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Z-drug Use and All-Cause Mortality: A Meta-Analysis of Observational Cohort Studies

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ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202530082

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 March 2025 and was last updated on 19 March 2025.

INTRODUCTION

Review question / Objective Non-benzodiazepine hypnotic drugs known as z-drugs (including zolpidem, eszopiclone, zopiclone, zaleplon) are commonly prescribed for insomnia patients worldwide. Z-drugs have been thought to be safer than benzodiazepines; however, several studies have raised controversy over the side effects of z-drug. This meta-analysis was conducted to evaluate the association between z-drugs and all-cause mortality.

Rationale This study is a meta-analysis of observational cohort studies, assessing the association between Z-drug use and all-cause mortality. Since we are not evaluating the direct effects of an intervention (such as a randomized controlled trial of Z-drugs vs. placebo), but rather investigating a potential risk factor and its long-term outcomes, this aligns more with prognostic or risk factor reviews rather than an intervention review.

Condition being studied The use of Z-drugs and their potential association with all-cause mortality, insomnia treatment and the safety profile of Z-drugs.

METHODS

Participant or population Individuals Prescribed Z-Drugs with insomnia.

Intervention Z-Drug Use.

Comparator This review does not have any comparators.

Study designs to be included Only nonrandomized study types will be included.

Eligibility criteria (1) human studies; (2) observational cohort studies; (3) studies reporting the association between z-drug use and mortality; (4) studies providing calculable data and effects estimates such as odds ratios (ORs), hazard ratios

(HRs) with 95% confidence intervals (CIs), or p-values; and (6) studies written in English.

Information sources Review timeline: Start date: 29 December 2021. End date: 14 March 2025. Only published studies will be sought. The main databases to be searched are Embase.com, PubMed and Scopus. The review will only include studies published in English. There are no search date restrictions.

Main outcome(s) The relationship between z-drug usage and all-cause mortality.

Additional outcome(s) There are no additional outcomes.

Quality assessment / Risk of bias analysis Study risk of bias or quality assessment
Risk of bias will be assessed using: Newcastle-Ottawa
Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.
Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.
Reporting bias assessment
Risk of bias due to missing results will be assessed.

Strategy of data synthesis Data Synthesis and Analysis

Statistical analyses were performed using the Comprehensive Meta-Analysis ver.2.2.064 software (Biostat Inc., Englewood, NJ, USA), with statistical significance set at $p<0.05$. We calculated the pooled HRs and corresponding 95% CIs to summarize the results of studies on whether z-drug usage increases all-cause mortality using the DerSimonian and Laird random-effects model. We assessed the degree of heterogeneity among the selected studies using the $\chi 2$-based Cochrane Q test and inconsistency score (I2). A p-value less than 0.05 from the $\chi 2$-based Cochrane Q test indicates significant heterogeneity.

A series of sensitivity and subgroup analyses were also performed. Sensitivity analysis was performed by excluding each included study individually, and the pooled HRs after excluding each study were compared. In addition, subgroup analyses were performed according to Western or Eastern countries, study duration of more or less than five years, and low or high study quality. Funnel plots, Begg and Mazumdar's rank correlation test, and Egger's regression test were further used to evaluate potential publication bias. We assessed asymmetry in the funnel plot and calculated the degree of asymmetry. $P < 0.05$ indicated significant publication bias.

Subgroup analysis Subgroup analyzes were performed according to Western or Eastern countries, study duration of more than or less than 5 years, and low or high study quality. Funnel plot, Begg and Mazumdar's rank correlation test, and Egger's regression test were used for evaluating potential publication bias . We observed the asymmetry of the funnel plot and calculated its degree. When $p<0.05$, it was considered that there was a significant publicationbias.

Sensitivity analysis Sensitivity analysis was done by excluding each included study one by one, and the pooled hazard ratios after removing each study were compared.

Language restriction The review will only include studies published inEnglish.

Country(ies) involved South Korea/Department of Family Medicine, Kyungpook National University Hospital.

Keywords z-drug, zolpidem, zopiclone, eszopiclone, zaleplon, meta-analysis, mortality.

Contributions of each author
Author 1 - Ji-Yeon Park - Drafted the manuscript, conducted the literature search, screened studies, and performed data extraction.
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Author 2 - Hae-Jin Ko - Designed the study, developed the search strategy, Reviewed and revised the manuscript for critical intellectual content. Conducted statistical analyses and interpreted the results.
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