Do the 2015 Beers Criteria predict medication-related harm in older adults? Analysis from a multicentre prospective study in the UK

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Key Words Inappropriate prescribing, Beers Criteria, medication harm, older adults, hospital discharge.

Key Points

- 1 in 5 older patients in England were discharged with potentially inappropriate medication (PIMs), defined by the 2015 Beers Criteria.
- Patients prescribed PIMs at hospital discharge were not at increased risk of hospitalisation or mortality, however multiple PIMs at discharge increased the risk of adverse drug reactions.
- The 2015 Beers Criteria may have a limited clinical utility in UK settings.

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Abstract

Objectives To investigate if inappropriate prescribing, defined by the Beers Criteria (2015 version), is associated with medication-related harm (MRH), hospital admission, and mortality in older adults.

Design Multicentre, prospective cohort study

Setting South-England

Participants 1280 older adults (median age 82 years) recruited at hospital discharge between 2013 and 2015 and followed-up by senior pharmacists in the community

Main outcomes MRH (harm from adverse drug reactions, non-adherence, and medication errors) was identified at 8-weeks post-discharge using three data sources; hospital readmissions, GP records, and, patient interview.   One-year mortality was determined using hospital records. Potentially inappropriate medications (PIMs) were determined using Beers 2015 criteria for medicines to avoid in older adults. Logistic regression was used to investigate the relationship between patients prescribed PIMs and adverse outcomes.

Results Two hundred and seventy-six patients (22%) were prescribed one or more PIMs at hospital discharge. The main PIM classes prescribed at hospital discharge were benzodiazepines and related drugs (30%) and antidepressants (27%). 1116 out of 1280 patients completed follow-up and 413 (37%) experienced MRH. In 51 cases (12%), MRH was attributable to a PIM. There was no significant relationship between patients prescribed PIMs and overall MRH, hospital readmission or all-cause one-year mortality. Multiple PIMs at discharge was independently associated with an increased risk of ADR (OR 2.32, 95% CI 1.03-5.23).

Conclusions The prescribing of PIMs is common at hospital discharge of older adults in England. The 2015 Beers criteria have a limited clinical value to predict adverse outcomes following hospital discharge in a UK setting.

Introduction

Reducing medication-related harm (MRH) has been designated the World Health Organisation's third global patient safety challenge, with risk during transitions of care a specific priority [1]. This term, MRH, includes harm to individuals from adverse drug reactions, non-adherence and medication errors. Older adults are at high risk of MRH due to their multimorbidity, polypharmacy and age-related changes in pharmacokinetics and pharmacodynamics[2]. A recent systematic review of MRH in older adults found that between 17-51% of older adults experience MRH within 30 days of hospital discharge[3]. In England, MRH is leading to an increasing number of hospital admissions[4]. The direct healthcare costs of MRH in older adults following hospital discharge in England is conservatively estimated at £400 million annually, of which 90% of cost is attributable to hospital readmission[5].

Inappropriate prescribing is an avoidable risk factor for MRH in older adults and can be defined as medicines with a higher probability of causing harm than benefit to the individual[6]. Numerous explicit lists of medicines to avoid in older adults are available (e.g. Beers, STOPP, EU-PIM, PRISCUS criteria etc.) [7]. They have generally been developed through Delphi consensus amongst expert geriatricians and clinical pharmacologists. The Beers Criteria were the first published guidance of potentially inappropriate medicines (PIMs) to avoid in older adults, developed in the USA in 1991 for use with nursing home residents[8]. They have been updated several times since 1991, and are arguably the most established of the available lists. Indeed, many other lists are derived from the Beers Criteria[7]. Crucially they are the only criteria where the strength of evidence for recommendations is reported [9]. The applicability of the Beers Criteria across care settings and in Europe has increased with updates[10]. In the UK, a cross-sectional analysis of almost 14000 primary care patients in 2012 found that 38% were prescribed at least one Beers Criteria inappropriate medicine[11]. However, there has not been an investigation in the UK to determine whether PIM use (as defined by the Beers Criteria) is associated with adverse clinical outcomes such as MRH, hospitalisation and mortality.

In this study, we sought to determine if the 2015 Beers Criteria can predict adverse clinical outcomes following hospital discharge in a large cohort of older adults in the UK.

Methods

This study was approved by the National Research Ethics Service, East of England (REC Reference 13/EE/0075).

To investigate the relationship between Beers Criteria PIMs and adverse outcomes, we used data from the multicentre, prospective cohort PRIME study[5,12]. Detailed methods are available in the published protocol.[12] Between 2013 and 2015, adults aged 65 years and over were recruited from medical wards in five hospitals in England just prior to hospital discharge. Patients were excluded if they were terminally ill, lacked capacity with no consultee, or if they were transferred to other healthcare units.

Trained research nurses collected baseline data from participants, and research pharmacists followed participants for 8 weeks in the community to identify MRH. Medication-related harm (MRH) included adverse drug reactions (ADR) and harm arising from a failure to receive medication owing to non-adherence. Harm arising from medication error was included where reported. Intentional overdose was excluded. This is a modified version of the definition by Strand *et al*.[13]

We identified MRH using three data sources; (1) participant (or carer if needed) telephone interview using a structured questionnaire, (2) General Practitioner (GP) records, and, (3) prospective review of hospital readmissions, in consultation with the admitting medical consultant. Where an ADR was suspected, we used the validated Naranjo Algorithm [14] to assess causality along with the British National Formulary and Summary of Product Characteristics. We assessed participants' non-adherence to medicine using a modified version of a validated questionnaire. [15]

An endpoint committee, independent from data collection, consisting of three senior geriatricians and a senior researcher in clinical pharmacy and therapeutics were provided structured case summaries of all cases of MRH by the research pharmacists. The committee reviewed, scrutinised and confirmed or rejected MRH cases by consensus. All-cause mortality was identified at one-year post-discharge using patient hospital records.

We determined inappropriate prescribing at hospital discharge using Table 2 of the Beers Criteria 'American Geriatrics Society 2015 criteria for potentially inappropriate medication use in older adults' [8]. We used these criteria, and cross-referenced to a published UK modification[11]. We applied the 2015 Beers Criteria that had a moderate (or above) grade of evidence.

Statistical analysis

The distributions of variables were examined using histograms and were described by their medians and interquartile ranges (IQR) due to evident skewness. For categorical variables, numbers and percentages were used to describe the data. Associations between variables and PIMs use was evaluated using the Mann-Whitney U-test for continuous variables and Fisher's Exact test for categorical variables. Logistic regression models were used to investigate the relationship between PIMs and adverse outcomes (MRH, ADR only, hospital readmissions and all-cause mortality). Models were adjusted for age, gender, socioeconomic status (using the Index of Multiple Deprivation for England), comorbidity (using the Charlson comorbidity index), number of drugs, and functional status (using the Barthel index). We analysed data using IBM SPSS Statistics, version 22, IBM Corporation, Armonk, NY.

Results

Baseline characteristics and PIMs prescribed at hospital discharge

We recruited 1280 older adults (median age 82, IQR 75-87 years; 58% female) close to the time of hospital discharge. The characteristics of the study population discharged with and without PIMs are shown in Table 1. Out of this cohort, a total of 276 (21.6%) patients were prescribed at least one PIM and 35 (2.7%) were prescribed two or more PIMs. Compared to patients without PIMs at hospital discharge, those patients with PIMs were more likely to be female, have a greater comorbidity burden, and a greater total number of medicines.

There was a total of 315 prescriptions for 36 different PIMs (see Table 2). The main PIMs prescribed at hospital discharge were benzodiazepines and related hypnotics (n=94, 30%) and antidepressants (n=85, 27%).

MRH identified at 8-week follow-up

Of those recruited, 164 (12.8%) did not complete follow-up to determine whether they experienced MRH and were therefore excluded from further analyses. There were no significant differences in the baseline characteristics between included and excluded participants, with the exception that included participants were more functionally dependent than excluded participants (Barthel Index 17 versus 18 out of 20, P=0.04). Out of the 1116 participants that completed follow-up, 240 (21.5%) had been discharged with at least one PIM (21.6% in the full cohort of 1280 participants) and 31 (2.8%) discharged with two or more PIMs (2.7% in the full cohort).

Four hundred and thirteen participants out of 1116 (37%) experienced MRH within 8-weeks post-discharge[5]. Antihypertensives (22.4%), opiates (17.2%), diuretics (12.2%) and antibiotics (10.5%) were implicated in the highest proportion of MRH events. Adverse drug reactions were responsible for MRH in 301 out of 413 cases (72.9%), non-adherence in 45 cases (10.9%), and a medication error in 14 cases (3.4%). In five cases (1.2%) the patient experienced harm from both an ADR and a medication error, and in 48 cases (11.6%) harm was due to both an ADR and non-adherence. Overall, 284 patients (25.4%) were readmitted to hospital within 8 weeks, and MRH was the primary reason for readmission in 87 (30.6%) out of the total number of readmissions. One year following hospital discharge, 240 participants had died (21.5%).

MRH due to PIMs at 8-weeks follow-up

We identified 51 participants that experienced MRH due to PIMs. This represents 12.3% of all participants who experienced MRH (n=413). There were 57 MRH events specifically attributable to PIMs. The PIMs that most commonly caused MRH were benzodiazepines and hypnotics (n=15, 26%), and antidepressants (n=14, 25%).

Table 3 shows the unadjusted and adjusted relationships between PIM use and adverse outcomes, including MRH, hospital readmission and all-cause mortality at one-year. On multivariable analysis, PIM use as defined by the 2015 Beers Criteria was not associated with MRH (OR 1.02, 95% CI 0.74-1.42, P=0.90), ADR specifically (OR 1.16, 95% CI 0.82-1.65, P=0.40), hospital readmission (OR 1.20, 95% CI 0.84-1.72, P=0.31), MRH-specific hospital readmission (OR 1.14, 95% CI 0.65-1.99, P=0.65) or all-cause mortality (OR 0.75, 95% CI 0.48-1.18, P=0.22). However, a statistically significant relationship was found between multiple PIMs use and ADRs (OR, 1.03 to 5.23, P=0.04).

Discussion

Our main findings are that 1 in 5 older people are prescribed PIMs at hospital discharge, defined by the 2015 Beers Criteria, however PIM use has a limited relationship with adverse clinical outcomes. Indeed, this might be expected given that MRH could only be attributed to PIMs in 12% of the 413 patients that experienced MRH in the study. The prescription of PIMs in our UK cohort did not confer a higher risk of MRH (ADR, harm from non-adherence and harm from medication error) or hospital readmission at 8-weeks post-discharge or increased mortality risk over one year. However multiple PIM prescription was associated with the incidence of ADR at an 8-week follow-up. This is the first UK study to investigate the relationship between the 2015 Beers Criteria PIMs and MRH. Hospital discharge is a crucial opportunity to optimise medicines and reduce patient risk of MRH, but it remains unclear what tool practitioners should use to identify high-risk individuals [16,17].

Using the UK Clinical Practice Research Datalink (CPRD), a retrospective analysis of almost 14000 older adults showed that 38% of the cohort had at least one PIM as defined by the 2012 Beers Criteria[11]. In our study, the prevalence was lower (22%) which might reflect a national drive in England to optimise medicines whilst patients are in the hospital setting[18,19]. Our prevalence rate of 22% was consistent with a large Italian study, which found that 24% of participants were discharged with a PIM based on Beers Criteria[20]. Previous studies that applied the Beers Criteria to predict MRH in a European setting have shown mixed results. In a prospective cohort study of older hospitalised patients in Ireland, 29% of patients were found to be prescribed a PIMs on admission (based on Beers 2003 version). However no significant relationship was found between PIMs use and medicines-related hospital admission (OR 1.28, 0.95-1.72; P=0.11)[21]. Similarly, no relationship was found between PIMs use (based on Beers 2012 version) and adverse clinical outcomes in a study of older Italians that were followed up for 3 months after hospital discharge (OR 0.88, 95% CI 0.49-1.51)[20]. In contrast, a multicentre study in Italy of 871 older inpatients, found that the 2012 Beers criteria did predict a combined adverse outcome of ADR and functional decline (OR 1.74, 95% CI 1.06-2.85) [22]. Additionally, a Dutch study of preventable medication-related hospital admission found that two or more PIMs (based on Beers 2012 criteria) independently predicted hospital admissions in older adults [23].

There are two important reasons that may explain the lack of association found in our study between PIMs use and adverse outcomes. Firstly explicit lists used in isolation fail to account for the interplay of biological, psychological and social complexities that places patients at high risk of MRH. A personalised approach that combines knowledge of both PIMs and patient-specific complexities is needed to prescribe appropriately. In the BELFRAIL cohort of older Belgian community-dwelling patients PIMs use was common, however in 30% of these patients the medicines were in fact not considered inappropriate by an expert panel (including a Geriatrician, General Practitioner and Clinical pharmacist) having considered the patient's full clinical picture [24]. A study of older outpatients of one large medical centre in the US similarly demonstrated the discordance between individualised medicine reviews by experts (physician/pharmacist pair) and medicines identified as inappropriate using two different explicit lists (Beers Criteria and Zhan Criteria).[25] In this study, 61% of medicines identified as inappropriate by the Beers Criteria were not judged to

be problematic based on individualised expert assessment (and 49% of medicines identified by the Zhan Criteria).   Another important reason that the Beers Criteria may not be predictive of adverse events is that many of the medicines listed are not licensed or commonly used in England.[11]

The STOPP criteria developed in Ireland through Delphi consensus methodology are an alternative tool to the Beers Criteria. Whilst there is some evidence that applying the STOPP criteria can prevent adverse outcomes for inpatient and care home populations, evidence for their ability to prevent adverse outcomes in community-dwelling older adults is limited[26]. A recent cross-European study trialled the use of the STOPP criteria within a risk prediction tool to identify hospital patients at high risk of ADR but the results showed limited clinical value (area under the receiver-operating-curve = 0.59) [27]. A similarly poor predictive ability was found in a Swedish study investigating the ability of STOPP to predict rehospitalisation and mortality in older patients following hospital discharge (area under the receiver-operating-curve = 0.57).[28]

There are some important limitations to our findings. Firstly, a sample size calculation was not specifically performed for the hypothesis tested in this study and the precision of our results should be interpreted in view of this. Secondly, in line with some other studies[20,29,30], we only applied the 2015 Beers Criteria for drugs to avoid in all older adults (excluding criteria for drug-disease combinations). One criterion (avoid use of proton-pump inhibitors (PPI) for more than 8 weeks unless for high-risk patients) was not applied due to incomplete information on duration of PPI use. Thirdly, our follow-up period for MRH was limited to 8 weeks as we were interested in the immediate post-discharge period, however MRH could have occurred after this observation period. Fourthly, 12.8% of patients were lost to follow-up which may introduce some selection bias, however there were no clinically significant differences between those included and excluded. Finally, our results are based on prescribing practices in hospitals in the South of England and may not be generalisable to other settings.

In conclusion, inappropriate prescribing, as defined by the 2015 Beers Criteria, was found to be common at hospital discharge in a large cohort of older adults from five UK hospitals. Patients prescribed PIMs were not at increased risk of MRH (inclusive of harm from ADR,

non-adherence and medication error), or hospital readmission, or one-year mortality. Patients prescribed multiple PIMs were, however, at increased risk of ADR post discharge. Identifying older patients at risk of MRH is clinically complex, and the 2015 Beers criteria had limited value to predict adverse clinical outcomes in a UK cohort of older adults.

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Table 1. Baseline characteristics of patients discharged with and without PIMs

Characteristic	Patients without PIM (n=1004)	Patients with PIM (n=276)	P-value
Age, median (IQR), years	81.9 (75.5-87.1)	80.7 (74.7-85.7)	*0.056*
Female, n (%)	567 (56.5)	178 (64.5)	*0.019*
Charlson comorbidity index, median (IQR)	2 (1-3)	2 (1-3)	*0.001*
Abbreviated Mental Test Score (AMTS), median (IQR)[a]	10 (8-10)	9 (9-10)	*0.621*
Barthel Index, median (IQR)	18 (13-20)	17 (13-19)	*0.374*
Number of discharge medicines, median (IQR)[b]	8 (6-11)	11 (9-13.8)	*<0.001*
Discharge to care home, n (%)	30 (2.9)	8 (3.0)	*>0.999*
Living alone after discharge, n (%)[c]	489 (48.9)	142 (51.6)	*0.454*
Socioeconomic status, median (IQR), IMD decile[d]	5 (3-8)	5 (2-8)	*0.240*
IQR, interquartile range; IMD, Index of Multiple Deprivation. Mann-Whitney U test for continuous variables and Fisher's Exact test for categorical variables. [a]1 missing;[b]4 missing;[c]6 missing;[d]101 missing.			

Table 2. Main classes of PIM prescribed at hospital discharge

Medicine Class	Medicines	Total Number (%)
Benzodiazepenes and related drugs	Zopiclone (24), Temazepam (19), Diazepam (17), Lorazepam (14), Nitrazepam (7), Zolpidem(6), Clonazepam (5), Lormetazepam (1), Oxazepam (1)	94 (29.8)
Antidepressants	Amitriptyline (68), Paroxetine (7), Nortriptyline (3), Trimipramine (3), Clomipramine (2), Imipramine (2)	85 (27.0)
Alpha-1-blocker	Doxazosin (46)	46 (14.6)
Propulsives	Metoclopramide (22)	22 (7.0)
Antihistamines	Chlorphenamine (12), Promethazine (4), Hydroxyzine (2)	18 (5.7)

Antipsychotics	Prochlorperazine (12), Haloperidol (2), Risperidone (2)	16 (5.1)
Other	Digoxin (9), Amiodarone (5), Nifedipine Immediate Release (5), Insulin sliding scale (3), Dipyridamole (2), Phenobarbital (2), Primidone (2), Ibuprofen (2), Naproxen (1), Dicyclomine (1), Oral Estrogen (1), Megestrol (1)	34 (10.8)

Table 3. Univariable and multivariable analysis of the relationship between PIM use and adverse outcomes (n=1116)

	MRH (n=413)	ADR only (n=301)	Hospital readmission (n=284)	MRH hospital readmission (n=87)	All-cause mortality at one-year (n=240)
Beers Criteria PIMs	*Univariable Odds Ratios (95% CI)*				
No PIM	Reference	Reference	Reference	Reference	Reference
≥ 1 PIM	1.23 (0.92-1.65)	1.28 (0.93-1.74)	1.45 (1.06-1.99)	1.53 (0.94-2.49)	0.78 (0.52-1.17)
≥ 2 PIM	2.11 (1.03-4.33)	2.29 (1.11-4.71)	1.21 (0.55-2.65)	2.98 (1.19-7.46)	0.54 (0.16-1.80)
Beers Criteria PIMs	*Adjusted Odds Ratios (95% CI)ᵃ*				
No PIM	Reference	Reference	Reference	Reference	Reference
≥ 1 PIM	1.02 (0.74-1.42)	1.16 (0.82-1.65)	1.20 (0.84-1.72)	1.14 (0.65-1.99)	0.75 (0.48-1.18)
≥ 2 PIM	1.80 (0.79-4.08)	2.32 (1.03-5.23)	1.02 (0.41-2.54)	2.49 (0.86-7.23)	0.66 (0.19-2.31)

ᵃ92 missing cases. Analyses adjusted for age, gender, socioeconomic status, Charlson Comorbidity Index, number of drugs, Barthel Index