

# Comparative Effects of Hypnotics in Adults with Primary Insomnia: A Systematic Review and Network Metanalysis

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## ABSTRACT

**OBJECTIVE:** Insomnia is highly prevalent in the modern society; however, the hierarchical selection of hypnotics in adults with insomnia remained unanswered.

To compare the efficacy and safety of different hypnotics for insomnia treatments in adults with insomnia.

**METHODS:** Four electronic databases, including the EMBASE, PubMed, Cochrane library, and ProQuest Dissertations and Theses A&I databases, were searched from inception up to December 15, 2021. References lists and relevant publications were manually searched. Only randomized control trials (RCTs) comparing hypnotics approved by the Food and Drug Administration, including estazolam, flurazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplon, zolpidem, doxepin, ramelteon, tasimelteon, suvorexant, butabarbital, secobarbital, daridorexant, lemborexant, as treatment arms, with either a placebo or one of the abovementioned hypnotics. The primary outcomes were objective total sleep time (oTST), objective sleep onset latency (oSOL), objective wake after sleep onset (oWASO), objective sleep efficiency (oSE), subjective total sleep time (sTST), subjective sleep onset latency (sSOL), subjective wake after sleep onset (sWASO), sleep quality (SQ), and adverse event (i.e., drowsiness), measured using the objective tools or sleep logs or valid questionnaires.

A random effect network meta-analysis in a frequentist framework was used for estimating treatment effects.

**RESULTS:** A total of 117 RCTs comprising 22,508 participants with mean age of 45.94 years were included. By simultaneously considering the effects of efficacy and daytime sleepiness of hypnotics, zolpidem improved all objective sleep parameters (i.e., oTST, oSOL, oWASO, and oSE) while zopiclone enhance the oTST, oSE, and reduce oSOL and daridorexant increased oTST and reduced oWASO. For subjective sleep outcomes, zolpidem has beneficial effects on sTST, sSOL, and sWASO with less daytime sleepiness. Zaleplon reduced sSOL while zopiclone was ranked as the suggestive hypnotic for improving SQ. The results of sensitivity analysis remained unchanged by excluding studies reporting long-term effects.

**CONCLUSION:** Zolpidem, and zaleplon are recommended for managing sleep-onset insomnia and sleep-maintenance insomnia but should be used with caution because of related behavioral effects. We suggest daridorexant as a new promising treatment agent for managing sleep-maintenance insomnia and increasing sleep duration.

**Keywords:** hypnotic for insomnia, hypnotic efficacy, network meta-analysis, adults