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CLINICAL INVESTIGATION

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Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs and the risk of peptic ulcers: A self-controlled study

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) should be used with caution in adults aged 65 years and older. Their gastrointestinal adverse event risk might be further reinforced when using concomitant cholinesterase inhibitors (ChEIs). We aimed to investigate the association between NSAIDs and ChEI use and the risk of peptic ulcers in adults aged 65 years and older.

Methods: Register-based self-controlled case series study including adults ≥65 years with a new prescription of ChEIs and NSAIDs, diagnosed with incident peptic ulcer in Sweden, 2007–2020. We identified persons from the Total Population Register individually linked to several nationwide registers. We estimated the incidence rate ratio (IRR) of peptic ulcer with a conditional Poisson regression model for four mutually exclusive risk periods: use of ChEIs, NSAIDs, and the combination of ChEIs and NSAIDs, compared with the non-treatment in the same individual. Risk periods were identified based on the prescribed daily dose, extracted via a text-parsing algorithm, and a 30-day grace period.

Results: Of 70,060 individuals initiating both ChEIs and NSAIDs, we identified 1500 persons with peptic ulcer (median age at peptic ulcer 80 years), of whom 58% were females. Compared with the non-treatment periods, the risk of peptic ulcer substantially increased for the combination of ChEIs and NSAIDs (IRR: 9.0, [6.8–11.8]), more than for NSAIDs alone (5.2, [4.4–6.0]). No increased risks were found for the use of ChEIs alone (1.0, [0.9–1.2]).

This work was submitted to the International Conference on Pharmacoepidemiology (ICPE), August 23–27, 2023, Halifax, Nova Scotia, Canada. The submission was accepted for the podium presentation.

Discussion: We found that the risk of peptic ulcer associated with the concomitant use of NSAIDs and ChEIs was over and beyond the risk associated with NSAIDs alone. Our results underscore the importance of carefully considering the risk of peptic ulcers when co-prescribing NSAIDs and ChEIs to adults aged 65 years and older.

KEYWORDS

cholinesterase inhibitor, dementia, non-steroidal anti-inflammatory drugs, peptic ulcer, pharmacoepidemiology

INTRODUCTION

Cholinesterase inhibitors (ChEIs) are used in persons living with dementia as symptomatic treatments to slow the progression of impairment in their cognition, memory, attention, and behavioral symptoms. However, their use might be associated with gastrointestinal side effects.[1] Similarly, non-steroidal anti-inflammatory drugs (NSAIDs), commonly used to reduce pain, inflammation, and fever, also have a known gastrointestinal adverse profile.[2] In a review of potential drug interactions with ChEIs, NSAIDs were suggested to cause a synergic pharmacodynamic interaction.[3] This may result in adverse gastrointestinal outcomes such as peptic ulcers, which are sores in the stomach lining or the first part of the small intestine.[4] To our knowledge, this drug–drug interaction has not previously been studied using real-world nationwide data.

NSAIDs and ChEIs have a long history of clinical use in their respective therapeutic areas. NSAIDs, prescribed for more than 10% of the Swedish population aged 65 years and older,[5] should be prescribed cautiously, mainly due to gastrointestinal adverse events, including peptic ulcers.[2,6–10] NSAIDs may cause peptic ulcers by damaging the gastroduodenal mucosa through a combination of systemic and local mechanisms. The primary mechanism considered responsible is the systemic inhibition of constitutively expressed cyclooxygenase 1-derived prostaglandins.[4] NSAIDs are therefore listed as potentially inappropriate medication in adults aged 65 years and older in the 2023 American Geriatrics Society Beers Criteria® and STOPP/START criteria.[11,12] Also, ChEIs-induced adverse reactions (e.g., vomiting, falls, nausea, diarrhea, bradycardia, and dizziness) have been frequently reported.[13,14] Contrary to NSAIDs, the association between ChEIs and peptic ulcers has only been highlighted in case reports and a handful of smaller studies.[15–19] Nonetheless, a clear mechanism of action is established: ChEIs increase the availability of the neurotransmitter acetylcholine, which stimulates the gastric secretion of hydrochloric acid and internal propulsion, which may lead to an increase in gastrointestinal adverse effects. Therefore, NSAIDs and ChEIs have potentially similar adverse effects on the gastrointestinal system. Co-administration could, therefore, result in an unfavorable drug–drug interaction that could augment the risk of peptic ulcers.[20]

Key points

- Self-controlled study of concomitant use of non-steroidal anti-inflammatory drug (NSAIDs) and cholinesterase inhibitors (ChEIs)
- Peptic ulcer risk was higher with ChEIs and NSAIDs than with NSAIDs alone
- An increased risk of peptic ulcers was not found for the use of ChEIs alone

Why does this paper matter?

Our results suggest the importance of carefully considering the risk of peptic ulcers when prescribing NSAIDs to ChEI users.

Peptic ulcer is a severe disease that impairs well-being and reduces the quality of life.[21] Its complications, for example, acute bleeding (e.g., melena, hematemesis, anemia), perforation, or penetration (e.g., severe abdominal pain, weight loss, loss of appetite, recurrent vomiting) may be fatal for people aged 65 years and older.[22] A systematic review reported that mortality within 30 days is estimated to be 9%−24% in the adult population depending on the severity of the peptic ulcer, age, and comorbidity.[23] Also, adults living with dementia have an excess risk of increased length of hospital stay and higher medical costs related to their peptic ulcer.[24] Preventing peptic ulcers remains the most important strategy to reduce mortality and morbidity for this condition.[4]

To provide helpful evidence to prescribers, the present study aimed to investigate the risk of peptic ulcer for people aged 65 years and older receiving both NSAIDs and ChEIs alone and in combination. In agreement with the biologically plausible interaction between these drugs, we hypothesized a substantially increased risk for combination use than NSAIDs or ChEIs alone.

METHODS

Data source

We used routinely collected administrative and health data with national coverage in Sweden. Data from the Total Population Register were linked using pseudonymised identifiers to the National Patient Register, the National Prescribed Drug Register, the National Cause of Death Register, and the Swedish Register of Education. A detailed description of the data sources can be found in Supplementary Table S1.

Study design

We used a self-controlled case series study design which has been widely utilized in pharmacoepidemiological studies investigating adverse drug reactions. People who experience both the outcome and the treatments of interest are included in the self-controlled case series method. It enables incidence rate ratio estimations of the outcome in time-varying exposure periods than non-treatment periods. Contrary to a cohort design where comparisons are between individuals, in this case, persons serve as their own controls, which eliminates intra-person time-constant confounders (e.g., genetic factors). Thereby, this study design investigates *when* the adverse event is more likely to occur, compared to cohort studies that assess *who* is more likely to experience the adverse event.[25] For more details see Supplementary Table S2.

Study population and follow-up

The source population included all adults aged ≥65 in Sweden, 2007–2020 ($n = 3{,}246{,}561$). From the source population, we identified people with a new prescription of both ChEIs and NSAIDs (either concomitant or not), who were diagnosed with incident peptic ulcer within the study period of January 1, 2007 to December 31, 2020 (Figure 1). The observation period began on January 1, 2007 for individuals equal to or older than 65 years at this date, otherwise on the 65th date of birth for those turning 65 years during the study period. End of the study period, death or emigration marked the end of the observation period. We excluded persons who used ChEIs or NSAIDs or had peptic ulcers during a one-year washout before their observation period. Including only new users of ChEIs and NSAIDs with no recent history of peptic ulcers in the study population ensures a clear temporal sequence of drug exposures and outcomes. We further excluded individuals who immigrated after the start of the washout period.

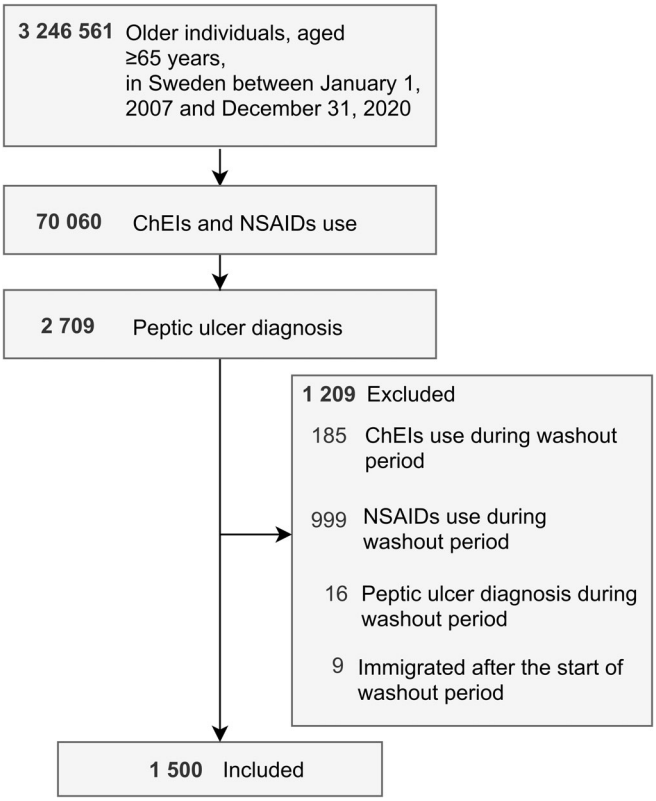

FIGURE 1 Flowchart of case identification.

Outcome and exposures

The outcome of peptic ulcer was defined based on the International Classification of Diseases, 10th Revision [ICD-10] codes of K25 (gastric ulcer), K26 (duodenal ulcer), K27 (peptic ulcer, site unspecified) from the National Patient Register. The K28 code was not used to identify peptic ulcer because in the Swedish ICD-10 codes it refers to recurrent ulcers after gastroenterostomy which were deemed irrelevant for the population of interest.[26] We included only the first occurrence of peptic ulcers because recurrent events are not independent.[27] Additionally, NSAIDs are contraindicated, and ChEIs should be used with caution after peptic ulcer, which suggests that

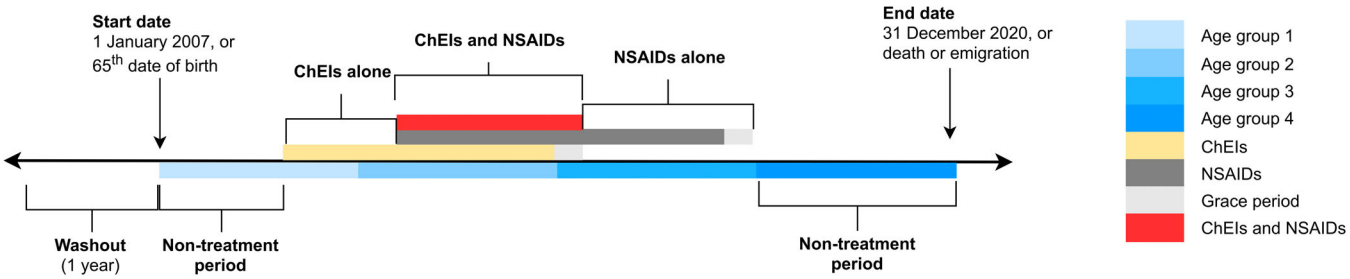

FIGURE 2 Study design and exposure risk period definitions for individuals with peptic ulcer.

comparisons should be limited to the first outcome occurrence as per recommendation.[22,28]

ChEIs and NSAIDs were identified based on the Anatomical Therapeutic Chemical (ATC) codes ("N06DA02" [donepezil], "N06DA03" [rivastigmin], "N06DA04" [galantamin], "M01A" [NSAIDs]) from the National Prescribed Drug Register. Over-the-counter NSAIDs, which are prevalent in Sweden (27 DDD/1000 inhabitants/day sold in 2016),[29] were not captured in our study. Topical agents or drugs dispensed in nursing home drug storerooms were also not included.

To define the length of drug use, we first calculated the prescribed daily dose with a text parsing algorithm based on the free text input of the prescriber. More details about the method are available elsewhere.[30] Then the length of use was constructed from the dispensing date until the end of the prescribed daily dose plus a 30-day grace period. Finally, overlapping drug exposure periods were merged into a single drug exposure window. Based on these drug exposure windows, we defined four mutually exclusive exposure risk periods: use of ChEIs alone, use of NSAIDs alone, use of a combination of ChEIs and NSAIDs, and a reference non-treatment period, similarly as done by Wang and colleagues.[31] Figure 2 displays the exposure risk periods.

Statistical analysis and covariates

We used descriptive statistics to assess the individual characteristics at the time of the peptic ulcer diagnosis. *Sex*, *age*, and *marital status* ("married", "single/divorced", "widowed") were extracted from the Swedish Total Population Register. We defined *education* as the highest attained educational level and categorized it into "primary", "secondary", and "tertiary" education based on the ISCED-97 classification system using the Swedish Register of Education.[32] The *drug sequence* ("ChEIs before NSAIDs", "NSAIDs before ChEIs", "initiated concomitantly") variable describes the first drug exposure during follow-up. We calculated the average *length of treatment periods* of ChEIs, NSAIDs, and combination treatment. We examined the *type of outcome* ("gastric ulcer", "duodenal ulcer", "peptic ulcer, site unspecified"), the *diagnostic setting* ("inpatient", "outpatient specialist care") and *diagnosis year* ("2007–2010", "2011–2015", "2016–2020") using the National Patient Register. We extracted *concurrent chronic diseases* (*multimorbidity*),[33] operationalized as the number of chronic diseases out of a list of 60 pre-defined conditions captured in the National Patient Register during a three-year period before the outcome (Supplementary Table S3). The co-prescribed medications were based on the list of Wang et al.[31] and additional medications that potentially increase the risk of peptic ulcers (e.g., antiplatelets, antidepressants)[34] or have gastroprotective effects (i.e., proton pump inhibitors).[35] Information on co-prescribed drugs was obtained from the National Prescribed Drug Register during a one-year period before the outcome (Supplementary Table S4). We present the proportions of the 10 most common comorbidities and co-prescribed drugs. The complete lists are available in Supplementary Tables S5 and S6. We investigated ICD-10 codes in the 90-day period before NSAID prescriptions to identify potential indications for the incident use (Supplementary Table S7).

We fitted a conditional Poisson regression model to estimate the incidence rate ratio (IRR) of the first peptic ulcer diagnosis for the risk periods: use of ChEIs alone, NSAIDs alone, the combination of ChEIs and NSAIDs, than the reference non-treatment period. Although the self-controlled case series method accounts for time-constant confounders by design, adjusting for important time-varying confounders is crucial. As age is linked to disease progression, we adjusted the analysis by age groups defined by quantiles of the age at the outcome, as recommended.[27] Other important confounders (e.g., alcohol consumption, smoking) were unavailable in the register data, but due to the self-controlled design, the impact of such residual confounding should be

minimized. To determine the minimum effect an unmeasured confounder would need to have with both the outcome and exposure to negate the observed association between the treatments and the outcome, we calculated E-values based on the work of Mathur and colleagues.[36] An E value of two, for example, means that the unmeasured confounder could "explain away" the observed association if it doubled the risk of the outcome for either exposure status and if it was twice as prevalent among exposed compared to unexposed.[37]

All analyses were performed with SAS software version 9.4[38] and R statistical software version 4.0.5.[39]

Subgroup and sensitivity analyses

We performed sex and age group stratified (65–79 years, 80+ years) subgroup analyses. Additionally, we undertook several sensitivity analyses to assess the robustness of the results. First, we excluded those who died within 4 weeks of the peptic ulcer diagnosis because they did not have the potential for subsequent treatment and censored the observation period, violating the assumptions of the self-controlled case series method. Second, we defined different pre-exposure risk periods (14 or 28 days) and repeated the main analyses because peptic ulcers may decrease the probability of subsequent treatment exposure and artificially reduce the incidence of the event in the non-treatment period. Third, we calculated the exposure risk periods using the dispensed amount in defined daily doses instead of relying on prescribed daily doses obtained from the text-parsing algorithm. Fourth, we repeated the analyses with a 14- and 60-day grace period. Fifth, we reduced the length of the washout period to 6 months for NSAIDs because the one-year washout period excluded many individuals. Sixth, we expanded the washout period to 3 years for peptic ulcers to reduce the possibility that previous peptic ulcers affected prescription decisions. Seventh, we adjusted for time-varying proton pump inhibitor use because they are commonly prescribed to prevent NSAIDs-induced peptic ulcers and thus might influence the results.[35] Lastly, we adjusted for time-varying antiplatelet, antidepressant, and systemic steroid use to control for their potential effect on the estimates.[34]

Guidelines and ethical approval

The present study was reported in keeping with the RECORD guidelines[40] (Supplementary Table S8) and was approved by the Regional Ethical Review Board of Stockholm (dnr: 2016/1001–31/4, 2020–03525; 2021–02004).

RESULTS

Characteristics of the study population

Out of the source population ($n = 3{,}246{,}561$), we identified 70,060 persons aged 65 years and older using both ChEIs and NSAIDs between 2007 and 2020. Of them, 2709 individuals (3.9%) had a peptic ulcer diagnosis registered during the study period. We excluded those using ChEIs ($n = 185$) and NSAIDs ($n = 999$) during the one-year washout period. Additionally, we removed 16 persons who had a peptic ulcer diagnosis during the washout period and nine individuals who immigrated after the start of the washout period. We included 1500 persons in the final study population.

The median age at peptic ulcer diagnosis was 80 years, 58% were females, 49% had primary education, and 49% were married (Table 1). Most individuals (84%) initiated NSAIDs earlier than ChEIs. The median length of treatment periods was 10.2 months for ChEIs alone, 2.4 months for NSAIDs alone, and 2.2 months for the combination of ChEIs and NSAIDs. Most individuals with peptic ulcers (68%) were diagnosed in an inpatient setting and had a median of 4 (IQR 2–6) concurrent chronic conditions besides their peptic ulcer. The most common concurrent chronic conditions were hypertension (44%) and dementia (25%). The most common co-prescribed medication during the year before peptic ulcer were antiplatelets (51%) and renin–angiotensin–aldosterone system inhibitors (42%). More than half (60%) died during the study follow-up.

Considering the type of ChEIs prescribed, most people received donepezil (77%), while rivastigmine (23%) and galantamine (12%) were less frequently prescribed. In addition, some individuals (11%) switched ChEIs during the study period. Regarding NSAIDs, more than half (57%) received a diclofenac prescription, 38% naproxen, and 29% ibuprofen (Supplementary Table S9).

The results of the self-controlled case series analysis are shown in Table 2. Compared with the non-treatment periods, the risk of peptic ulcer was higher with the use of NSAIDs alone (adjusted IRR: 5.2, 95% confidence interval: 4.4–6.0, E-value: 9.8) and further increased with the combination of ChEIs and NSAIDs (9.0, 6.8–11.8, E-value: 17.5). No increased risk were found for the use ChEIs alone (1.0, 0.9–1.2, E-value: 1.2).

Subgroup and sensitivity analyses

In the subgroup analyses, the adjusted IRR of ChEIs and NSAIDs combination treatment was higher for females (10.4, 7.4–14.8, E-value: 20.4) than for males (6.9, 4.3–10.9, E-value: 13.2), and for the people aged more

TABLE 1 Characteristics of individuals aged ≥65 years at the time of first peptic ulcer diagnosis in Sweden, 2007–2020.

	Study population ($n = 1500$)
Age at time of event	
Median (P_{25}–P_{75}), years	79.5 (74.8–83.7)
No. (%)	
65–74 years	389 (25.9%)
75–84 years	833 (55.5%)
85 years and older	278 (18.5%)
Sex, No. (%)	
Females	863 (57.5%)
Males	637 (42.5%)
Education	
Tertiary	212 (14.1%)
Secondary	537 (35.8%)
Primary	734 (48.9%)
Missing	17 (1.1%)
Marital status	
Married	741 (49.4%)
Single/divorced	322 (21.5%)
Widowed	437 (29.1%)
Drug sequence	
ChEIs before NSAIDs	237 (15.8%)
NSAIDs before ChEIs	1260 (84.0%)
Initiated concomitantly	3 (0.2%)
Median length of treatment periods, (P_{25}–P_{75}), months	
ChEIs alone	10.2 (4.45–19.9)
NSAIDs alone	2.44 (1.71–3.75)
Combination	2.32 (1.51–3.42)
Outcome type	
Gastric ulcer (ICD-10: K25)	909 (60.6%)
Duodenal ulcer (ICD-10: K26)	511 (34.1%)
Peptic ulcer, site unspecified (ICD-10: K27)	80 (5.3%)
Outcome diagnosis setting	
Outpatient specialist care	487 (32.5%)
Inpatient	1013 (67.5%)
Outcome diagnosis year	
2007–2010	470 (31.3%)
2011–2015	632 (42.1%)
2016–2020	398 (26.5%)
Died during study period no. (%)	892 (59.5%)
Number of concurrent chronic diseases	
Median (P_{25}–P_{75})	4.00 (2.00–6.00)
No. (%)	
0–1	296 (19.7%)
2–3	439 (29.3%)
4–5	371 (24.7%)
≥6	394 (26.3%)
Concurrent chronic diseases (10 most prevalent)[a]	
Hypertension	653 (43.5%)
Dementia	373 (24.9%)
Anemia	351 (23.4%)
Cataract and other lens diseases	348 (23.2%)
Ischemic heart disease	298 (19.9%)
Esophagus, stomach and duodenum diseases	247 (16.5%)
Other eye diseases	231 (15.4%)
Diabetes	204 (13.6%)
Atrial fibrillation	201 (13.4%)
Solid neoplasms	187 (12.5%)
Co-prescribed drug (10 most prevalent)	
Antiplatelets	768 (51.2%)
Renin-angiotensin-aldosterone system inhibitors	624 (41.6%)
Proton-pump inhibitors	618 (41.2%)
Beta-blockers	591 (39.4%)
Lipid modifying agents	580 (38.7%)
Antidepressants	462 (30.8%)
Diuretics	453 (30.2%)
Hypnotics and sedatives	447 (29.8%)
Calcium channel blockers	360 (24.0%)
Anxiolytics	300 (20.0%)

Abbreviations: ChEIs, cholinesterase inhibitors; ICD-10, international classification of diseases, 10th revision; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]We extracted concurrent chronic diseases out of a list of 60 pre-defined conditions captured in the National Patient Register during a three-year period before the outcome (Supplementary Table S3).[33]

80 years and older (12.6, 8.5–18.5, E-value: 24.6) compared to the people aged 65 to 79 (6.9, 4.5–10.6, E-value: 13.3).

In the sensitivity analyses, we obtained a comparable IRR estimate to the main analysis for combination treatment when we excluded individuals who died within 4 weeks of the peptic ulcer diagnosis (8.0, 6.0–10.7, E-value: 15.5) or when the 60-day grace period was applied (7.4, 5.7–9.7, E-value: 14.4). The additions of

TABLE 2 Incidence rate ratio of first peptic ulcer diagnosis stratified by exposure risk periods.

	Number of events	Person-years of follow-up	Incidence rate (95% CI) per 100 person-years	Incidence rate ratio (95% CIs)		E-value[b]
				Unadjusted	Adjusted[a]	
Exposure risk periods						
Non-treatment	850	12,375.8	6.87 (6.42–7.34)	Ref.	Ref.	Ref.
NSAIDs alone	284	1063.8	26.70 (23.71–29.92)	4.95 (4.26–5.74)	5.16 (4.44–6.00)	9.80
ChEIs alone	278	3333.6	8.34 (7.4–9.36)	1.25 (1.08–1.46)	1.02 (0.86–1.21)	1.18
Combination of NSAIDs and ChEIs	88	169.1	52.04 (41.91–63.69)	10.55 (8.04–13.85)	8.98 (6.81–11.84)	17.45

Abbreviations: ChEIs, cholinesterase inhibitors; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Estimates from the conditional Poisson regression of the self-controlled case series analysis, adjusted by age groups.
[b]E-value estimated for the adjusted incidence rate ratio.

pre-exposure risk periods produced almost identical IRR estimates to the main result, with no meaningfully increased risk during the 14-day (1.3, 0.9–2.0, E-value: 1.9) or 28-day pre-treatment periods (1.3, 1.0–1.8, E-value: 2.0). The analysis where the NSAIDs washout window was reduced to 6 months to keep more persons in the study population produced equivalent estimates to the main analysis but based on a 15% larger population ($n = 1729$ vs. 1500). Lastly, after additionally controlling for time-varying proton pump inhibitor, antiplatelet antidepressant, and systemic steroid use, the estimates remained unchanged. Detailed subgroup and sensitivity analyses results are presented in Supplementary Table S10–S19.

DISCUSSION

In this nationwide self-controlled case series analysis of adults aged 65 years and older living with dementia, we found a synergic drug–drug interaction when NSAIDs and ChEIs are concurrently used. We observed a nine-fold increase in the risk of peptic ulcer associated with concomitant use of NSAIDs and ChEIs, which was substantially higher than the risk associated with NSAIDs alone. Females and individuals aged 80 years and older had even further increased risks of peptic ulcer. Our estimates of the risks with NSAID therapy alone align well with the literature.[2,7–10] No excess risk was observed for ChEIs alone, contrary to what other studies suggest.[15–18] Our results support the cautious prescribing of NSAIDs to adults aged 65 years and older, particularly among people living with dementia.

Previous studies on individual NSAIDs and upper gastrointestinal complications found that all NSAIDs cause gastrointestinal adverse events. However, the risk ratios of toxicity vary between <2 to 12, with lower toxicity for COX-2 inhibitors and highest for ketorolac.[2] Our analysis did not stratify by the type of NSAIDs due to the low number of individuals, but we found an average five-fold increase of peptic ulcer compared to no use among individuals aged 65 years and older. Using a similar self-controlled case series analysis study design, Tata and colleagues found an almost three-fold increase in gastrointestinal bleeding for NSAID users among people aged 18 years and older.[7] Other studies have found three to five times the risk of peptic ulcer with NSAIDs compared to no treatment in the adult population.[8–10]

Pharmacoepidemiological studies on ChEIs and the risk of peptic ulcers are scarce. However, other types of studies mention their potential association. For example, two case reports presented a man and a woman, both aged 86 years, with no prior medical history besides their dementia diagnosis. Both were diagnosed with a peptic ulcer which the physicians attributed to their ChEI use.[15,16] Two clinical trials reported low proportions of gastrointestinal bleeding (1% and 7%), which were not significantly different from placebo.[17,18] A cohort study reported a higher incidence of gastrointestinal adverse events for rivastigmine (14%) and galantamine (24%) compared to donepezil (6%).[19] Systematic reviews for ChEIs only report the common adverse events of diarrhea, nausea, vomiting and dizziness.[41,42] Nonetheless, utilizing nationwide data, we estimated no excess risk of peptic ulcer associated with ChEIs use alone compared to non-treatment periods in adults aged 65 years and older. This might be because the current doses of treatments are low enough to avoid peptic ulcers. Alternatively, peptic ulcer risk might only be linked with upward dose titration of ChEIs,[15] which we could not capture in our analysis.

Regarding the co-administration of NSAIDs and ChEIs, a review article highlights the possibility of a pharmacodynamic interaction between these drugs with a synergic effect on peptic ulcers.[3] Our analysis aligns with a possible synergic effect given the estimated

nine-fold increase in the risk of peptic ulcer with the co-administration of these drugs. Furthermore, the age and sex-stratified sensitivity analyses revealed that individuals aged 80 years and older and females are at a higher risk of peptic ulcer during the combined use of NSAIDs and ChEIs than their counterparts. These findings confirm that increased age is a risk factor for gastrointestinal toxicity,[6] and contributes to filling the knowledge gap in sex-related differences in drug safety research.[43]

Clinical implications

In terms of clinical practice, our findings suggest that physicians should consider deprescribing NSAIDs in chronic users if possible (e.g., for people without inflammatory arthropathies) who are starting ChEI treatment and instead consider alternative solutions. Further, chronic ChEI users should refrain from starting NSAID treatment. Maybe, NSAIDs should be substituted with an alternative drug (e.g., paracetamol or acetaminophen for pain relief) to prevent unnecessary complications for an individuals aged 65 years and older. We suggest including the ChEIs and NSAIDs drug–drug interaction in potentially inappropriate medication use criteria to raise awareness among prescribers.[11,44] Unmet pain needs in conditions treated with ChEIs (e.g., dementia, cognitive impairment) is a substantial problem that should be assessed, managed, and intervened,[45,46] but potentially with other pharmacological (or non-pharmacological) treatments than NSAIDs.

Strength and limitations

The study's strengths include large-scale, routinely collected data with nearly 100% nationwide coverage, which enabled us to study rare drug adverse events with sophisticated statistical methods that control for the time-constant confounders by design.

Our findings should be interpreted cautiously due to the following limitations. First, the National Prescribed Drug Register only contains data about prescription drugs dispensed through pharmacies and machine-dispensed drugs packed in disposable bags ("apodos").[47] Over-the-counter medications or nursing home drug storerooms (which only exist in some nursing homes) are not included, which might have led to an underestimation of NSAIDs and antiplatelets use. However, older adults in Sweden (particularly those living with dementia) usually have their medications prescribed within their high-cost reimbursement scheme and are not expected to purchase over-the-counter NSAIDs or antiplatelets. Second, we could not differentiate between bleeding and non-bleeding peptic ulcers because we only accessed the three-digit ICD-10 category codes. Moreover, the peptic ulcer events were obtained from the National Patient Register, which does not contain diagnoses from primary care. However, most persons with symptoms should undergo an endoscopic examination by a gastroenterologist to confirm the diagnosis,[48] and in Sweden, most endoscopic units are linked to the National Patient Register.[26] In addition, the low proportion of persons diagnosed with dementia in our sample probably also reflects the lack of primary care data. Third, the drug exposure periods might not represent the actual consumption period. The drug exposure periods were constructed based on register data where it is impossible to ascertain whether the individual consumed the dispensed drug, that is, data on adherence is missing. Some persons may have stopped using the treatments earlier than prescribed or used the drugs (e.g., NSAIDs) following on a need basis that prolonged the drug use compared to what we could measure. Fourth, the relatively low number of events, in comparison to the number of individuals starting ChEIs and NSAIDs, indicates that peptic ulcer may hold a moderate clinical importance in absolute terms (e.g., $n = 88$ among persons with a combination of NSAIDs and ChEIs). This prevented us from performing stratified analysis based on the type of NSAIDs and ChEIs. Nevertheless, the self-controlled case series design requires outcomes to be rare, as it is in our study.[49] Fifth, our study does not fully consider the complexity of drug use in adults aged 65 years and older. People had multiple drugs prescribed during the study period that might have also increased or decreased the risk of peptic ulcer. However, sensitivity analysis showed that results remain unchanged after adjusting for time-varying proton-pump inhibitor, antiplatelet, antidepressant, and systemic steroid use. Sixth, register data do not provide enough information to determine the clinical and ethical appropriateness of each prescribing or whether it resulted in health benefits for the individuals. Still, our population-level findings may inform prescribers about the potential risks of combining NSAIDs and ChEIs. Seventh, official statistics regarding race/ethnicity were not available from the databases used in the study because there is no official data collected about ethnic, linguistic, or cultural affiliation in Sweden. Finally, our results may only be generalizable to settings similar to Sweden.

Conclusion

We found that the risk of peptic ulcer associated with the concomitant use of NSAIDs and ChEIs was over and beyond the risk associated with NSAIDs alone. Our

results underscore the importance of carefully considering the risk of peptic ulcers when co-prescribing NSAIDs and ChEIs to adults aged 65 years and older. Further research is warranted to validate the effect size estimates using an even larger population.

AUTHOR CONTRIBUTIONS

Máté Szilcz, Géric Maura, and Jonas W. Wastesson conceived and designed the study. Máté Szilcz performed the statistical analysis, interpreted the data, drafted and critically revised the manuscript. Jonas W. Wastesson, Amaia Calderón-Larrañaga, Pierre-Olivier Blotière, Géric Maura, Daniel Prieto-Alhambra, and Kristina Johnell interpreted the data and critically revised the manuscript. Kristina Johnell obtained funding and acquired the data. Kristina Johnell, Jonas W. Wastesson, Amaia Calderón-Larrañaga, and Daniel Prieto-Alhambra provided supervision. Kristina Johnell and Máté Szilcz are the guarantors of the study and data integrity. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no actual conflict of interest regarding this article. Potential conflict of interest unrelated to the present study: MS received consulting fees from Parexel, Pfizer, and Macanda AB.

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The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1. Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs and the risk of peptic ulcers: a self-controlled study—Supplementary materials.

Supplementary Table S1: Data sources.

Supplementary Table S2: Assumptions of the self-controlled case series design.

Supplementary Table S3: Details of diagnosis codes and drugs used to detect chronic conditions.

Supplementary Table S4: Details of drugs used to identify co-prescribed medications.

Supplementary Table S5: Distribution of co-prescribed medications.

Supplementary Table S6: Distribution of chronic comorbidities.

Supplementary Table S7: Diagnosis codes related to first NSAIDs prescription (20 most common).

Supplementary Table S8: RECORD statement.

Supplementary Table S9: Distribution of individual NSAIDs and ChEIs during the study period for the total number of individuals (n = 1500).

Supplementary Table S10: Subgroup analysis (stratified by sex).

Supplementary Table S11: Subgroup analysis (stratified by age group).

Supplementary Table S12: Sensitivity analysis (Defined Daily Dose used for treatment period calculation).

Supplementary Table S13: Sensitivity analysis (individuals died within 4 weeks of outcome were excluded).

Supplementary Table S14: Sensitivity analysis (grace period: 14 days and 60 days).

Supplementary Table S15: Sensitivity analysis (NSAIDs washout window: 6 months).

Supplementary Table S16: Sensitivity analysis (included a 14-day or a 28-day pretreatment risk periods).

Supplementary Table S17: Sensitivity analysis (3-year washout for peptic ulcer).

Supplementary Table S18: Sensitivity analysis (adjusted for proton pump inhibitor use).

Supplementary Table S19: Sensitivity analysis (adjusted for proton pump inhibitor, antiplatelets, antidepressant and systemic steroid use).

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