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Histamine-2 Receptor Antagonist Use and Incident Dementia in an Older Cohort

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Abstract

OBJECTIVE—Examine whether histamine-2 receptor antagonist (H2RA) therapy is associated with a lower incidence of all-cause dementia or Alzheimer disease (AD) compared to nonuse, as some studies have suggested.

DESIGN—Prospective population-based cohort

SETTING—Group Health, an integrated health maintenance organization, Seattle, Washington

PARTICIPANTS—2923 participants aged 65 and older without dementia at baseline with initial recruitment between 1994 and 1996

MEASUREMENTS—Follow-up occurred every 2 years to identify incident dementia and AD using standard criteria. Exposure to H2RAs was based on automated pharmacy data. Three aspects of exposure (time-varying) were examined based on standard daily dose (SDD): cumulative use, intensity of use (highest SDD in any prior two year window), and cumulative use stratified by recency (1–3 years versus > 3 years prior).

RESULTS—Over a mean follow-up of 6.7 years, 585 subjects developed dementia (453 developed AD). Total cumulative exposure was not associated with dementia (p=0.35; omnibus test) or AD (p=0.23). The adjusted HR for the highest exposure category (>1080 SDD) compared

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to light or nonuse was 1.28 (95% confidence interval [CI] 0.95–1.72) for dementia and 1.41 (95% CI 1.00–1.97) for AD. Intensity of use was not associated with dementia (p=0.39) or AD (p=0.63). Examining exposure according to recent and distant cumulative use also showed no association with dementia (p=0.11) or AD (p=0.30).

CONCLUSION—We found no association between H2RA use and reduced risk of all-cause dementia or AD using more detailed and extensive information about past H2RA use than any prior study.

Keywords

dementia; Alzheimer disease; pharmacoepidemiology; cohort study; histamine-2 receptor antagonist

INTRODUCTION

Histamine-2 receptor antagonist (H2RA) medications were the first agents available to treat gastric acid-related disorders prior to the introduction of proton pump inhibitors. Four H2RAs (cimetidine, ranitidine, famotidine, and nizatidine) are currently available by prescription and also over the counter (OTC) at lower doses. Ranitidine remains among the top 50 generic prescriptions dispensed in the US,[1] with 12,645,000 prescriptions dispensed in 2007.[2] Thus, even with the advent of proton pump inhibitors, H2RAs remain widely used.

Histamine is an excitatory neurotransmitter and plays an important role in attention and vigilance.[3,4] Several epidemiological studies have examined the effects of H2RAs on diverse cognitive outcomes including cognitive impairment,[5] Alzheimer's disease[6,7] or combined outcomes (cognitive impairment or dementia)[8] with mixed results. Some [7,9] but not all[10] cross-sectional studies reported an association between H2RA use and lower occurrence of AD. However, 2 longitudinal studies did not confirm this association, [5,6] and a third longitudinal study found that H2RA use was associated with an increased risk for AD or cognitive decline in African Americans.[8] In a randomized, placebo controlled trial, nizatidine had no effect on cognitive function in subjects with AD.[11] Current H2RA use has been associated with delirium and psychosis.[12]

The reasons for these discrepant results are not clear. A limitation of prior longitudinal studies is the lack of detailed information on past H2RA use. For example, one study only had information on current use,[8] and another relied on self-reported duration of use.[6] No prior study has had information about exposure occurring in the several years prior to study enrollment. A strength of the Adult Changes in Thought (ACT) study is the availability of detailed pharmacy data extending back to 1977, which is 15+ years prior to the first ACT enrollment. This extent of past use is important because it has been proposed that an intervention may be most effective in the preclinical stage of dementia which may be several years prior to symptom onset.[13] The objective of this study was to examine the association between H2RA exposure and incident all-cause dementia or AD. Our hypothesis was that sustained long-term use of H2RAs may be associated with a reduced risk of these outcomes.

METHODS

Participants

ACT is a population-based prospective cohort study of incident dementia and AD. ACT study methods have been described in detail elsewhere.[14] Briefly, study participants, aged 65 years and older, were randomly sampled from Seattle-area members of Group Health (GH). The research protocol for this study was reviewed and approved by the GH and

University of Washington's institutional review boards. The original cohort of 2581 cognitively intact men and women was enrolled between 1994 and 1996. An additional 811 participants were enrolled between 2000 and 2002, and in 2004 the study began continuous enrollment (n=620 to date), to replace those who die or drop out for a total of 4012 study participants. For our analyses we required subjects to have at least 10 years of continuous GH membership prior to baseline to ensure a thorough accounting of prior H2RA exposure and to have at least one follow-up visit. Applying these inclusion criteria yielded a cohort of 2923 participants.

Ascertainment of Dementia and AD

At baseline and biennial follow-up visits, cognitive function was evaluated using the Cognitive Assessment Screening Instrument (CASI).[15] The CASI is a 100-point test of global cognitive functioning used in several population-based epidemiological studies. Participants whose CASI scores fell below 86 underwent a standardized dementia diagnostic evaluation, including a physical and neurological examination by a study neurologist, geriatrician or internist, and a one-hour battery of neuropsychological testing. Relevant laboratory tests and brain CT or MRI imaging studies were performed or results were obtained from GH records. Diagnoses were assigned at consensus diagnostic conferences using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria for dementia,[16] and criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association for AD.[17] Participants with new onset dementia underwent at least one annual follow-up examination for verification of dementia status. The date of onset was assigned by convention as the midpoint between the ACT study visit that triggered a positive dementia evaluation and the preceding study visit. For these analyses, the two outcomes of interest were incident all-cause dementia and possible or probable AD.

Exposure measurement

The GH pharmacy database includes all prescriptions dispensed from March 1977 to the present, including drug name, strength, and amount dispensed. Since cimetidine was first approved by the FDA in 1979, this database covers the entire time period of H2RA marketing. In prior studies, 96% of older GH members report filling all or most of their prescriptions at GH pharmacies.[18] Self-reported OTC H2RA use was collected at each biennium interview, but dose and duration was not available. For each H2RA agent, we established an equivalent daily dose based on usual daily doses.[19] Equivalent daily doses were ranitidine (300 mg), cimetidine (800 mg), nizatidine (300 mg) and famotidine (40 mg). Then for each H2RA prescription in the GH pharmacy database, we calculated the number of standard daily doses (SDD) dispensed by multiplying the number of tablets dispensed by the tablet strength and dividing by the equivalent daily dose. We then distributed the SDD equally across the time to the next fill or 90 days, whichever was earliest.

Since the precise nature of the relationship between H2RA and dementia risk is not known, we developed three time-varying measures of H2RA exposure, each capturing a different facet of exposure: cumulative use (exposure 1), intensity of use (exposure 2), and recency of cumulative use (exposure 3). For cumulative use (exposure 1), we summed the total SDD from all of a participant's prior prescriptions and categorized levels of use as follows: ≤30 (nonuse or less than 1 month of usual use), 31–180 (roughly 1–6 months of usual use), 181–540 (roughly 6–18 months of usual use), 541–1080 (roughly 18–36 months of usual use), and >1080 SDD (greater than 36 months of usual use). For intensity of use (exposure 2), we measured the maximum total number of SDD ever dispensed to an individual in any 2-year period (categorized as: ≤30, 31–180, 181–540, and >540 SDD). Exposure 2 sought to determine whether sustained, high intensity use at any time was associated with decreased

risk of dementia. For exposure 3 (recent/distant use), we created 9 mutually exclusive categories based on all possible combinations of 3 levels of recent use (total cumulative SDD accumulated 1 to 3 years prior, categorized as 0–30, 31–180, or >180 SDD) and 3 levels of distant use (total cumulative SDD accumulated more than 3 years prior, categorized as ≤30, 31–540, or >540 SDD). All exposure measures were lagged by 1 year to avoid consideration of H2RA use that might have been influenced by the onset of dementia.

Potential confounders

At study baseline and each follow-up visit, information was collected on demographic factors, self-reported medical history, and health behaviors. Demographic factors considered included age, gender, and years of education. Participants were asked whether a doctor had ever told them that they had angina, congestive heart failure, hypertension, diabetes mellitus, asthma, or chronic obstructive pulmonary disease (COPD). Coronary heart disease (CHD) was defined as a self-reported history of heart attack, angina, angioplasty, or coronary artery bypass surgery. Cerebrovascular disease was defined as a self-reported history of stroke, cerebral hemorrhage, small strokes or transient ischemic attack, or carotid endarterectomy. Health and lifestyle characteristics included body mass index (BMI) calculated from measured weight and height, self-assessed health, and physical activity. Regular exercise was defined as self-report of performing one of several listed activities for at least 15 minutes, three times per week.[20] Exposure to non-steroidal anti-inflammatory drugs (NSAID) was expressed as total cumulative use (SDD) and was created as described for H2RA exposure 1.

Statistical Analyses

Descriptive analyses were stratified by baseline level of H2RA use and presented as number and percentages for categorical variables. To analyze the association between H2RA exposure and risk of all-cause dementia, we estimated hazard ratios (HR) from Cox proportional hazards regression models with participant age as the time scale,[21] and the event time taken to be the age at dementia onset. Individuals not diagnosed with dementia were censored at time of their last ACT visit or at time of disenrollment from GH, whichever was earlier. In addition, for the AD-specific analysis, individuals were censored at the time of any dementia diagnosis not attributed to possible or probable AD. We fit separate models for each of the 3 time-varying H2RA exposure characterizations. All models adjusted for ACT cohort, gender, education, time-varying use of NSAIDs, time-varying measures of diabetes mellitus, hypertension, cerebrovascular disease, CHD, pulmonary disease (asthma or COPD), regular exercise, and self-reported health, and baseline BMI. For exposure 2 (intensity of use), the model was additionally adjusted for time since most intense use. Hazard ratios for all-cause dementia and AD are presented relative to a referent group of 0–30 SDD H2RAs. The p-values provided are from omnibus Wald tests which jointly assess the effects across the H2RA exposure categories. We assessed proportional hazards assumptions by testing for an interaction between the exposures of interest and age at dementia onset. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Sensitivity Analysis—H2RAs became available as OTC products beginning in 1995, which coincided with ACT study initiation. Thus complete ascertainment of H2RA use prior to baseline is available from GH automated pharmacy files for most subjects. The strength of OTC H2RAs is typically ½ of the prescription strength, with the exception of ranitidine. To address potential misclassification by unaccounted OTC use, we performed sensitivity analyses for exposure 1 incorporating self-reported OTC H2RA use. At each visit in which a participant indicated OTC H2RA use, 100 SDD was added to the total cumulative dose (e.g. equivalent to once-daily use of OTC ranitidine 75 mg 4 days a week over the prior 2 years).

In order to assess the potential impact of more extreme OTC use, this analysis was repeated using 250 SDD for each OTC H2RA self-report.

RESULTS

Table 1 provides baseline characteristics of the 2923 eligible ACT participants, stratified by H2RA exposure level at baseline. The median age at cohort entry was 74 years (interquartile range 70 to 79). Approximately 60% were female, 91% were white, and more than 60% had at least some college education. The analytic sample based on all inclusion criteria did not differ meaningfully at baseline from the full ACT cohort with regard to the distribution of health and socio-demographic characteristics (not shown). Missing data were ≤2% for all variables.

Of the 2,923 participants, 2076 (71.0%) had light or no cumulative H2RA use at baseline (≤30 cumulative SDD), while 413 (14.1%) had between 30 and 180 SDD, 205 (7.0%) had between 180 and 540 SDD, and 229 (7.8%) had more than 540 SDD. Among people who used H2RAs prior to baseline, the median number of prescriptions per participant was 7 (interquartile range 3–20), whereas the median total SDD per participant was 194 (interquartile range 75–595). Participants with heavier use had more co-morbid conditions and adverse health characteristics than light or non-users. The predominant H2RA agents prescribed were cimetidine and ranitidine, each of which accounted for approximately half of the prescriptions and SDD.

Over a mean (SD) follow-up of 6.7 (3.9) years, 585 subjects developed dementia and of these, 453 developed probable or possible AD. The results for all-cause dementia and AD are given in tables 2 and 3 respectively. We saw no overall association between the categorized levels of cumulative H2RA use (Exposure 1) and risk of all-cause dementia or AD (omnibus test; p-value 0.35 and 0.23, respectively). However, the highest exposure category (>1080 SDD) gave some indication of elevated risk compared to light or nonuse for all-cause dementia (HR, 1.28; 95% CI 0.95–1.72) and for AD (HR, 1.41; 95% CI 1.00–1.97). In analyses examining intensity of use (Exposure 2), the maximum number of SDD ever accumulated in a 2 year period was not related to risk of all-cause dementia or AD (omnibus test; p-value 0.39 and 0.63 respectively). For this exposure, the adjusted HR for the highest use category (>540 SDD) was 1.09 (95% CI 0.79–1.52) for all-cause dementia and 1.13 (95% CI 0.78–1.64) for AD. A test for an interaction between the maximum 2-year exposure level and time since last achieving that exposure level was not statistically significant (p-value 0.62 for all-cause; p-value 0.48 for AD).

In the analysis which characterized participants into discrete categories of recent and distant exposure, there was no overall association between H2RA use and risk for dementia (p=0.11) or AD (p=0.30). For example, when examining the risk associated with high recent use; relative to users who had light or nonuse (SDD ≤30 for recent and distant), the HR for all-cause dementia was 0.92, 1.25, and 0.88 for heavy distant/heavy recent, moderate distant/heavy recent, and light distant/heavy recent users, respectively. No interactions were observed between any exposure and age at dementia onset.

Sensitivity Analysis: Self-reported OTC use

Over the study follow-up, 440 participants reported OTC H2RA use across a total of 838 visits. Approximately 50% of this self-reported OTC use occurred in those who were already in the highest exposure category (SDD>1080) based on automated pharmacy files. In general, the results were not appreciably changed and were attenuated toward the null when we assigned 100 or 250 SDD for each self-report of OTC use. For example, for all-cause dementia in relation to total cumulative use of ≥1080 SDD, the HR was 1.25 (0.93–

1.68) for the analysis adding 100 SDD and 1.18 (0.88–1.57) for 250 SDD, compared to an HR of 1.28 (0.95–1.72) in our primary analysis (data available upon request).

DISCUSSION

In this population-based, longitudinal study of persons aged 65 years and older, we found no association between H2RA use and reduced risk of all-cause dementia or AD using three different exposure characterizations. For both AD and all-cause dementia, the group with the highest cumulative exposure (>1080 SDD) had if anything a slightly increased risk for these outcomes compared to the light/nonuse group (e.g. HR 1.41, 95% CI 1.00–1.97 for AD), but importantly, there was no association overall and there was no dose-response trend. Further, no association was suggested for any exposure group in the analysis of intensity of exposure in any two year window or when use was stratified by recency of use.

The first study to examine the association between H2RA exposure and AD risk was published in 1995. In a cross-sectional analysis of siblings, those with sustained H2RA exposure experienced a later onset of AD than those without H2RA exposure.[7] A cross-sectional analysis of data from the Cache County study also reported an association of lower AD prevalence with H2RA use,[9] whereas a cross-sectional analysis of data from the Rotterdam study did not (HR 0.95, 95% CI 0.52–1.75).[10] A subsequent longitudinal analysis of data from Cache County study did not demonstrate an association between H2RA exposure and AD risk (adjusted HR 1.09, 95% CI 0.63–1.79).[6] H2RA use was not associated with a reduction in incident cognitive decline (adjusted RR 1.51, 95% CI 0.93–2.47) in a longitudinal sample followed for 7 years.[5] Most recently, in a sample of 1,558 community-dwelling African Americans aged 65 and older, H2RA use was found to be associated with an *increased* risk for incident AD or cognitive impairment. A limitation of that study was that it was not clear that the exposure preceded outcome for all individuals.[8]

A clear mechanism for how H2RA exposure may be protective for all-cause dementia or AD has not been elucidated. In the central nervous system, histamine is an excitatory neurotransmitter and plays an important role in attention and vigilance.[3,4] There is some evidence that a decrease in histamine transmission (e.g. through histamine receptor blockade) could improve cognition; there is also evidence suggesting the contrary. [3] However, H2RA agents have been shown to have serum anticholinergic activity which could contribute to cognitive impairment.[22] We attempted to address this issue by ignoring H2RA exposure during the 1 year prior to diagnosis, and thus only counting exposure that corresponds roughly to use prior to the visit with the last normal CASI score.

Strengths of this study include the large community based sample, the average of over 6 years of follow-up, use of standard definitions for dementia and AD ascertainment, and the extensive detailed exposure ascertainment preceding dementia onset. As all participants had at least 10 years of pharmacy data available prior to baseline, we had the flexibility to categorize three different facets of H2RA exposure which extends prior research in this area. Misclassification of exposure is possible because of OTC H2RAs availability beginning in 1995, although a prior study indicated that GH automated pharmacy files still capture a considerable extent of acid suppressive therapy (proton pump inhibitors and H2RAs) use compared with self-report.[23] We conducted sensitivity analyses incorporating information about self-reported OTC use and found that in general, our results were attenuated toward the null. Thus it seems very unlikely that misclassification due to OTC use could be sufficient to reverse our findings, causing the HR to cross the null, as would be needed to suggest that H2RAs are indeed associated with reduced dementia risk.

Despite the strength of our pharmacy exposure data, a few limitations should be noted. We lacked daily dose and days supply information for each prescription, so we were not able to precisely determine dose or duration of use but instead used a methodology (SDD) that has been utilized extensively.[19, 24] Further, the small size of some of the exposure groups precluded our ability to fully investigate certain combinations of recent and distant use in more detail (exposure 3). Lastly, as in any observational study, unmeasured or residual confounding could introduce bias in our estimates. In particular, the elevated risk noted in the highest exposure category could be related to the overall worse health status of this group which we may not have adequately accounted for with the available self-reported comorbidity information. The accuracy of self-report for many of the conditions (diabetes mellitus, hypertension, MI, stroke, angioplasty, or coronary artery bypass surgery) we adjusted for has been found to be very good to excellent in prior studies.[25–27]

The relationship between H2RA use and AD risk has been the subject of scrutiny over the years, yet the relationship, if any, has remained unclear. Early cross-sectional studies reported a lower occurrence of AD in users of H2RA medications, which subsequently was not confirmed in longitudinal studies, including the current study. In fact, some studies have suggested an increased risk of AD with H2RA use. Further complicating this picture are case reports suggesting that H2RAs may precipitate delirium in susceptible individuals. Our study has extended prior work in this area by utilizing considerably more detailed and extensive information about past H2RA use than any study to date. Our results do not support an association between H2RA use and lower risk of dementia or AD among community-dwelling older adults. Limiting the unnecessary use of H2RAs, which are available to patients as OTC products, is prudent given the possibility of acute negative effects on cognition as has been reported in the literature.

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References

1. 2008 Top 200 generic drugs by total prescriptions; Drug Topics. 2009. p. 4-6.Accessed on http://www.modernmedicine.com/modernmedicine/data/articlestandard/drugtopics/192009/597084/article.pdf
2. Top 200 generics drugs by unit in 2007. Drug Topics. 2008. http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/072008/491181/article.pdf
3. Esbenshade TA, Browman KE, Bitner RS, et al. The histamine H3 receptor: An attractive target for the treatment of cognitive disorders. Br J Pharmacol. 2008; 154:1166–1181. [PubMed: 18469850]
4. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev. 2008; 88:1183–1241. [PubMed: 18626069]
5. Hanlon JT, Landerman LR, Artz MB, et al. Histamine2 receptor antagonist use and decline in cognitive function among community dwelling elderly. Pharmacoepidemiol Drug Saf. 2004; 13:781–787. [PubMed: 15386717]
6. Zandi PP, Anthony JC, Hayden KM, et al. Reduced incidence of AD with NSAID but not H2 receptor antagonists: The Cache County Study. Neurology. 2002; 59:880–886. [PubMed: 12297571]

7. Breitner JC, Welsh KA, Helms MJ, et al. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. Neurobiol Aging. 1995; 16:523–530. [PubMed: 8544901]
8. Boustani M, Hall KS, Lane KA, et al. The association between cognition and histamine-2 receptor antagonists in African Americans. J Am Geriatr Soc. 2007; 55:1248–1253. [PubMed: 17661965]
9. Anthony JC, Breitner JC, Zandi PP, et al. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study. Neurology. 2000; 54:2066–2071. [PubMed: 10851364]
10. Launer LJ, Jama JW, Ott A, et al. Histamine H2 blocking drugs and the risk for Alzheimer's disease: The Rotterdam Study. Neurobiol Aging. 1997; 18:257–259. [PubMed: 9258905]
11. Carlson MC, Tschanz JT, Norton MC, et al. H2 histamine receptor blockade in the treatment of Alzheimer disease: A randomized, double-blind, placebo-controlled trial of nizatidine. Alzheimer Dis Assoc Disord. 2002; 16:24–30. [PubMed: 11882746]
12. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: Incidence, prevention and management. Drug Saf. 1999; 21:101–122. [PubMed: 10456379]
13. Montine TJ, Larson EB. Late-life dementias: Does this unyielding global challenge require a broader view? JAMA. 2009; 302:2593–2594. [PubMed: 20009062]
14. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: A prospective cohort study. Arch Neurol. 2002; 59:1737–1746. [PubMed: 12433261]
15. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): A practical test for cross-cultural epidemiological studies of dementia. Int Psychogeriatr. 1994; 6:45–58. discussion 62. [PubMed: 8054493]
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. Washington, D.C: American Psychiatric Association; 1994. p. 886
17. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
18. Saunders, KWDR.; Stergachis, A. Group Health Cooperative. In: Strom, BL., editor. Pharmacoepidemiology. Chichester: John Wiley & Sons; 2005. p. 234
19. Breitner JC, Haneuse SJ, Walker R, et al. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology. 2009; 72:1899–1905. [PubMed: 19386997]
20. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006; 144:73–81. [PubMed: 16418406]
21. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. Am J Epidemiol. 1997; 145:72–80. [PubMed: 8982025]
22. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008; 56:1333–1341. [PubMed: 18510583]
23. Boudreau DM, Doescher MP, Saver BG, et al. Reliability of Group Health Cooperative automated pharmacy data by drug benefit status. Pharmacoepidemiol Drug Saf. 2005; 14:877–884. [PubMed: 15931653]
24. in t' Veld BA, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med. 2001; 345:1515–1521. [PubMed: 11794217]
25. Heckbert SR, Kooperberg C, Safford MM, et al. Comparison of self-report, hospital discharge codes, and adjudication of cardiovascular events in the Women's Health Initiative. Am J Epidemiol. 2004; 160:1152–1158. [PubMed: 15583367]
26. Okura Y, Urban LH, Mahoney DW, et al. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol. 2004; 57:1096–1103. [PubMed: 15528061]
27. Simpson CF, Boyd CM, Carlson MC, et al. Agreement between self-report of disease diagnoses and medical record validation in disabled older women: Factors that modify agreement. J Am Geriatr Soc. 2004; 52:123–127. [PubMed: 14687326]

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Table 1

Baseline characteristics according to level of histamine 2 receptor antagonist use prior to study entry*

	All (n=2932)		SDD ≤ 30 (n=2076)		30 < SDD ≤ 180 (n=413)		180 < SDD ≤ 540 (N=205)		SDD > 540 (n=229)	
	N	%	N	%	N	%	N	%	N	%
DEMOGRAPHICS										
Age, yrs										
≤ 70	818	28.0	611	29.4	121	29.3	41	20.0	45	19.7
71 – 75	844	28.9	597	28.8	104	25.2	69	33.7	74	32.3
76 – 80	670	22.9	473	22.8	96	23.2	48	23.4	53	23.1
81 – 85	400	13.7	265	12.8	57	13.8	37	18.0	41	17.9
86 – 90	150	5.1	99	4.8	29	7.0	7	3.4	15	6.6
> 90	41	1.4	31	1.5	6	1.5	3	1.5	1	0.4
Female	1,750	59.9	1,222	58.9	257	62.2	144	70.2	127	55.5
Some college	1827	62.5	1329	64	261	63.2	106	51.7	131	57.2
White	2,659	91.1	1,886	90.9	373	90.3	184	90.2	216	94.3
COMORBIDITIES										
Asthma/COPD	481	16.6	306	14.8	78	19.0	48	23.8	49	21.5
Diabetes	290	9.9	195	9.4	43	10.4	25	12.2	27	11.8
Hypertension	1,171	40.3	776	37.6	188	45.6	92	44.9	115	50.4
Stroke	93	3.2	61	2.9	12	2.9	9	4.4	11	4.8
Myocardial Infarction	264	9.1	162	7.8	47	11.4	25	12.2	30	13.1
Congestive heart failure	119	4.1	74	3.6	20	4.9	16	7.8	9	3.9
Cerebrovascular disease	295	10.2	189	9.2	41	10.1	29	14.4	36	15.7
HEALTH CHARACTERISTICS										
Exercise 15+ min ≥ 3 times/week	2,085	71.4	1,507	72.7	289	70.1	147	71.7	142	62.0
Fair/poor Self-rated health	483	16.6	286	13.7	76	18.4	58	28.3	63	27.5
Body mass index, kg/m^2										
< 25.0 (underweight/normal)	954	33.4	716	35.1	125	31.3	58	29.7	55	24.6
25.0–29.9 (overweight)	1,181	41.3	840	41.1	174	43.6	78	40.0	89	39.7
≥ 30 (obese)	727	25.4	488	23.9	100	25.1	59	30.3	80	35.7

*Percentages based on non-missing data

SDD Standardized daily dose; COPD Chronic obstructive pulmonary disease;

Table 2

Adjusted hazard ratios of risk for all-cause dementia according to histamine 2 receptor antagonist exposure

	Exposure at End of Follow-up*			Minimally Adjusted†		Fully Adjusted‡, §		
	N	%	Events	HR	95% CI	HR	95% CI	P value
Exposure 1: Total cumulative use								
SDD > 1080	301	10.3	59	1.37	1.04–1.81	1.28	0.95–1.72	0.35
540 < SDD ≤ 1080	157	5.4	33	1.09	0.77–1.56	1.01	0.69–1.48	
180 < SDD ≤ 540	306	10.5	66	1.28	0.99– 1.66	1.19	0.89–1.57	
30 < SDD ≤ 180	517	17.7	87	0.97	0.77–1.23	0.93	0.72–1.20	
SDD ≤ 30	1,642	56.2	340	1.00	Reference	1.00	Reference	
Exposure 2: Highest intensity in 2-yr period								
SDD > 540	276	9.4	50	1.20	0.89– 1.63	1.09	0.79–1.52	0.39
180 < SDD ≤ 540	381	13.0	87	1.29	1.01–1.65	1.21	0.93–1.58	
30 < SDD ≤ 180	573	19.6	100	0.97	0.76–1.24	0.94	0.73–1.21	
SDD ≤ 30	1,693	57.9	348	1.00	Reference	1.00	Reference	
Exposure 3: Distant use/Recent Use								
High/High	186	6.4	32	1.01	0.71–1.45	0.92	0.62–1.35	0.11
High/Moderate	54	1.8	18	2.50	1.57–3.98	2.25	1.34–3.77	
High/Low	163	5.6	30	1.42	0.97–2.08	1.37	0.91–2.06	
Moderate/High	74	2.5	22	1.32	0.86–2.04	1.25	0.79–1.97	
Moderate/Moderate	115	3.9	24	1.20	0.79–1.83	1.14	0.73–1.76	
Moderate/Low	552	18.9	92	0.98	0.78–1.24	0.96	0.76–1.23	
Low/High	39	1.3	6	0.94	0.43–2.05	0.88	0.38–2.06	
Low/Moderate	83	2.8	19	1.30	0.83–2.04	1.16	0.69–1.94	
Low/Low	1,657	56.7	342	1.00	Reference	1.00	Reference	

SDD Standardized daily dose; HR hazard ratio; CI confidence intervals

Distant Use: High (SDD>540); Moderate (30<SDD≤ 540); Low (SDD≤30)

Recent Use: High (SDD>180); Moderate (30<SDD≤ 180); Low (SDD≤30)

*This column displays the number of people exposed to H2RA at end of follow-up for each participant.

†Adjusted for age (via the time scale), ACT cohort

[‡]Adjusted for age (via the time scale), ACT cohort, gender, education, time-varying use of non-steroidal anti-inflammatory drugs (NSAIDs), time-varying measures of diabetes mellitus, hypertension, cerebrovascular disease, coronary heart disease, pulmonary disease, regular exercise, and self-reported health, and baseline body mass index

[§]P-value for omnibus test for overall association with histamine 2 receptor antagonist use

Table 3

Adjusted hazard ratios of risk for Alzheimer disease according to histamine 2 receptor antagonist exposure*

		Minimally Adjusted†		Fully Adjusted‡		
	Events	HR	95% CI	HR	95% CI	P value§
Exposure 1: Total cumulative use						
SDD > 1080	47	1.41	1.04–1.93	1.41	1.00–1.97	0.23
540 < SDD ≤ 1080	23	0.98	0.64–1.49	0.95	0.60–1.49	
180 < SDD ≤ 540	51	1.27	0.95–1.71	1.26	0.92–1.73	
30 < SDD ≤ 180	70	1.00	0.77–1.31	1.01	0.76–1.33	
SDD ≤ 30	262	1.00	Reference	1.00	Reference	
Exposure 2: Highest intensity in 2-yr period						
SDD > 540	39	1.17	0.83–1.66	1.13	0.78–1.64	0.63
180 < SDD ≤ 540	65	1.20	0.91–1.59	1.19	0.88–1.61	
30 < SDD ≤ 180	79	0.95	0.72–1.25	0.98	0.74–1.30	
SDD ≤ 30	270	1.00	Reference	1.00	Reference	
Exposure 3: Distant use/Recent Use						
High/High	25	1.02	0.68–1.53	0.98	0.63–1.52	0.30
High/Moderate	10	1.80	0.97–3.34	1.77	0.90–3.47	
High/Low	27	1.64	1.09–2.47	1.66	1.07–2.57	
Moderate/High	18	1.39	0.86–2.26	1.34	0.79–2.27	
Moderate/Moderate	18	1.17	0.73–1.89	1.30	0.81–2.11	
Moderate/Low	73	1.00	0.77–1.29	1.02	0.78–1.34	
Low/High	4	0.80	0.31–2.04	0.71	0.25–2.04	
Low/Moderate	14	1.23	0.73–2.10	1.11	0.61–2.03	
Low/Low	264	1.00	Reference	1.00	Reference	

SDD Standardized daily dose; HR hazard ratio; CI confidence intervals

Distant Use: High (SDD>540); Moderate (30<SDD≤ 540); Low (SDD≤30)

Recent Use: High (SDD>180); Moderate (30<SDD ≤180); Low (SDD≤30)

*Based on National Institute of Neurological and Communicative Disorders and Stroke criteria, including possible/probable categories.

†Adjusted for age (via the time scale), ACT cohort

[‡]Adjusted for age (via the time scale), ACT cohort, gender, education, time-varying use of non-steroidal anti-inflammatory drugs (NSAIDs), time-varying measures of diabetes mellitus, hypertension, cerebrovascular disease, coronary heart disease, pulmonary disease, regular exercise, and self-reported health, and baseline body mass index

[§]P-value for omnibus test for overall association with histamine 2 receptor antagonist use