Impact of specific Beers Criteria medications on associations between drug exposure and unplanned hospitalisation in elderly patients taking high-risk drugs: a case-time-control study in Western Australia

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Abstract

Background: Certain broad medication classes have previously been associated with high rates of hospitalisation due to related adverse events in elderly Western Australians, based on clinical coding recorded on inpatient summaries. Similarly, some medications from the Beers Criteria, considered potentially inappropriate in older people, have been linked with an increased risk of unplanned hospitalisation in this population.

Objective: To determine whether risk estimates of drug-related hospitalisations are altered in elderly patients taking 'high-risk drugs' (HRDs) when specific Beers potentially inappropriate medications (PIMS) are taken into consideration.

Methods: Using the pharmaceutical claims of 251,305 Western Australians aged ≥65 years (1993-2005) linked with other health data, we applied a case-time-control design to estimate odds ratios (ORs) for unplanned hospitalisations associated with anticoagulants, antirheumatics, opioids, corticosteroids and four major cardiovascular drug groups, from which attributable fractions (AFs), number and proportion of drug-related admissions were derived. The analysis was repeated taking exposure to eight specific PIMs into account, and results compared.

Results: 1,899,699 index hospitalisations were involved. Twelve to 57% of index subjects were exposed to each HRD at the time of admission, although the proportions taking both a HRD and one of the selected PIMs were much lower (generally ≤2%, but as high as 8% for combinations involving temazepam and for most PIMs combined with hypertension drugs). PIMs included (indomethacin, naproxen, temazepam, oxazepam, diazepam, digoxin, amiodarone, and ferrous sulphate) all tended to increase ORs, AFs and drug-related hospitalisation estimates in HRD combinations, although this was less evident for opioids and corticosteroids. Indomethacin had the greatest overall impact on HRD ORs/AFs. Indomethacin (OR 1.40; 95% CI 1.27-1.54) and naproxen (OR 1.22; 1.14-1.31) were associated with higher risks of unplanned hospitalisation than other antirheumatics (overall OR 1.09; 1.06-1.12). Similarly, among cardiac rhythm regulators, amiodarone (OR 1.22; 1.13-1.32) was riskier than digoxin (OR 1.08; 1.04-1.13). For comparisons of drug-related hospitalisation estimates, temazepam yielded the greatest absolute increases, especially with hypertension drugs.

Conclusions: Indomethacin and temazepam should be prescribed cautiously in elderly patients, especially in drug combinations. Furthermore, it appears other antirheumatics should be favoured over indomethacin/naproxen and, in situations where both drugs may be appropriate, digoxin over amiodarone. Our methodology may help assess the safety of new medications in drug combinations in preliminary pharmacovigilance investigations.

1 Introduction

Adverse drug events (ADEs) are common in ageing patients [1, 2]. Older people are major consumers of medication, and are more susceptible to ADEs due to physiological deterioration (e.g. renal and liver function decline; cognitive, sensory and motor function impairment); increasing number of comorbidities; polypharmacy; and other age-related factors. These factors can lead to pharmacokinetic and pharmacodynamic complications; propensity for drug-drug and drug-disease interactions; and difficulties adhering to physicians' instructions about medication intake, all of which are associated with drug-related problems [3-9]. In America, ADEs account for nearly 100,000 emergency hospitalisations annually in people aged ≥65 years [10]. In Australia, 15-22% of unplanned hospital admissions are drug-related in this age group [11].

Furthermore, medications considered potentially inappropriate in the elderly are frequently prescribed in older people. A number of lists of such medications have been developed in the last few decades [12-15], the Beers Criteria [16-19] being the most commonly referenced. Prevalence estimates of Beers medications vary in different elderly populations, but most are around 10-40% [20, 21].

A widespread approach for reporting ADE-related hospitalisations at the population level involves the use of clinical coding from inpatient records [22, 23]. This approach is not only subject to under-reporting, but is also restricted to broad medication categories due to constraints of the coding scheme [22-26]. Nonetheless, using this approach, Western Australian (WA) studies have identified anticoagulants, antirheumatics, opioids, corticosteroids, cytotoxics and cardiovascular agents as broad drug classes associated with high rates of ADE-related hospitalisations [24-26].

Our own investigations, which linked WA pharmaceutical claims with inpatient and other records, estimated that 7-45% of unplanned hospital admissions in older patients exposed to medications from each of these drug classes (cytotoxics excluded) were likely attributable to their drug exposure (although two cardiovascular sub-groups appeared protective) [27]. Our research also examined Beers' medications using similar methods, identifying 14 potentially inappropriate medications (PIMs) that seemed to increase the risk of unplanned hospitalisation significantly in the elderly [28]. Results from these two separate studies led us to the

following question: “To what extent are risk estimates of unplanned hospital admissions altered in elderly patients taking medications from broad classes of high-risk drugs (HRDs) when exposure to specific Beers medications is taken into consideration?” Detection of an increased risk of serious adverse events (i.e. unplanned hospitalisations) when a PIM of interest was taken in combination with medications from certain broad HRD classes (versus the estimated HRD risk overall), would prompt physicians not to rely on estimated safety figures for these drug classes as a whole when assessing the HRD risk in patients who are also taking the PIM in question. Conversely, assessment of the risk associated with the combined effect of specific PIMs with medications from HRD groups would also provide a better estimate of the likelihood of serious harm in subgroups of patients taking various HRDs, when a specific PIM was being considered as an additional prescription drug. The increased potential for interactions when therapeutic drugs are taken in combination, over and above the independent effect of each medication, suggested to us that an increase in risk was likely [1], but to what extent?

This paper presents the results of our analyses in relation to this question. Using a case-time-control design [29, 30], we assessed the impact of exposure to specific PIMs in elderly Western Australians taking HRDs in terms of unplanned hospitalisation. For some PIMs, we also compared associations between specific PIMs and unplanned hospitalisation against those of the broad drug classes to which they belong. Given the potential for confounding by indication in observational studies of this nature, we sought to enhance our study design to the greatest extent possible in an attempt to overcome related issues.

2 Methods

2.1 Data linkage and participant selection

This study linked Australian Pharmaceutical Benefits Scheme (PBS) [31, 32], Medicare [33, 34] and residential aged care [35] data with inpatient, death and electoral roll records from the WA Data Linkage System [36, 37] through probabilistic linkage. This linkage involved full names and addresses, phonetic compression and other identifiers. A previous evaluation of linked chains for WA core datasets has estimated that <0.3% contained incorrect links [36]. For the Australian (i.e. national) data sources, the linkage was performed on key fields from a patient register (rather than individual records), for which a unique person identifier was available. Once

linkage between the WA Data Linkage System and the patient register was completed (based on key patient details), data custodians were able to retrieve all health records belonging to each patient, using their person identifier. The study protocol was approved by The University of WA's Human Research Ethics Committee. Participants were not required to provide informed consent as identification details were not released to the researchers.

Participants included people aged ≥65 years by the end of 2004, who continuously lived in WA during 1993-2005 (until death) and had at least one pharmaceutical claim during that time, thus ensuring that those included had ascertainable drug exposures. Due to problem data (e.g. records post-death, no gender on any record), 8% were subsequently excluded. Comparisons against official statistics of the WA estimated residential population aged ≥65 years [38] suggest that our ultimate cohort captured 80-85% of WA elderly residents annually.

2.2 Establishment of drug reference database

Details of all PBS items from available schedules (August 1991-June 2007) [39] were assembled into a reference database, reconciling Anatomical Therapeutic Chemical (ATC) codes with the 2007 World Health Organization (WHO) ATC classification [40, 41]. Average daily doses were determined for each item by comparing prescription statistics from BEACH (Australian Bettering the Evaluation and Care of Health) [42-44], MIMS Australia [45-47], and the 2008 WHO ATC Defined Daily Doses (DDDs) [48, 49], taking drug form, route and strength into account. Precedence was given to the most appropriate information applicable to older Australians. Additionally, each drug's elimination half-life was obtained (predominantly from MIMS [45-47]), from which the period of drug effect, defined as five times the drug's half-life [50, 51], was estimated. Finalised entries were merged to the PBS master file.

2.3 Definition of HRD groups and domains

Previously identified HRDs included anticoagulants, antirheumatics (mostly non-steroidal antiinflammatory drugs (NSAIDs)), corticosteroids, opioids, cytotoxics and cardiovascular agents [24-26]. Cytotoxics were excluded from this study because they were predominantly administered in public hospitals for which prescriptions were not recorded in the PBS data. Cardiovascular agents were expanded to include cardiac rhythm regulators, beta-blockers, hypertension drugs and serum lipid-

reducing agents. Code definitions for each of these medication groups were established using the 2007 ATC classification [40, 41]. ATC definitions for corresponding 'drug domains' were also agreed, where each drug domain consisted of medications used to treat similar conditions to those treated by the related HRD. Patients taking medications from each drug domain (i.e. 'patient domain') were considered to be potential candidates for being prescribed a HRD of interest. They formed the cohort of participants associated with each HRD sub-study. ATC definitions for each HRD group and corresponding drug domain are provided in a previous publication [27].

2.4 Case-time-control design

Associations between HRDs and unplanned hospital admissions were expressed as odds ratios (ORs) derived from a case-time-control design [29, 30]. Thus, index subjects acted both as cases and as their own historical controls, while background time trends in exposure due to ageing, disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group selected from the same patient domain as the index subjects. As already mentioned, in this study the patient domain included everyone in the overall cohort who had been prescribed a therapeutic drug used to treat similar conditions to the indications for the HRD group of interest during 1993-2005.

Index subjects were individuals within the patient domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31 December 2005 whilst aged ≥67 years. These additional age and time constraints ensured sufficient lead-up time for the control observation period. Many patients were included in the analysis as multiple index subjects, although a few (≤0.1%) who had >50 index admissions were excluded given concerns about representativeness. Two records were created for each index subject, one for the 'case time' (i.e. the admission date) and the other for the 'control time' (usually 365 days prior). When index subjects were in hospital at this preferred control time (2-3% of instances), the admission date of that earlier hospitalisation was used as control time instead.

Each index subject was matched by gender, general practitioner (GP) coverage category for the entire study period, and year of birth to a randomly selected reference subject from the sub-study's patient domain. To determine the GP coverage category, each GP visit identified in the Medicare dataset was allocated a

'coverage' period of 61 days, overlapping periods for each person being merged together. The GP coverage category was then derived from the proportion of days with GP coverage over the study period, categories loosely based on quartiles applicable to the study cohort. Persons born before 1900 were allocated a year of birth of 1900 for matching purposes only. Case and control time records were created for each reference subject as per the index subjects, ensuring case and control dates were matched with those of corresponding index subjects as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the time-dependent variables required to adjust for potential confounding in the regression models, including nursing home status at the case or control time; hospital days, overall Charlson comorbidity index [52] and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall count of daily doses taken (for any drug) and a daily dose count for each broad drug category.

Additionally, PBS records were processed to determine whether the subject was exposed to any medications from the sub-study's HRD drug group at each case and control date. If a prescription was found for a relevant drug and if the time period bound by its supply date and exposure effect end date overlapped with the case or control date, the exposure status was set to 'exposed'. The exposure effect end date was calculated by adding the number of drug consumption days associated with the script (i.e. total quantity / average daily dose) to the supply date (-1) plus the period of drug effect (up to seven days) and a seven-day latency period. Thus, the exposure status did not strictly identify whether the subject was taking a relevant HRD at the case or control time. Instead, it was used to reflect whether the effects of HRD exposure could potentially have caused a hospital admission at the case or control time.

For each HRD sub-study, conditional logistic regression models were applied using the SAS 9.2 PHREG procedure, with stratification based on a unique identifier for each subject [53]. The COVS option was specified to ensure the generation of robust Sandwich covariance estimates [54], thus accounting for the potential within-cluster correlation associated with multiple hospitalisations per person. The OR of

primary interest was derived from the coefficient of the cross-product between exposure and the binary index/reference indicator, which represented the association between exposure and unplanned hospitalisation in the index subjects, over and above apparent time-trend effects that applied to both index and reference subjects [29]. The adjusted model controlled for all health and drug consumption indicators mentioned earlier (refer to last footnote in Table 2), except for the three-month count of daily doses for the drug group of interest.

2.5 Estimation of unplanned hospitalisations attributed to drug group

Using the OR derived as above, the attributable fraction (AF) of unplanned hospitalisations associated with each HRD group (within the exposed) was calculated, where AF=(OR-1)/OR. The estimate of unplanned hospitalisations attributed to each HRD group was then derived as AF x number of exposed index subjects [55-58].

2.6 Derivation of PIM-refined estimates

Using a process analogous to that described for HRDs, our previous research produced ATC definitions for all medications from the 2003 Beers Criteria [18] and corresponding drug domains, and applied a case-time-control design to all 'general' PIMs from the Beers list (i.e. drugs to avoid in all elderly independent of diagnosis) that were available in WA over the study period. Of the 43 individual PIMs examined, 14 demonstrated significant associations with unplanned hospitalisations in adjusted models.[28] All were initially included in this study. However, as some PIMs (meperidine/pethidine, thioridazine, bisacodyl, oxybutynin, nitrofurantoin and promethazine) did not affect HRD ORs significantly (predominantly due to low prevalence), the list was subsequently restricted to eight, as follows: indomethacin, naproxen, temazepam, oxazepam, diazepam, digoxin, amiodarone and ferrous sulphate. Please refer to the footnotes of Tables 1 and 2 for ATC definitions of these medications. Exposure to these PIMs was ascertained for all index and reference subjects at the case and control times, as per exposure to HRDs. This was repeated for each HRD sub-study. It should be noted that indomethacin and naproxen, as well as being specific PIMs in the analyses, were also members of the antirheumatic HRD group. Similarly, digoxin and amiodarone were treated as both specific PIMs and as members of the cardiac rhythm regulator HRD group.

Once this exposure information had been obtained, the following covariates were added to the existing HRD conditional logistic regression models: the binary exposure variable for a given PIM (e.g. PIM1exp); the interaction term between this PIM exposure variable and the HRD group's exposure status (e.g. PIM1exp*HRDexp); and the interaction term between PIM exposure and the cross-product between HRD exposure and the binary index/reference indicator (e.g. PIM1exp*HRDexp*index). The ORs of interest were those that applied to index subjects only in relation to their exposure to both the HRD and the PIM of interest. They were calculated as follows:

$$OR = e^{a + b}$$

where a = model coefficient for HRDexp*index and b = model coefficient for PIM1exp*HRDexp*index. The 'b' term represented the added effect associated with the use of PIM1 in index subjects taking medication from the HRD group.

As per the overall analysis for HRDs, the ORs involving PIM terms were adjusted for potential confounding using all available covariates. Furthermore, these adjusted ORs were used to derive corresponding AFs and estimates of hospital admissions attributed to drug exposure when both the specified PIM and a medication from the HRD group were taken.

Finally, estimates of hospitalisations attributed to drug exposure were refined according to PIM exposure by splitting the index subjects exposed to medications from each HRD group based on their additional exposure to specific PIMs and applying the most appropriate AF to each subset. Where refinements involved two PIMs, the AFs originated from regression models in which PIM exposure was represented as a class variable. Differences were then calculated between the PIM-refined estimates and those obtained by multiplying corresponding 'PIM-negative' AFs by the total number of index subjects exposed to each HRD, where 'PIM-negative' referred to patients who were exposed to a given HRD but not to PIMs involved in the refinement process.

3 Results

An overview of participants and index subjects for each HRD sub-study is presented in Table 1. The overall study cohort consisted of 251,305 individuals. However, participants in each HRD patient domain (i.e. sub-study cohort) numbered between

39,596 (cardiac rhythm regulators) and 193,196 (opioids). These people received 569,369-4,825,066 prescriptions during the study period. Overall, 1,899,699 unplanned admissions ('index subjects') were included, each sub-study yielding 128,241-358,570 admissions, which were associated with 29,919-108,513 patients. Around 45-46% of the index subjects were male and the mean age was 78-79 years.

The proportion of index subjects exposed to a medication from each HRD group at the time of admission ranged between 12-13% (anticoagulants and opioids) and 57% (hypertension drugs). Proportions of index subjects exposed to a HRD as well as a PIM were much lower (generally ≤2%). However, these proportions were higher for exposure to a HRD with temazepam and for most PIMs combined with hypertension drugs (up to 8.1% for both). For the sub-study on cardiac rhythm regulators, the proportions specifically taking digoxin and amiodarone (both of which are cardiac rhythm regulators) at the time of admission were 26.6% and 9.1% respectively.

Adjusted ORs for unplanned hospital admissions, corresponding AFs, and estimates of hospital admissions attributed to HRDs overall and in combination with selected PIMs are presented in Table 2. When no consideration was given to individual PIMs, adjusted ORs for hypertension and serum lipid-reducing agents were below one, suggesting that these drugs may have had an overall protective effect against unplanned hospitalisations. Adjusted ORs for the other HRD groups (without consideration for concurrent PIM exposure) ranged between 1.08 (95% CI 1.05-1.11) for beta-blockers and 1.81 (1.75-1.88) for opioids, and corresponding AFs ranged between 7.4% and 44.9%.

We compared HRD ORs involving PIM combinations with both the ORs for the HRD groups as a whole and with ORs for those not taking the specified PIMs (i.e. PIM-negative ORs). However, as PIM-negative ORs were almost identical to overall ORs for most PIMs, only the overall ORs are shown in Table 2. For temazepam, PIM-negative ORs were slightly lower than overall ORs though (e.g. 1.11 vs. 1.13 for anticoagulants), except for the opioid sub-study (1.83 vs. 1.81).

Most PIM/HRD combinations produced higher ORs for unplanned hospitalisation than corresponding overall and PIM-negative ORs. This was particularly evident for indomethacin, which appeared to increase the hospitalisation risk significantly for all HRD groups except corticosteroids. Naproxen and temazepam also raised a number

of ORs, although naproxen had a greater effect on results for anticoagulants, corticosteroids and opioids, whereas temazepam produced higher ORs consistently for broad cardiovascular drug groups. Similarly, oxazepam seemed to augment ORs related to cardiovascular drug groups, despite not demonstrating much effect on results for other HRDs. Diazepam, digoxin, amiodarone and ferrous sulphate also affected results for some HRDs, although none of these PIMs had much effect on opioid and corticosteroid ORs.

In terms of the HRD groups, ORs for the hypertension medications were the most affected by drug combinations with PIMs. Other cardiovascular drug groups, antirheumatics and anticoagulants were affected by several PIMs as well. Conversely, with only a few exceptions, ORs for opioids and corticosteroids seldom seemed to be affected when exposure to PIMs was taken into consideration.

Figure 1 compares the unplanned hospitalisation ORs associated with specific antirheumatic and cardiac rhythm regulator PIMs against the overall ORs obtained for the broad HRD group to which they belong. For antirheumatics, both indomethacin and naproxen (which accounted for 5.9% and 10.8% of the antirheumatic exposure, respectively), were associated with a significantly higher risk of unplanned hospitalisation than the group of antirheumatic drugs as a whole. Furthermore, ORs suggested that indomethacin was possibly linked to a higher hospitalisation risk than naproxen (although the difference in the strength of these associations was not statistically significant). For cardiac rhythm regulators, the OR for amiodarone was higher than that for digoxin. Neither was significantly different from the OR for the entire HRD group, which was expected since 98.3% of the exposure to cardiac rhythm regulators involved digoxin (72.3%), amiodarone (22.1%) or both (3.9%).

Figures 2 and 3 compare the overall AF for those exposed to a medication from each HRD group with that of elderly people exposed to both the main drug group and a specified PIM. These figures concentrate on non-cardiovascular and cardiovascular HRDs, respectively. For the sake of simplicity, PIM-negative AFs for each PIM are not shown; most would be slightly lower than the overall AF. Most AFs were greater when drug exposure involved a combination of a medication from a main drug group with a specific PIM. Indomethacin exposure in combination with most HRDs generally produced the greatest AF increases (as opposed to other PIM exposure),

except for corticosteroids and hypertension drugs; naproxen and diazepam had the greatest influence for the latter, respectively. AFs for opioids and corticosteroids were the least affected when these drugs were combined with individual PIMs, whereas the AF for hypertension drugs was most affected.

Figure 4 shows differences between PIM-refined and PIM-negative estimates of hospitalisations considered attributable to drug exposure for each HRD group. PIM-refined estimates were those obtained by applying specific AFs to subsets of index subjects exposed to HRDs depending upon their concurrent PIM exposure status, whereas PIM-negative ones were those that would be expected if all index subjects exposed to a HRD were unexposed to the PIMs under consideration. Index subjects taking hypertension drugs were most affected by additional exposure to specific PIMs in terms of increases in estimated hospital admissions attributed to drug exposure, although those taking serum lipid-reducing agents, beta-blockers and antirheumatics were also noticeably affected. For most broad drug groups, the PIM associated with the greatest absolute difference in attributable hospital admissions was temazepam. This was particularly apparent for index subjects taking hypertension drugs, for which a difference of 7,145 admissions was estimated over the study period when temazepam exposure was taken into account.

4 Discussion

This study investigated whether intake of specific PIMs from the Beers Criteria affected risk estimates of unplanned hospitalisation in elderly Western Australians exposed to medications from broad classes of 'high-risk drugs'. The linkage of pharmaceutical claims data with inpatient and other records not only allowed us to bring together exposure and outcome information for each person and to use different techniques to estimate excess hospitalisations associated with medication exposure, but also permitted the isolation of individual medications in this process (which was not possible from clinical coding). Furthermore, our large cohort and the extended study duration gave us the power to evaluate individual drugs on their own as well as in combination with other medications.

4.1 Major findings

Our results suggest that most of the Beers medications we investigated tended to increase the risk estimates associated with drug exposure and unplanned

hospitalisation for at least some, if not most of the broad drug groups included in the study. This was not only evident when comparing ORs, but was also reflected in corresponding AFs and derived estimates of unplanned hospitalisations considered attributable to medication exposure. This is not surprising, given that Beers medications have been identified as drugs to be avoided in the elderly due to their potential harm [18]. Furthermore, concurrent use of multiple medications can lead to drug interactions, which may increase the risk of adverse drug reactions [1].

One could argue that the proportion of unplanned hospitalisations associated with exposure to these drug combinations is fairly low, each combination generally affecting <2% of our index subjects. However, in our elderly population, which consisted of ~170,000 older WA residents annually, >32,000 unplanned hospitalisations were attributed to these drug combinations between July 1994 and December 2005, an average of 2,785 per year. For those patients potentially affected, this undoubtedly represents a very important issue.

With respect to individual PIMs, indomethacin had the greatest impact on relative effect measures for most HRD groups and their association with unplanned hospitalisation, although naproxen and diazepam were also strong modifiers. In absolute terms, temazepam, which was the most commonly prescribed PIM in combination with HRDs, appeared to be the most influential. Thus, clinicians should be particularly cautious when contemplating the use of these PIMs in patients who are already taking medications from a relevant HRD group (or vice versa).

For HRD classes, it is difficult to single out which group of patients warrant the most precaution when contemplating therapy combinations involving the PIMs discussed in this paper. Although elderly patients taking hypertension drugs were most affected by an apparent increase in risk of unplanned hospitalisation when taking the majority of these PIMs, hypertension drugs demonstrated an overall protective effect against unplanned hospitalisation when these PIMs were not taken into consideration. Conversely, older people taking opioids and corticosteroids seemed least affected by the additional intake of any given PIM. However, this may relate to the fact that medications from these broad drug groups were already associated with a very high risk of unplanned hospitalisation (81% and 48% increases compared with the unexposed), which may not have been altered substantially by the introduction of an additional medication.

Our comparisons of ORs for individual PIMs against those of the broad drug class to which they belong should also be highlighted. Although the apparent increase in risk of unplanned hospitalisation in those taking antirheumatics was a modest 9% overall when compared with the unexposed, the corresponding figures for indomethacin and naproxen were much higher (40% and 22%, respectively). Fortunately, the prescribing of these two drugs has been declining in the Western Australian population and most likely elsewhere, as newer and safer drugs are being introduced onto the market. In any event, these differences illustrate the need to exert caution when examining risk-related results for broad drug classes, as these results may not be applicable uniformly to individual medications within these drug classes. For cardiac rhythm regulators, comparisons against overall results for the entire drug class are less relevant, since 98% of the exposed were taking a PIM of interest. Nonetheless, our ORs do suggest a higher increased risk of unplanned hospitalisation for amiodarone (22%) than digoxin (8%). These two drugs are generally prescribed for somewhat different indications (in Australia at least) – amiodarone (Class III antiarrhythmic) used in various cases of tachyarrhythmia, digoxin (cardiac glycoside) in the treatment of congestive heart failure [46, 47]. However, in situations where both drugs may be appropriate (e.g. maintenance therapy for atrial fibrillation), digoxin should be favoured over amiodarone for safety.

4.2 Perusal of the literature and review of ADE mechanisms

Identifying other study results that are directly comparable with ours has proved difficult. Most publications on the potential adverse effects of drug combinations have focused on the prevalence of potential drug-drug interactions, as defined in various compendia [59-63]. In these publications, digoxin, amiodarone, and NSAIDs (e.g. indomethacin, naproxen) are prominent on lists of major drug-drug interactions [59-72]. Studies reporting more specifically on multi-drug adverse events [59, 60, 70-74] have indicated that counts of actual ADEs resulting from exposure to drug combinations were considerably lower than corresponding counts of potential drug-drug interactions; associated lists of the most common drug combinations seldom provided statistics that represented a relative risk or rate of occurrence with respect to drug exposure; the medications most frequently implicated in ADEs generally reflected drug consumption patterns in the study population; and several studies

were not specific to the elderly. Thus, this information is mostly peripheral to our research.

However, the literature does explain the likely mechanisms responsible for potential ADEs, in support of our findings regarding PIMs and high-risk drug combinations. For instance, the interaction between NSAIDs and anticoagulants such as warfarin is well established. Most NSAIDs, including indomethacin and naproxen, inhibit platelet aggregation and cause gastrointestinal toxicity that may lead to inflammation and ulceration, thus predisposing patients to gastrointestinal and other bleeding [75-79]. Therefore, it is not surprising that older patients taking anticoagulants in our study, who were also exposed to indomethacin or naproxen, were at a much increased risk of unplanned hospitalisation compared with anticoagulant users who were not. Similarly, NSAIDs inhibit COX-2 and prostaglandin synthesis, which leads to decreased sodium excretion, subsequent expansion of intravascular volume and fluid retention.[77, 80] Consequently, NSAIDs may interfere with antihypertension therapy and have been linked with the aggravation of heart failure, other cardiovascular events and renal impairment, all of which may affect patients who are taking a range of cardiovascular drugs [77-79]. The Beers Criteria also warn against the use of indomethacin due to its adverse effects related to the central nervous system [18]. This may possibly explain the increased risk of unplanned hospitalisation associated with indomethacin in patients taking opioids, and the higher risk associated with indomethacin overall compared with naproxen.

Comparing digoxin and amiodarone is also interesting when considering the ADE mechanisms involved. In the early 1970s, toxicity was of major concern in people taking digoxin, one study reporting that 25% of patients taking this PIM were diagnosed with definite toxicity [81]. Symptoms of toxicity include acute fatigue, anorexia, nausea, visual disturbances, confusion, drowsiness and others [81, 82]. Subsequently, recommended dosage levels were lowered, and by the mid-1990s, the prevalence of digoxin toxicity had been reduced to ~4% in patients being treated with this medication [81]. Nonetheless, patients with renal failure remain at higher risk, as well as those taking diuretics and calcium channel blockers [81, 82]. Digoxin toxicity is not the only potential adverse effect associated with this PIM, however. Combinations of digoxin with calcium channel blockers (hypertension drugs) can lead

to complete heart block in some situations, whereas digoxin with beta-blockers may induce bradycardia [80, 82].

In contrast, amiodarone has not been linked with a high prevalence of toxicity. However, it may lead to a heart block in combination with a calcium channel blocker, as per digoxin [82]. Additionally, amiodarone may interact with other drugs through the inhibition of cytochrome P450 enzymes, increasing patients' sensitivity to most NSAIDs, warfarin, beta-blockers, calcium channel blockers, statins and a number of benzodiazepines (e.g. diazepam). This may possibly lead to overdose and associated symptoms [83]. This latter mechanism may account for the higher impact of amiodarone than digoxin on the risk of unplanned hospitalisation in several groups of study participants taking high-risk drugs.

Diazepam, temazepam and oxazepam are benzodiazepines, a class of drugs with strong sedative and other central nervous system properties that may lead to cognitive impairment, confusion, falls, fractures and other related adverse outcomes [84-87]. They are associated with a high level of ADEs even in monotherapy [87]. Although clinically significant interactions have been identified between benzodiazepines and other medications, most drug classes involved have not been included in this study, with one exception: opioid analgesics [87]. Surprisingly, our results have not demonstrated an elevated risk of unplanned hospitalisation in patients taking opioids when used in combination with any of the three benzodiazepine PIMs included in our analysis.

For completeness, we also mention ferrous sulphate, which is known to cause constipation when taken in high doses [18, 73]. Publications reporting major drug interactions in the elderly do not generally mention this substance. However, one would expect other drugs also associated with constipation (e.g. opioids, calcium channel blockers) [73] to exacerbate the problem if taken in combination with iron supplements. Our findings for hypertension drugs appear to support this premise, but our opioid results do not. The strong impact of ferrous sulphate on the risk of unplanned hospitalisation for anticoagulant and beta-blocker groups is also difficult to interpret in our results. The residual effects of protopathic bias are possible with this medication, whereby the underlying reason for prescribing iron supplements (e.g. anaemia, which may be associated with other, potentially undiagnosed conditions)

may be the source of the apparent interaction [88]. Further investigations would be required to ascertain whether this is the case, but this would require additional data.

4.3 Study limitations

Like most research involving administrative health data, this study was subjected to data quality and availability issues. Although the WA Data Linkage System is a well-established data linkage facility [36, 37], a slightly greater proportion of invalid links than usual were likely created in this instance, given the lesser quality of the linkage fields extracted from Australian (i.e. national) sources. Additional staff members were appointed to identify and resolve improbable links, but some would likely have been missed. Nonetheless, given the large size of the datasets, it is unlikely that the few glitches would have impacted on the results to any great extent.

Similarly, the researchers also conducted an extensive clean-up and cross-validation process upon receipt of the data, addressing most problems, but they could not have eliminated them entirely. In particular, ascertainment of drug exposure at specific times was difficult, as no information was available on the daily dose specifically prescribed for each dispensed drug, nor on patient adherence. Much attention was devoted to the derivation of exposure status from average recommended daily doses, but this could not have been completely accurate for every subject.

Furthermore, our PBS dataset had some coverage limitations. It excluded medications prescribed within public hospitals, over-the-counter drugs, and prescriptions for which a PBS claim could not be made [89]. However, since our elderly participants likely had a concession card and very low co-payment requirements, most non-hospital scripts for medications of interest would have been recorded in this age group. Consequently, these coverage issues were not expected to affect our results to any great extent.

Our own exclusions also eliminated elderly people with no PBS record during 1993-2005 and those who appeared not to have lived in WA for the entire study period (until death). Since the excluded individuals were probably younger, healthier and wealthier than the study population average, we expect our overall results may have slightly overestimated the impact of drug exposure on unplanned hospitalisation compared with corresponding figures applicable to all older people living in WA or possibly elsewhere.

Additionally, we acknowledge that the case-time-control design is dependent upon inherent assumptions and conditions, especially in relation to time trend bias [29, 30, 90]. Our preliminary work has demonstrated that our enhanced approach appears to control reasonably well against related confounding, improving internal validity compared with the case-control and case-crossover designs, and the basic case-time-control design without adjustment for measurable time-variant confounders [27]. Nonetheless, it is unlikely that our models were able to fully adjust for potential protopathic (reverse causation) bias, a form of systematic error that arises when early manifestations of the outcome prior to its formal ascertainment drive up exposure [88].

Given the ongoing development of new therapeutic drugs since the start of our project, a repeat of our study using more recent data and updated drug definitions would certainly be beneficial. Still, all of the selected PIMs continue to be available in Australia [91] and all but one were included in the latest revision of the Beers Criteria [19]. Ferrous sulphate was excluded as a PIM, not due to lack of evidence of the drug's potential harm in older people, but because the associated problems are not restricted to the elderly [92].

5 Conclusions

This study used robust methods involving pharmaceutical claims, linked data and a case-time-control design to examine individual drugs in combination or in comparison with broad classes of HRDs and their associations with unplanned hospitalisation in the elderly. Based on our results, indomethacin and temazepam appear particularly problematic in terms of hospitalisation risk when used with HRDs. Clinicians should be particularly cautious in prescribing these medications to their elderly patients, especially in drug combinations. Furthermore, from a safety perspective, our results suggest that other antirheumatics should be favoured over indomethacin and naproxen and, in situations where both drugs may be appropriate, digoxin over amiodarone.

Our methodology has broader applications, however. Additional research seems warranted to compare a wide range of individual drugs within each HRD group, to determine which ones appear to be potential drivers of adverse outcomes. This need not be limited to the drug groups identified in this study. For instance, a number of PIMs from the Beers Criteria belong to other drug classes. One could investigate

various anxiolytics or sedatives, for example, to determine which ones appear safest or most dangerous. Of course, our methods would be quite useful in investigations of the potential harm associated with combinations of individual medications, especially those suspected of elevating the risk of ADEs. In particular, we propose our approach as an additional tool for assessing the potential harm of new medications and their combined effects with other drugs in preliminary pharmacovigilance investigations.

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Tables

Table 1 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - profile of study population and medication exposure status[a] of index subjects at the time of admission

Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
Domain participants (people in sub-study cohort)[b]	90,124	174,585	193,196	84,960	39,596	89,017	180,539	100,787
Domain prescription count (all drugs)	1,697,870	3,317,418	4,825,066	569,369	614,754	2,717,155	12,236,135	4,517,199
Number (%) participants contributing as index subjects	57,609 (63.9%)	92,903 (53.2%)	108,513 (56.2%)	53,369 (62.8%)	29,919 (75.6%)	55,179 (62.0%)	99,635 (55.2%)	50,295 (49.9%)
Index subjects (i.e. unplanned admission cases)	212,187	307,276	358,570	197,385	128,241	195,311	335,259	165,470
Male index subjects (%)	99,926 (47.1%)	138,319(45.0%)	160,977 (44.9%)	90,258 (45.7%)	58,402 (45.5%)	88,532 (45.3%)	151,908 (45.3%)	82,445 (49.8%)
Index subjects' mean age at admission (years)	78.1	78.3	78.5	78.0	79.5	78.2	78.5	76.4
Index subjects exposed to main drug group (all)	26,088 (12.3%)	61,595 (20.0%)	45,772 (12.8%)	30,740 (15.6%)	44,730 (34.9%)	60,755 (31.1%)	192,674 (57.5%)	69,286 (41.9%)
Index subjects exposed to main drugs+indomethacin	216 (0.1%)	3,675 (1.2%)	1,117 (0.3%)	393 (0.2%)	498 (0.4%)	737 (0.4%)	2,166 (0.6%)	662 (0.4%)
Index subjects exposed to main drugs+naproxen	259 (0.1%)	6,741 (2.2%)	1,862 (0.5%)	819 (0.4%)	714 (0.6%)	1,232 (0.6%)	3,800 (1.1%)	1,174 (0.7%)
Index subjects exposed to main drugs+temazepam	3,994 (1.9%)	9,465 (3.1%)	10,477 (2.9%)	5,445 (2.8%)	7,553 (5.9%)	8,102 (4.1%)	27,098 (8.1%)	8,779 (5.3%)
Index subjects exposed to main drugs+oxazepam	1,018 (0.5%)	3,172 (1.0%)	3,261 (0.9%)	1,679 (0.9%)	2,142 (1.7%)	2,694 (1.4%)	8,834 (2.6%)	2,647 (1.6%)
Index subjects exposed to main drugs+diazepam	743 (0.4%)	2,692 (0.9%)	3,048 (0.9%)	1,349 (0.7%)	1,450 (1.1%)	2,105 (1.1%)	6,381 (1.9%)	2,176 (1.3%)
Index subjects exposed to main drugs+digoxin	8,312 (3.9%)	5,096 (1.7%)	4,006 (1.1%)	3,074 (1.6%)	34,122 (26.6%)	5,825 (3.0%)	23,836 (7.1%)	5,485 (3.3%)
Index subjects exposed to main drugs+amiodarone	2,997 (1.4%)	1,618 (0.5%)	1,532 (0.4%)	1,128 (0.6%)	11,632 (9.1%)	2,458 (1.3%)	8,614 (2.6%)	3,695 (2.2%)
Index subjects exposed to main drugs+ferrous sulphate	1,056 (0.5%)	2,104 (0.7%)	1,837 (0.5%)	1,086 (0.6%)	2,138 (1.7%)	1,827 (0.9%)	7,258 (2.2%)	1,926 (1.2%)

[a] Table entries for the medication exposure status provide the count and proportion (in parentheses) of index subjects considered exposed to the specified drugs at the time of admission. For the World Health Organization Anatomical Therapeutic Chemical (ATC) [40, 41] code specifications for the high-risk drug groups, please refer to *Price et al. (2013)*. [27] ATC definitions for the specified Beers potentially inappropriate medications are as follows: indomethacin (M01AB01); naproxen (M01AE02); temazepam (N05CD07); oxazepam (N05BA04); diazepam (N05BA01); digoxin (C01AA05); amiodarone (C01BD01); and ferrous sulphate (B03AA07, B03AD03).

[b] Domain participants for each sub-study were selected from an overall cohort of 251,305 individuals.

Table 2 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - adjusted odds ratios and estimates of hospital admissions attributed to drug exposure[a] for combinations of high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria[b]

Beers Criteria medication	Statistics	Anti-coagulants	Anti-rheumatics	Opioids	Cortico-steroids	Cardiac rhythm regulators	Beta-blockers	Hypertension drugs	Serum lipid-reducing agents
None (i.e. PIM	Adjusted odds ratio (OR)[c]	1.13	1.09	1.81	1.48	1.11	1.08	0.92	0.85
intake not	95% confidence interval	(1.07-1.19)	(1.06-1.12)	(1.75-1.88)	(1.42-1.54)	(1.07-1.15)	(1.05-1.11)	(0.90-0.94)	(0.82-0.88)
considered)	Attributed admissions (%)	2,960 (11.3%)	5,138 (8.3%)	20,539 (44.9%)	9,913 (32.2%)	4,360 (9.7%)	4,500 (7.4%)	-17,669 (-9.2%)	-12,323 (-17.8%)
Indomethacin	Adjusted odds ratio (OR)[c]	2.36	1.40	2.97	1.54	1.72	1.47	1.13	1.26
(Antirheumatic)	95% confidence interval	(1.43-3.90)	(1.27-1.54)	(2.40-3.67)	(1.12-2.11)	(1.31-2.25)	(1.21-1.80)	(1.00-1.28)	(1.01-1.56)
	Attributed admissions (%)	124 (57.6%)	1,048 (28.5%)	741 (66.3%)	137 (34.9%)	208 (41.9%)	236 (32.0%)	254 (11.7%)	135 (20.4%)
Naproxen	Adjusted odds ratio (OR)[c]	1.87	1.22	2.13	2.11	1.11	1.32	1.05	0.96
(Antirheumatic)	95% confidence interval	(1.26-2.79)	(1.14-1.31)	(1.81-2.51)	(1.69-2.64)	(0.90-1.35)	(1.14-1.53)	(0.96-1.14)	(0.82-1.11)
	Attributed admissions (%)	121 (46.6%)	1,216 (18.0%)	989 (53.1%)	431 (52.7%)	68 (9.6%)	299 (24.3%)	174 (4.6%)	-55 (-4.7%)
Temazepam	Adjusted odds ratio (OR)[c]	1.30	1.22	1.79	1.57	1.27	1.30	1.17	1.05
(Hypnotic/	95% confidence interval	(1.14-1.48)	(1.14-1.30)	(1.65-1.95)	(1.41-1.75)	(1.16-1.38)	(1.20-1.40)	(1.11-1.23)	(0.97-1.13)
sedative)	Attributed admissions (%)	915 (22.9%)	1,694 (17.9%)	4,630 (44.2%)	1,979 (36.3%)	1,592 (21.1%)	1,850 (22.8%)	3,898 (14.4%)	394 (4.5%)
Oxazepam	Adjusted odds ratio (OR)[c]	1.15	1.16	1.77	1.58	1.34	1.24	1.03	1.05
(Anxiolytic)	95% confidence interval	(0.90-1.47)	(1.05-1.29)	(1.54-2.03)	(1.33-1.88)	(1.16-1.55)	(1.10-1.40)	(0.95-1.11)	(0.92-1.20)
	Attributed admissions (%)	132 (13.0%)	440 (13.9%)	1,417 (43.4%)	617 (36.7%)	546 (25.5%)	523 (19.4%)	249 (2.8%)	126 (4.8%)
Diazepam	Adjusted odds ratio (OR)[c]	1.37	1.38	1.78	1.60	1.22	1.18	1.25	1.01
(Anxiolytic)	95% confidence interval	(1.05-1.78)	(1.23-1.54)	(1.55-2.04)	(1.32-1.93)	(1.03-1.44)	(1.03-1.34)	(1.15-1.37)	(0.88-1.15)
	Attributed admissions (%)	199 (26.8%)	737 (27.4%)	1,337 (43.9%)	505 (37.5%)	261 (18.0%)	317 (15.0%)	1,292 (20.3%)	15 (0.7%)
Digoxin	Adjusted odds ratio (OR)[c]	1.09	1.20	1.79	1.49	1.08	1.23	0.98	0.96
(Cardiac rhythm	95% confidence interval	(1.00-1.18)	(1.09-1.31)	(1.55-2.06)	(1.29-1.72)	(1.04-1.13)	(1.12-1.34)	(0.92-1.03)	(0.86-1.07)
regulator)	Attributed admissions (%)	672 (8.1%)	835 (16.4%)	1,767 (44.1%)	1,015 (33.0%)	2,586 (7.6%)	1,078 (18.5%)	-611 (-2.6%)	-240 (-4.4%)
Amiodarone	Adjusted odds ratio (OR)[c]	1.41	1.32	1.85	1.67	1.22	1.42	1.10	1.10
(Cardiac rhythm	95% confidence interval	(1.23-1.61)	(1.10-1.58)	(1.45-2.36)	(1.27-2.19)	(1.13-1.32)	(1.20-1.67)	(1.00-1.22)	(0.95-1.27)
regulator)	Attributed admissions (%)	865 (28.9%)	390 (24.1%)	703 (45.9%)	451 (40.0%)	2,098 (18.0%)	725 (29.5%)	790 (9.2%)	330 (8.9%)
Ferrous sulphate	Adjusted odds ratio (OR)[c]	1.54	1.24	1.62	1.50	1.16	1.46	1.08	0.98
(Iron preparation)	95% confidence interval	(1.22-1.95)	(1.09-1.42)	(1.35-1.94)	(1.21-1.85)	(1.00-1.34)	(1.26-1.69)	(0.99-1.17)	(0.85-1.15)
	Attributed admissions (%)	372 (35.2%)	407 (19.4%)	702 (38.2%)	362 (33.3%)	289 (13.5%)	574 (31.4%)	531 (7.3%)	-31 (-1.6%)

[a] Estimates of hospital admissions attributed to drug exposure in exposed index subjects (and corresponding proportions in parentheses) are shown in the table for each medication combination in rows labelled "Attributed admissions (%)'; proportion = attributable fraction (AF) = (OR-1)/OR and count = AF x number of index subjects exposed to PIM/HRD combination (as specified) at the time of hospital admission.

[b] For the World Health Organization Anatomical Therapeutic Chemical (ATC) [40, 41] code specifications for the high-risk drug groups, please refer to *Price et al. (2013)*.[27] ATC definitions for the specified Beers potentially inappropriate medications are as follows: indomethacin (M01AB01); naproxen (M01AE02); temazepam (N05CD07); oxazepam (N05BA04); diazepam (N05BA01); digoxin (C01AA05); amiodarone (C01BD01); and ferrous sulphate (B03AA07, B03AD03).

[c] Conditional logistic regression models were adjusted for the following time-dependent variables: nursing home status at the case or control time; hospital days, overall Charlson comorbidity index [52] and GP coverage percentage, all for the previous year; and a drug consumption profile for the preceding 90 days (plus the case or control date), which included the number of broad medication categories involved, the overall number of daily doses consumed (for any drug) and a count of daily doses for each broad drug category (except the high-risk drug group of interest).

Figure captions

Fig. 1 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - adjusted odds ratios and 95% confidence intervals for antirheumatics and cardiac rhythm regulators and for specific medications from the Beers Criteria included in these broad classes of high-risk drugs

Fig. 2 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - estimated proportions of hospital admissions attributed to drug exposure[a] for combinations of non-cardiovascular high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria

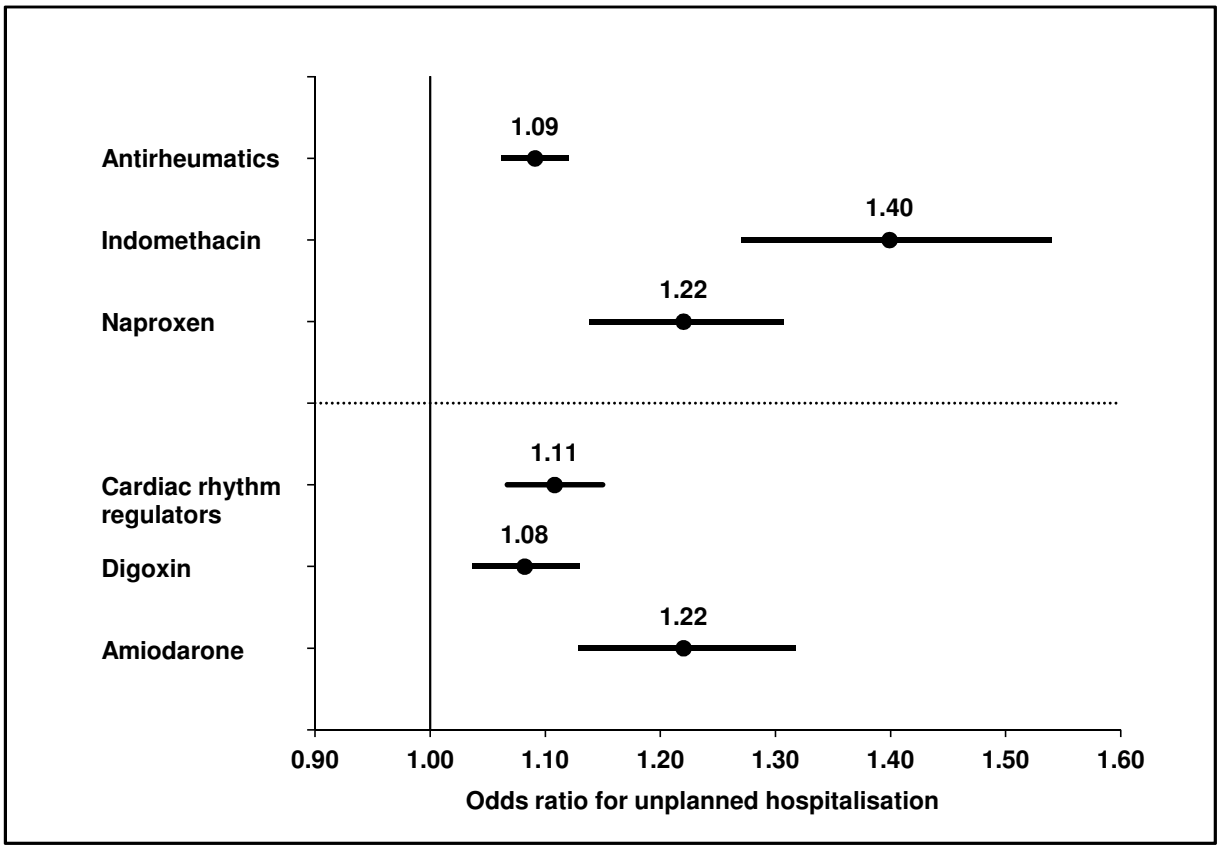
[a] Percentages shown in the diagrams represent estimated proportions of hospital admissions attributed to drug exposure in index subjects exposed to the main HRD group, overall or in combination with a given PIM (as specified); they are the attributable fractions (AFs) associated with the specified drug combination, where AF=(OR-1)/OR and OR=adjusted odds ratio.

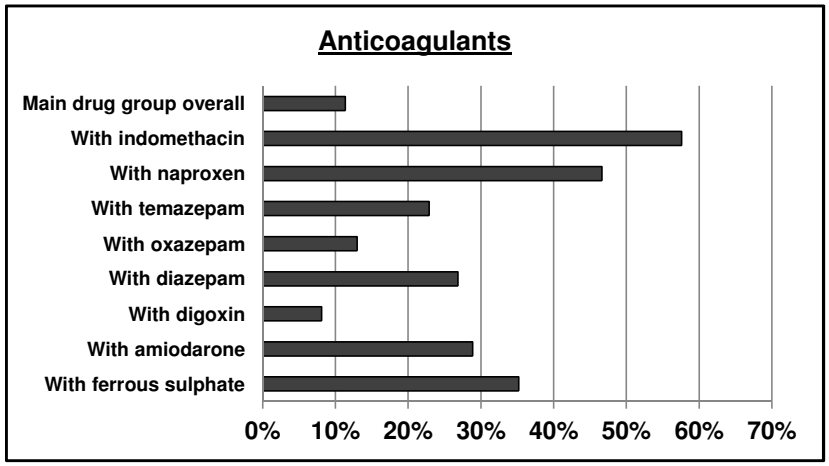
Fig. 3 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - estimated proportions of hospital admissions attributed to drug exposure[a] for combinations of cardiovascular high-risk drugs (HRDs) with specific potentially inappropriate medications (PIMs) from the Beers Criteria

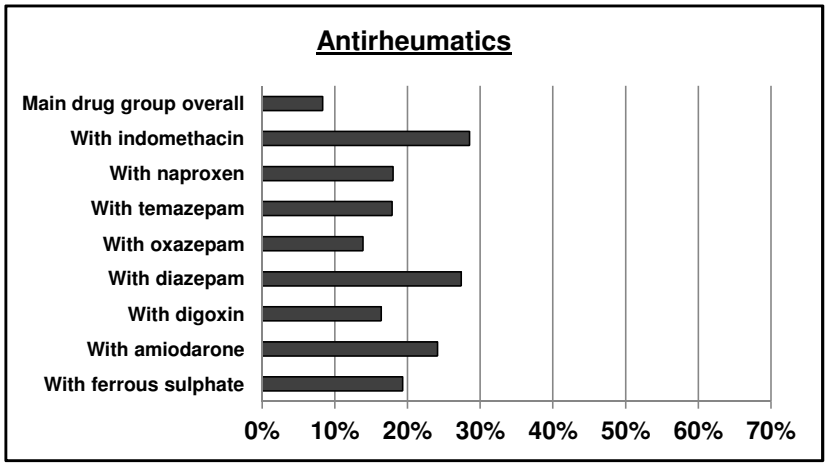
[a] Percentages shown in the diagrams represent estimated proportions of hospital admissions attributed to drug exposure in index subjects exposed to the main HRD group, overall or in combination with a given PIM (as specified); they are the attributable fractions (AFs) associated with the specified drug combination, where AF=(OR-1)/OR and OR=adjusted odds ratio.

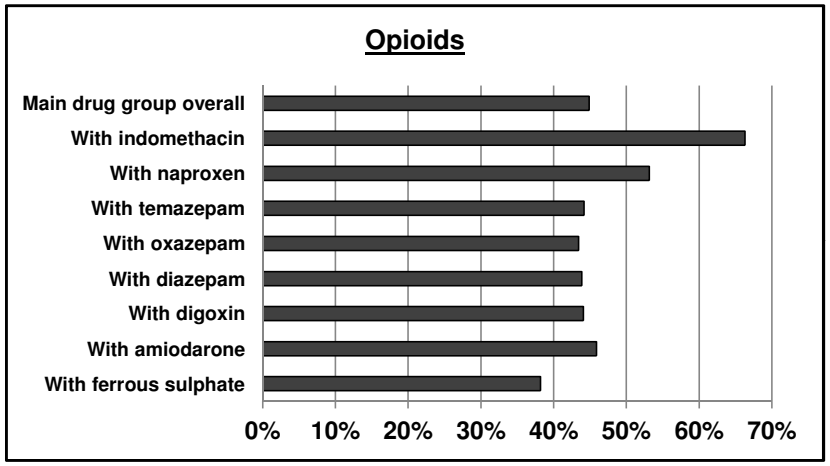
Fig. 4 High-risk medications and unplanned hospitalisations in Western Australian elderly (1993-2005) - differences[a] in the estimated counts of hospital admissions attributed to drug exposure with concurrent intake of specific potentially inappropriate medications (PIMs) from the Beers Criteria

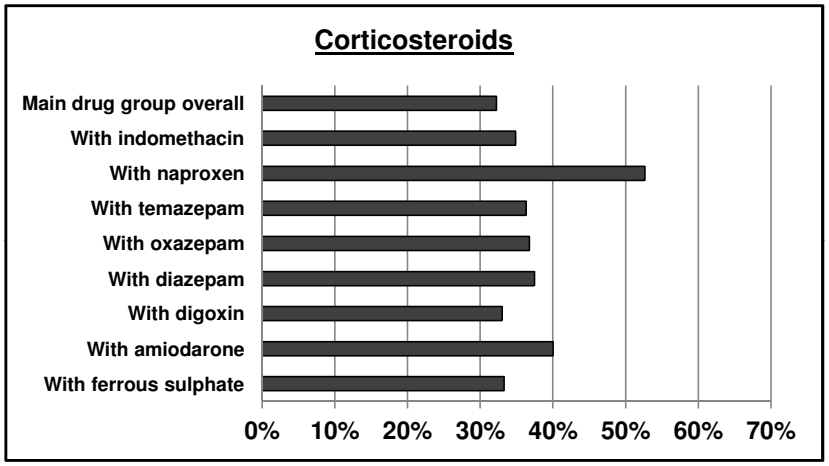
[a] The differences shown were obtained by subtracting the 'PIM-negative' estimates (i.e. counts of unplanned hospitalisations that would be expected if all index subjects exposed to a HRD were unexposed to the specified PIMs) from the 'PIM-refined' estimates (i.e. those obtained by applying more explicit attributable fractions (AFs) to subsets of index subjects exposed to HRDs depending upon their concurrent PIM exposure status). For cardiac rhythm regulators, the difference related to digoxin/amiodarone has been suppressed as 98% of index subjects exposed to cardiac rhythm regulators were taking at least one of these two PIMs.

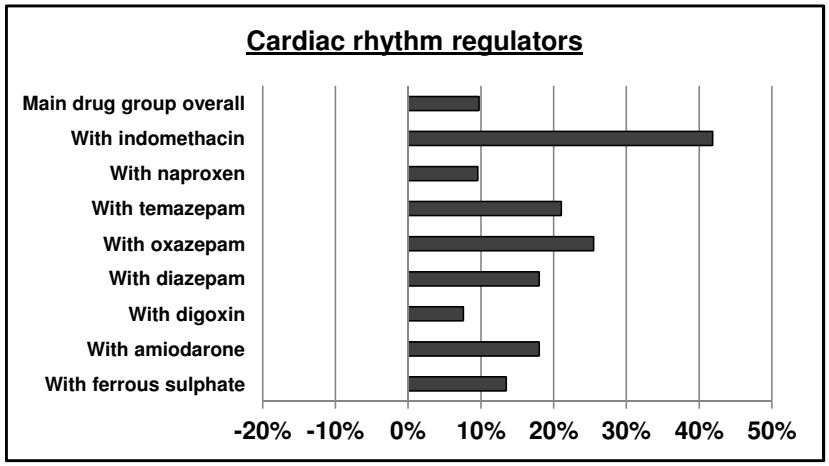

Antirheumatics
1.09
Indomethacin
1.40
Naproxen
1.22
Cardiac rhythm regulators
1.11
Digoxin
1.08
Amiodarone
1.22
0.90
1.00
1.10
1.20
1.30
1.40
1.50
1.60
Odds ratio for unplanned hospitalisation

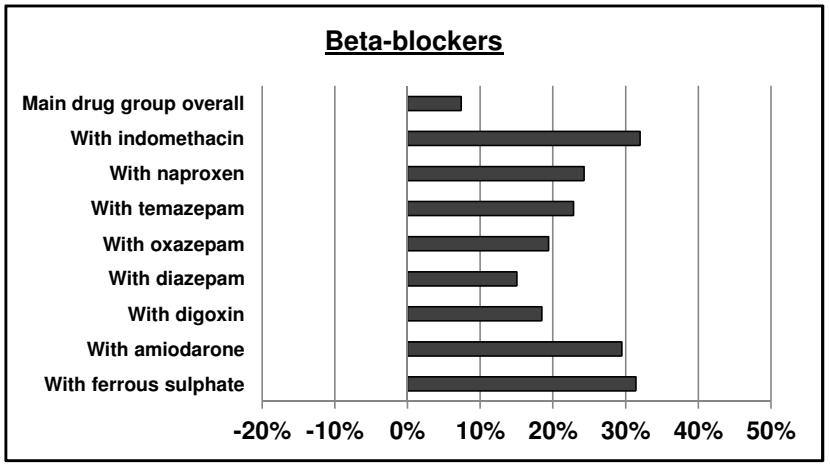

Anticoagulants
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
0%
10%
20%
30%
40%
50%
60%
70%

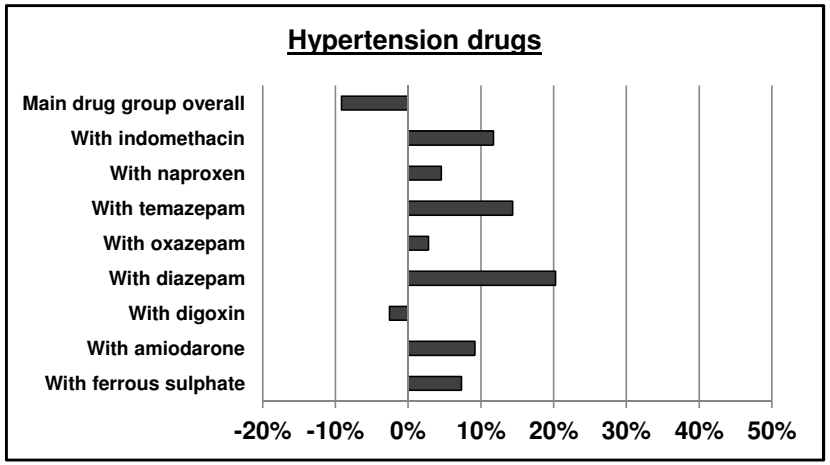

Antirheumatics
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
0%
10%
20%
30%
40%
50%
60%
70%

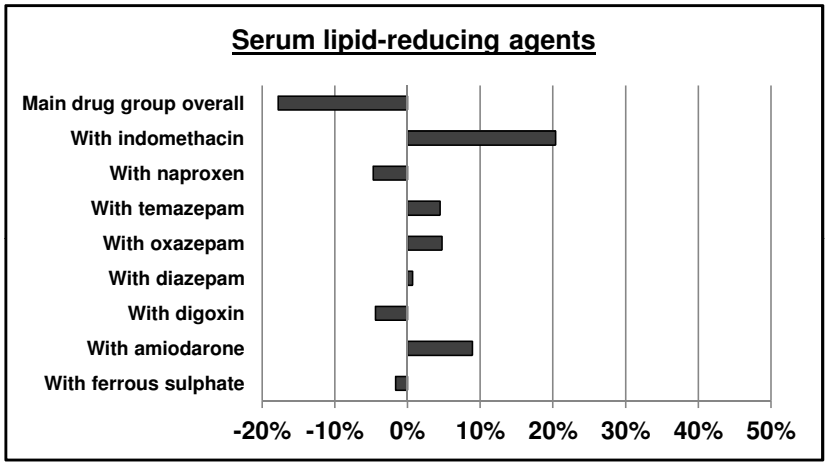

Opioids
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
0%
10%
20%
30%
40%
50%
60%
70%

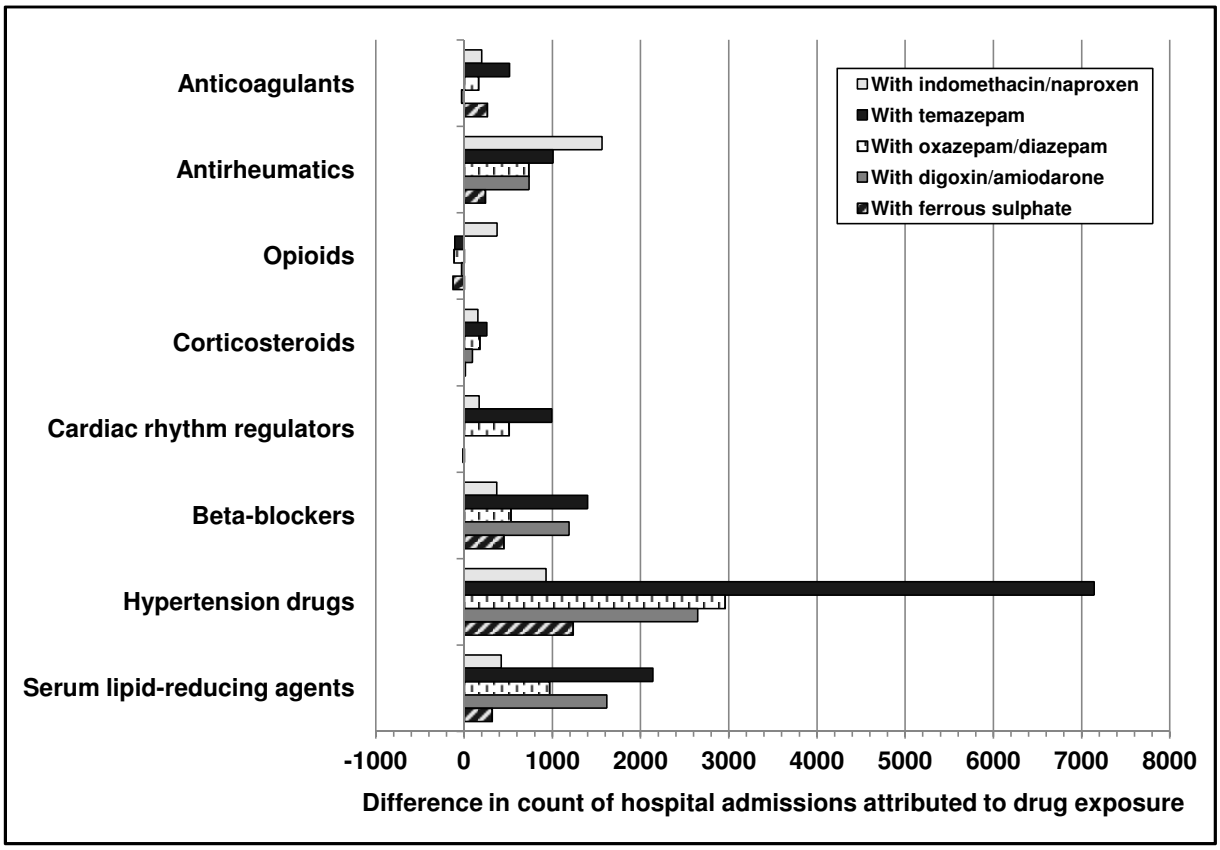

Corticosteroids
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
0%
10%
20%
30%
40%
50%
60%
70%


Cardiac rhythm regulators
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
-20% -10% 0% 10% 20% 30% 40% 50%


Beta-blockers
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
-20% -10% 0% 10% 20% 30% 40% 50%


Hypertension drugs
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
-20% -10% 0% 10% 20% 30% 40% 50%


Serum lipid-reducing agents
Main drug group overall
With indomethacin
With naproxen
With temazepam
With oxazepam
With diazepam
With digoxin
With amiodarone
With ferrous sulphate
-20% -10% 0% 10% 20% 30% 40% 50%


Anticoagulants
Antirheumatics
Opioids
Corticosteroids
Cardiac rhythm regulators
Beta-blockers
Hypertension drugs
Serum lipid-reducing agents
With indomethacin/naproxen
With temazepam
With oxazepam/diazepam
With digoxin/amiodarone
With ferrous sulphate
-1000
0
1000
2000
3000
4000
5000
6000
7000
8000
Difference in count of hospital admissions attributed to drug exposure

Author/s:
Price, SD; Holman, CDJ; Sanfilippo, FM; Emery, JD

Title:
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