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REVIEW

Antihistamine use and the risk of injurious falls or fracture in elderly patients: a systematic review and meta-analysis

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Abstract

Summary Despite their anticholinergic side effects, first-generation antihistamines are widely prescribed to elderly patients. A systematic review was conducted to synthesize real-world evidence. First-generation antihistamine use is considerably associated with an increased risk of injurious falls or fracture among the elderly.

Introduction First-generation antihistamines are considered potentially inappropriate for elderly patients owing to anticholinergic side effects. We aimed to determine whether elderly patients taking antihistamines are at increased risk of injurious falls or fracture.

Methods We identified studies in MEDLINE, EMBASE, and several local databases through November 2016. Observational studies on the association between antihistamine use and the risk of injurious falls or fracture were selected. Quality of the studies and the level of evidence were assessed. The random-effects model was employed for meta-analysis, and heterogeneity was examined based on I-square and Cochrane's Q test. Subgroup analyses were performed when the heterogeneity among studies could not be explained.

Results From 473 identified studies, five (three case-control studies, one cohort study, and one case-crossover study) were included in our analysis based on eligibility criteria. First-generation antihistamine use showed significantly increased risk of injurious falls or fracture (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.49–2.76, heterogeneity: $p = 0.41$, $I^2 = 0\%$). Studies including antihistamines of all generations or containing no generation information were dealing with falls during hospitalization. Among these studies, the association was statistically significant without heterogeneity (OR 2.89, 95% CI 1.71–4.89, heterogeneity: $p = 0.42$, $I^2 = 0\%$). Due to the small number of studies included and unadjusted results, meaningful interpretation based on subgroup analysis was limited.

Conclusions First-generation antihistamine use is considerably associated with increased risk of injurious falls or fracture among the elderly. Clinicians need to exercise caution when prescribing first-generation antihistamines to elderly patients.

Keywords Aged · Antihistamines · Falls · Fracture · Meta-analysis

Introduction

Approximately one in three adults aged 65 years or over falls at least once a year [1]. With the rapidly aging society, falls among the elderly have become a critical health issue [2]. Among older adults, falling is a leading cause of unintentional injuries and accounts for two thirds of the deaths resulting from unintentional injuries. It is estimated that approximately 10–15% of people who fall suffer serious consequences, such as fractures [3]. Falls in the elderly patients could cause fractures of the hip, wrist, pelvis, proximal humerus, ankle, and elbow [4].

Many studies have identified risk factors of falling. One of the causes is pharmacotherapy, which can increase the risk of injurious falls and fracture via sedation, orthostatic reactions, balance disorder, muscle weakness, cognitive impairment, and/or osteoporosis [5]. In addition, drug clearance decreases as people become older due to the aging process, which leads to prolonged adverse effects [6]. The evidence of the relation

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between anticholinergic drugs (e.g., tricyclic antidepressants, proton pump inhibitors, and antiparkinsonian drugs) and the risk of injurious falls and fracture has been established by meta-analysis [7–9]. As far as we know, however, there is no systematic literature review or meta-analysis regarding the risk of injurious falls or fracture in relation to antihistamine use.

H1-antihistamines are drugs that block the H1-histamine receptors in the body [10]. They have been commonly used to treat histamine-mediated allergic reactions such as allergic rhinitis, atopic dermatitis, and urticaria since the 1940s [11, 12]. Generally, H1-antihistamines are categorized into two classes: first-generation antihistamines (FGAHs) and second-generation antihistamines (SGAHs). FGAHs have been widely used for decades, but they are likely to have adverse effects because they readily cross the blood–brain barrier (owing to high lipophilicity) and cross-react with other receptors [13]. As an alternative, SGAHs were developed in an attempt to reduce anticholinergic side effects associated with FGAHs.

According to the Screening Tool of Older Persons' Prescriptions (STOPP) and Beers criteria, the two most frequently used instruments for assessing the suitability of prescription drug use in the elderly population, FGAHs are considered potentially inappropriate due to anticholinergic side effects [14, 15]. Nonetheless, the prevalence of FGAH prescriptions has remained high in clinical settings [16, 17]. Therefore, given the potential for adverse effects of FGAHs on the elderly population, a systematic review is needed for the synthesis of real-world evidence regarding the increased risk of injurious falls or fracture. The objective of this study was to investigate the association between FGAHs and injurious falls or fracture on the basis of published studies.

Materials and methods

The search strategy and data source

For this systematic review and meta-analysis, we followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [18, 19]. We developed a protocol in advance to specify the objective, outcome, eligibility criteria, search strategy, methods for study selection, data extraction, and data synthesis for this meta-analysis. Before conducting the literature search, we defined a structured research question following the Population, Intervention, Comparison, Outcome (PICO) format: "In elderly patients (Population), does taking first-generation antihistamines (Intervention), compared to not taking them (Comparison), increase the risk of falls or fracture (Outcome)?"

We searched two core databases (MEDLINE and EMBASE) and five Korean core databases (KoreaMed, KMbase, KISS, NDSL, and KiSTi) published by November 14, 2016 (the date of the last search) to identify studies on the association between FGAH use and the risk of injurious falls or fracture in the elderly population. The following search terms were used: "aged" and "elderly," for population; "antihistamine*," "histamine H1 antagonists," "histamine H1 blockers," "brompheniramine," "carbinoxamine," "chlorpheniramine," "clemastine," "cyproheptadine," "dexbrompheniramine," "dexchlorpheniramine," "dimenhydrinate," "diphenhydramine," "doxylamine," "hydroxyzine," "meclizine," "promethazine," and "triprolidine" for intervention; "fall*," "fracture*," "accidental falls," and "fractures, bone" for outcome. Search terms belonging to each group (population, intervention, and outcome) were co6mbined using "OR," while population, intervention, and outcome were combined via "AND." The FGAH active ingredients listed above were derived from 2012 Beers criteria.

Study selection

Two reviewers (H.C. and J.M.) independently screened the titles and abstracts for the eligibility criteria. Subsequently, the full text of the studies that potentially met the inclusion criteria was evaluated to reach a decision on final inclusion. Any disagreements were resolved by reaching a consensus through mutual discussion or consulting a third reviewer (H.-Y.K.).

Studies were included if they met the following eligibility criteria: (1) they presented original data from observational studies (e.g., a cohort study, case-control study, or case-crossover study); (2) the population of interest was the elderly population aged 65 years or older; (3) the outcome of interest was clearly defined as injurious falls or fracture; (4) the treatment of interest was antihistamine medication; (5) they reported the odds ratio (OR), the relative risk (RR), or the hazard ratio (HR) of injurious falls or fracture associated with the use of FGAHs, and the corresponding 95% confidence interval (CI). We also included studies that did not clearly provide information on the generation of antihistamines. Studies were excluded if both reviewers agreed that they did not meet the eligibility criteria. Nonetheless, studies were excluded if they were not specific to antihistamine use (e.g., anticholinergic drugs), even though they presented original data. Review articles, editorials, case series, conference abstracts, and letters to the editor were not included. Duplicate studies and studies for which we were not able to obtain full-text articles were excluded.

Data extraction and quality assessment

Two independent reviewers (H.C. and J.M.) extracted data from the selected articles on the following items: the name of the first author, the year of publication, the country where the study was conducted, study design, study population and baseline characteristics, exposure, the type of outcome, risk estimates (OR, RR, or HR and its 95% CI), and adjusted covariates.

The risk of bias in each observational study was evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) version 2.0, which showed moderate reliability, promising feasibility, and validity [20]. RoBANS version 2.0 consists of the following six domains: selection of the participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Two reviewers (H.C. and J.M.) independently categorized the quality of evidence into four levels (very low, low, moderate, or high) in accordance with the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method [21]. Any controversy was resolved by discussion.

The main analysis and subgroup analysis

We investigated the association between the use of FGAHs and the risk of injurious falls or fracture by means of adjusted risk estimates, if available. Due to a lack of studies, we considered "injurious falls or fracture" one combined outcome to conduct the meta-analysis. To understand the underlying clinical and methodological heterogeneity across the studies, we performed subgroup analysis by type of study design, adjustment for any confounder, and generation of antihistamines. We performed the test for subgroup differences available in the Review Manager 5.3 software to determine whether the results for subgroups were significantly different.

Statistical analysis

A generic inverse-variance method was employed to pool the ORs of injurious falls or fracture associated with the use of FGAHs and the corresponding 95% CIs [22]. The random-effects model was chosen instead of the fixed-effect model, considering the high likelihood of between-study variance and the likelihood of producing more conservative estimates.

Heterogeneity was assessed statistically by means of Cochran's Q statistic and Higgins I^2 statistic [23, 24]. Statistical significance was set to the 10% level owing to low power of the test. The magnitude of heterogeneity was interpreted as not important (0–30%), moderate (30–50%), substantial (50–70%), or considerable (70–100%).

All analyses were conducted in the Review Manager 5.3 software (London, UK) from the Cochrane Collaboration. Data with a two-sided p value of less than 0.05 were considered significant.

Results

Search results

Figure 1 shows the strategy used to identify the relevant studies for the meta-analysis. After the search strategy was applied, 473 potentially relevant articles were identified in our initial literature search. This number was reduced to 411 articles after excluding duplication. After screening of the titles and abstracts, 371 studies were excluded, mainly because they were not relevant to our study objective. Three studies published before 1995 were excluded because we could not obtain full-text articles. After full-text assessment, five studies satisfied the eligibility criteria [25–29]. No additional studies were identified in our manual search of references in published articles.

Study characteristics

Table 1 summarizes the main characteristics of the five studies that were included in the analysis. They were published between 2011 and 2016. Among them, three were case-control studies [25–27], one was a cohort study [29], and one article was a case-crossover study [28]. The data sources of three studies were medical records [26–28], a patient-safety reporting system with computerized medical records [25], and national veterans affairs administrative data [29]. Geographically, four studies were from Asia [25–28], and one from the USA [29]. Three studies defined their outcome of interest as falls [25, 27, 28], one study as hip fracture [26], and one study as falls or fracture [29]. In three studies, results were adjusted for potential confounders [26, 27, 29]. As to the generation of antihistamines, two studies included FGAHs [26, 29], and three studies did not clearly define the generation of antihistamines [25, 27, 28]. As for the eligible studies that did not provide information on the generation of antihistamines, we tried to contact the authors for further information. Lee (2011) responded that all generations of antihistamines were used in the study [27]. Although we could not acquire relevant information from the other authors, we did not exclude these studies for the following reason: they deal with medication that causes sedation and drowsiness, implying high probability of FGAH [25, 27, 28]. The risk of bias analysis revealed little concern, aside from two studies where the key covariates were not adjusted for confounding variables [25, 28]. We conducted subgroup analysis because of this concern to make an unbiased interpretation. The quality of evidence was moderate according to the GRADE method.

The main analysis and subgroup analysis

Five studies were included in the analysis, and the results showed increased risk of injurious falls or fracture in patients exposed to antihistamines without heterogeneity among the studies (OR 2.22, 95% CI 1.70–2.90, heterogeneity: $p = 0.45$, $I^2 = 0\%$). Although five studies were finally selected, we included only two studies in the main analysis that clearly focused on FGAHs [26, 29]. Figure 2 shows the pooled estimate of the two included studies assessing the risk of injurious

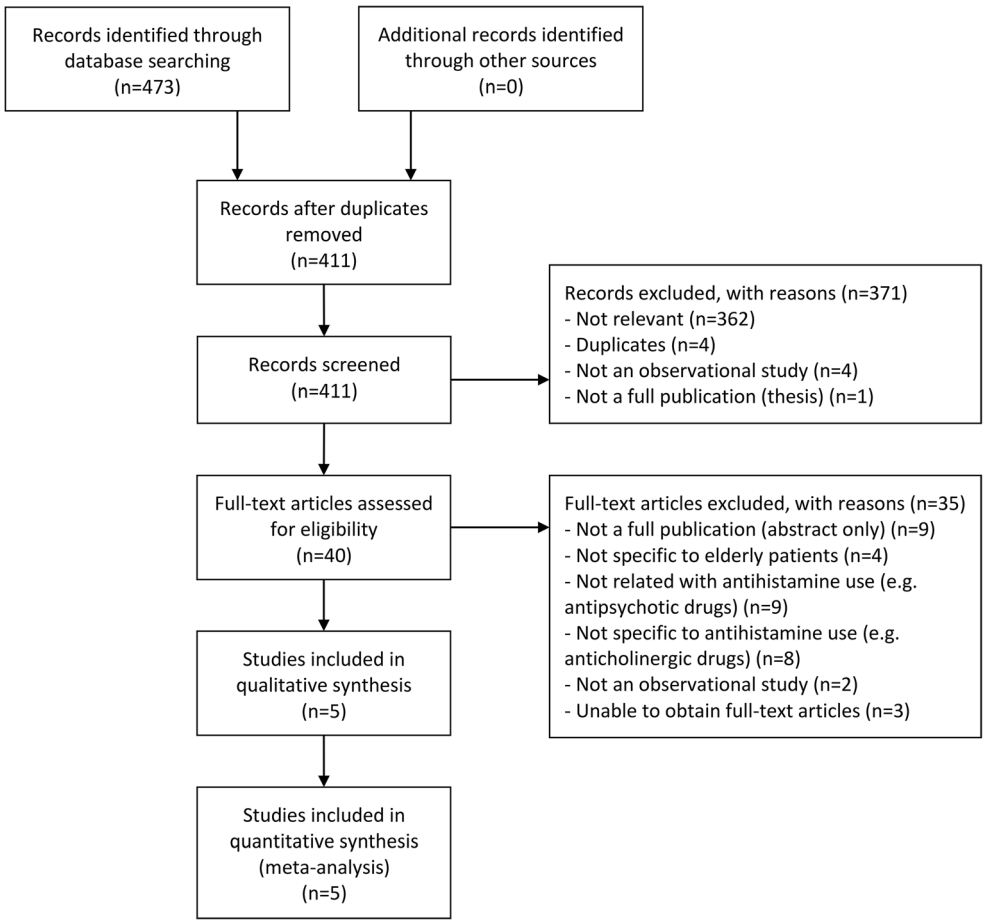

Fig. 1 The flowchart for identification of relevant studies

falls or fracture relevant to the use of FGAHs. This use considerably correlated with the risk of injurious falls or fracture without heterogeneity (OR 2.03, 95% CI 1.49–2.76, heterogeneity: $p = 0.41$, $I^2 = 0\%$).

On the other hand, the results on all generations of antihistamines or without a clear mention of the generation of antihistamines in terms of injurious falls or fracture were also significant without heterogeneity (OR 2.89, 95% CI 1.71–4.89, heterogeneity: $p = 0.42$, $I^2 = 0\%$). Although no statistical heterogeneity was detected, we conducted subgroup analysis according to the type of study design, adjustment for any confounder, and the generation of antihistamines to assess potential clinical and methodological heterogeneity (Table 2). Overall, an increased risk of injurious falls or fracture associated with the use of antihistamines was observed in all subgroups. There was a tendency among case-control studies to be associated with a higher OR (OR 3.79, 95% CI 1.80–7.96, heterogeneity: $p = 0.41$, $I^2 = 0\%$) in comparison with the case-crossover study (OR 2.20, 95% CI 1.04–4.64, heterogeneity: not applicable). Two studies on antihistamines not clearly mentioning the generation and not adjusted for a potential confounder seemed to show lower risk estimates of injurious falls or fracture (OR 2.49, 95% CI 1.39–4.44, heterogeneity: $p = 0.61$, $I^2 = 0\%$) than did a study on all-generation antihistamines that was adjusted for a potential confounder (OR 5.80, 95% CI 1.67–20.18, heterogeneity: not applicable). Nevertheless, the test for subgroup differences did not yield statistically significant results.

Discussion and conclusions

We conducted a meta-analysis to examine the association between FGAH use and the risk of injurious falls or fracture on the basis of all eligible studies. In the main analysis, we obtained clear evidence that the relative risk of injurious falls or fracture is considerably increased among FGAH users (OR 2.03, 95% CI 1.49–2.76, heterogeneity: $p = 0.41$, $I^2 = 0\%$). Our results support other meta-analyses (regarding anticholinergic drugs), which have shown an increased risk of injurious falls and fracture associated with anticholinergic medication such as tricyclic antidepressants, proton pump inhibitors, and antiparkinsonian drugs [7–9].

On the other hand, there were two other studies that did not clearly indicate the generation of antihistamines, and one study that included all generations of antihistamines. The results of these studies showed higher OR without statistical heterogeneity (OR 2.89, 95% CI 1.71–4.89, heterogeneity: $p = 0.42$, $I^2 = 0\%$)

Table 1 Characteristics of five studies included in the meta-analysis

First author's name	Year of publication	Location of study	Study design	Age of study subjects	Data sources	Exposure	Outcome definition	No. of cases	No. of controls	Odds ratio (95% CI)	Were variables adjusted?
Chang et al. [25]	2011	Taiwan	Case-control	≥ 65 years	Taiwan Patient-Safety Reporting System and computerized medical records	Antihistamines	Falls in the hospital	165	165	3.00 (1.19–7.56)	Unadjusted
Lee et al. [26]	2016	Hong Kong	Case-control	≥ 65 years	Electronic patient records	1st-generation antihistamines	Falls resulting in hip fractures	170	170	3.18 (1.04–9.66)	Adjusted for benign prostatic hyperplasia and lower urinary tract symptoms, antiparkinsonian medications, osteoporosis, use of walking aids, betahistine, hyperlipidemia, congestive heart failure, gastritis, atrial fibrillation or atrial flutter, trimetazidine, serum creatinine
Lee [27]	2011	Korea	Case-control	≥ 65 years	Medical records	All-generation antihistamines	Falls during hospitalization	34	68	5.80 (1.67–20.18)	Not given (adjusted variables are selected using stepwise logistic regression)
Choi et al. [28]	2012	Korea	Case-cross-over	≥ 65 years	Electronic medical records	Antihistamines	Falls during hospitalization	168	168	2.20 (1.04–4.64)	Unadjusted
Alvarez et al. [29]	2015	USA	Cohort	≥ 65 years	National Veterans Affairs administrative data	1st-generation antihistamines	Hospitalization for falls or fractures	30,029	30,029	1.95 (1.41–2.69)	Adjusted for risk factors for mortality, hospitalizations, ED visits, falls, and fractures.

Abbreviations. *ASA* acetylsalicylic acid, *CI* confidence interval, *ED* emergency department, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRI* selective serotonin reuptake inhibitor

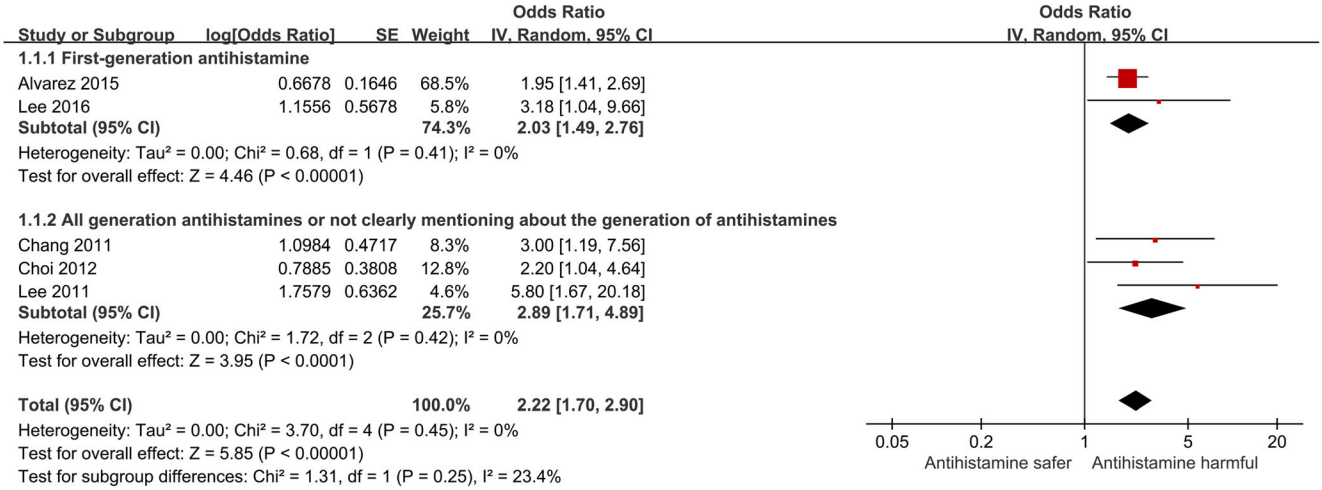

Fig. 2 Antihistamine use and the risk of injurious falls or fracture according to the random-effects model. CI confidence interval, IV inverse variance, SE standard error.

compared to the main analysis. It is notable that the study population was hospitalized patients in these articles [25, 27, 28], whereas that of the main analysis was mostly outpatients. In addition, the outcome of these studies was injurious falls, whereas that of the main analysis included fracture that resulted from injurious falls [4]. The difference in severity in terms of study population and outcome measurement may explain why the main analysis showed lower OR than that of the other articles.

Four studies were conducted in Asian countries, and each study presented increased risk of injurious falls or fracture among antihistamine users. According to Dhanwal et al., who analyzed geographical variation of hip fractures, it is estimated that a half of hip fractures will occur in Asia in 2050 [30]. Appropriate interventions that are intended to reduce potentially inappropriate antihistamine prescribing may help to lower the incidence rate of hip fracture. It is notable that three of the included articles deal with falls of hospitalized patients in a hospital. Careful monitoring is needed when elderly patients are prescribed antihistamines because falls among elderly patients are becoming more prevalent in hospitals [31].

Our study has several potential limitations. First, only a few studies were included in the main analysis owing to limited information about the generation of antihistamines in the other included studies. Because SGAHs are known to have smaller anticholinergic side effects, thus possibly

Table 2 Subgroup analysis for the use of antihistamines and the risk of injurious falls or fracture

Factor	No. of studies	Odds ratio (95% CI)	Heterogeneity	
			I^2 statistic (%)	Q statistic (p value)
Study design				
Case-control	2	3.79 (1.80–7.96)	0	0.41
Case-crossover	1	2.20 (1.04–4.64)	NA[a]	NA[a]
Test for subgroup differences: $\chi^2 = 1.02$, df = 1 ($P = 0.31$), $I^2 = 2.4\%$				
Adjustment for any confounder				
Crude OR	2	2.49 (1.39–4.44)	0	0.61
Adjusted OR	1	5.80 (1.67–20.18)	NA[a]	NA[a]
Test for subgroup differences: $\chi^2 = 1.46$, df = 1 ($P = 0.23$), $I^2 = 31.4\%$				
Generation of antihistamines				
Not clearly mentioning the generation	2	2.49 (1.39–4.44)	0	0.61
All generations	1	5.80 (1.67–20.18)	NA[a]	NA[a]
Test for subgroup differences: $\chi^2 = 1.46$, df = 1 (P = 0.23), $I^2 = 31.4\%$				

Abbreviations. *CI* confidence interval, *NA* not applicable

[a] Heterogeneity was not assessed because there was only one study

Subgroup analysis was conducted for the studies including all generations of antihistamines or not clearly mentioning the generation of antihistamines

resulting in biased estimates, we excluded studies including all generations of antihistamines or not clearly mentioning the generation of antihistamines from the main analysis. Therefore, to establish a more robust relation between FGAHs and injurious falls or fracture, more empirical research is required. Second, we combined two different conditions—injurious falls and fracture—for the same outcome variable because there were relatively few eligible studies. As a result, clinical heterogeneity may be present. Nevertheless, these outcomes are not completely different, given that among older people, fracture is frequently caused by falls [4]. Especially, hip fracture is mostly a consequence of falls [32, 33]. Third, the study population varied among the studies in terms of gender distribution. Lee et al. (2016) mostly included female elderly patients, whereas the study by Alvarez et al. (2015) predominantly included elderly male patients [26, 29]. Fourth, it was not confirmed whether appropriate statistical methods (conditional logistic regression) were used in two matched case-control studies [26, 27]. Fifth, publication bias was not assessed by means of a funnel plot. Because of the relatively small number of studies, publication bias tests may be inappropriate [34]. Lastly, we compared FGAH users with non-FGAH users in the present study because there was no study comparing FGAH users versus SGAH users. Further real-world empirical research is needed to determine the impact of FGAHs and to confirm the safety of SGAHs. Despite these limitations, to the best of our knowledge, this study is the first systematic review and meta-analysis to explore the correlation between antihistamine use and the risk of injurious falls or fracture on the basis of real-world evidence.

In conclusion, our findings revealed that FGAH use is considerably associated with an increased risk of injurious falls or fracture as compared to nonuse of FGAH. Clinicians need to exercise caution when prescribing FGAHs to elderly patients. We expect that our findings will provide evidence supporting Beers and STOPP criteria that discourage prescription of FGAHs to elderly patients.

Compliance with ethical standards

Conflicts of interest None

References

1. Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly persons living in the community. N Engl J Med 319: 1701–1707
2. Gelbard R, Inaba K, Okoye OT, Morrell M, Saadi Z, Lam L, Talving P, Demetriades D (2014) Falls in the elderly: a modern look at an old problem. Am J Surg 208:249–253
3. Butt DA, Mamdani M, Austin PC, Tu K, Gomes T, Glazier RH (2013) The risk of falls on initiation of antihypertensive drugs in the elderly. Osteoporos Int 24:2649–2657
4. Ensrud KE (2013) Epidemiology of fracture risk with advancing age. J Gerontol A Biol Sci Med Sci 68:1236–1242
5. Kragh A, Elmstahl S, Atroshi I (2011) Older adults' medication use 6 months before and after hip fracture: a population-based cohort study. J Am Geriatr Soc 59:863–868
6. Brawn LA, Castleden CM (1990) Adverse drug reactions. An overview of special considerations in the management of the elderly patient. Drug Saf 5:421–435
7. Tan L, Wang Y, Zhou L, Shi Y, Zhang F, Liu L, Nie S (2014) Parkinson's disease and risk of fracture: a meta-analysis of prospective cohort studies. PLoS One 9:e94379
8. Zhou B, Huang Y, Li H, Sun W, Liu J (2016) Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 27:339–347
9. Wu Q, Qu W, Crowell MD, Hentz JG, Frey KA (2013) Tricyclic antidepressant use and risk of fractures: a meta-analysis of cohort and case-control studies. J Bone Miner Res 28:753–763
10. Canonica GW, Blaiss M (2011) Antihistaminic, anti-inflammatory, and antiallergic properties of the nonsedating second-generation antihistamine desloratadine: a review of the evidence. World Allergy Organ J 4:47–53
11. Sim TC, Grant A (1996) H1-receptor antagonists in chronic urticaria. In: Simons FER (ed) Histamine and H1-receptor antagonists in allergic disease, 2nd edn. Marcel Dekker, New York, pp 273–296
12. Nightingale CH (1996) Treating allergic rhinitis with second-generation antihistamines. Pharmacotherapy 16:905–914
13. Simons FE, Simons KJ (1994) The pharmacology and use of H1-receptor-antagonist drugs. N Engl J Med 330:1663–1670
14. Campanelli CM (2012) American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 60:616–631
15. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P (2015) STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44:213–218
16. Jensen LL, Romsing J, Dalhoff K (2017) A Danish survey of antihistamine use and poisoning patterns. Basic Clin Pharmacol Toxicol 120:64–70
17. Cho H, Choi J, Kim YS, Son SJ, Lee KS, Hwang HJ, Kang HY (2017) Prevalence and predictors of potentially inappropriate prescribing of central nervous system and psychotropic drugs among elderly patients: a national population study in Korea. Arch Gerontol Geriatr 74:1–8
18. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283:2008–2012
20. Kim SY, Park JE, Lee YJ, Seo H-J, Sheen S-S, Hahn S, Jang B-H, Son H-J (2013) Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 66:408–414
21. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S (2004) Grading quality of evidence and strength of recommendations. BMJ 328:1490
22. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

23. Higgins J, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
25. Chang CM, Chen MJ, Tsai CY, Ho LH, Hsieh HL, Chau YL, Liu CY (2011) Medical conditions and medications as risk factors of falls in the inpatient older people: a case-control study. Int J Geriatr Psychiatry 26:602–607
26. Lee VW, Leung TP, Lee VW (2016) Outpatient medication use in Chinese geriatric patients admitted for falls: a case-control study at an acute hospital in Hong Kong. Am J Ther 23:e1729–e1735
27. Lee YJ (2011) Medication use as a risk factor for falls in hospitalized elderly patients in Korea. Korean J Clin Pharm 21:243–248
28. Choi SY, Park YH, Kim JY, Gwak HS, Song YC (2012) Fall risk in hospitalized elderly patients with drugs that induce the fall. J Kor Soc Health-Syst Pharm 29:182–187
29. Alvarez CA, Mortensen EM, Makris UE, Berlowitz DR, Copeland LA, Good CB, Amuan ME, Pugh MJ (2015) Association of skeletal muscle relaxers and antihistamines on mortality, hospitalizations, and emergency department visits in elderly patients: a nationwide retrospective cohort study. BMC Geriatr 15:2
30. Dhanwal DK, Dennison EM, Harvey NC, Cooper C (2011) Epidemiology of hip fracture: worldwide geographic variation. Indian J Orthop 45:15–22
31. Hayes N (2004) Prevention of falls among older patients in the hospital environment. Br J Nurs 13:896–901
32. Silva MJ (2007) Biomechanics of osteoporotic fractures. Injury 38(Suppl 3):S69–S76
33. Foster KW, Eiff P, Grayzel J (2014) Hip fractures in adults. UpToDate. https://www.uptodate.com/contents/hip-fractures-in-adults. Accessed 11 Oct 2017
34. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I (2006) The case of the misleading funnel plot. BMJ 333:597–600