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Association Between the Use of Non-benzodiazepine Hypnotics and Cognitive Outcomes: A Systematic Review

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Abstract

Purpose of Review: Adverse effects of sedative-hypnotic medications on cognition are concerning. Past studies have examined benzodiazepine (BZD) use and cognitive outcomes; however, few studies have examined newer non-BZD hypnotic agents (nBHs; e.g. zolpidem). This systematic review examined observational studies assessing the association between nBH use and cognitive outcomes.

Recent Findings: Five studies met eligibility requirements and were included in the review. Most studies did not find an association between nBH use and dementia diagnosis; however, we found no studies assessing other cognitive outcomes such as cognitive performance (e.g., word

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Conflict of Interest

Dr. Kaufmann, Dr. Moore, and Dr. Hart each declare no potential conflicts of interest.

Dr. Murphy reports personal fees from Boston Consulting Group, outside the submitted work

Dr. Malhotra reports his role as a PI on NHLBI grants and has received consulting income from Merck related to medical education. ResMed provided a philanthropic donation to UC San Diego in support of a sleep center.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

recall tasks). Characterization of nBH use mostly consisted of incident new use; one study assessed nBH dosing; none examined duration of use. Studies included were of strong quality.

Summary: This review found no association between nBH use and dementia diagnosis, although there is a need for more research on more cognitive outcomes and nBH use patterns.

Keywords

dementia; Alzheimer's disease; sleep medications; insomnia; non-benzodiazepine hypnotics

INTRODUCTION

Sedative-hypnotic medications are used for the treatment of sleep and anxiety disorders, among other indications. The most common sedative-hypnotic medications are benzodiazepines (BZDs; e.g. alprazolam, clonazepam, lorazepam, etc.) and non-BZD hypnotics (nBHs; e.g. zolpidem, zaleplon, eszopiclone) [1]. BZDs were developed in the 1950s but concerns about their safety [2] prompted the development of the nBHs in the 1990s as safer alternatives to BZDs specifically for the treatment of insomnia [1]. The nBHs were designed to bind to some but not all GABA-A receptor subtypes as compared to BZDs. There are concerns about the use of these agents, especially in vulnerable groups like older adults, as their use has been shown to be associated with adverse health outcomes such as falls [3, 4] and hip fractures [5, 6], and decline in function [7–9]. These concerns have led medical organizations to recommend against using these medications specifically in older adults [10–12]. Most recently, the Food and Drug Administration implemented a new Blackbox Warning for common nBHs due to concerns of complex behaviors during sleep (e.g., sleep walking, sleep driving, etc.) possibly leading to serious injury [13].

Sedative-hypnotic use has also been associated with cognitive outcomes, including lower cognitive performance [14–17] and diagnosis of Alzheimer's disease and related dementias (ADRD) [18–26]. The vast majority of these studies have focused on BZD use and have had mixed findings. Studies using cognitive performance measures show common BZD cognitive adverse effects to include problems with learning and memory [14–17], speed of processing [14, 27, 28], attention [14, 27–29], and visual-spatial ability [14, 27, 30]. There is also evidence from epidemiologic studies of associations of BZD with ADRD diagnosis [18–26]—studies have shown that BZD use is associated with increased risk of ADRD, although the evidence is less consistent pertaining to other aspects of BZD use including duration of use. As an example, Billioti de Gage et al. showed BZD use to be associated with new diagnosis of ADRD with a dose response relationship for duration of use (i.e., those using for longest duration were at almost 84% greater risk of ADRD compared to non-users) [20]. Gray et al. also found an association between BZD use and ADRD diagnosis, although the association was modest and there were no differences across varying durations of use, which did not support a causal relationship [22].

Despite the data on BZDs and risk for poor cognitive outcomes, there has been less focus on the newer nBHs. Since the 1990s, a number of clinical trials have demonstrated the safety of nBHs related to cognition, showing that there was no adverse effect or only minimal impairment on cognitive performance [31–33]. However, these initial trials mostly recruited

a select sample of healthy participants who were introduced to treatment with nBHs for the first time. These participants may not be representative of patients using nBHs in the community especially older adults. For example, Kaufmann et al. found that there was a 140% increase in use of nBHs between 1993-2010 [34], and that much of this increase was driven by long-term prescribing [35] and increased rates of long-term use [36]. Because of this trend, there is a need for a synthesis of population-based observational studies examining the association between nBH use and cognitive outcomes.

To the best of our knowledge, there have been no systematic reviews of studies examining nBH use and cognition. To address this gap, we conducted a systematic review of the literature examining associations between use of nBHs and cognitive outcomes. Specifically, we reviewed observational studies pertaining to outcomes related to either cognitive performance and/or risk of developing ADRD. We ultimately sought to identify critical gaps in literature to identify future research directions.

METHODS

Study Eligibility

In this systematic review, we focused on observational population-based epidemiologic studies examining the association between nBH use and cognitive and/or ADRD outcomes, and included at least some older adult persons within the sample (over age 65 years). To examine nBH use only, we excluded articles that examined nBH use but combined reporting with other agents like BZDs. We also excluded case reports, review articles, and studies from clinical trials

Search Strategy

We searched both PubMed and EMBASE for articles that were published on or before September 15th, 2019 (our last search date). We chose not to have a start date to ensure all necessary articles were captured. For PubMed, we used the following search strategy: “(zolpidem OR zaleplon OR eszopiclone OR ambien OR lunesta OR sonata OR sleep medications OR z-drug) AND (cognition OR dementia OR Alzheimer’s disease).” For EMBASE, we used a similar search strategy based upon indexed words in their database: “(‘zolpidem’ OR ‘zaleplon’ OR ‘eszopiclone’ OR ‘zolpidem tartrate’ OR ‘sleep medications’ OR ‘z drug’) AND (‘cognition’ OR ‘dementia’ OR ‘Alzheimer disease’)”. For our search in EMBASE, we excluded articles that were also indexed in PubMed.

For each article obtained from PubMed and EMBASE, two reviewers (CNK and LAH) independently reviewed titles and abstracts iteratively to ascertain whether inclusion criteria were met. Following screening of titles and abstracts, we reviewed the full-text article to make a final determination of study eligibility. Discrepancies in inclusion decisions between reviewers were discussed in person to reach a consensus.

Data Abstraction and Study Quality

Data abstraction was completed independently by reviewers based on full-text articles to ascertain study characteristics and information. Data abstracted included year of publication,

location of study, characteristics of population (e.g., sampling frame, age ranges, diagnoses, etc.), study design, sample size, main predictors, cognitive outcomes, confounders measured, and main findings. In addition to extracting these data, we also assessed study quality using the Newcastle-Ottawa Scale for observational studies [37]. The Newcastle-Ottawa Scale utilizes a star rating system to evaluate studies on three broad domains: 1) selection of study groups, 2) comparability of study groups, and 3) ascertainment of exposure of interest (for case-control studies) or outcome of interest (for cohort studies). We also used a modified version of the Newcastle-Ottawa scale for cross-sectional studies that has been used in a previous study [38]. Studies were considered to be of good quality if they received a rating of 7 or more stars, a threshold which has been used previously [39]. Any discrepancies in data abstraction and study quality assessment were discussed among the two reviewers to obtain consensus.

RESULTS

Description of Included Studies

In total, we retrieved 758 articles in PubMed and an additional 82 from EMBASE, ultimately yielding five eligible studies [40–44]. Figure 1 depicts a flow diagram of inclusion/exclusion decisions for study selection. A total of five observational studies were included in this review: 3 cohort studies [42, 41, 43], 1 case-control study [44], and 1 cross-sectional study [40] (Table 1). Three of the studies were in international settings, including United Kingdom [44], Japan [40], and Taiwan [43], and two were from the United States [42, 41]. The mean age of participants in the studies ranged from 71.6 to 82.6 years. Almost all studies used administrative data (e.g., claims, data from medical records, etc.) and had large sample sizes (N > 6,700 individuals) with the exception of a study by Hosoya et al. which included data from patients seen in a clinic setting with a smaller sample size (N = 269) [40].

Medications Examined in Studies

Among included studies, three studies evaluated zolpidem specifically [42, 41, 43]. Two other studies evaluated nBH use more broadly, without examining the specific agents individually [40, 44]. Characteristics of nBH use examined included new-onset use (e.g., first mention of an nBH in the medical record) and prevalent use, and one study examined nBH dosage as defined by “defined daily dose” (DDD).

Cognitive Outcomes Evaluated

The main cognitive outcomes examined were diagnosis of dementia [42, 44], MCI [41], and delirium [40]. One study evaluated dementia diagnosis more broadly [44], and two studies evaluated Alzheimer’s disease specifically [42, 43]. One study evaluated delirium among patients hospitalized for stroke [40]. An additional study evaluated mild cognitive impairment [MCI], focusing on how zolpidem might modify the association between sleep disturbance and MCI [41]. Importantly, none of the studies examined change in cognitive performance on specific cognitive tests or in specific cognitive domains as measured by multiple cognitive tests.

Confounders Assessed

The confounders assessed among the studies varied. Richardson et al. [44] and Cheng et al. [43] both assessed a large range of covariates, including various health conditions such as diabetes, cardiovascular conditions (e.g., hypertension, heart failure, myocardial infarction), and psychiatric diagnoses (e.g., anxiety, depression). Of note, they both measured insomnia or sleep problems. They both also measured medication use, notably antidepressants, with Cheng et al. including several other medication classes such as antihypertensive medications and anticoagulants. The studies by Burke et al. [42, 41] evaluated sleep disturbance and APOE e4 carrier status with a focus on how sleep medications (e.g., zolpidem) might moderate the hazard of MCI and Alzheimer's disease. These studies also included demographic characteristics. The study by Hosoya et al. did not appear to adjust for any covariates [40].

Summary of Findings

For the most part, almost all included studies found either no or small associations between nBH use and cognitive outcomes. Richardson et al. found a small association between nBH exposure and incidence of dementia in bivariate analyses, but this was no longer statistically significant after adjusting for confounders [44]. The Burke et al. studies found that zolpidem use modifies the association between sleep disturbance and MCI and probable Alzheimer's disease such that there was no association between sleep disturbance and these outcomes for those using zolpidem whereas there was a positive association for those not using zolpidem [42, 41]. While the Cheng et al. study found no association with zolpidem use overall and Alzheimer's disease diagnosis, they found that zolpidem use at higher cumulative DDD yielded a nearly three times greater risk of developing Alzheimer's disease as compared to those who were non-users [43].

Study Quality

Most studies were of high-quality, as per evaluation with the Newcastle-Ottawa Scale. The case-control study by Richardson et al. included in this review received a rating of 8 stars, as did the cohort study by Cheng et al. [43, 44] The other cohort studies by Burke et al. each received a star rating of 7 stars [41, 42]. The cross-sectional study by Hosoya et al. received a star rating of 3 stars [40]. More detail about study quality is outlined in Table 2.

DISCUSSION

This study is among the first systematic reviews to examine the association between use of nBHs and cognitive outcomes. Overall, the five studies included in our review [42, 41, 43, 40, 44] found little evidence for an association between use of nBHs and development of dementia/MCI. There appeared to be some evidence for higher doses of nBHs to be associated with dementia incidence, but this notion was only assessed in the Cheng et al. study [43]. The studies examined were either cohort, case-control, or cross-sectional studies, tending to use administrative data (e.g., claims or data from medical records, etc.) and had relatively large sample sizes. Overall, the quality of studies was strong.

Of note, only five studies met our eligibility requirements. Through the process of screening studies, a number of studies examined nBHs but reported results combined with other sedative-hypnotic medications such as BZDs, rather than reporting nBHs separately [45–48]. As BZDs were introduced earlier in the 1950s, the prevalence of BZD use is much higher than nBHs [36, 35, 34], and one reason for fewer studies for nBHs may be due to insufficient sample sizes for nBH users. It will be important that as the use of nBHs in the population continues to grow, more studies will examine the association between nBH use and cognitive outcomes.

For the most part, the studies examined did not find an association between use of nBHs and ADRD diagnosis, although one found an association with higher doses. While it is possible that nBHs have few adverse effects on cognition, it is also possible that it is the *way* nBHs are used rather than simply starting use, that put patients at risk for adverse cognitive outcomes. For example, the majority of the studies in our review focused on new onset use of nBHs, which may have not considered specific use patterns such as long-term use. There is evidence suggesting that long-term use of nBHs is common and a growing problem particularly in the US [36, 35]. As the Cheng et al. study shows, higher cumulative doses of zolpidem were associated with greater risk of ADRD [43], and therefore there is reason to believe that examining longer use of nBHs may identify higher risks for adverse cognitive outcomes. The possibility of reverse causation must also be considered when examining this literature given that insomnia is common in early Alzheimer's disease (e.g. from irregular sleep wake disorder). For example, Alzheimer's disease may drive insomnia increasing hypnotic requirement rather than toxicity of the hypnotics per se. Thus, we emphasize the need for mechanistic research before drawing definitive conclusions.

There appeared to be some critical gaps in the literature reviewed in this study. First, all studies assessed a diagnosis for a cognitive disorder as the outcome, and did not assess biological cognitive outcomes including markers of ADRD (e.g., beta-amyloid burden) and data from brain imaging. Second, the most common nBH medication studied was zolpidem, and there were few studies examining outcomes from other nBHs such as zaleplon and eszopiclone. Third, studies did not include measures of cognitive performance and various domains of cognition (e.g., memory, visual-spatial ability, executive functioning, etc.). It may be important to identify whether nBH use is associated with pre-clinical or subsyndromal symptoms that may not rise to the level of a dementia diagnosis, but could indicate cognitive impairment. Finally, only two studies came from the United States but these studies used the same dataset (National Alzheimer's Coordinating Center Uniform Dataset). The remaining studies came from other countries. Given that the US may have unique patterns of healthcare utilization as compared to other countries, it may be important for more research into nBH use with cognitive outcomes in the US.

The quality and methodological design of existing studies was high overall. However, it is important to note that two of the studies evaluated how sleep medications (e.g., zolpidem) moderate the hazard of sleep disturbance on development of MCI or Alzheimer's disease, rather than directly evaluating the association between zolpidem and cognitive outcomes. It will be important for additional well-designed observational studies to be conducted evaluating the association between nBH use and cognitive outcomes.

CONCLUSIONS

Past studies have examined the association between BZD use and cognitive outcomes, although there are fewer studies examining these associations for nBH use. We systematically reviewed the literature on nBH use and cognitive outcomes. While reviewed studies for the most part showed nBH use to not be associated with diagnosis of dementia, it will be important that future studies a) examine duration and quantity of nBH use, and b) use other measures of brain health, including neuroimaging and performance on individual cognitive tests. Because there is evidence of medical use patterns of nBHs contrary to clinical recommendations (e.g., long-term use), it is important that further delineating this potential association be done for the purpose of promoting successful aging for those with sleep disturbance.

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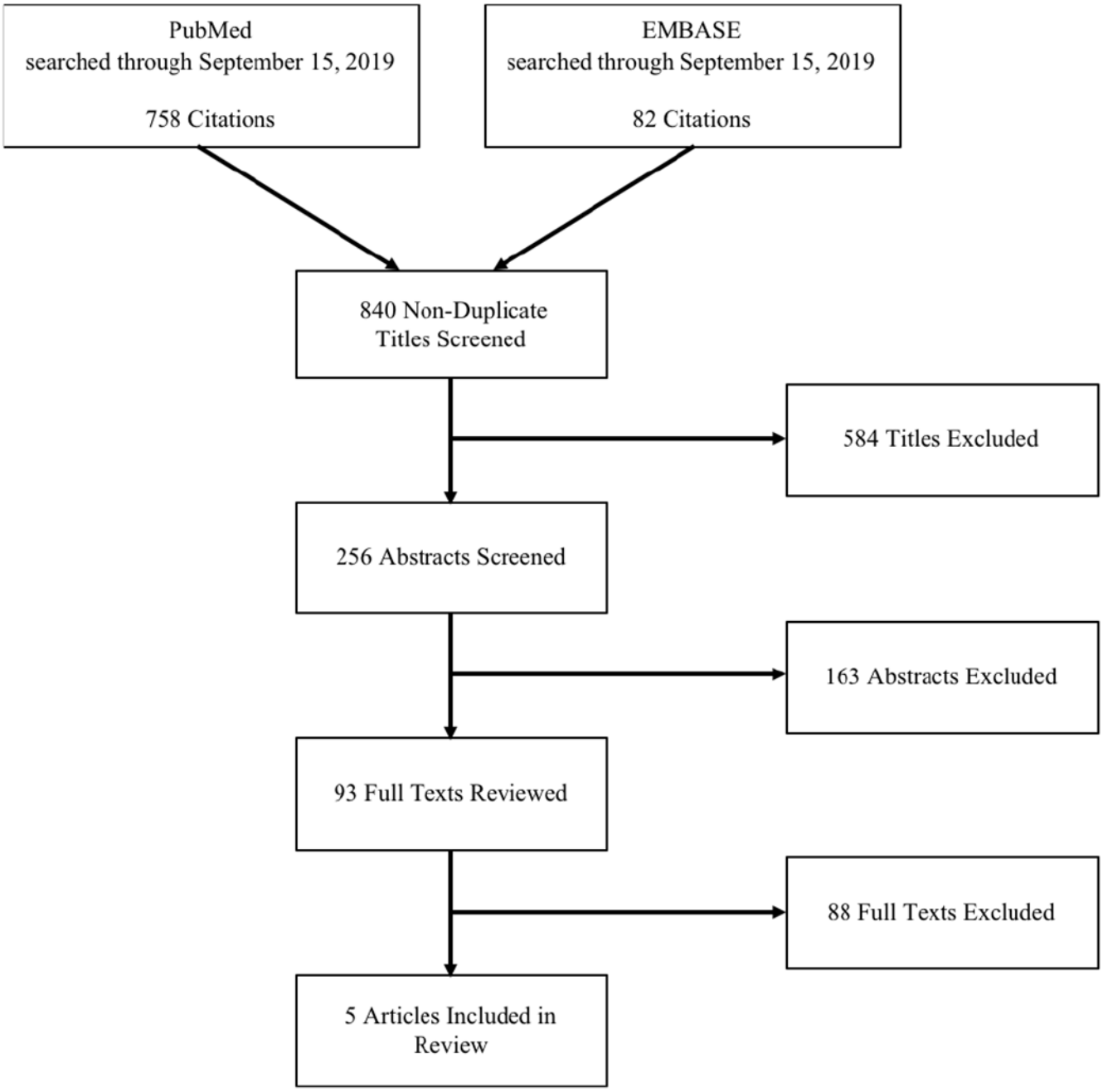

Figure 1.
Flow Diagram of Study Inclusion/Exclusion

Table 1.

Summary of Findings

Article, Country	Population	Study Design	Sample Size	Main Predictors	Cognitive Outcome	Confounders Measured	Main Findings	Study Quality Star Rating
Richardson et al. (2019), United Kingdom	Patients seen in general practice, mean age 82.6 ± 6.8 years	Nested case-control study	N=324,703 • Cases with dementia = 40,770 • Controls = 283,933	Drug-exposure period 1 year after up-to-standard data recorded (and up to 20 years before index date), and ending 4 years prior to index date Number of DDDs prescribed for nBHs	Incidence of dementia	Health conditions: Diabetes, cardiovascular conditions, urinary incontinence, Parkinson's disease, depression, anxiety, insomnia/ sleep problems, pain Medications: SSRI, TCA, antipsychotic Health status and history: Smoking, BMI, alcohol use, fall history	No association between use of nBHs and dementia incidence While small association seen in bivariate analyses, adjusting for confounders removed association	8
Burke et al. (2018), United States	Participants of Alzheimer's Disease Research Centers, mean age 71.62 ± 9.97 years	Retrospective cohort study	N=6,798 with normal cognition at baseline	Sleep disturbance (as measured by Neuropsychiatric Inventory Questionnaire) Zolpidem used in past two weeks (self-report)	Onset of MCI	Sleep disturbance, APOE e4 carrier status Demographic characteristics: age, sex, race/ethnicity, education level	Hazard of MCI higher for those with sleep disturbance (unadjusted HR=1.36, 95% CI=1.11-1.67; adjusted HR=1.39, 95% CI=1.13-1.72) Among those using zolpidem, there was no association between sleep disturbance and MCI (unadjusted HR=1.14, 95% CI=0.60-2.17; adjusted HR=1.06, 95% CI=0.55-2.04). Among those not using zolpidem, there was an association between sleep disturbance and MCI (unadjusted HR=1.40, 95% CI=1.13-1.74; adjusted HR=1.45, 95% CI=1.16-1.81)	7
Burke et al. (2019),	Participants of	Retrospective cohort study	N=6,782	Zolpidem used in past two	First diagnosis of	Sleep disturbance, APOE e4 carrier	Among those using	7

Article, Country	Population	Study Design	Sample Size	Main Predictors	Cognitive Outcome	Confounders Measured	Main Findings	Study Quality Star Rating
United States	Alzheimer's Disease Research Centers, mean age 71.60 ± 9.97 years			weeks (self-report)	probable Alzheimer's disease	status Demographic characteristics: age, sex, race/ethnicity, education level	zolpidem, there was a significant association with development of probable AD (HR=3.56 , 95% CI=1.02, 12.46), but statistical significance was lost after adjusting for confounders Among those not using zolpidem, there was a significant association with development of probable AD (HR=1.69 , 95% CI=1.11, 2.58)	
Hosoya et al. (2018), Japan	Patients hospitalized in stroke care unit	Cross-sectional study	N=269 • With delirium=97 • Without delirium=172	Use of antianxiety agents and sleep-aids (from medical record)	Presence of delirium (score of ≥4 on Intensive Care Delirium Screening Checklist)	Did not adjust for covariates Conducted multivariate analysis to evaluate importance of factors on delirium onset (e.g., clinicodemographic information, medical information, and classification of medications that were significant in univariate analysis)	Prior use of nBHs not associated with having delirium (p=0.7265)	3
Cheng et al. (2017), Taiwan	Patients aged 65+years	Retrospective cohort study	N=6,922 • Zolpidem users=3,4 61 • Propensity score matched controls=3,461	Use of zolpidem Zolpidem cumulative DDD (<28, 28-90, 91-180, 180+)	First diagnosis of Alzheimer's disease	Demographics: age, sex Health conditions: diabetes, cardiovascular conditions, depression, anxiety, sleep disorder, psychotic-related disorder, alcohol related disorder, Parkinson's disease, head injury Medications: antihypertensives, anti-diabetic agents, anticoagulants, anti-hyperlipidemia, antidepressants,	Zolpidem use was not associated with Alzheimer's disease However, zolpidem users with high cumulative DDD (>180 cDDD) strongly associated with Alzheimer's disease (reference non-users: HR=2.97, 95%	8

Article, Country	Population	Study Design	Sample Size	Main Predictors	Cognitive Outcome	Confounders Measured	Main Findings	Study Quality Star Rating
						benzodiazepines, anti-Parkinson, antipsychotics Physician visits: total outpatient and emergency visits for neurology and psychiatry clinics in pre-index period	CI=1.61-5.49; reference those with <28 cDDD: HR=4.18, 95% CI=1.77-9.86)	

Notes: nBH = non-benzodiazepine hypnotics, MCI = Mild Cognitive Impairment; DDD = Defined Daily Dose; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; APOE = apolipoprotein E

Table 2.

Study Quality Assessment (Newcastle-Ottawa Scale)

Cohort Studies								
	Selection				**Comparability**	**Outcome**		
Study	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough up of for outcomes to occur**	**Adequacy of follow up of cohorts**
Burke (2019)	Selected group of users (volunteers)	* Drawn from same community as the exposed cohort	* Structured interview	* Yes	* Study controls for sleep disturbance * Study controls for any additional factor	* Independent blind assessment	* Yes	No statement
Burke (2018)	Selected group of users (volunteers)	* Drawn from same community as the exposed cohort	* Structured interview	* Yes	* Study controls for sleep disturbance * Study controls for any additional factor	* Independent blind assessment	* Yes	No statement
Cheng (2017)	* Truly representative of the average population	* Drawn from same community as the exposed cohort	* Secure record	* Yes	* Study controls for sleep disturbance * Study controls for any additional factor	* Record linkage	* Yes	No statement
Case-Control Studies								
	Selection				**Comparability**	**Exposure**		
Study	**Is case definition adequate?**	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability of cases and controls on basis of design or analysis**	**Ascertainment of exposure**	**Same ascertainment for cases and controls**	**Non-response rate**
Richardson (2019)	Yes Record linkage	* Consecutive or obviously representative	* Community	* No history of disease	* Study controls for sleep disturbance * Study controls any additional factor	* Secure record	* Yes	* Same rate for both groups
Cross-Sectional Studies								
	Selection				**Comparability**	**Outcome**		
Study	**Representativeness of the sample**	**Sample size**	**Non-respondents**	**Ascertainment of exposure**	**Control of confounding factors**	**Assessment of outcome**	**Statistical test**	
Hosoya (2018)	Selected group of users	Non-justified	N/A	Non-validated	Does not control	** Independent blind assessment	* Described, appropriate	

Note: Newcastle-Ottawa Scale evaluates studies on: 1) selection of study groups, 2) comparability of study groups, and 3) ascertainment of exposure (for case-control studies) or outcome (for cohort studies). Assessment of cross-sectional studies came from a modified version from a previous study [38]. Good study quality threshold set at 7 stars.