Pharmacodynamic and Pharmacokinetic Characteristics of Zolpidem and Z-drugs in Old-aged adults

노인에서의 졸피뎀 약력학/약동학 특성

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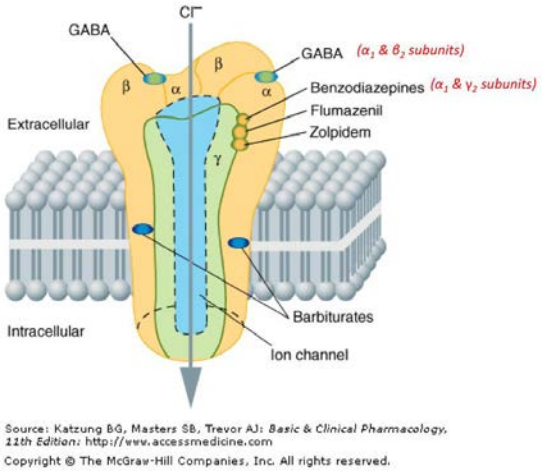
2022. 12. 09

I. Introduction

zolpidem

- Zolpidem is a sedative used to treat patients with insomnia characterized by difficulties with sleep initiation.
- Mechanism of action:
  - Binding to $GABA_A$ receptor -> enhances GABAergic inhibition of neurotransmission in the CNS
- Actions: sleep latency shortened, prolongs sleep time
- PK characteristics
  - rapid absorption (Tmax ~2 hrs)
  - absolute BA 70%
  - Half-life 2~3 hrs



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

II. PK(Pharmacokinetics) of zolpidem in elderly

First approval of zolpidem in 1992

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DOSAGE AND ADMINISTRATION

The dose of Ambien should be individualized.

The recommended dose for adults is 10 mg immediately before bedtime.

Downward dosage adjustment may be necessary when Ambien is administered with agents having known CNS depressant effects because of the potentially additive effects.

Elderly, debilitated patients, and patients with hepatic insufficiency may be especially sensitive to the effects of Ambien. An initial 5 mg dose is recommended in these patients (see PRECAUTIONS).

The total Ambien dose should not exceed 10 mg.

Pharmacokinetics

The pharmacokinetic profile of AMBIEN is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{½}$) in healthy subjects. In a single dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range 29-113) and 121 (range 58-272) ng/ml, respectively, occurring at a mean time (t_{max}) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4-4.5) and 2.5 (1.4-3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is converted to inactive metabolites that are eliminated primarily by renal excretion. AMBIEN demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/ml. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

A food effect study in 30 healthy male volunteers compared the pharmacokinetics of AMBIEN 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hours). The half-life remained unchanged. These results suggest that, for faster sleep onset, AMBIEN should not be administered with or immediately after a meal.

In the elderly, the dose for AMBIEN should be 5 mg (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{½}$ and AUC were significantly increased when compared to results in young adults. In one study of 8 elderly subjects (>70 years), the means for C_{max}, $T_{½}$ and AUC significantly increased by 50% (255 vs 384 ng/ml), 32% (2.2 vs 2.9 hr) and 64% (955 vs 1,562 ng·hr/ml), respectively, as compared to younger adults (20-40 yrs) following a single 20 mg oral zolpidem dose. AMBIEN did not accumulate in elderly subjects following nightly oral dosing of 10 mg for one week.

PRECAUTIONS

Use in the Elderly and/or Debilitated Patients - Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended AMBIEN dosage is 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients should be closely monitored.

Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men

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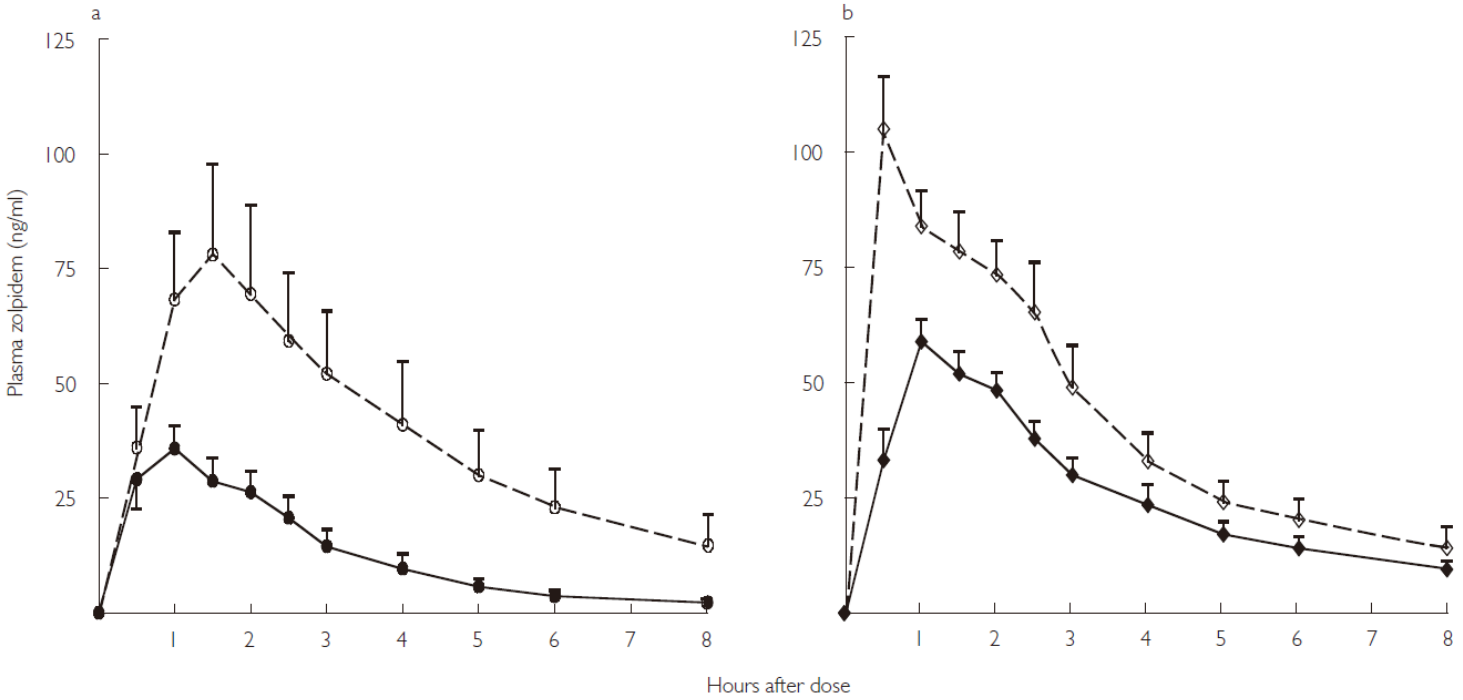

Figure 1 Mean (± SEM) serum zolpidem concentrations–time plots for young (●, ◆) and elderly (○, ◇) male (a) and female (b) volunteers.

Table 2 Pharmacokinetic parameters (mean (± SD)).

	Young male	*Elderly male*	*Kruskal–Wallis test*	*Young female*	*Elderly female*	*Kruskal–Wallis test*	*Difference in mean value between young and elderly* *Men*	*Women*
C_{max} (ng ml^{-1})	40 (± 16) [26, 53]	93 (± 45) [56, 131]	$P < 0.01$	60 (± 19) [49, 70]	108 (± 30) [83, 133]	$P < 0.001$	54 [17, 90]	48 [27, 69]
t_{max} (h)	0.8 (± 0.3) [0.6, 1.2]	1.1 (± 0.4) [0.7, 1.4]	NS	1.2 (± 0.4) [0.9, 1.4]	0.8 (± 0.7) [0.2, 1.4]	NS	0.25 [−0.12, 0.62]	−0.34 [−0.83, 0.14
Total AUC (ng ml^{-1} h)	110 (± 68) [54, 167]	400 (± 326) [127, 672]	$P < 0.01$	249 (± 133) [178, 320]	398 (± 189) [241, 557]	$P < 0.05$	289 [37, 542]	150 [12, 287]
Clearance (ml min^{-1})	820 (± 445) [448, 1193]	276 (± 179) [126, 425]	$P < 0.01$	376 (± 271) [232, 520]	209 (± 122) [107, 311]	$P < 0.05$	−545 [−909, −181]	−167 [−377, 44]
(ml min^{-1} kg^{-1})	11.0 (± 6.4) [5.6, 16.3]	3.8 (± 2.5) [1.6, 5.9]	$P < 0.01$	5.8 (± 4.8) [3.3, 8.4]	3.0 (± 1.9) [1.4, 4.5]	$P < 0.02$	−7.2 [−12.4, −2.0]	−2.9 [−6.5, 0.8]
Half-life (h)	1.5 (± 0.5) [1.1, 1.8]	2.7 (± 1.2) [1.7, 3.6]	$P < 0.03$	2.4 (± 0.9) [1.9, 3.9]	2.3 (± 0.7) [1.7, 2.9]	NS	1.2 [0.2, 2.1]	−0.2 [−0.9, 0.6]

95% confidence intervals are shown in square brackets.

Zolpidem case

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2007 label

NDA 19908 S027 FDA approved labeling 4.23.08

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN

Ambien® (zolpidem tartrate) tablets Ⓒ

Initial US Approval: 1992

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	03/2007
Warnings and Precautions	
Severe anaphylactic and anaphylactoid reactions (5.2)	03/2007
Abnormal thinking and behavioral changes (5.3)	03/2007
Special populations (5.6)	03/2007

----------INDICATIONS AND USAGE----------

Ambien is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

----------DOSAGE AND ADMINISTRATION----------

- Adult dose: 10 mg once daily immediately before bedtime (2.1)
- Elderly/debilitated patients/hepatically impaired: 5 mg once daily immediately before bedtime (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants (2.3)
- Should not be taken with or immediately after a meal (2.4)

2014 label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN safely and effectively. See full prescribing information for AMBIEN

AMBIEN® (zolpidem tartrate) tablets, for oral use, C-IV

Initial US Approval: 1992

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Severe Injuries (5.8)	10/2014

----------INDICATIONS AND USAGE----------

AMBIEN, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. AMBIEN has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

----------DOSAGE AND ADMINISTRATION----------

- Use the lowest dose effective for the patient (2.1)
- Recommended initial dose is 5 mg for women and 5 or 10 mg for men, immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening (2.1)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 5 mg for men and women (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN (2.3)
- The effect of AMBIEN may be slowed if taken with or immediately after a meal (2.4)

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness *[see Warnings and Precautions (5.1)]*. The total dose of AMBIEN should not exceed 10 mg once daily immediately before bedtime. Ambien should be taken as a single dose and should not be readministered during the same night.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

8.6 Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men. C_{max} and AUC parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of AMBIEN for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of AMBIEN in geriatric patients is 5 mg regardless of gender.

scientific reports

OPEN

Effect of CYP3A4 metabolism on sex differences in the pharmacokinetics and pharmacodynamics of zolpidem

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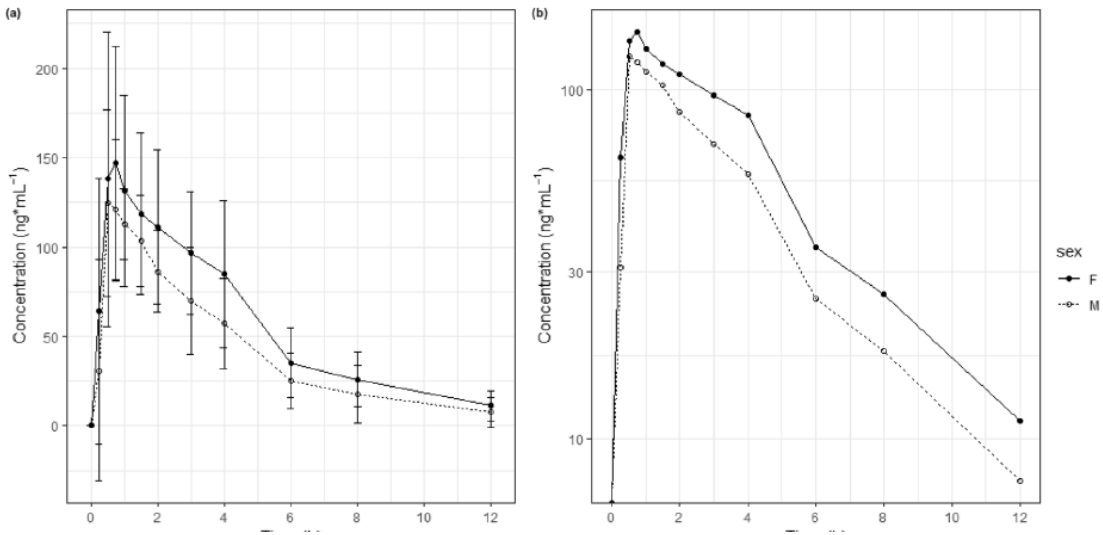

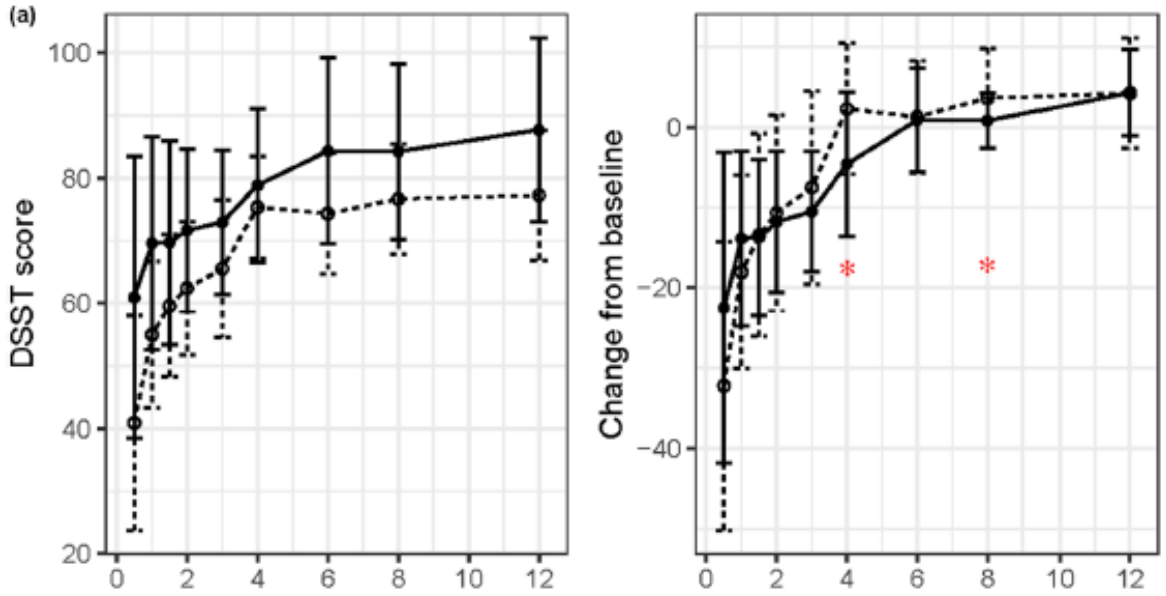

Ⅲ. PD(Pharmacodynamics) of zolpidem in elderly

Eur Psychiatry 1997;12(Suppl 1):21s–29s

General safety profile of zolpidem: safety in elderly, overdose and rebound effects

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Table IV. Zolpidem studies in elderly population.

Studies	*Year*	*Country*	*Design*	*Subjects*	*Number*	*Age (mean)*	*Treatment Doses/Comparison (mg)*	*Treatment duration (days)*
Kurtz et al	1991	France	SB, CO, pla	Eld HV	12	66.2	Zol 10, pla	7
Scharf et al	1991b	USA	DB, CO, pla	Eld chronic insomn	24	68	Zol 1.25 to 10 tria 0.125	2
Scharf et al	1991a	USA	DB, CO, pla	Eld chronic insomn	33	67.8	Zol 5 to 20, pla	2
Roger et al	1991	France	DB, PG, tria 0.25	Insomn dis	111	78	Zol 10 to 30, pla	1
Rhodes et al	1990	UK	DB, PG, pla	Eld HV	21	69	Zol 10, pla	1
Fairweather et al	1992	UK	DB, CO, pla	Eld HV	24	65	Zol 5 , 10, pla	7
Roger et al	1993	France	DB, PG, tria	Insomn dis	221	65	Zol 5, 10, tria 0.25	21
Shaw et al	1992	UK	DB, PG	Insomn dis Adult & eld	119	74.5	Zol 10, 20	21
Benoît et al	1994	UK	DB, CO, pla	Eld HV	11	70	Zol 10, pla	21
Emeriau et al	1988	France	DB, PG	Insomn dis	84	83.0	Zol 10, 20/fluni 1	28
Ochs et al	1992	USA	DB, PG, pla	Insomn dis	335	69	Zol 5, tria 0.125 tema 15, pla	28
Kummer et al	1988	Germany	SB	Insomn dis	14	68.0	Zol 20	180
Sauvanet et al	1988	France	Open	Insomn dis	42	81	Zol 10 to 30	60 to 360

SB: single blind; CO: cross over; DB: double blind; PG: parallel groups; Eld HV: elderly healthy volunteers without insomnia; Eld chronic insomn: elderly chronic insomnia; Isomn dis: insomnia defined according to difficulty for sleep, sleep reduction, awakenings; fluni: flunitrazepam; pla: placebo; tema: temazepam; tria: triazolam; zol: zolpidem.

- Scharf et al (199 la)
  - no clinically significant rebound insomnia was detected, and no consistent effects on memory, performance or alertness were observed the morning after drug intake.
- Kurtz et al (1991), Rhodes et al (1990) and Fairweather et al (1992), 4-7 days treatment
  - the absence of day-time cognitive impairment and of nocturnal respiratory disturbances with zolpidem 5 mg or 10 mg/day
- Emeriau et al (1988), Ochs et al (1992), Shaw et al (1992) and Roger et al (1993), 3-4 weeks treatment
  - adverse events were reported in about 10% of the patients. CNS effects (eg drowsiness or headache) were less with zolpidem than with temazepam or triazolam (Ochs et al, 1992).

Systematic review of zolpidem in elderly

Experimental Gerontology 136 (2020) 110962

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

More than a quarter century of the most prescribed sleeping pill: Systematic review of zolpidem use by older adults

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1) the efficacy and/or effectiveness to treat sleep disorders in older adults and
2) the safety (adverse events, rebound insomnia, residual, dependence, tolerance and abstinence effects) of zolpidem use to be used by older adults.

Table 1
PICOS structure used in the article search strategy.

Criterion	Parameter
Population	Elderly individuals ≥60 years old of both sexes
Intervention	Zolpidem
Comparison	Placebo or other hypno-sedatives
Outcome	efficacy (and/or effectiveness) for sleep disorders; safety
Study design	Clinical study; comparative study; observational study

- Outcomes evaluated
  - sleep latency (SL), total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), the number of nocturnal awakenings and global subjective assessments of sleep quality (SQ)

Results of systematic review

- 32 articles
  - Efficacy and/or effectiveness – 16 studies
  - Safety – 27 studies

Table 2
Characteristics of studies concerning zolpidem efficacy and/or safety to treat sleep disorders in elderly patients, according to the quality of the evidence provided.

Authors	General evidence quality	Study population	Purpose of study	Design, sample size[a], intervention	Primary outcome variables	Instruments or sources	Conclusion
Allain et al., 2003	Unclear[b]	Primary insomnia without comorbidities.	To assess the hypnotic effects of ZOL, zopiclone and lormetazepam on postural oscillation, memory under real life conditions and subjective sleep evaluations.	RCT crossover design; 48 individuals; 64–79 y ($\bar{x}$ = 68.5 y); 57.1% ♀. ZOL 5 mg, zopiclone 3.75 mg, lormetazepam 1 mg or placebo. Intervention duration: 1 d.	- Repeated measures of body sway, and reaction times (attention and memory); - Subjective assessments: ease of getting to sleep, sleep quality, ease of awakening from sleep and behavior following wakefulness; - Safety: adverse events.	- SASQ; - Cognitive tests; - Balance tests; - VAS.	- The active drugs ↑ body sway; effect disappeared after 5 h of ZOL use and after 8 h with lormetazepam or zopiclone use; - Subjects fell asleep more easily and slept better with lormetazepam, ZOL or zopiclone than placebo or with lormetazepam vs. ZOL; - ZOL showed no effect on memory functions or attention as assessed by the Simple reaction time and Consonant trigrams test; - No serious adverse events.
Berry et al., 2013	Low[c]	Diagnosis of hip fracture.	To assess the association between non-benzodiazepine hypnotic drugs (ZOL, eszopiclone, zaleplon) and risk of hip fracture in long-stay residents.	Observational, case-crossover study; 15,528 individuals; ≥50 y ($\bar{x}$ = 81 y); 77.6% ♀. Users of either ZOL, eszopiclone or zaleplon.	- Hip fracture rates; - Use or non-use of non-BZDs during the fracture period.	- Online survey, certification, and reporting database (patient medical records).	- Risk of hip fracture ↑ among users of a non-BZD hypnotic (OR = 1.66, 95% CI = 1.45–1.90); - The association between non-BZD hypnotics and hip fracture was higher among new users (OR = 2.20, 95% CI = 1.76–2.74).
Cheng et al., 2017	Low[c]	Elderly patients exposed to zolpidem.	To assess association between ZOL use and the risk of Alzheimer's disease (AD) among older people	Retrospective cohort study; 6922 individuals; ≥65 y ($\bar{x}$ = 72 y); 62.1% ♀. ZOL 10 mg (DDD); follow-up: 6 y.	- Exposure and mean cumulative dose of ZOL; - Occurrence of AD.	- Data from the Taiwan National Health Insurance Research Database (NHIRD).	- Zol users with a high cumulative dose (> 180 cDDD) had a significantly greater risk of AD than non-users (OR = 2.97; 95% CI = 1.61–5.49) or users of a low cumulative dose (< 28 cDDD) (OR = 4.18; 95% CI = 1.77–9.86). - Possible confounding effects of immeasurable risk factors were not eliminated.

F.V. Machado, et al.

Efficacy and/or effectiveness

- Sleep latency
  - Polysomnography
    - Primary insomnia (2 studies)
      - Reduction ranging from 5 to 15 min in SL associated with zolpidem administration, even with different formulations and doses.
    - Healthy elderly without insomnia (2 studies)
      - a significant reduction of 10 up to 28 min in objective SL was also observed at all evaluated doses (5 to 20 mg/night).
  - Subjective questionnaire
    - Primary insomnia without comorbidities (5 studies)
      - Significant reduction in subjective SL at all doses
      - Only one study found no significant differences in SL estimates
  - Overall, significant decreases in both objectively measured and subjectively reported sleep latency

Efficacy and/or effectiveness

- Total sleep time
  - Subjective and objective measurement (8 studies)
    - General significant increase in TST under zolpidem IR use at doses of 5-20mg (gain of 26 to 110 min objectively and 24 to 138 min subjectively)
  - Perception of the nursing staff and prescribers
    - Significantly higher TST for various doses, gains of 24 up to 138 min.
  - In summary, the available evidence support an increase in sleep duration

Efficacy and/or effectiveness

- Sleep efficiency
  - Polysomnography (5 studies)
    - Statistically significant increases ranging from 0.07% up to 22% in SE, with an average 8.3% increase
- Nocturnal awakenings (9 studies)
  - Fewer counts of nocturnal awakenings per night (7 studies)
- Wake after sleep onset (7 studies)
  - Reduction in WASO
- Sleep quality (15studies)
  - Significant improvement was observed
  - Two studies described unclear or inconsistent patterns of improvement

- Risk of falls and fracture (6 studies)
  - Exposure information
    - Kajiwara et al. 2016 – both dosage and days of exposure
    - 4 studies – exposure
    - 1 study – no information
  - Kajiwara et al., 261 elderly individuals >80 years of age
    - Most frequent AE decreased balance and/or occurrence of falls (1.8%) and morning drowsiness (1.3%)
  - Kang et al., significantly increased the risk of fracture in the elderly
    - Adjusted OR = 1.72 (95% CI 1.37-2.16)
  - Wang et al.,
    - significant increase in the risk of hip fracture (aOR=1.95; 95% CI=1.09 -3.51)
  - Berry et al.
    - Increased risk of hip fracture (OR= 1.66; 95% CI = 1.45 -1.90)

- Cognitive and/or psychomotor changes (11 studies)
  - 7 studies minimal psychometric and/or psychomotor performance during nighttime awakenings and/or morning residual effect
  - 2 studies, healthy elderly
    - Clinically significant balance and cognitive impairments upon awakening after short-term (1 to 3d) treatment.
  - 1 study, changes in mental status
  - 1 study (retrospective population-based case-control study)
    - Significant association between isolated use of zolpidem and risk for dementia in this age strata (aOR=1.33;95% CI=1.24 -1.41)

- Rebound insomnia (7 studies)
  - 4 studies (long-term treatment)
    - No shown insomnia rebound insomnia
  - 3 studies (short-term treatment)
    - No studies identified higher rebound insomnia

- Summary
  - efficacy and effectiveness in the elderly, evidence tends to suggest improved sleep parameters with short term use, notably in SL, TST, SE and WASO along with bettered perception of SQ, possibly by helping sleep onset and continuance at all studied doses and formulations.
  - its prescription should take into account the possible risk of fractures, cognitive impairment and dependence.
  - In addition, there is limited evidence of the effects of zolpidem on architecture, and the risk of adverse events over long time periods (years), which should be further documented

Amari *et al. BMC Geriatrics* (2022) 22:484
https://doi.org/10.1186/s12877-022-03165-6

BMC Geriatrics

RESEARCH Open Access

Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines

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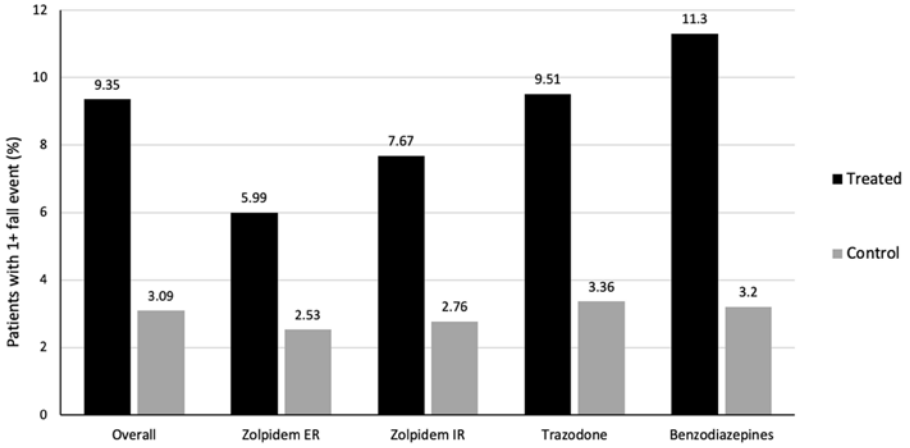
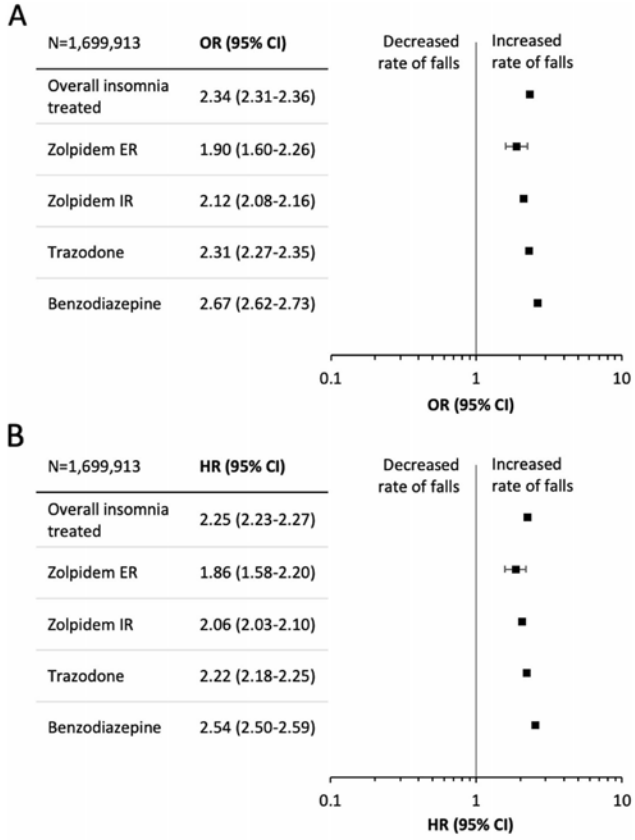


"Fall events" were defined as receipt of ≥1 diagnostic code for falls, hip fractures, or traumatic brain injuries, regardless of claim position or point of service. See methods for additional details.

Fig. 1 Percentage of patients with 1 + falls in the overall and stratified insomnia treated and matched control cohorts



Abbreviations: CI, confidence interval; OR, odds ratio; HR, hazard ratio.
OR and HR estimated using a generalized linear model with a Gamma distribution and log link function while adjusting for age, sex, race, geographic region and Charlson Comorbidity Index score. "Fall events" were defined as receipt of ≥1 diagnostic code for falls, hip fractures, or traumatic brain injuries, regardless of claim position or point of service. See methods for additional details.

Fig. 2 **a** Odds ratio (OR) for fall events in the insomnia treated cohort. **b** Hazard ratio (HR) for fall events in the insomnia treated cohort

Aging & Mental Health, 2016
Vol. 20, No. 6, 611–615, http://dx.doi.org/10.1080/13607863.2015.1031640

Routledge Taylor & Francis Group

Safety analysis of zolpidem in elderly subjects 80 years of age or older: adverse event monitoring in Japanese subjects

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(*Received 17 December 2014; accepted 10 March 2015*)

Table 1. Distribution of the characteristics of the patients with or without adverse symptoms during zolpidem use.

	Total[a]			Male			Female		
	Without Symptoms $n = 941$	With Symptoms $n = 58$	OR[b] [95% CI]	Without Symptoms $n = 291$	With Symptoms $n = 22$	OR[b] [95% CI]	Without Symptoms $n = 650$	With Symptoms $n = 36$	OR[b] [95% CI]
Age									
50–79 years old (%)	629 (66.8)	47 (81.0)	1	205 (70.4)	18 (81.8)	1	424 (65.2)	29 (80.6)	1
≥80 years old (%)	251 (26.7)	7 (12.1)	**0.39 [0.17–0.88]**	68 (23.4)	1 (4.5)	0.16 [0.02–1.23]	183 (28.2)	6 (16.7)	0.54 [0.22–1.33]
<50 years old (%)	61 (6.5)	4 (6.9)	0.85 [0.29–2.45]	18 (6.2)	3 (13.6)	2.22 [0.58–8.59]	43 (6.6)	1 (2.8)	0.30 [0.04–2.30]
Concomitant alcohol drinking									
Never used hypnotic after drinking (%)	784 (83.3)	44 (75.9)	1	191 (65.6)	15 (68.2)	1	593 (91.2)	29 (80.6)	1
Used hypnotic after drinking (%)	157 (16.7)	14 (24.1)	1.40 [0.72–2.71]	100 (34.4)	7 (31.8)	0.89 [0.35–2.29]	57 (8.8)	7 (19.4)	**2.44 [1.01–5.92]**
Dose									
≤median (%)	599 (63.7)	39 (67.2)	1	165 (56.7)	12 (54.5)	1	434 (66.8)	27 (75.0)	1
>median (%)	342 (36.3)	19 (32.8)	0.81 [0.46–1.43]	126 (43.3)	10 (45.5)	1.03 [0.43–2.50]	216 (33.2)	9 (25.0)	0.68 [0.31–1.48]
Duration of zolpidem use (day)	23.8 ± 16.2	25.8 ± 14.6	1.01 [0.99–1.02]	23.1 ± 14.9	20.5 ± 9.7	0.98[0.94–1.02]	24.2 ± 16.8	29.1 ± 16.2	1.01 [1.00–1.03]
Sex									
Male (%)	291 (30.9)	22 (37.9)	1	–	–	–	–	–	–
Female (%)	650 (69.1)	36 (62.1)	0.80 [0.45–1.44]	–	–	–	–	–	–

[a] 12 cases were excluded because of their missing value.
[b] Adjusted for the factors listed in this table.

Ⅲ. Other Z-drugs

Z-drugs

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Z-drug	Dose	Dose for elderly	Effects on sleep	Adverse effects	Formulations
Zopiclone (Eszopiclone)	7.5mg	3.75mg	sleep-onset latency Sleep maintenance	Headache, unpleasant taste, dizziness, dry mouth	Oral tablet
Zolpidem	10 mg	5 mg	sleep-onset latency	Headache, dry mouth, dizziness, hallucinations, delirium, nausea, vomiting.	Immediate-release tablet Controlled-release (CR) tablet Sublingual tablet Oral spray mist
Zaleplon	5/10 mg	5 mg	sleep-onset latency	Headache, vomiting, abdominal pain, rhinitis, dizziness, CNS-depressant effects.	Sonata capsules (5mg and 10mg)

Age and Ageing 2018; **47:** 201–208
doi: 10.1093/ageing/afx167
Published electronically 25 October 2017

Z-drugs and risk for falls and fractures in older adults—a systematic review and meta-analysis

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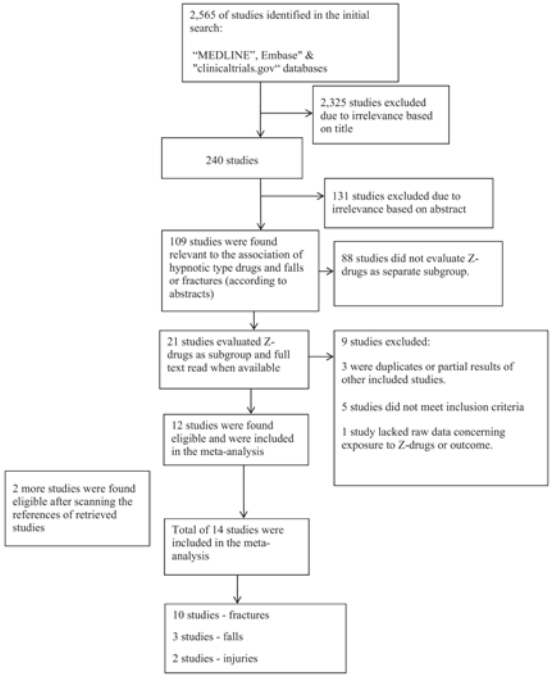

Figure 1. Flow diagram of systematic literature review.

Table 1. Main characteristics of studies included in the meta-analysis

References	Design	Exposure	Outcome	Population of control	Quality score[a]
Chang *et al.* (2011)	Case–control	Zolpidem	Falls	Hospitalised	3
Chung *et al.* [25]	Cohort study	Zolpidem	Injuries and fractures	Cohort	7
Kang *et al.* [15]	Case-crossover	Zolpidem	Fractures	Case-crossover	6
Kolla BP *et al.* (2013)	Cohort study	Zolpidem	Falls	Patients prescribed but not treated with zolpidem	6
Lai MM *et al.* (2014)	Cohort study	Zolpidem	Injuries	Cohort	5
Lai SW *et al.* (2015)	Case–control	Zopiclone	Hip fractures	Randomly selected matched by age	5
Landi *et al.* [24]	Cohort study	Z-drugs[b]	Falls	Cohort	4
Lin FY *et al.* (2014)	Cohort study	Zolpidem	Hip fractures	Cohort	6
Pierfitte C *et al.* (2001)	Case–control	Zolpidem and zopiclone	Hip fractures	Hospitalised for another reason	5
Tamiya *et al.* (2015)	Case–control	Z-drugs	Fractures	Hospitalised	4
Tang *et al.* [21]	Case-crossover	Zolpidem	Fractures	Case-crossover	6
Vestergaard *et al.* (2008)	Case–control	Z-drugs	Fractures	Randomly selected matched by age	5
Wang PS *et al.* (2001)	Case–control	Zolpidem	Hip fractures	Randomly selected matched by age	5
Zint K *et al.* (2010)	Case–control	Z-drugs	Hip fractures	Matched hospitalised control	2

[a]0 indicates lowest quality, 9 the highest.
[b]Z-drugs: including the exposure of zolpidem, zaleplon and zopiclone or eszopiclone.

Study or Subgroup	Z-drugs Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 cohort studies						
Chung et al 2013	520	77036	232	77036	11.6%	2.25 [1.93, 2.63]
Lin et.al 2014	119	1533	259	6046	10.0%	1.88 [1.50, 2.35]
Subtotal (95% CI)		78569		83082	21.7%	2.10 [1.76, 2.49]
Total events	639		491			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.67$, df = 1 ($P = 0.20$); $I^2 = 40\%$						
Test for overall effect: $Z = 8.41$ ($P < 0.00001$)						
1.2.2 case control studies						
Kang et al 2012	236	958	1272	6582	11.6%	1.36 [1.16, 1.60]
Lai et al 2015	170	207	10826	19090	7.1%	3.51 [2.46, 5.01]
Pierfitte et al 2001	29	112	216	946	5.6%	1.18 [0.75, 1.85]
Tamiya et al 2015	194	655	623	2697	10.8%	1.40 [1.16, 1.69]
Tang et al 2015	487	2242	5523	27808	12.7%	1.12 [1.01, 1.24]
Vestergaard et al 2008	20538	61719	104117	436898	13.6%	1.59 [1.57, 1.62]
Wang et al 2001	20	54	1202	6070	4.2%	2.38 [1.37, 4.15]
Zint et al 2010	482	2162	16716	101026	12.7%	1.45 [1.31, 1.60]
Subtotal (95% CI)		68109		601117	78.3%	1.53 [1.31, 1.77]
Total events	22156		140495			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 72.77$, df = 7 ($P < 0.00001$); $I^2 = 90\%$						
Test for overall effect: $Z = 5.48$ ($P < 0.00001$)						
Total (95% CI)		146678		684199	100.0%	1.63 [1.42, 1.87]
Total events	22795		140986			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 95.33$, df = 9 ($P < 0.00001$); $I^2 = 91\%$						
Test for overall effect: $Z = 6.98$ ($P < 0.00001$)						
Test for subgroup differences: $Chi^2 = 7.38$, df = 1 ($P = 0.007$), $I^2 = 86.4\%$						

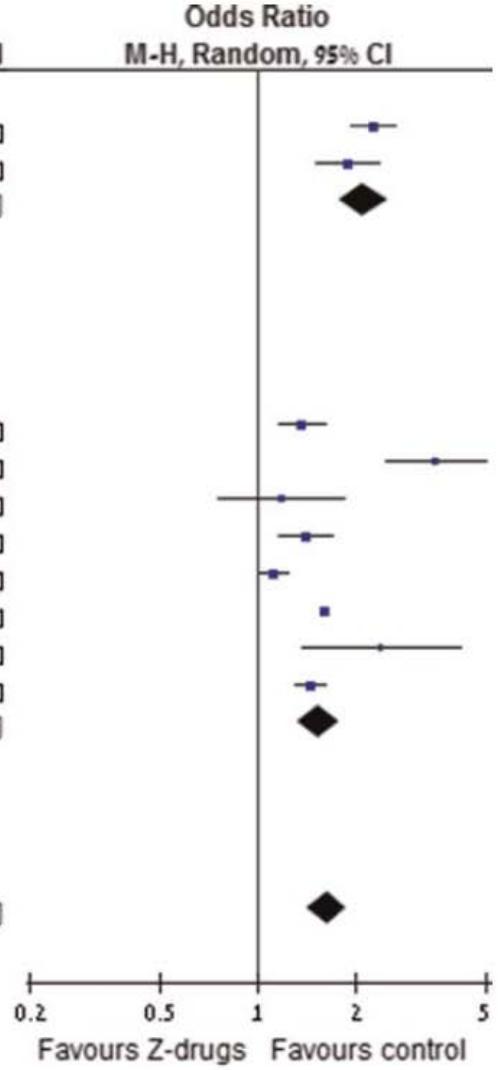

Figure 2. Forest plot of odds ratio for fractures under the exposure of Z-drugs, using a random-effect model.

Study or Subgroup	Z-drugs Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.4.1 cohort studies							
Landi et al 2005	118	280	943	2574	35.9%	1.26 [0.98, 1.62]	2005
Kolla et al 2013	151	4962	81	11358	35.7%	4.37 [3.33, 5.74]	2013
Subtotal (95% CI)		**5242**		**13932**	**71.6%**	**2.34 [0.69, 7.93]**	
Total events	269		1024				
Heterogeneity: Tau² = 0.76; Chi² = 43.47, df = 1 (P < 0.00001); I² = 98%							
Test for overall effect: Z = 1.37 (P = 0.17)							
1.4.2 case-control studies							
Chang et al 2011	19	27	146	303	28.4%	2.55 [1.08, 6.01]	2011
Subtotal (95% CI)		**27**		**303**	**28.4%**	**2.55 [1.08, 6.01]**	
Total events	19		146				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.15 (P = 0.03)							
Total (95% CI)		**5269**		**14235**	**100.0%**	**2.40 [0.92, 6.27]**	
Total events	288		1170				
Heterogeneity: Tau² = 0.65; Chi² = 43.56, df = 2 (P < 0.00001); I² = 95%							
Test for overall effect: Z = 1.79 (P = 0.07)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%							

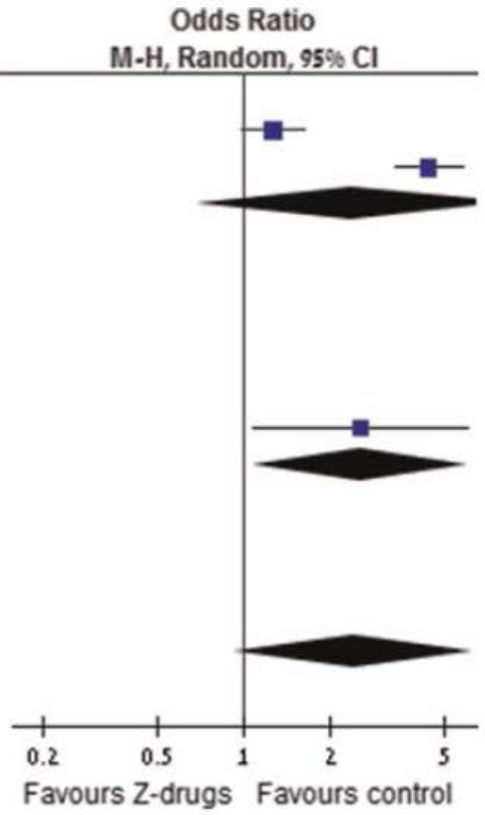

Figure 3. Forest plot of odds ratios for falls under the exposure to Z-drugs, using a random-effect model.

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