3–3.5 mg)[a]	n.s.[b,d]
WASO[e] (min)	decrease (1–3.5 mg)[a]	decrease (3 mg)[a,d]
Total sleep time (min)	---	---
Sleep efficiency (%)	increase (1–3.5 mg)[a]	increase (2–3 mg)[a,d]
Sleep architecture		
Stage 1 sleep (min or %)	decrease (3.5 mg)[a]	n.s.[b,d]
Stage 2 sleep (min or %)	increase (3.5 mg)[a]	increase (2–3 mg)[a,d]
Slow wave sleep (stage 3/4) (min or %)	n.s.[b]	n.s.[b,d]
REM latency (min)	---	---
REM sleep (min)	---	n.s.[b,d]
REM sleep (% of TST)[c]	decrease (3.5 mg)[a]	---
Subjective sleep parameters		
Sleep latency	decrease (1–3.5 mg)[a]	decrease (2–3 mg)[a,d]
Number of awakenings	decrease (1–3.5 mg)[a]	---
WASO	decrease (3–3.5 mg)[a]	decrease (3 mg)[a,d]
Total sleep time	increase (2–3.5 mg)[a]	increase (2–3 mg)[a,d]
Quality of sleep	increase (2–3.5 mg)[a]	increase (2–3 mg)[a,d]
Rebound insomnia	---	present on the first night after discontinuation of treatment with 2 mg eszopiclone
Tolerance	---	absent

[a]Significantly different from placebo ($p < 0.05$)
[b]n.s. = non-significant
[c]TST = total sleep time
[d]Average of nights 1, 15 and 29
[e]WASO = wake time after sleep onset

Table 2b Effects of eszopiclone on sleep parameters in normal subjects with transient insomnia, and non-elderly and elderly subjects with chronic primary insomnia

	Krystal et al (2003)	**Scharf et al (2005)**	**McCall et al (2006)**
Study design	randomized double-blind placebo-controlled	randomized double-blind placebo-controlled	randomized double-blind placebo-controlled
Number of patients	788 (471 completed the study)	231 (210 completed the study)	264 (255 completed the study)
Mean age (years)	43.8 (range 21–69)	72.3 (range 64–85)	71.1
Diagnostic criteria	DSM-IV criteria for primary insomnia	DSM-IV criteria for primary insomnia	DSM-IV criteria for primary insomnia
Number of drug evaluation nights	6 months	2 weeks	2 weeks
Dosage (mg)	placebo (n = 196); eszopiclone 3 mg (n = 595)	placebo (n = 80); eszopiclone 1 mg (n = 72); 2 mg (n = 79)	placebo (n = 128); eszopiclone 2 mg (n = 136)
Assessment of sleep	interactive voice response system	interactive voice response system	polysomnography: nights 1, 2, 13 and 14; patients reports: nights 1 to 14
Objective sleep parameters			
Sleep induction			
NREM sleep latency (min)	---	---	decrease[a]
Sleep maintenance			
Number of awakenings	---	---	n.s.
WASO (min)	---	---	decrease[a]
Total sleep time (min)	---	---	increase[a]
Sleep efficiency (%)	---	---	increase[a]
Sleep architecture			
Stage 1 sleep (min or %)	---	---	n.s.
Stage 2 sleep (min or %)	---	---	increase[a]
Slow wave sleep (stage 3/4) (min or %)	---	---	n.s.
REM latency (min)	---	---	---
REM sleep (min)	---	---	n.s.
REM sleep (% of TST)	---	---	increase[a]
Subjective sleep parameters			
Sleep latency	decrease[a]	decrease (1–2 mg)[a]	decrease[a]
Number of awakenings	decrease[a]	n.s.	decrease[a]
WASO	decrease[a]	decrease (2 mg)[a]	decrease[a]
Total sleep time	increase[a]	increase (2 mg)[a]	increase[a]
Quality of sleep	increase[a]	increase (2 mg)[a]	increase[a]
Rebound insomnia	---	---	---
Tolerance	absent	---	---

[a]Significantly different from placebo ($p < 0.05$)

15 to determine intermediate-term efficacy, and night 29 for analysis of long-term effectiveness. Efficacy was evaluated in addition to subject reports on nights 1, 15, 29, and 43/44. Subjects returned to the sleep laboratory on nights 45 and 46 to assess the occurrence of rebound insomnia.

The effects of eszopiclone or a placebo are summarized in Table 2a. Stage 2 sleep latency showed a significant decrease after either dose of eszopiclone relative to placebo. On the other hand, the number of nocturnal awakenings was not significantly modified by the hypnotic drug. The assessment of sleep continuity measures showed a significant reduction of WASO after the 3 mg dose and an increase of SE after the 2- and 3 mg doses.

During the first withdrawal night WASO was significantly increased and SE decreased relative to baseline in the eszopiclone 2 mg group. Changes tended to resolve by the second night after eszopiclone discontinuation. Sleep induction and maintenance did not deteriorate in the eszopiclone 3 mg group during nights 45 and 46.

Tolerance was not observed after the 3 mg dose of the derivative.

With respect to sleep architecture, the inferred increase of non-rapid eye movement (NREM) sleep was coupled with significantly higher levels of stage 2. Stages 3 and 4 were not significantly different between 2 mg and 3 mg eszopiclone and placebo. A similar outcome was observed in relation to time spent in REM sleep.

Subjective evaluation was correlated with the sleep laboratory findings. Accordingly, eszopiclone 2 mg and 3 mg improved subjective ratings of the perceived ease of getting to sleep, the duration of sleep, and the quality and depth of sleep. Less subject-reported WASO was obtained only after eszopiclone 3 mg. DSST scores were not significantly different after nights 1, 15, and 29 relative to placebo. Somnolence and unpleasant taste were the most common treatment-related side-effects.

Thus the study by Zammit et al (2004) confirms the hypnotic efficacy of eszopiclone compared with placebo in non-elderly subjects with chronic primary insomnia. Eszopiclone reduced the stage 2 SOL and WASO whereas it increased the SE. Values corresponding to stage 2 were augmented, while slow wave sleep and REM sleep showed no significant changes. Tolerance did not develop during the eszopiclone 3 mg administration period whereas rebound insomnia was present during the first withdrawal night in the 2 mg group.

The efficacy and use of eszopiclone to improve sleep architecture over a longer period of time has also been evaluated (Krystal et al 2003; Zammit et al 2004). Observations were carried out at 70 sites and initially included 788 subjects with a mean age of 43.8 years suffering from chronic primary insomnia. However, the treatment was completed by only 471 subjects. The study was conducted according to a double-blind, placebo-controlled design with randomization. The efficacy of eszopiclone and of placebo was assessed once each week using an interactive voice response system. Eszopiclone significantly reduced SOL, WASO, the number of awakenings per night, and the number of nocturnal awakenings per week, whereas total sleep time was increased compared with baseline at the end of the first week (short-term efficacy) and through months 1 to 6. Sleep quality, daytime ability to function, alertness, and physical well-being also improved significantly. No significant differences were observed in the placebo group. The type of side-effects encountered during active treatment (unpleasant taste, headache) corresponds well with what has been reported in previous studies.

In summary, during the active treatment period eszopiclone induced significant improvements over baseline values in the population of subjects with chronic primary insomnia. Eszopiclone hypnotic activity was maintained throughout the 6-month study period without any tolerance phenomena.

Insomniac patients frequently take hypnotic medication for months or years despite the lack of information on their long-term effects. This applies not only to BZD hypnotics but also to most of the non-BZD derivatives. The finding that eszopiclone maintains its efficacy over 6 months of nightly treatment gives scientific support for its clinical value in its long-term use.

Roth et al (2005) evaluated the safety of eszopiclone during an additional 6-month period in subjects originally included in the study by Krystal et al (2003). The study was conducted open-label and comprised 471 non-elderly subjects with a diagnosis of chronic primary insomnia. In order to weekly assess sleep variables the study authors made use of an interactive voice response system. The evaluation was completed by only 382 subjects (placebo: n = 86; eszopiclone 3 mg: n = 296). The sustained improvement in sleep and daytime function reported by Krystal et al (2003) during the double-blind phase of the investigation was confirmed during the second 6-month phase of the study. Accordingly, the decrease of SOL, number of awakenings, and number of nights with one awakening, and the increase of TST and sleep quality remained significantly different from baseline during the 6 months of open-label treatment (Table 2b). There was no evidence of tolerance.

Chronic primary insomnia in elderly subjects

Sleep disturbance is very common among elderly people. Foley et al (1995) found that between 23% and 34% of subjects aged 65 years and older have symptoms of primary or secondary insomnia.

Scharf et al (2005) and McCall et al (2006) assessed the effects of eszopiclone administration in elderly subjects with primary insomnia for a 2-week period. These were randomized, double-blind, placebo-controlled studies. Subjects between the ages of 65 years and 86 years who met the DSM-IV definition for primary insomnia were included in the studies.

The study by Scharf et al (2005) comprised 231 subjects who were given either placebo or eszopiclone 1 mg or 2 mg nightly for 2 weeks. Efficacy was assessed using an interactive voice response system. Eszopiclone 2 mg was effective in reducing SOL and WASO while total sleep time was increased and sleep quality and depth, daytime alertness, and quality of life were improved compared with placebo (Table 2b). The number of awakenings per night was not significantly different from placebo during the double-blind period. The efficacy of eszopiclone 1 mg was limited to a reduction of SOL. Four side-effects were most frequently reported during eszopiclone 1 or 2 mg: headache, unpleasant taste, somnolence, and dyspepsia. Tolerance was not observed during the study.

The study by McCall et al (2006) included 255 subjects who received either eszopiclone 2 mg or placebo for 2 weeks. Efficacy was assessed by means of PSG recordings and subjects' reports. The subjects spent nights 1, 2, 13, and 14 in the sleep laboratory and reported efficacy measures during nights 1 to 14. The effects of eszopiclone 2 mg on sleep induction and maintenance are summarized in Table 2b. Eszopiclone administration significantly reduced latency to persistent sleep and WASO whereas TST and SE showed significant increments. The hypnotic drug significantly increased stage 2 sleep whereas stage 1, SWS (stages 3 and 4), and REM sleep in min were not significantly modified. Subjective evaluation was relatively well correlated with the sleep laboratory findings.

Insomnia coexisting with major depressive disorder

While both sleep and mood disorders share a commonality based on the underlying neurochemical cascades, sleep complaints are cardinal manifestations in patients with mood disorders. Such PSG characteristics include prolonged SOL and WASO, reduced TST and SE, and increased wakefulness. Assessment of sleep architecture shows that stage 1 sleep and REM sleep are increased whereas SWS and REM onset latency (REMOL) are reduced in a relatively small number of depressed patients. Although insomnia related to depression may be alleviated by treating the underlying mood disorder with antidepressant drugs (reviewed elsewhere, Jindal and Thase 2004); however, this is not always the case since a stimulant-like effect may appear during treatment. This is particularly true with the selective serotonin reuptake inhibitors (SSRIs), which according to pharmacoEEG studies behave as activating antidepressants (Oberndorfer et al 2000). Acute or subchronic administration of SSRIs to patients with major depression prolongs SOL, increases the number of awakenings and stage 1 sleep, and reduces TST and SE. Subjective evaluations indicate that the disruption of sleep continuity is more pronounced after fluoxetine administration compared with the other SSRIs.

Recently, Fava et al (2006) evaluated the effect of adding eszopiclone to fluoxetine in non-elderly patients who met DSM-IV criteria for MDD and comorbid insomnia. Patients who had been receiving fluoxetine (dose range 20–40 mg/day) were randomized to receive either eszopiclone 3 mg or placebo double-blind for 8 weeks. Patient self-reports of various sleep parameters, daytime functioning, and depressive symptoms were obtained with an interactive voice recording system. Sleep induction, sleep maintenance, and daytime function showed a significant improvement in the patients in the eszopiclone plus fluoxetine group compared with the placebo plus fluoxetine group during the 8-week treatment period. In addition, scores on the Hamilton Depression-17 Rating Scale were significantly lower at week 4 and week 8. The treatment with eszopiclone was well tolerated and the type and frequency of side-effects were similar to those reported in subjects with chronic primary insomnia.

In summary, the co-administration of eszopiclone with fluoxetine improved comorbid insomnia related to fluoxetine administration and the psychiatric disease, without interfering with the SSRI antidepressant effect.

Insomnia during peri-menopause and early post-menopause

In another recent randomized controlled study, Soares and co-workers (2006) evaluated the efficacy of 3 mg of eszopiclone for the treatment of insomnia in perimenopausal and early postmenopausal women (n = 410; aged 40–60 years

old). The study concluded with the finding that eszopiclone significantly improved many sleep characteristics (sleep induction, maintenance, duration, quality, and next day functioning). The study also showed a positive impact on the mood, quality of life (QoL), and other subjective menopausal-related symptoms in post-menopausal women with insomnia.

Comparison of zopiclone with placebo and benzodiazepine hypnotics

There are no published trials that compare eszopiclone with other hypnotic drugs. On the other hand, zopiclone has been extensively compared not only with placebo but also with benzodiazepine hypnotics in subjects with chronic insomnia. However, none of the studies used neither systematic nor objective scaling methods for classifying sleep disturbance (ie, DSM-IV or ICSD). Moreover, in most trials there was no adherence to a strict double-blind placebo-controlled design, nor in most cases were attempts made to combine subjective assessments with objective PSG measures for evaluating sleep and daytime impairment.

In studies comparing zopiclone 7.5 mg with placebo in patients with chronic insomnia the active drug was found to reduce both SOL and the number of awakenings, and to increase TST and sleep quality (Duriez et al 1979; Chaudoir et al 1983; Mamelak et al 1983; Beaumont and Holland 1990; Pecknold et al 1990). In addition, zopiclone decreased stage 1 sleep, increased stage 2 sleep, reduced or had no effect on stages 3 and 4, and did not significantly modify the duration of REM sleep. There was no rebound insomnia upon drug withdrawal (Mamelak et al 1983; Pecknold et al 1990). The potential for tolerance was assessed in two studies where subjects with chronic insomnia received zopiclone 7.5 mg/day for 8 and 17 weeks, respectively. In all of the studies no significant evidence was found for tolerance to the effects of zopiclone (Fleming et al 1988; Pecknold et al 1990).

A number of trials have compared the hypnotic effects of zopiclone with the long-acting (flurazepam, nitrazepam), intermediate-acting (flunitrazepam, temazepam), and short-acting (triazolam, midazolam) benzodiazepine hypnotics. In this respect it has been found that zopiclone 7.5 mg, flurazepam 30 mg, and nitrazepam 5 mg have similar overall hypnotic efficacy in adult patients with chronic insomnia (Petre Quadens et al 1983; Tamminen and Hansen 1987). In addition, the active agents were significantly better than placebo according to clinicians' and/or subjects' global impressions (Anderson 1987; Ponciano et al 1990). Daytime sedation was more likely to occur after flurazepam or nitrazepam administration.

It was initially established by Wickstrom et al (1983) that zopiclone 7.5 mg and flunitrazepam 2 mg improve to an almost similar extent sleep induction, sleep maintenance, and condition in the morning of insomniac subjects. Hajak et al (1994) also compared zopiclone 7.5 mg with flunitrazepam 1 mg and placebo in subjects suffering from insomnia. The treatments were given for 28 nights. Zopiclone significantly reduced the SOL and the number of nocturnal awakenings, and increased the TST compared with placebo. Daytime well-being was also improved. In contrast, the response rate in the flunitrazepam 1 mg group was not significantly different from that of placebo.

Zopiclone 7.5 mg has been compared also with temazepam 20 mg in subjects with chronic insomnia. The results of the studies have shown that zopiclone and temazepam are almost equally effective with respect to sleep induction, sleep maintenance, and quality of sleep (Wheatley 1985; van der Kleijn 1989).

Comparisons of the hypnotic effects of zopiclone and triazolam have produced consistent results. Hajak et al (1994) compared zopiclone 7.5 mg against triazolam 0.25 mg, and placebo in private practice patients with insomnia. Zopiclone was significantly more effective than placebo in improving sleep induction and sleep maintenance, while no such difference occurred with the benzodiazepine derivative. Further, Autret et al (1987) found that zopiclone 7.5 mg was significantly superior to triazolam 0.5 mg for improving sleep quality in subjects with chronic insomnia.

Begg et al (1992) compared the efficacy (based on LSEQ) and tolerance of zopiclone 7.5 mg and midazolam 15 mg in subjects with sleep disorders (n = 88; 18+ years old). The authors concluded that the zopiclone daily improved all items on the LSEQ than daily administration of midazolam but was associated with significant rebound insomnia. Notwithstanding this, there were no significant differences between the hypnotic drugs in comparisons between groups.

Adverse events

Table 3 shows the incidence of treatment-emergent adverse events in non-elderly subjects who received eszopiclone 3 mg for 44 nights, and elderly patients who were given the hypnotic agent at a dose of 2 mg for 14 nights. The most commonly reported side-effect was unpleasant or bitter taste followed by headache, dyspepsia, pain, diarrhea, dry mouth, dizziness, and accidental injury.

Table 3 Dosage, onset of action and adverse events of eszopiclone in non-elderly and elderly subjects with chronic primary insomnia

	Non-elderly subjects[a]	Elderly subjects[b]
Dosage (mg)	2–3	1–2
Onset of action (h)	0.5–1	0.5–1
Adverse events	unpleasant taste	headache
	viral infection	urinary tract infection
	headache	unpleasant taste
	somnolence	dry mouth
	dry mouth	dizziness
	dizziness	pain
	dyspepsia	accidental injury
	nausea	diarrhea
	rash	nervousness
	anxiety	neuralgia
	respiratory infection	
	confusion	

[a]Non-elderly subjects: 3 mg – n = 106
[b]Elderly subjects: 2 mg – n = 215

Dosage and administration

The recommended starting dose of eszopiclone for non-elderly insomniac patients is 2 mg. If necessary the amount of drug can be increased to 3 mg. Elderly patients should receive initially 1 mg eszopiclone immediately before bedtime. The dose can be increased to 2 mg if difficulty staying asleep is not satisfactorily resolved.

Taking into account that the metabolic clearance of eszopiclone is impaired in patients with severe hepatic insufficiency, its administration is to be avoided; alternatively, a dose of no greater than 1 mg can be administered, but with close monitoring.

Rebound insomnia

Rebound insomnia following withdrawal of eszopiclone has been examined only in the study by Zammit et al (2004). Discontinuation of the active treatment with 2 mg was followed by a significant increase of WASO and a reduction of sleep efficiency on the first night of withdrawal compared with baseline. Following cessation of eszopiclone 3 mg there was no significant rebound on the first or the second night after discontinuation.

Of note, withdrawal of zopiclone 7.5 mg was followed by mild (Lader and Frcka 1987; Fleming et al 1990) or no rebound insomnia (Jovanovic and Dreyfus 1983; Mamelak et al 1983; Petre Quadens et al 1983; Tiberge et al 1988) in patients with chronic insomnia.

Tolerance

Based on the available clinical evidence, eszopiclone is generally well tolerated. In the randomized controlled study of Soares et al (2006), no evidence of tolerance to eszopiclone over the 4-week study period was noted. In other studies on the long-term effects of eszopiclone use, Krystal et al (2003) and Roth et al (2005) found that, at the 3 mg dose level, the drug showed no evidence of producing tolerance effects after 6 and 12 months of administration. Interestingly, in several studies where zopiclone was administered over periods of up to 17 weeks, the activity of the hypnotic drug was maintained throughout the whole treatment period (Hindmarch 1990).

Memory impairment

Impairment of short-term memory is a particularly undesirable effect of the BZD hypnotics. The possibility of such impairment of memory with eszopiclone has been investigated in comparison with placebo.

In a study designed to determine the long-term effects of eszopiclone 3 mg in 595 adult subjects with chronic primary insomnia, memory impairment occurred in 1.3% of subjects (Krystal et al 2003). Furthermore, in a 6-week study in non-elderly subjects of nightly administered placebo (n = 99), eszopiclone 2 mg (n = 104), or 3 mg (n = 105), the rates for memory impairment were 1%, 1%, and 0%, respectively (Zammit et al 2004).

It should be noted that in volunteers tested 1 hour after zopiclone 7.5 mg administration, short-term memory processes were impaired, as evidenced by significant decrements in visual memory, digit learning, and reaction time. On the other hand, long-term memory assessed 10 and 24 hours after zopiclone administration had already regained placebo levels (Fossen et al 1983; Subhan and Hindmarch 1984; Harrison et al 1985; Griffiths et al 1986; Warot et al 1987).

Withdrawal symptoms, abuse and dependence

In the 6-week study of Zammit et al (2004) in elderly subjects, single blind placebo was administered on the first 2 nights of discontinuation. New adverse events were recorded during the withdrawal period beginning with day 45, up to 14 days after discontinuation. Withdrawal symptoms reported by 1.0% and 2.9% of subjects taking eszopiclone 2 and 3 mg, respectively, comprised anxiety, abnormal dreams, hyperesthesia, nausea, and upset stomach. This finding warrants further investigation to determine whether progressive eszopiclone dosage reduction is necessary.

There is no evidence of the addicting potential of eszopiclone in individuals without known histories of drug abuse. In an unpublished report that refers to patients with known dependence for BZDs, eszopiclone at doses of 6 and 12 mg produced euphoria effects similar to those of diazepam 20 mg (Scharf 2006). The reinforcing properties of eszopiclone compared with BZDs in drug addicts justifies its classification as a Schedule IV controlled substance in the United States.

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References

[APA] American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington DC: APA.

Anderson AA. 1987. Zopiclone and nitrazepam:a multicenter placebo controlled comparative study of efficacy and tolerance in insomniac patients in general practice. *Sleep*, 10 (Suppl 1):54–62.

Ator NA, McCann UD. 2005. New insights into the $GABA_A$ receptor. *CNS Spectrums*, 10:20.

Autret E, Maillard F, Autret A. 1987. Comparison of the clinical hypnotic effects of zopiclone and triazolam. *Eur J Clin Pharmacol*, 31:621–3.

Bardone MC, Ducrot R, Garret C, et al. 1978. Benzodiazepine-like central effects of RP 27267, a dihidro-7-oxo-5H-pyrrolo[3,4-b]pyrazine derivative. Int Congr Pharmacology, Abstract No. 2319. London: Pergamon Press.

Beaumont G, Holland RL. 1990. A multi-centre open study in general practice to evaluate the efficacy and acceptability of zopiclone 7.5 mg nocte in patients requiring the prescription of a hypnotic. *Int Clin Psychopharmacol*, 5 (Suppl 2):11–20.

Becquemont L, Mouajjah S, Escaffre O, et al. 1999. Cytochrome P-450 3A4 and 2C8 are involved in zopiclone metabolism. *Drug Metab Dispos*, 27:1068–73.

Begg EJ, Robson RA, Frampton CM, et al. 1992. A comparison of efficacy and tolerance of the short acting sedatives midazolam and zopiclone. *NZ Med J*, 105:428–9.

Buysee D, Reynolds C, Kupfer D, et al. 1994. Clinical diagnoses of 216 insomnia patients using the International Classification of Sleep Disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV field trial. *Sleep*, 17:630–7.

Chaudoir PJ, Jarvie MB, Wilcox GJ. 1983. The acceptability of a non-benzodiazepine hypnotic (zopiclone) in general practice. *J Int Med Res*, 11:333–7.

Carlson JN, Haskew R, Wacker J, et al. 2001. Sedative and anxiolytic effects of zopiclone´s enantiomers and metabolite. *Eur J Pharmacol*, 415:181–9.

Coleman R, Roffwarg H, Kennedy S, et al. 1981. Sleep-wake disorders based on a polysomnographic diagnosis. *JAMA*, 247:997–1003.

Depoortere H, Decobert M, Granger P, et al. 1986. Hypnotics:clinical value of pharmaco-EEG methods. *Neuropsychobiology*, 16:157–62.

Doble A. 1999. New insights into the mechanism of action of hypnotics. *J Psychopharmacol*, 13:S11–20.

Drover DR. 2004. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives. *Clin Pharmacokinet*, 43:227–38.

Duriez R, Barthélémy CI, Rives H, et al. 1979. Traitement des troubles du sommeil par la zopiclone. Essais cliniques en double insu contre placébo. *Thérapie*, 34:317–25.

Ebert B, Wafford KA, Deacon S. 2006. Treating insomnia:current and investigational pharmacological approaches. *Pharmacol Ther*, 112:612–29.

Fava M, McCall W, Krystal A, et al. 2006. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry*, 59:1052–60.

Fernández C, Maradeix V, Gimenez F, et al. 1993. Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. *Drug Metab Dispos*, 21:1125–8.

Fernández C, Martin C, Gimenez F, et al. 1995. Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet*, 29:431–41.

Fleming JA, Bourgouin J, Hamilton P. 1988. A sleep laboratory evaluation of the long-term efficacy of zopiclone. *Can J Psychiatry*, 33:103–7.

Fleming JA, McClure DJ, Mayes C, et al. 1990. A comparison of the efficacy, safety and withdrawal effects of zopiclone and triazolam in the treatment of insomnia. *Int Clin Psychopharmacol*, 5 (Suppl 2):29–37.

Foley DJ, Monjan AA, Brown SL, et al. 1995. Sleep complaints among elderly persons:an epidemiologic study of three communities. *Sleep*, 18:425–32.

Fossen A, Godlibsen OB, Loyning Y, et al. 1983. Effects of hypnotics on memory. *Pharmacology*, 27 (Suppl 2):116–26.

Griffiths AN, Jones DM, Richens A. 1986. Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam. *Br J Clin Pharmacol*, 21:647–53.

Hajak G, Clarenbach P, Fischer W, et al. 1994. Zopiclone improves sleep quality and daytime well-being in insomniac patients: comparison with triazolam, flunitrazepam and placebo. *Int Clin Psychopharmacol*, 9:251–61.

Harrison C, Zubhan Z, Hindmarch I. 1985. Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. *Drugs Exp Clin Res*, 11:823–9.

Harvey SC. 1980. Hypnotics and sedatives. In Goodman Gilman A, Goodman LS, Gilman A (eds). The pharmacological basis of therapeutics. 6th ed. New York: MacMillan. p. 339–76.

Hindmarch I. 1990. Immediate and overnight effects of zopiclone 7.5 mg and nitrazepam 5 mg with ethanol, on psychomotor performance and memory in healthy volunteers. *Int Clin Psychopharmacol*, 5 (Suppl 2):105–13.

International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2005. 2nd ed. Westchester: American Academy of Sleep Medicine.

Jindal RD, Thase ME. 2004. Treatment of insomnia associated with clinical depression. *Sleep Med Rev*, 8:19–30.

Jovanovic UJ, Dreyfus JF. 1983. Polygraphical sleep recordings in insomniac patients under zopiclone or nitrazepam. *Pharmacology*, 27 (Suppl 2):136–45.

Julou L, Bardone MC, Blanchard JC, et al. 1983. Pharmacological studies on zopiclone. *Pharmacology*, 27 (Suppl 2):46–58.

Julou L, Blanchard JC, Dreyfus JF. 1985. Pharmacological and clinical studies of cyclopyrrolones:Zopiclone and suriclone. *Pharmacol Biochem Behav*, 23:653–59.

Korpi ER. 2006. $GABA_A$ receptor subtypes in sedation and hypnosis. In Lader M, Cardinali DP, Pandi-Perumal SR (eds). Sleep and sleep disorders: a neuropsychopharmacological approach. Texas and New York, USA: Landes Bioscience/Eurekah.com and Springer Science + Business Media, Inc., pp. 3–9.

Koshorek G, Roehrs T, Sicklesteel J, et al. 1988. Dose effects of zolpidem on transient insomnia. *Sleep Res*, 17:47.

Krystal AD, Walsh JK, Laska E, et al. 2003. Sustained efficacy of eszopiclone over 6 months of nightly treatment:Results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep*, 26:793–9.

Lader M, Frcka G. 1987. Subjective effects during administration and on discontinuation of zopiclone and temazepam in normal subjects. *Pharmacopsychiatry*, 20:67–71.

Lichstein KL. 2000. Secondary insomnia. In Lichstein KL, Morin CM (eds). Treatment of late-life insomnia. London: Sage Publications. p. 297–319.

Lichstein KL, Gellis LA, Stone KC, et al. 2006. Primary and Secondary Insomnia. In. Clinical Pharmacology of Sleep, S.R. Pandi-Perumal and J.M. Monti (eds.), pp. 1–9. Basel, Switzerland: Birkhauser Verlag.

Mamelak M, Scima A, Price V. 1983. Effects of zopiclone on the sleep of chronic insomniacs. *Pharmacology*, 27(Suppl 2):156–64.

McCall WV, Erman M, Krystal AD et al. 2006. A polysomnographic study of eszopiclone in elderly patients with insomnia. *Curr Med Res Opin*, 22:1633–42.

Momose T. 1983. Effectiveness of zopiclone as a preoperative hypnotic. *Pharmacology*, 27(Suppl 2):196–204.

Monti JM. 2004. Primary and secondary insomnia:Prevalence, causes and current therapeutics. *Curr Med Chem – CNS Agents*, 4:119–37.

Monti JM, Boussard M, Olivera S, et al. 1993. The effect of midazolam on transient insomnia. *Eur J Clin Pharmacol*, 44:525–7.

Monti JM, Monti D. 2006. Overview of currently available benzodiazepine and nonbenzodiazepine hypnotics. In Pandi-Perumal SR, Monti JM (eds). Clinical Pharmacology of Sleep. Basel: Birkhäuser. p. 207–23.

Moon CAL, Hindmarch I, Holland, RL. 1990. The effect of zopiclone 7.5 mg on the sleep, mood and performance of shift workers. *Int Clin Psychopharmacol*, 5(Suppl):79–83.

Najib J. 2006. Eszopiclone, a nonbenzodiazepine sedative-hypnotic agent for the treatment of transient and chronic insomnia. *Clin Ther*, 28:491–516.

Nicholson AN, Stone BM. 1983. Zopiclone:Sleep and performance studies in healthy man. In Nicholson AN, Schlosberg A, Dreyfus JF (eds). Zopiclone:A Third Generation of Hypnotics. Basel:Karger. p. 92–7.

Noble S, Langtry HD, Lamb HM. 1998. Zopiclone:An update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs*, 55:277–302.

Oberndorfer S, Saletu-Zyhlarz G, Saletu B. 2000. Effects of selective serotonin reuptake inhibitors on objective and subjective sleep quality. *Neuropsychobiology*, 42:69–81.

Pecknold J, Wilson R, Le Morvan P. 1990. Long-term efficacy and withdrawal of zopiclone:a sleep laboratory study. *Int Clin Psychopharmacol*, 5(Suppl 2):57–67.

Petre Quadens O, Hoffman G, Buytaert G. 1983. Effects of zopiclone as compared to flurazepam on sleep in women over 40 years of age. *Pharmacology*, 27(Suppl 2):146–155.

Ponciano E, Freitas F, Camara J, et al.1990. A comparison of the efficacy, tolerance and residual effects of zopiclone, flurazepam and placebo in insomniac outpatients. *Int Clin Psychopharmacol*, 5 (Suppl 2):69–77.

Rosenberg R, Caron J, Roth T, et al. 2005. An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults. *Sleep Med*, 6:15–22.

Roth T, Walsh JK, Krystal A, et al. 2005. An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med*, 6:487–95.

Sanger DJ. 2004. The pharmacology and mechanisms of action of new generation, non-benzodiazepine hypnotic agents. *CNS Drugs*, 18 (Suppl 1):9–15.

Scharf M. 2006. Eszopiclone for the treatment of insomnia. *Expert Opin Pharmacother*, 7:345–356.

Scharf M, Erman M, Rosenberg R, et al. 2005. A 2-week efficacy and safety study of eszopiclone in elderly patients with primary insomnia. *Sleep*, 28:720–7.

Soares CN, Joffe H, Rubens R, et al. 2006. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. *Obstet Gynecol*, 108:1402–10.

Subhan Z, Hindmarch I. 1984. Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. *Neuropsychobiology*, 12:244–8.

Tamminen T, Hansen PP. 1987. Chronic administration of zopiclone and nitrazepam in the treatment of insomnia. *Sleep*, 10(Suppl 1):63–72.

Tiberge M, Calvet V, Khayi N, et al. 1988. Comparison des effets de la zopiclone et du triazolam sur le sommeil du sujet sain. *Encéphale*, 14:319–324.

Ueki S, Watanabe S, Yamamoto T, et al. 1987. Behavioral and electroencephalographic effects of zopiclone, a cyclopyrrolone derivative. *Japan J Pharmacol*, 43:309–26.

Van der Kleijn E. 1989. Effects of zopiclone and temazepam on sleep, behavior and mood during the day. *Eur J Clin Pharmacol*, 36:247–51.

McCall WV, Erman M, Krystal AD, et al. 2006. A polysomnography study of eszopiclone in elderly patients with insomnia. *Curr Medical Res Opin*, 22:1633–42.

Warot D, Bensimon G, Danjou P, et al. 1987. Comparative effects of zopiclone, triazolam and placebo on memory and psychomotor performance in healthy volunteers. *Fund Clin Pharmacol*, 1:145–52.

Wheatley D. 1985. Zopiclone:A non-benzodiazepine hypnotic. Controlled comparison to temazepam insomnia. *Br J Psychiatry*, 146:312–4.

Wickstrom E, Barbo SE, Dreyfus JF, et al. 1983. A comparative study of zopiclone and flunitrazepam in insomniacs seen by general practitioners. *Pharmacology*, 27(Suppl 2):165–72.

Zammit GK, McNabb LJ, Caron J, et al. 2004. Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia. *Curr Med Res Opin*, 20:1979–91.