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Association between potentially inappropriate medications from the Beers Criteria and the risk of unplanned hospitalization in elderly patients

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Running head: Beers PIMs & unplanned hospitalizations in elderly patients

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Abstract

BACKGROUND: Predisposition to adverse drug events with advancing age has led to the development of lists of potentially inappropriate medications (PIMs) to be avoided in the elderly, such as the Beers Criteria. The prevalence of Beers medications has been studied widely, but it is still unclear whether PIM use is predictive of adverse events in older people

OBJECTIVES: To examine potential associations between exposure to PIMs from the general Beers list and unplanned hospitalizations in elderly Western Australians.

METHODS: Using an enhanced case-time-control design and conditional logistic regression applied to the pharmaceutical claims and other linked health data of 251,305 Western Australians aged ≥ 65 years (1993-2005), odds ratios for unplanned hospitalization were obtained, from which attributable fractions, number and proportion of hospitalizations associated with drug exposure were derived.

RESULTS: Based on the health profiles of 383,150 hospitalized index subjects, overall PIM exposure was associated with an elevated risk of unplanned hospitalization (adjusted OR 1.18; 95% CI 1.15-1.21), this estimated risk increasing with the number of different PIMs and PIM quantity taken. Fifteen percent of unplanned hospitalizations in exposed index subjects (1,980 per year) were attributed to PIM exposure. Patients taking meperidine (pethidine), nitrofurantoin, promethazine, indomethacin, and thioridazine appeared to be at particularly high risk of unplanned hospitalization, whereas temazepam, oxazepam, diazepam, digoxin, amiodarone, ferrous sulphate, and naproxen were attributed the greatest numbers of unplanned hospitalizations.

CONCLUSIONS: Due caution prescribing Beers medications in the elderly seems justified, paying particular attention to PIMs listed above and to the concurrent use of multiple PIMs. Our results also support the retention of specific medications on PIM lists in future developments.

Introduction

Due to physiological deterioration, increasing comorbidities, polypharmacy and other age-related factors, adults generally become more susceptible to adverse drug events (ADEs) with advancing age.¹⁻³ In America, ADEs account for nearly 100,000 emergency hospitalizations each year in people aged ≥ 65 years.⁴ In Australia, 15-22% of unplanned hospitalizations are drug-related in this age group.⁵ This has led to the development of lists of ‘potentially inappropriate medications’ (PIMs) to be avoided in the elderly. Among them, the Beers Criteria⁶⁻⁹ are the most commonly referenced.

Numerous studies have examined the prevalence of medications from the Beers Criteria in elderly populations worldwide. However, it is still unclear whether the use of Beers medications is predictive of adverse events in older people. Earlier reviews¹⁰⁻¹² have concluded that the evidence linking medications from the Beers list with adverse health outcomes was generally weak and contradictory. Most of the reviewed studies used early versions (1991/97)^{6,7} of the Beers Criteria though and had important limitations. More recently, additional research projects based on Beers 2003⁸ have produced results supporting the association of PIM exposure with adverse outcomes in older people,¹³⁻²⁴ although these findings are far from universal. For example, research by Budnitz et al. estimated that only 6.6% of elderly Americans hospitalized due to ADEs following an Emergency Department visit were due to Beers medications.⁴ Many studies are still limited in terms of participant numbers, duration of study period or ability to control for important confounding factors. Furthermore, most of this research has concentrated on the effects of overall PIM exposure, with few studies reporting on the adverse outcomes of individual medications from the Beers list.

This paper presents the results of a large population-based linked-data study (1993-2005), which sought to identify associations between exposure to PIMs from the ‘general’ Beers list (i.e. excluding disease-specific PIMs) and unplanned hospitalizations in Western Australian (WA) residents aged ≥ 65 years. The study not only examined associations related to overall exposure to these medications, but also assessed the impact of concurrent exposure to multiple PIMs, and estimated unplanned hospitalization outcomes for each individual PIM. Although PIM use was defined according to the 2003 Beers Criteria,⁸ differences between the latter and the 2012 updated version⁹ are examined briefly in the paper’s Discussion, within the context of this study.

Methods

DATA LINKAGE AND COHORT SELECTION

This study linked Australian Pharmaceutical Benefits Scheme (PBS),^{25,26} Medicare^{27,28} and System for Payment of Aged Residential Care (SPARC)²⁹ data with inpatient, death and electoral roll records from the WA Data Linkage System³⁰ through probabilistic linkage. The study protocol was approved by The University of WA's Human Research Ethics Committee.

The cohort was restricted to people who were ≥ 65 years old by the end of 2004, continuously lived in WA during 1993-2005 (until death) and had at least one PBS prescription filled during that time, thus ensuring that those included in the study had ascertainable drug exposures. Ninety-two percent of people who met these criteria participated in the study, the remainder excluded due to problem data (e.g. records post-death, no gender on any record). Our ultimate cohort captured 80-85% of WA residents aged ≥ 65 years.

ESTABLISHMENT OF DRUG REFERENCE DATABASE

Details of all drug items from available PBS schedules (August 1991-June 2007)³¹ were assembled into a large reference database. Relevant prescription details were extracted from the last published entry for each item. Anatomical Therapeutic Chemical (ATC) codes were reconciled with the 2007 World Health Organization (WHO) ATC classification.³²

Since PBS claims did not include the prescribed dose, average daily doses for each item were determined from comparisons between average prescribed daily doses from the Australian Bettering the Evaluation and Care of Health (BEACH)³³ general practice data, the MIMS Australia³⁴ registered drug information and the 2008 WHO ATC Defined Daily Doses (DDDs),³⁵ according to drug form, route and strength. Furthermore, each drug's elimination half-life was obtained (predominantly from MIMS),³⁴ from which the period of drug effect, defined as five times the drug's half-life,^{36,37} was estimated.

DEFINITION OF DRUG GROUPS AND DOMAINS

To identify medications of interest, each item from the 2003 Beers list⁸ was defined according to the 2007 ATC classification.³² Once patient and drug reference variables had been merged to the PBS master data file for 1993-2005, the ATC code list for 'general' PIMs (i.e. excluding disease-specific criteria, but including PIMs with dosage or duration constraints irrespective of the dose/duration likely prescribed) was applied to determine which of these PIMs were supplied to WA residents aged ≥ 65 years during the study period. Forty of the 43

individual drugs identified through this process were included in the study and grouped into 20 broad drug classes (corresponding to 20 drug-defined domains of exposed patients) as per Table 2, each class consisting of medications used to treat similar conditions to those treated by related PIMs. Diphenhydramine, dicyclomine, and oestriol were omitted from the analysis due to very low prevalence.

CASE-TIME-CONTROL DESIGN

Associations between PIMs and unplanned hospitalizations were expressed as odds ratios (ORs) obtained from a case-time-control design.^{38,39} This approach involved index subjects that acted both as cases and as their own historical controls, while background time trends in exposure due to ageing, natural disease progression and treatment patterns were adjusted using similarly constructed case and control observation windows in a reference group drawn from the same drug-defined domain of patients as the index subjects. In this instance, the domain for each PIM included everyone in the study cohort who had ever been prescribed a drug from the PIM's broad medication class during 1993-2005. The motivation for restriction of reference group sampling to the same patient domain as each index subject was to achieve enhanced comparability between index and reference observations, thus reducing the potential for differential exposure time trends under the null hypothesis, a problem that may affect poorly constructed case-time-control designs.^{40,41} Essentially, the approach conferred advantages similar to those of a case-case-time-control design,^{40,41} but rather than conditioning on all patients sustaining observed outcomes, our design achieved a similar ends of a relatively homogenous study base by restricting each analysis to members of the same drug-defined patient domain.

Index subjects were patients within the drug-defined domain who had experienced an unplanned (i.e. emergency) hospital admission between 1 July 1994 and 31 December 2005 whilst aged ≥ 67 years, thus ensuring sufficient lead-up time for the control observation period. Many individuals were included in the analysis as multiple index subjects, although a few ($\leq 0.1\%$) with >50 index admissions were excluded due to concerns about representativeness. Two records were created for each index subject, one representing the 'case time' (i.e. the admission date) and the other the 'control time' (usually 365 days before the admission date but, if the patient was in hospital at this preferred control time, the admission date of that earlier hospitalization was used instead).

Each index subject was matched by gender, general practitioner (GP) coverage category and year of birth to a randomly selected reference subject from the drug-defined domain. For GP coverage, each GP visit identified in the Medicare dataset was allocated a 'coverage' period of 61 days (overlapping periods for each patient being merged together), from which patients' number and proportion of 'GP coverage' days over the study period was ascertained. Categories were then derived, loosely based on related quartiles. For year of birth, subjects born prior to 1900 were allocated a birth year of 1900 for matching purposes only. 'Case time' and 'control time' records were created for each reference subject as per the corresponding index subjects, matching the case and control dates as closely as possible.

Once created, the case and control time records for index and reference subjects were populated with the variables required to control for potential confounding, including nursing home status at the time specified on the record (i.e. case or control time); hospital days, overall Charlson comorbidity index⁴² 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.

Additionally, PBS records were checked to ascertain exposure status at each case and control date. If a prescription was found for a PIM of interest and if the time period bound by its supply date and exposure effect end date overlapped with the case or control time, the PIM's exposure status was set to 'exposed'. The end date was calculated by adding the number of drug consumption days associated with the script (i.e. total drug 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 indicated the potential for a hospital admission at the case or control time to have resulted from the effects of PIM exposure.

For each PIM sub-study, conditional logistic regression models with robust analysis of variance were applied using the SAS 9.2 PHREG procedure, with the COVS option and stratification based on a unique identifier for each subject. The baseline model included the binary exposure variable and the cross-product between exposure and the binary index/reference indicator, the OR of primary interest being derived from the coefficient of this interaction term.³⁸ The adjusted model controlled for all health and drug consumption indicators mentioned earlier, excluding the three-month count of 'daily doses' for the PIM of interest.

The analysis was repeated for each individual PIM and for all PIMs combined. For the latter, drug consumption adjustments covered all medications, including PIMs. Furthermore, additional regression models were applied to the overall PIM study, substituting the PIM exposure dichotomous variable with the number of different PIMs and the total number of PIM ‘daily doses’ taken in the three-month period prior to the case or control time. These model variations enabled the estimation of effects of PIM polypharmacy and dose-response, respectively.

ESTIMATION OF UNPLANNED HOSPITALIZATIONS ATTRIBUTED TO PIMS

Using the OR derived from the interaction term in the adjusted model described above, it was possible to calculate the attributable fraction (AF), in the form of an incidence density fraction, of unplanned hospitalizations associated with each PIM within the exposed, where $AF = (OR - 1) / OR$. An estimate of the number of unplanned hospitalizations attributed to each medication was then derived as $AF \times$ the number of exposed index subjects.^{43,44}

IDENTIFICATION OF ADE-RELATED HOSPITALIZATIONS FROM ICD CODES

For comparison, the count of ADE-related unplanned hospitalizations in cohort members considered exposed to each PIM was determined based on relevant ICD external cause codes for accidental drug poisoning and adverse drug reactions^{45,46} recorded on inpatient discharge summaries. These derivations more closely reflected the conventional approach for identifying ADE-related hospitalizations using inpatient data. However, other studies would not necessarily have restricted their hospitalization counts to exposed patients as exposure status is not always readily available.

Results

Table 1 presents summary results for the overall study of associations between PIM exposure and unplanned hospitalizations. From an initial cohort of 251,305 participants, 245,436 (97.7%) had either taken a PIM from the ‘general’ Beers list during 1993-2005 or a drug used to treat conditions similar to the indications for prescribing these PIMs. They comprised the patient domain for this study. Of these, 187,616 (76.4%) had actually been prescribed a PIM. Overall, 383,150 unplanned hospitalizations (‘index subjects’) were included, which involved 120,332 patients. Index subjects were 45.5% males, their mean age was 78.4 years, and 149,289 (39.0%) were considered exposed to a PIM at the time of admission.

Exposure to a PIM was associated with a significant increase in unplanned hospitalizations - odds ratio (OR) 1.18; 95% confidence interval (CI) 1.15-1.21, after adjusting for general time trends (through the inclusion of reference subjects), and changes in patients' health profile and medication intake over time. Based on the derived attributable fraction, 15.3% (13.3-17.1%) of unplanned hospitalizations were attributed to PIMs in exposed subjects, yielding 22,773 (19,922-25,500) hospitalizations from July 1994 to December 2005 (1,980 per year). By comparison, only 9,172 of the exposed index subjects (6.1%) had an International Classification of Diseases (ICD) external cause code related to ADEs on their inpatient summary record over the same period.

The estimated risk of unplanned hospitalization depended on both the number of different PIMs taken and the PIM quantity consumed. For instance, the OR increased progressively from 1.18 (95% CI 1.16-1.19) to 5.07 (4.42-5.81) as the number of different PIMs increased from one to ten in the three-month period preceding a potential hospital admission (Figure 1). Similarly, the OR rose from 1.00 (1.00-1.00) to 2.20 (1.83-2.63) when a total of one to 900 PIM 'daily doses' were taken over the same time period (Figure 2).

Table 2 provides summary results for all general PIMs prescribed in our cohort during 1993-2005 (excluding diphenhydramine, dicyclomine, and oestriol due to very low prevalence). The number of participants in each drug-defined domain varied, ranging between 115 (psychostimulants) and 193,196 (hypertension medications), as did the number of index subjects (between 390 and 358,570 for the corresponding domains). Thirteen of the 20 domains yielded >100,000 index subjects, and all but one produced >25,000. Twenty-five of the 40 PIMs were associated with >1,000 'exposed' index subjects (i.e. those considered exposed to the drug of interest at the time of hospital admission), although the number of exposed index subjects was also wide-ranging - from 28 (hydroxyzine) to 34,122 (digoxin).

Most adjusted ORs derived from the case-time-control design were above one, suggesting that exposure to individual PIMs was generally associated with a higher risk of unplanned hospitalization. However, our results were not all statistically significant, in some instances possibly due to insufficient power. Adjusted ORs tended to be similar to or lower than the corresponding unadjusted ORs, but not always.

Statistical significance was achieved for sixteen PIMs (Figure 3). Of these, fourteen were associated with an increase in unplanned hospitalizations, with adjusted ORs ranging between 1.07 (1.03-1.11) for digoxin (a cardiac glycoside) and 2.37 (1.25-4.50) for

meperidine/pethidine (an opioid analgesic more frequently prescribed to WA inpatients than to those in a community setting). Other PIMs associated with an elevated hospitalization risk included indomethacin and naproxen (non-steroidal anti-inflammatory drugs); promethazine (systemic antihistamine); thioridazine (antipsychotic); oxazepam and diazepam (anxiolytics); temazepam (hypnotic sedative); amiodarone (cardiac rhythm regulator); ferrous sulphate (iron supplement); bisacodyl (laxative); oxybutynin (urinary antispasmodic); and nitrofurantoin (urinary tract antibacterial). Nifedipine, a calcium channel blocker (OR 0.89; 0.83-0.95), and conjugated oestrogens (OR 0.89; 0.80-0.98) appeared to have a protective effect against unplanned hospitalizations.

Figure 4 presents estimates of the number and proportion of unplanned hospitalizations attributed to the drug of interest in exposed index subjects, for PIMs associated with a significantly higher risk of hospitalization. The proportion of unplanned hospitalizations attributed to these PIMs (in the exposed) ranged from 6.3% (2.4-10.1%) for digoxin to 57.8% (19.9-77.8%) for meperidine/pethidine, although most proportions were between 13% and 33%. The estimated number of unplanned hospitalizations attributed to each of these 14 PIMs in our study population (July 1994 to December 2005) ranged between 97 (meperidine/pethidine) and 5,144 (temazepam). The most commonly prescribed PIMs tended to yield higher counts of unplanned hospitalizations, despite not necessarily having the highest proportions of hospitalizations attributed to drug exposure. Temazepam, oxazepam, diazepam, digoxin, amiodarone, and ferrous sulphate were all associated with >100 unplanned hospitalizations per year, naproxen closely following at 99 per year. These counts arose in a population averaging approximately 167,000 residents aged ≥ 65 years annually.

Discussion

PRINCIPAL FINDINGS

Using linked health data, this study applied a case-time-control design to a large population of elderly Western Australians to examine associations between PIMs from the general Beers' list and unplanned hospitalizations. In our study, overall PIM exposure was associated with an elevated risk of unplanned hospitalization (adjusted OR 1.18; 1.15-1.21), this risk increasing with the number of different PIMs and PIM quantity taken. Fifteen percent of unplanned hospitalizations in exposed index subjects (1,980 per year) were attributed to PIM exposure.

Sixteen PIMs demonstrated a statistically significant effect on unplanned hospitalizations, which appeared protective for two drugs - nifedipine and conjugated oestrogens. Of the 14 others, meperidine (pethidine) was associated with the highest risk of unplanned hospitalization (adjusted OR 2.37; 1.25-4.50), whilst exposure to nitrofurantoin, promethazine, indomethacin, thioridazine, temazepam, diazepam, oxazepam, amiodarone, naproxen, ferrous sulphate, oxybutynin, bisacodyl, and digoxin appeared to increase the likelihood of unplanned hospitalization by 7-50%, depending on the drug. Furthermore, 6-58% of unplanned hospitalizations in exposed index subjects were considered attributable to exposure to each of these 14 PIMs. PIMs attributed the greatest hospitalization counts included temazepam, oxazepam, diazepam, digoxin, amiodarone, ferrous sulphate, and naproxen.

We were unable to ascertain from our research why certain PIMs were associated with a greater risk of unplanned hospitalization than other drugs. Our methods were more likely to detect a significant risk for more common high-risk drugs, for medications with serious adverse outcomes, and for those associated with acute rather than long-term effects. Many of the PIMs we have highlighted have strong sedative properties and other symptoms related to the central nervous system, which could potentially have led to confusion, disorientation, and ultimately falls and fractures. Alternatively, the cause of related cognitive problems may have been difficult to detect, and patients may have been hospitalized for further investigation. Other PIMs of interest were associated with heart and renal complications, which are often quite serious and also have multiple causal pathways. Further research in this area, beyond the scope of our study, seems justified.

COMPARISON WITH OTHER STUDIES

A number of recent investigations based on the 2003 Beers list have provided some evidence in support of adverse health outcomes related to PIM exposure,¹³⁻²⁴ despite inconclusive results from earlier reviews.¹⁰⁻¹² If we specifically focus on the likelihood of hospitalization, three American studies,^{14,22,23} each involving several thousands of elderly people, reported significantly higher rates of hospitalizations in patients taking Beers medications. Fick et al.¹⁴ also demonstrated that PIM users were much more likely to have problems directly related to their medication, whereas Albert et al.²² showed an association between hospitalization risk and both the number of PIMs prescribed and recency of PIM use. Conversely, Budnitz et al. estimated that only 6.6% of elderly Americans hospitalized due to ADEs following an

emergency department (ED) visit were due to Beers medications.⁴ However, cases included in the Budnitz study were those explicitly attributed to drug use by the treating clinician and two-thirds related to unintentional drug overdose. Given the ambiguous nature of some medication side-effects, some of which are associated with multiple causes, it is possible that the Budnitz study was too restrictive, concentrating on ADEs with very obvious links to drug exposure, such as unintentional drug overdoses. This would include bleeding in relation to warfarin and oral antiplatelet agents, as well as hypoglycemia in relation to insulins and oral hypoglycemic agents, which were likely more readily recognized by physicians.

Two Taiwanese studies, one involving 574 ambulatory care patients¹⁶ and the other ~1.5 million ED presentations,¹⁷ both concluded that exposure to Beers medications was linked to an increased risk of hospitalization, the first reporting an adjusted OR of 1.62 (1.04-2.53) for PIM users and the other demonstrating a significantly higher mean count of hospitalizations over a one-year period in patients prescribed PIMs during ED visits. Similarly, a one-year Japanese study²⁴ revealed a 68% higher rate of hospitalization and a 33% increase in medical costs in patients prescribed Beers medications. Furthermore, Ruggiero et al.²⁰ found higher odds of hospitalization in Italian nursing home residents using PIMs from the Beers list, particularly in those taking ≥ 2 PIMs (OR 1.73; 1.14-2.60).

Passarelli et al.⁴⁷ initially reported that exposure to Beers' 2003 PIMs was a strong predictor of ADEs (OR 2.32; 1.17-4.59) in Brazilian inpatients aged ≥ 60 years, although only 11.3% of these ADEs were the likely cause of hospitalization. A subsequent study in the same setting failed to extend this association to ADE-caused hospitalizations, however.⁴⁸ Similarly, in an Irish study of 597 acute hospitalizations, Gallagher et al.¹⁵ first reported that nearly half the patients exposed to Beers medications were admitted due to an ADE related to their PIM exposure. Yet, this seemingly strong link between Beers PIMs and ADE hospitalizations could not be replicated in later investigations in the same environment.^{49,50}

With one exception, our elderly cohort was much larger than that of other studies. This not only increased the overall power of our study, but also allowed us to investigate the apparent effects of individual PIMs, the impact of multiple PIMs, and dose-response effects, which most other investigations could not achieve reliably. Moreover, some of the other studies did not attempt to ascertain the PIM exposure status of patients at the time of admission as we have, and most were not restricted to unplanned hospitalizations. However, Fick et al.,¹⁴ Budnitz et al.,⁴ as well as the Irish^{15,49,50} and Brazilian^{47,48} research, sought to identify explicitly the hospital-related events that likely resulted from adverse drug effects, which we

were unable to achieve due to study limitations. This design variation, as already mentioned, may not necessarily have been a weakness in our study, given that explicit selection of cases known to be ADE-related may be too restrictive. In any event, although our case-time-control design was different to the approaches used elsewhere, our ORs were similar to comparable results from other studies.

STRENGTHS AND LIMITATIONS

A strength of our study is its large sample sizes. This generated narrow confidence intervals for the overall PIM study and for a number of the sub-studies within drug-defined domains. Admittedly, for some of the more specialized medications, especially those less commonly prescribed, confidence limits were still fairly wide.

Additionally, unlike the more conventional method of examining ICD external cause codes on inpatient records to identify potential ADEs, our approach took patients' drug exposure status upon admission into account and was able to examine individual medications (not being constrained by broad ICD categories).

Furthermore, our study applied three levels of defence against confounding: a crossover configuration to control for fixed confounders (known and unknown); matched reference subjects selected from a group taking medications with similar indications to the PIMs of interest to control for unmeasured and unknown time-variant confounders; and regression modelling to adjust for measured patient-specific time-variant confounders (e.g. health and medication profile over time). Although these measures may not have fully controlled for the potential time-trend bias associated with the basic case-time-control design (e.g. reverse causation bias),^{38,39,51} our preliminary work in this field, which applied sensitivity analysis, stratification and negative controls in our regression models, has demonstrated superior internal validity compared with the standard case-control and case-crossover designs, and the basic case-time-control design without adjustment for measurable time-variant confounders.⁵² Analogous to the case-case-time-control design,^{40,41} we restricted the sampling frame for reference subjects to the same drug-defined domain as each index subject to confer an important advantage by more complete adjustment for time-trend bias.

Difficulties in the ascertainment of drug exposure at the specific times of interest were also of concern, as no information was available on the daily dose specifically prescribed for each dispensed drug, nor on patient compliance. 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. Assuming similar levels of exposure misclassification at both ‘case time’ and ‘control time’ for each subject (i.e. non-differential measurement error), our estimated ORs may possibly have been attenuated slightly (i.e. pushed towards null) as a result,⁵³ perhaps counter-balancing some of the OR inflation resulting from unadjusted reverse causation bias.

Furthermore, our pharmaceutical data had some coverage limitations. It excluded drugs prescribed in public hospitals, over-the-counter medications, and prescriptions for which a pharmaceutical claim could not be made. However, unlike other situations described in the literature,⁵⁴ the problem of a ‘sick-stopper’ effect from unmeasured exposure during inpatient care was reduced in this study by the use of unplanned hospitalization (not death) as the outcome and avoidance of exposure ascertainment windows that overlapped inpatient stays. Moreover, in our population of elderly people, most of whom would have had very low co-payment requirements, these coverage issues unlikely impacted on study results to any great extent, as most non-hospital scripts for medications of interest would have been recorded in this age group.

THE 2012 BEERS CRITERIA UPDATE

In April 2012, the American Geriatrics Society published an updated version of the Beers Criteria.⁹ Although resource constraints have prevented us from repeating our analysis with these more recent definitions, we believe that most of our results would still be applicable with the current Beers list. Of the PIMs included in our study, only five have been removed from the latest Beers update. Two (propoxyphene and ethacrynic acid) are no longer or seldom prescribed⁵⁵ (in America and Australia). They are examples of some of the PIMs for which the lack of statistical significance in our results may possibly reflect a low prevalence of exposure rather than a low risk of unplanned hospitalization. Due to their low prevalence, it is also unlikely that exclusion of these drugs from the list of Beers medications would affect our overall results (i.e. for all PIMs) to any great extent.

Two other drugs (ferrous sulphate and fluoxetine) were omitted because related concerns are not restricted to older patients.⁵⁵ Since our study only included people aged ≥ 65 years, we are unable to compare estimated risks for these PIMs between older and younger adults. Our results do suggest an elevated risk of unplanned hospitalization in older people taking ferrous sulphate, although this is less clear for fluoxetine. These Beers exclusions are worth highlighting, especially in relation to the Budnitz findings.⁴ The Beers Criteria list

medications for which elderly patients are at greater risk of ADEs than other adults, a fact that is often forgotten. We suspect that the subsets of antithrombotics and diabetes medications identified by Budnitz as high-risk drugs in the elderly in relation to emergency hospitalization may have been omitted from the 2003 Beers list not because they were considered low-risk in older people, but because they were judged equally problematic in both young and older adults. Would clinicians more readily endorse a PIM list for the elderly if it incorporated all medications associated with a high risk of potential harm in older people, including those that are also problematic in younger adults? This point may warrant further debate.

Of the five PIMs on our list that were omitted from the 2012 Beers Criteria, bisacodyl was the only one excluded due to insufficient evidence.⁵⁵ This is interesting, since we have estimated a 15% (95% CI 4-26%) increase in unplanned hospitalization in elderly patients taking this medication. Should other studies report similar results, bisacodyl may perhaps find its way back onto the Beers list.

The revised Beers Criteria also include a number of new medications, most of which are drugs that were introduced to the American market in the last decade. As many belong to the same drug classes as PIMs from the 2003 Beers Criteria, they may be associated with similar risks as related PIMs from the previous version, but not necessarily. One may argue that, being newer they are likely safer. However, given the more rigorous approach to the selection of Beers medications in this latest round, we suspect that some new drugs may also be associated with quite high risks or potential harm in older people. It is beyond the scope of this paper to examine them all individually. Obviously, future studies in this area should include these more recent PIMs in their research protocols, as well as disease-specific PIMs, when feasible. Of particular interest is the estimated effect of sliding-scale insulin treatment, which now appears on the current Beers list.

CONCLUSIONS

Medications listed in the Beers Criteria have long been the subject of ongoing debate. Do we prevent harmful effects by avoiding them (where possible) in elderly patients? Our study adds support to the mounting evidence that PIMs from the 2003 Beers Criteria are associated with adverse outcomes, especially in relation to general PIMs (i.e. drugs to be avoided in all elderly patients) and their association with unplanned hospitalizations. Moreover, our study has identified 14 individual PIMs linked to a significantly high risk of unplanned hospitalization, exposure to which may possibly account for up to one third or even one half

of all unplanned hospitalizations in exposed elderly patients. Thus, restraint when considering prescribing Beers medications in the elderly seems justified, paying particular attention to PIMs associated with a high risk of hospitalization and to the concurrent use of multiple PIMs. In situations where these drugs cannot be avoided, older patients should be monitored closely.

For countries developing their own criteria for medications deemed potentially inappropriate in the elderly, our results highlight particular drugs to consider in the development of these criteria.

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Tables

Table 1 Potentially inappropriate medications (PIMs) in Western Australians aged ≥ 65 years (1993-2005)^a: associations between exposure to any PIM and unplanned hospitalizations

Statistics	Results
Individual participants ^b (number of people in study cohort)	245,436
Number/proportion of participants contributing as index subjects	120,332 (49.0%)
Number of index subjects (i.e. unplanned hospitalization cases)	383,150
Number/proportion of male index subjects	174,453 (45.5%)
Index subjects' mean age at hospital admission (years)	78.4
Number of exposed index subjects (Exp Idx) & proportion	149,289 (39.0%)
Unadjusted odds ratio (Unadj OR) ^c	1.31 (1.28-1.33)
Unadjusted odds ratio p-value	<0.0001
Adjusted odds ratio (OR) ^c	1.18 (1.15-1.21)
Adjusted odds ratio p-value	<0.0001
Attributable fraction: $AF = (OR-1) / OR$ (%) ^c	15.3% (13.3-17.1%)
Estimate of index hospitalizations attributed to PIM ($AF \times \text{Exp Idx}$) ^c	22,773 (19,922-25,500)
Number/proportion of exposed index subjects with drug ecode ^d	9,172 (6.1%)

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥ 67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b Individual participants were those who took medications used to treat similar conditions to those indicated for any of the PIMs included in the study (i.e. medications from the same broad drug classes and corresponding drug-defined domains); these people were considered to be part of the study's population at risk.

^c 95% confidence interval shown in parentheses

^d Exposed index subjects with drug ecode refers to hospitalizations among index subjects who were exposed to a general PIM from the Beers list at the time of admission and for which any ICD external cause code (ecode) related to accidental poisoning or adverse drug effect was recorded on the corresponding inpatient discharge summary. Acceptable codes included those in the ranges E850-E858 and E930-E949 (ICD-9-CM)⁴⁵ or X40-X44 and Y40-Y59 (ICD-10-AM).⁴⁶

Table 2 Potentially inappropriate medications (PIMs) in Western Australians aged ≥65 years (1993-2005)^a: associations between exposure to individual PIMs and unplanned hospitalizations

Domain drug class	PIM	Participants ^b	Index subjects ^c	Index exposure ^c	Unadjusted OR ^d	Adjusted OR ^d	PIM attribution ^e
Antirheumatics	Indomethacin	174,585	307,276	3,675 (1.2%)	1.36 (1.25-1.48)	1.38 (1.25-1.52)	1,008 (27.4%)
	Naproxen			6,741 (2.2%)	1.21 (1.14-1.29)	1.20 (1.12-1.29)	1,138 (16.9%)
	Piroxicam			5,487 (1.8%)	0.97 (0.90-1.03)	1.01 (0.94-1.09)	76 (1.4%)
Analgesics	Dextropropoxyphene	193,196	358,570	211 (0.1%)	1.16 (0.77-1.75)	1.24 (0.78-1.98)	41 (19.6%)
	Meperidine/pethidine			168 (<0.1%)	2.59 (1.46-4.59)	2.37 (1.25-4.50)	97 (57.8%)
	Orphenadrine	10,017	27,545	33 (0.1%)	1.43 (0.60-3.40)	1.14 (0.44-2.96)	4 (12.4%)
Anti-Parkinson drugs	Hydroxyzine	25,064	68,355	28 (<0.1%)	1.10 (0.35-3.44)	1.05 (0.25-4.45)	1 (4.3%)
Antihistamines (systemic)	Cyproheptadine			1,492 (2.2%)	1.08 (0.96-1.23)	1.08 (0.95-1.24)	112 (7.5%)
	Promethazine			886 (1.3%)	1.49 (1.25-1.77)	1.50 (1.24-1.81)	294 (33.2%)
	Thioridazine	79,914	188,508	1,058 (0.6%)	1.30 (1.09-1.54)	1.35 (1.11-1.63)	273 (25.8%)
Antipsychotics	Oxazepam	60,497	146,960	14,988 (10.2%)	1.29 (1.22-1.36)	1.22 (1.15-1.30)	2,743 (18.3%)
Anxiolytics, hypnotics/sedatives	Alprazolam			1,229 (0.8%)	1.23 (1.01-1.49)	1.16 (0.94-1.43)	171 (13.9%)
	Diazepam			10,963 (7.5%)	1.34 (1.27-1.42)	1.26 (1.18-1.34)	2,241 (20.4%)
	Temazepam			24,125 (16.4%)	1.35 (1.29-1.41)	1.27 (1.21-1.34)	5,144 (21.3%)
Antidepressants	Amitriptyline	90,128	215,207	8,922 (4.1%)	1.11 (1.04-1.18)	1.07 (0.99-1.14)	545 (6.1%)
	Doxepin			4,958 (2.3%)	1.03 (0.94-1.12)	1.01 (0.92-1.12)	64 (1.3%)
	Fluoxetine			2,870 (1.3%)	1.08 (0.96-1.22)	1.07 (0.93-1.22)	180 (6.3%)
Psychostimulants	Dexamphetamine	195	390	56 (14.4%)	1.62 (0.74-3.52)	1.27 (0.49-3.28)	12 (20.9%)
Cardiac rhythm regulators	Disopyramide	39,596	128,241	168 (0.1%)	1.00 (0.63-1.59)	1.24 (0.77-1.99)	32 (19.2%)
	Digoxin			34,122 (26.6%)	1.12 (1.08-1.17)	1.07 (1.03-1.11)	2,143 (6.3%)
	Amiodarone			11,632 (9.1%)	1.28 (1.19-1.37)	1.21 (1.12-1.30)	2,003 (17.2%)
Hypertension drugs	Methyldopa	180,539	335,259	2,038 (0.6%)	1.08 (0.94-1.24)	1.13 (0.97-1.32)	239 (11.7%)
	Nifedipine			11,699 (3.5%)	0.83 (0.78-0.88)	0.89 (0.83-0.95)	-1,431 (-12.2%)
	Clonidine			261 (0.1%)	1.27 (0.91-1.78)	1.06 (0.74-1.53)	15 (5.9%)
High ceiling diuretics	Ethacrinic acid	74,222	227,139	227 (0.1%)	1.79 (1.16-2.75)	1.53 (0.94-2.51)	79 (34.8%)
Antithrombotics	Dipyridamole	90,124	212,187	3,548 (1.7%)	1.10 (0.98-1.23)	1.01 (0.89-1.15)	35 (1.0%)
	Ticlopidine			109 (0.1%)	1.49 (0.75-2.97)	1.50 (0.69-3.25)	36 (33.3%)
	Chlorpropamide	37,032	83,666	68 (0.1%)	0.62 (0.33-1.15)	0.76 (0.39-1.45)	-22 (-32.3%)
Diabetes drugs	Ferrous sulphate	35,918	117,120	11,259 (9.6%)	1.21 (1.15-1.28)	1.19 (1.12-1.25)	1,758 (15.6%)
Iron preparations	Cimetidine	132,452	284,092	2,989 (1.1%)	1.02 (0.93-1.13)	1.09 (0.98-1.22)	252 (8.4%)
Peptic ulcer/reflux drugs	Bisacodyl	53,653	164,718	4,505 (2.7%)	1.32 (1.22-1.43)	1.15 (1.04-1.26)	574 (12.7%)
Laxatives	Belladonna alkaloids	5,791	18,195	506 (2.8%)	1.21 (0.98-1.49)	1.22 (0.98-1.53)	92 (18.2%)
Bowel disorder drugs/belladonna & derivatives	Propantheline	9,798	28,127	91 (0.5%)	1.17 (0.73-1.88)	1.38 (0.81-2.35)	25 (27.6%)
Urinary antispasmodics	Oxybutynin			3,497 (12.4%)	1.22 (1.11-1.35)	1.16 (1.04-1.30)	493 (14.1%)
Urinary tract antibacterials	Nitrofurantoin	173,341	331,509	1,980 (0.6%)	1.52 (1.34-1.73)	1.50 (1.30-1.73)	658 (33.2%)
Oestrogen-only medication	Ethinylloestradiol	33,242	53,332	69 (0.1%)	1.35 (0.78-2.33)	1.50 (0.85-2.64)	23 (33.3%)
	Oestradiol			1,889 (3.5%)	0.91 (0.80-1.04)	0.94 (0.81-1.08)	-131 (-7.0%)
	Oestrone			2,954 (5.5%)	1.01 (0.91-1.13)	1.07 (0.96-1.20)	196 (6.6%)
	Oestrogens-conjugated			2,429 (4.6%)	0.85 (0.78-0.94)	0.89 (0.80-0.98)	-313 (-12.9%)
	Fosfestrol sodium			147 (0.3%)	1.76 (1.01-3.07)	1.41 (0.74-2.70)	43 (29.0%)

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b In each sub-study, participants were those who took medications from the domain drug class (i.e. drugs used to treat similar conditions to those indicated for PIMs of interest).

^c 'Index subjects' refers to unplanned hospitalization cases, each participant potentially contributing multiple times as an index subject; 'index exposure' gives count/proportion of index subjects exposed to PIM at time of admission.

^d Odds ratios (OR), both unadjusted and adjusted for potential confounding factors, are presented with 95% confidence intervals.

^e 'PIM attribution' provides an estimate of the count/proportion of hospitalizations attributed to PIM in exposed index subjects; proportion = attributable fraction (AF) = (OR-1)/OR and count = AF x no. exposed index subjects.

Figures

Fig 1 Potentially inappropriate medications (PIMs) in Western Australians aged ≥ 65 years (1993-2005)^a: associations between PIM exposure and unplanned hospitalizations based on number of different PIMs taken over three months^b (adjusted odds ratios and 95% confidence intervals)

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥ 67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b Number of different PIMs taken was determined based on drug consumption during the three-month period preceding the case and control times (including the case/control dates).

Fig 2 Potentially inappropriate medications (PIMs) in Western Australians aged ≥ 65 years (1993-2005)^a: associations between PIM exposure and unplanned hospitalizations based on total number of PIM 'daily doses' taken over three months^b (adjusted odds ratios and 95% confidence intervals)

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥ 67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b Total number of PIM 'daily doses' taken was determined based on drug consumption during the three-month period preceding the case and control times (including the case/control dates). Each 'daily dose' represented exposure to one medication for one day, where the quantity taken was the average dose recommended per day, based on drug form, route and strength.

Fig 3 Potentially inappropriate medications (PIMs) in Western Australians aged ≥ 65 years (1993-2005)^a: associations between exposure to specific PIMs^b and unplanned hospitalizations (adjusted odds ratios and 95% confidence intervals)

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥ 67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b PIM exposure was determined based on exposure status at case and control times.

Fig 4 Potentially inappropriate medications (PIMs) in Western Australians aged ≥ 65 years (1993-2005)^a: estimates of number^c and proportion^b of unplanned hospitalizations attributable to PIM exposure for specified PIMs

^a Although the study period covered 1993-2005 in this population, index cases related to unplanned hospital admissions between July 1994 and December 2005 only, in patients aged ≥ 67 years upon admission; these additional constraints were required to ensure sufficient lead-up time for the control observation period.

^b The proportion of hospitalizations considered to be attributable to the specified PIM was based on the attributable fraction (AF) derived from the primary adjusted odds ratio (OR) for the corresponding regression analysis, where $AF = (OR - 1) / OR$.

^c The number of hospitalizations considered to be attributable to the specified PIM was calculated as the product of the attributable fraction (AF) multiplied by the number of exposed index subjects (i.e. patients exposed to the PIM at the time of hospital admission).