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Review Article

COMPREHENSIVE ANALYSIS OF HISTAMINE-2 RECEPTOR ANTAGONISTS ON DEMENTIA RISK: A SYSTEMATIC REVIEW OF COHORT STUDIES

Yong Yee Wen[1], *Vivien Puspitasari*[1,2]

[1]Medical Profession Program, Faculty of Medicine, Pelita Harapan University, Tangerang, Banten, Indonesia; yongyeewen1804@gmail.com
[2]Department of Neurology, Siloam Hospitals Lippo Village, Tangerang, Banten, Indonesia

ABSTRACT

Introduction : Histamine-2 Receptor Antagonist (H2RA) are widely used to manage upper gastrointestinal diseases (UGID). However, growing concerns have emerged regarding their potential neurocognitive side effect, particularly an increased dementia risk. H2RAs are often preferred over proton pump inhibitors (PPIs) for enhanced therapeutic efficacy in clinical settings.
Material and methods : This research adhered to the PRISMA guidelines to select studies and assess biases. Databases (PubMed, Scopus, and Cochrane) are systematically searched from 2020-2025, and available studies are further evaluated for eligibility and risk of bias using the Cochrane risk of bias assessment tools for non-randomized studies of interventions (ROBINS-I).
Discussion : Six studies were analyzed, with four cohort studies showing no significant association between H2RA use and dementia risk. However, H2RA use was associated with accelerated cognitive decline in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). The anticholinergic effects of H2RAs may contribute to cognitive impairment by disrupting histamine's role in the central nervous system and vitamin B12 absorption. However, the pathophysiological mechanisms remain unclear and the findings across studies are inconsistent. Further randomized controlled trials (RCTs) with larger sample sizes are needed to elucidate the potential long-term effects of H2RAs on cognitive health.
Conclusion : This systematic review found no clear association between H2RA use and an increased risk of dementia, but noted accelerated cognitive decline in MCI and AD patients.

Keywords: alzheimer's disease; cognitive impairment; dementia; gastric acid-suppressive agents; histamine-2 receptor antagonists

INTRODUCTION

Histamine-2 Receptor Antagonists (H2RAs) are commonly prescribed for the management of upper gastrointestinal diseases (UGID) and are considered safe for use in children and adolescents. They work by binding to histamine H2 receptors, reducing gastric acid secretion. H2RAs are well-absorbed by oral administration and can be used either for symptomatic relief or prophylactically, typically taken 30 to 60 minutes prior to known food or beverages triggers, with common dosing regimens involving twice-daily administration.[1] However, concerns have been raised regarding

the potential long-term cognitive effects of H2RA use, particularly its association with dementia. Histamine plays a key role in cognitive function, and H2RAs may contribute to cognitive impairment by inhibiting histamine and reducing gastric absorption of vitamin B12, potentially leading to neurological damage.[2,3]

Several studies have examined the relationship between H2RA use and cognitive impairment, but the results remain inconclusive.[2,4,6-9] A systematic review and meta-analysis by Northuis et al. in 2023, examining the effects of similar gastric acid suppressive agents such as proton-pump inhibitors (PPIs), reported prolonged PPI use linked to a 33% higher dementia risk[10], while 2023 review by Ahn et al. found no clear evidence of such an association.[11] These mixed findings, alongside H2RAs' clinical preference due to their therapeutic benefits, highlight the need for further research. This systematic review aims to assess the association between H2RA use and dementia risk and examine the reasons for conflicting results in the current literature.

MATERIAL AND METHODS

This systematic review adheres to the PRISMA guidelines for study selection. Cohort studies involving adult patients over 18 years of age, which examine the use of H2RAs as the primary intervention, were eligible for inclusion. Studies included in this review report on the risk of dementia associated with H2RAs, with the primary outcome being the incidence of dementia, including AD, VD, or other diagnoses related to cognitive impairment. The secondary outcome involves comparing the effects of H2RAs with those of PPIs. Studies were excluded if they were not cohort designs, were published in languages other than English, did not provide full-text access, lacked sufficient data for analysis, or did not specifically address the use of H2RAs.

Relevant studies were identified through electronic searches of PubMed, ScienceDirect, and Cochrane databases Articles published within five years prior to March 7th, 2025, were screened. Full texts of all potentially relevant studies were then reviewed to determine final selection. These

studies were then assessed for eligibility and risk of bias using the Cochrane risk of bias assessment tools for non-randomized studies of interventions (ROBINS-I) tool. Only studies with low-to-moderate quality were included in the final analysis.

DISCUSSION

Identification of relevant study data

A total of 325 articles were screened for eligibility, and six studies investigating the association between H2RAs and dementia risk were included in the review.

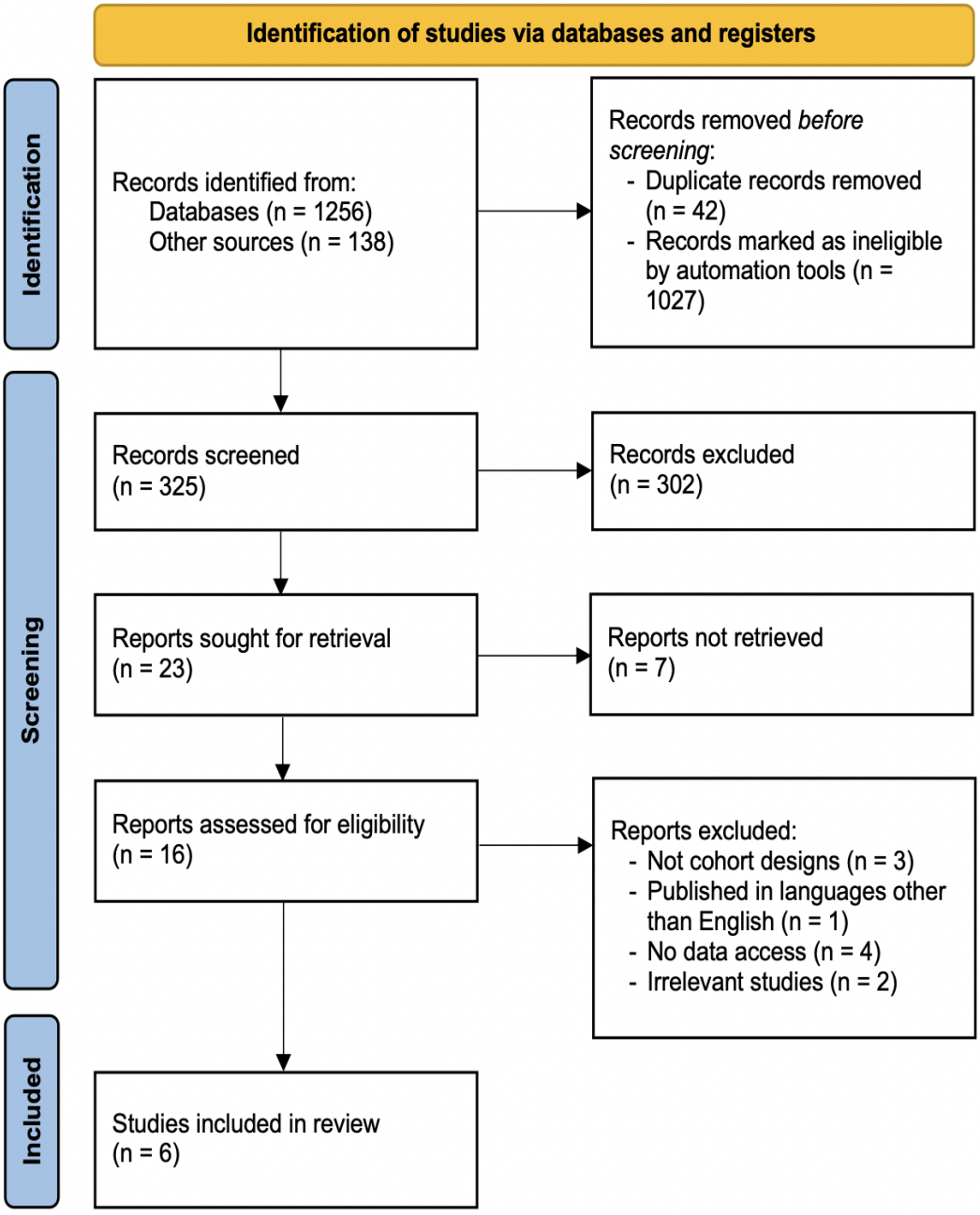

Figure 1. Study identification PRISMA flow diagram

Impact on patients with normal cognitive function or without prior dementia

A 2020 cohort study conducted by Chen et al. found that H2RA use was linked to a higher risk of dementia (adjusted HR, 1.84; 95% CI, 1.49-2.20) in patients without prior dementia. H2RAs may contribute to cognitive decline through their anticholinergic effects, which inhibit histamine's role in cognitive function. Additionally, histamine plays a role in gastric vitamin B12 absorption, and its inhibition by H2RAs may impair DNA synthesis, contributing to cognitive decline and neurological damage.[2] A similar study by Lin et al. 2021 (n = 1,679) found an increased dementia risk with H2RAs (adjusted HR, 1.357; 95% CI, 1.098-1.678). These drugs may also disrupt the gut microbiota, potentially affecting the central nervous system via the microbiota-gut-brain axis.[4] Compared to H2RAs, PPIs are associated with a higher dementia risk, likely due to the impairment of β-amyloid (Aβ) degradation by lysosomes in microglial cells, and greater impact on the gut microbiome and oral-to-gut transmission.[5]

In contrast, a study by Wu et al. in 2021 found no significant association between H2RA use and cognitive impairment (adjusted HR, 1.067; 95% CI, 0.807-1.410).[6] A subsequent cohort study by Wu et al. in 2022 also reported no link between the use of H2RAs and cognitive impairment (adjusted HR, 0.94; 95% CI, 0.71-1.242).[7] Both studies suggested a potential dose-response relationship, indicating that cumulative effects and the anticholinergic burden scale of H2RAs may influence dementia risk. However, the precise maximum dose, duration, and frequency thresholds that might lead to cognitive impairment remain unidentified in the existing literature.[6,7] Similar findings were reported by Wu et al. in 2020 (adjusted HR, 0.95; 95% CI, 0.74-1.22) and Mehta et al. in 2023 (adjusted HR, 1.00; 95% CI, 0.59-1.74), who also found no association between H2RAs and dementia. These inconclusive results across studies may stem from variations in study populations, exposure assessment methods, drug exposure levels, and key confounding factors not accounted for in positive studies, including race or ethnicity, body

mass index, smoking status, alcohol consumption, concomitant medications, and educational level.[8,9]

Impact on patients with a history of cognitive impairment or prior dementia

Based on the study conducted by Wu et al. in 2021, patients with mild cognitive impairment (MCI) had a significantly higher risk of developing dementia (adjusted HR, 1.402; 95% CI, 1.085-1.811), similar to patients with clinically diagnosed AD (adjusted HR, 0.783; 95% CI, 0.671-0.915).[6] In 2022, Wu et al. reported that H2RA use was associated with a 40.2% increased risk of dementia in MCI patients (adjusted HR, 1.40; 95% CI, 1.09-1.81) and accelerated memory decline in individuals with mild-moderate AD (adjusted HR, 0.76; 95% CI, 0.64-0.92).[7] The anticholinergic effects of H2RAs may exacerbate existing cholinergic deficiencies in MCI or AD patients, potentially accelerating cognitive decline by inhibiting acetylcholine, which is crucial for memory and learning.[6,7]

Table 1. Summary of included studies characteristics

Author; Year	Study Location	Design	Demography			Intervention	Outcome	Follow-up	Findings
			Patient characteristics	Sample size	Groups				
Chen et al.; 2020[2]	Taiwan	Retrospective Cohort	Inclusion Criteria: Asian patient aged ≥65 years old Patient who had not received any H2RA or PPI therapy for 12 months prior to the first prescription Exclusion Criteria: Patient who had received H2RAs before 1 January 2000 Patient aged <65 years old Patient had all-cause dementia diagnosed before 1 January 2000 Incomplete demographic data	62,574	Group 1: H2RA users (*n* = 21,939) Group 2: Non-H2RA users (*n* = 21,939) Group 3: PPI users (*n* = 9,348) Group 4: Non-PPI users (*n* = 9,348)	Clinical use of H2RA (Cimetidine, Ranitidine, Famotidine, Roxatidine) or PPI (Omeprazole, Pantopraozle, Lansoprazole, Esomeprazole, and Rabeprazole), supply days, and total number of pills dispensed from the outpatient pharmacy prescription database. Cumulative dosage of H2RAs or PPIs during the study period was calculated and presented as: **Defined Daily Dosage (DDD)** = (Total Amount of Drug) / (Amount of Drug in a DDD) Cumulative DDD (cDDD) = $DDD_{H2RA} + DDD_{PPI}$ *(1 January 2000 - 31 December 2013)* Dosage categories of	Primary diagnosis of dementia, confimed by a board-certified psychiatrist or neurologist, based on ICD-9 and DSM-IV	13 years	Patients treated with H2RAs demonstrate a significant higher risk of developing dementia as compared to those not treated with H2RAs (adjusted HR, 1.84; 95% CI, 1.49-2.20). As a secondary outcome, PPI users had significantly elevated risk of dementia compared to non-PPI users (adjusted HR, 1.42; 95% CI, 1.07-1.84).

					H2RAs or PPIs use were classified based on quartile distribution of cDDD			
Lin et al.; 2021[4]	Taiwan	Retrospective Cohort	Inclusion Criteria: Patients administered between 1 January 2000 - 31 December 2015 Exclusion Criteria: Patient with UGID who had received gastric acid-suppressive agents before 2000 Patient had all-cause dementia diagnosed before 1 January 2000 Patient receiving gastric acid-suppressive agents <90 days within 365 days after first being administered	20,133	Group 1: Patients with UGID receiving gastric acid-suppressive agents (*n* = 6,711) Group 2: Patients with UGID without gastric acid-suppressive agents (*n* = 6,711) Group 3: Patients without UGID and gastric acid-suppressive agents (*n* = 6,711)	Use of gastric acid-suppressive agents, defined as a prescription for at least one type of PPI (Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole, or Rabeprazole) or H2RA (Cimetidine, Ranitidine, Famotidine, Nizatidine, or Roxatidine) for at least 90 days within 365 days after first being administered one of these agents.	Diagnosis of dementia, based on ICD-9	10 years	Both H2RAs and PPIs increase the risk of dementia, with patients receiving PPIs exhibiting greater risk (adjusted HR, 1.886; 95% CI, 1.377-2.582) than H2RAs (adjusted HR, 1.357; 95% CI, 1.098-1.678). Overall, patients with UGID receiving gastric acid-suppressive agents had higher incidence of dementia (adjusted HR, 1.470; 95% CI, 1.267-1.705).
Wu et al.; 2022[7]	United States	Retrospective Cohort	Inclusion Criteria: Patients with clinically diagnosed mild-moderate AD,	2,968	Group 1: Mild-moderate AD with H2RA use (*n* = 157)	Use of H2RAs or PPIs	Delayed recall memory, assessed using the Wechsler Memory Scale Revised-Logical Memory Test IIA (score range from	5 years	H2RA use was associated with an earlier progression from MCI to dementia in those

	MCI, and normal cognition; classified using prevailing clinical diagnostic criteria and Clinical Dementia Rating (CDR). Exclusion Criteria: Patients with cancer or on chemoterapy Patients with global CDR of 0 on a drug for dementia Patients with CDR Sum of Boxes (CDR-SOB) >0.5 for normal individuals; >4 for those with MCI; >15 for those with mild-moderate AD Patients using both H2RA and PPI at baseline	and with PPI use (*n* = 471) Global CDR score of 1 or 2 Met NIA and Alzheimer's Association (NIA-AA) or National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association Group 2: MCI with H2RA use (*n* = 205) and PPI use (*n* = 615) Global CDR score of 0.5 Met the	0 to 25; better scores indicate better performance in episodic memory)	with MCI (adjusted HR, 1.40; 95% CI, 1.09-1.81), as well as more rapid decline in memory over a 5-year period in individuals with mild-moderate AD (adjusted HR, 0.76; 95% CI, 0.64-0.92). However, no longitudinal associations with cognitive decline were observed in individuals with normal cognition (adjusted HR, 0.94; 95% CI, 0.71-1.242).

				Petersen's criteria Group 3: Normal cognition with H2RA use (*n* = 380) and PPI use (*n* = 1,140) Global CDR score of 0				
Wu et al.; 2021[6]	United States	Retrospective Cohort	Inclusion Criteria: Patients with clinically diagnosed mild-moderate AD, MCI, and normal cognition; classified using prevailing clinical diagnostic criteria and CDR. Exclusion Criteria: Patients with global CDR of 0 on a drug for dementia Patients with CDR-SOB >0.5 for normal	5,333	Group 1: Normal cognition patients with H2RA use (*n* = 547) and PPIs use (*n* = 2,237) Group 2: MCI patients with H2RAs use (*n* = 288) and PPIs use (*n* = 1,413) Group 3: Mild-moderate AD patients with H2RAs use (*n* = 212) and PPIs use (*n* =	Use of H2RAs or PPIs	Delayed recall memory, assessed using the Wechsler Memory Scale Revised-Logical Memory Test IIA (score range from 0 to 25; better scores indicate better performance in episodic memory)	5 years	The use of H2RAs was associated with more rapid cognitive decline in patients with MCI (adjusted HR, 1.402; 95% CI, 1.085-1.811) and AD (adjusted HR, 0.783; 95% CI, 0.671-0.915). However, no differential associations with cognitive decline were observed in cognitively normal older people (adjusted HR, 1.067; 95% CI, 0.807-1.410).

			individuals; >4 for those with MCI; >15 for those with mild-moderate AD Patients using both H2RA and PPI at baseline		636)				
Wu et al.; 2020[8]	Taiwan	Retrospective Cohort	Inclusion Criteria: Patients administered between 1 January 2000 - 31 December 2015 Exclusion Criteria: Patient aged <40 years old Incomplete information during the insurance period or withdrawal from the insurance program in 2000 Any use of PPIs or H2RA in 2000 Patient had all-cause dementia diagnosed (ICD-9-CM code: 290.xx, 294.1, 331.0) before 1	96,181	Group 1: PPI users (*n* = 2,778) PPIs >60 cDDD H2RA = 0 cDDD Group 2: H2RA users (*n* = 6,165) PPIs = 0 cDDD H2RA >60 cDDD Group 3: Non-users (*n* = 86,238) PPIs = 0 cDDD H2RA = 0 cDDD	H2RAs and PPIs prescriptions, identified in ambulatory visits and contracted pharmacies during the follow-up period, using the anatomical therapeutic chemical code (ATC code) for classification. Cumulative dosage of H2RAs or PPIs during the study period was calculated and presented as: **Defined Daily Dosage (DDD)** = (Total Amount of Drug) / (Amount of Drug in a DDD) Cumulative DDD (cDDD) = $DDD_{H2RA} + DDD_{PPI}$ *(2001 - 2010)* Total of 3 propensity-score matching (PSM) was	Primary diagnosis of dementia following at least 2 ambulatory visits during the follow-up period, confimed by psychiatrists or neurologist, based on DSM-IV	According to the date of **cDDD >60** in each groups to prevent immorial time bias Mean follow-up duration of each PSM = 4,0 - 4,4 years	Compared to non-users, H2RAs (adjusted HR, 0.95; 95% CI, 0.74-1.22) users did not show a significant risk of developing dementia. There was also no difference between PPIs and H2RAs users in the risk of developing dementia (adjusted HR, 0.82; 95% CI, 0.58-1.17). Therefore, no association was observed between the use of gastric acid-suppressive agents and the risk of developing dementia.

			January 2000 Diagnosis of thyroid disease (ICD-9-CM code: 240.xx-246.xx), human immunodeficiency virus (ICD-9-CM code: 042), or cancer (ICD-9-CM code: 140.xx-239.xx) from 2000 to 2010 A follow-up period of less than 1 year			done: PPIs users with non-users (*n* = 2,583) H2RAs users with non-users (*n* = 5,955) PPIs users with H2RA users (*n* = 2,675)			
Mehta et al.; 2023[9]	United States & Australia	Prospective Cohort	Inclusion Criteria: Patient administered in ASpirin in Reducing Events in the Elderly (ASPREE) trial Exclusion Criteria: Patient died before their first annual visit during ASPREE-eXTension	18,934	Group 1: PPIs users (*n* = 6,711) Group 2: H2RAs users (*n* = 6,711)	Use of Gastric acid-suppressive agents, defined as a prescription for at least one type of PPI (Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole, or Rabeprazole) or H2RA (Cimetidine, Ranitidine, Famotidine, Nizatidine, or Roxatidine) for at least 90 days within 365 days after first being administered one of these agents.	During ASPREE, cognitive testing was performed at baseline, then at years 1, 3, 5, and at a final visit. During ASPREE-XT, cognitive testing was performed annually. 4 cognitive tests were administered: 3MS (global cognition) The Hopkins Verbal Learning Test-Revised (episodic memory) The Symbol Digit	≥6 weeks after the initial dementia flag	There was no association between H2RA use and AD (adjusted HR, 1.00; 95% CI, 0.59-1.74), probable AD (adjusted HR, 0.73; 95% CI, 0.27-1.99), and mixed presentation (adjusted HR, 1.15; 95% CI, 0.59-2.24). H2RA use also exhibited no associations with incident CIND

	(ASPREE-XT) Patient had missing baseline covariate information Patient had cardiovascular disease, dementia, or physical disability, or <5 years survival rate	Modalities Test (psychomotor speed) The Single Letter (F) Controlled Oral Word Association Test (language and executive function) **DEMENTIA** Triggers for further evaluation of dementia: 3MS score <78 A drop of >10 points from the predicted score based on their own baseline 3MS, adjusted or age and education Report of memory concerns or other cognitive problems to a specialist A clinician diagnosis of dementia in the medical records or a prescription of antidementia drugs Dementia also subclassified as: Alzheimer Disease (AD) Probable AD	(adjusted HR, 1.02; 95% CI, 0.79-1.31).

		Mixed presentations (non-AD causes) **COGNITIVE IMPAIRMENT, NO DEMENTIA (CIND)** Patients met dementia trigger but did not met adjudication criteria for dementia

CONCLUSION

This systematic review found no definitive link between H2RA use and an increased risk of dementia. However, it observed accelerated cognitive decline in patients with MCI and AD. The variability in findings may be due to potential dose-response relationships and various confounding factors. To better understand the long-term impact of H2RAs on cognitive health, further randomized controlled trials (RCTs) with larger sample sizes are essential, particularly those that account for confounding variables.

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