Which drugs cause preventable admissions to hospital? A systematic review

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Aims
Previous systematic reviews have found that drug-related morbidity accounts for 4.3% of preventable hospital admissions. None, however, has identified the drugs most commonly responsible for preventable hospital admissions. The aims of this study were to estimate the percentage of preventable drug-related hospital admissions, the most common drug causes of preventable hospital admissions and the most common underlying causes of preventable drug-related admissions.

Methods
Bibliographic databases and reference lists from eligible articles and study authors were the sources for data. Seventeen prospective observational studies reporting the proportion of preventable drug-related hospital admissions, causative drugs and/or the underlying causes of hospital admissions were selected. Included studies used multiple reviewers and/or explicit criteria to assess causality and preventability of hospital admissions. Two investigators abstracted data from all included studies using a purpose-made data extraction form.

Results
From 13 papers the median percentage of preventable drug-related admissions to hospital was 3.7% (range 1.4–15.4). From nine papers the majority (51%) of preventable drug-related admissions involved either antiplatelets (16%), diuretics (16%), nonsteroidal anti-inflammatory drugs (11%) or anticoagulants (8%). From five studies the median proportion of preventable drug-related admissions associated with prescribing problems was 30.6% (range 11.1–41.8), with adherence problems 33.3% (range 20.9–41.7) and with monitoring problems 22.2% (range 0–31.3).

Conclusions
Four groups of drugs account for more than 50% of the drug groups associated with preventable drug-related hospital admissions. Concentrating interventions on these drug groups could reduce appreciably the number of preventable drug-related admissions to hospital from primary care.

Introduction

Drug-related problems are an important cause of morbidity and mortality and a significant burden on healthcare resources [1, 2]. Previous systematic reviews have shown that 4.9–7.7% of admissions are related to adverse drug events [3, 4] and a median of 4.3% of admissions are considered to be drug-related and preventable [3]. These reviews have largely concentrated on the proportion of admissions that are drug related. One review assessed which drugs most commonly con-

tributed to drug-related morbidity, but combined events which had occurred in hospital with those which occurred in a community setting [5]. Little is known about which drugs are most frequently responsible for preventable drug-related hospital admissions, or the most common underlying causes of these admissions.

We undertook a systematic review to address the following questions:

- What proportion of hospital admissions are drug related and preventable?
- What are the most common drug causes of preventable hospital admissions?
- What are the most common underlying causes of preventable drug-related admissions?

Methods

Searching

We sought to identify both published and unpublished studies using a high-sensitivity, low-specificity search of the following databases: the Cochrane controlled trials register, Cochrane database of systematic reviews, Index UK, US Dissertation abstracts, International Pharmaceutical Abstracts, MEDLINE, EMBASE, Cinahl, Pharmline, National Research Register, Psychinfo, Science Citation Index and SIGLE.

In addition, bibliography lists of published reviews were searched for relevant papers [3–5]. Where possible, corresponding authors were contacted for further information. Details of the search strategy are available from the corresponding author.

Selection and abstraction

Two reviewers (S.S. and S.R.) independently screened titles for relevance, resolving disagreements through discussion. The same reviewers independently reviewed the abstracts of articles considered to be relevant. Full papers were retrieved for detailed analysis and assessed according to the inclusion criteria. Two reviewers (S.S. and R.L.H.) abstracted data from papers meeting these criteria and a third reviewer (A.J.A.) verified the data.

Our inclusion criteria were as follows:

- Types of studies: studies eligible for inclusion prospectively identified patients admitted with preventable drug-related admissions to hospital using medical record review. Studies reported the number and proportion of preventable drug-related admissions and at least one of the following: types of medication associated with preventable drug-related admissions and underlying causes of preventable drug-related admissions.
- Types of participants: patients aged ≥16 years.

- Types of admissions: admissions to hospital from primary care judged to be drug related and preventable. Admissions caused by adverse drug reactions, under- or overtreatment and problems with patient adherence to medication were included.

Studies excluded from the review were those that: did not use medical record review to identify admissions; focused on specific diseases or treatments, a single drug-related problem, or admissions to a single specialist unit; focused on admissions attributed to drugs of abuse or intentional overdose; focused on hospital readmissions only; focused on events occurring in hospital.

Quality assessment

Papers were assessed as suitable for inclusion if they met the inclusion criteria detailed above. For the purposes of subgroup and sensitivity analyses, we also recorded other methodological and participant characteristics of included studies.

Categorization of drugs into classes and groups

Drugs associated with admissions were categorized into groups using British National Formulary subchapter headings wherever possible [6].

Data synthesis

Summary statistics for our chosen outcomes were calculated from the selected papers using Microsoft Excel (2000) and are reported as follows:

- The median (range) percentage of all hospital admissions (as reported by study authors) which were drug related and preventable.
- The frequency of drug causes of admissions, reported as the proportion of all drug causes (i.e. greater than the number of admissions, as more than one drug can contribute to a single admission)
- The median percentage (range) of all hospital admissions attributed to an underlying cause (as reported by the study authors). Underlying causes included: prescribing problems (admissions which could have been avoided by prescribing an alternative drug or dose of drug), monitoring problems (admissions which could have been avoided by closer monitoring for adverse effects of medication) and adherence problems (admissions which could have been avoided if patients had taken the drugs according to the prescribed directions).
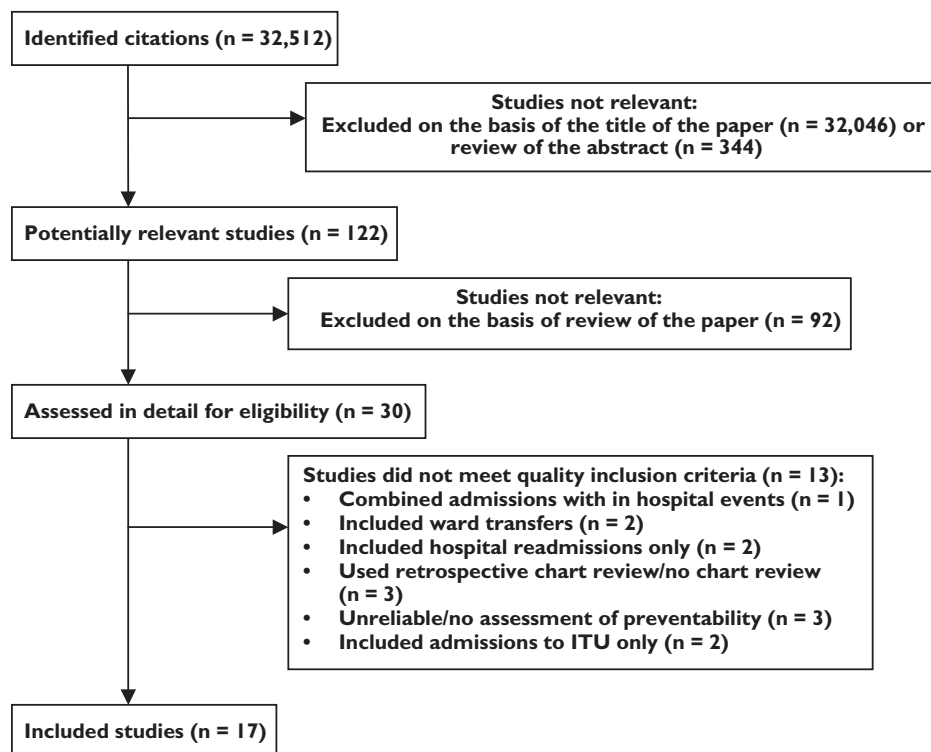
Results

Description of studies

We identified 122 potentially relevant studies, of which 17 satisfied our inclusion criteria. The main reasons for

Figure 1
Selection process of eligible studies

excluding studies are summarized in the QUOROM flow diagram (see Figure 1). A brief description of the studies included in the review is presented in Table 1. Hallas *et al.* conducted a series of studies covering a range of hospital wards (general medical, cardiac, older people, gastrointestinal and respiratory) [7–11]. Details of the drugs associated with preventable hospital admissions are published in five papers [7–11], whilst a sixth paper summarized the percentage of preventable drug-related admissions for all the units studied [12]. A seventh paper by Hallas *et al.* reported the results of a survey of admissions following an intervention which had been developed as a result of the earlier work [13].

Percentage of admissions that were drug-related and preventable
The search identified 13 papers which met the inclusion criteria. These were conducted between 1983 and 2002. Five studies were conducted in the UK [14–18], two in Denmark [12, 13], two in the USA [19, 20], two in Australia [21, 22], one in Canada [23] and one in Italy [24]. Four studies included adults aged ≥65 years [14, 17, 21, 23], whilst the remaining studies included adults of all ages. Four studies included only admissions caused by adverse drug reactions [16–19], whilst the remaining nine studies included a wider definition of admissions due to under- and overtreatment. Seven stud-

ies included admissions due to problems with patient adherence to medication [12, 13, 15, 21–24]. Eleven studies used multiple reviewers to assess causality and preventability [12, 14–23] and 10 studies used guidelines or specific criteria to assign causality and preventability [12–18, 21–23]. A meta-analysis of the data reported was deemed inappropriate due to the heterogeneity between studies.

The median (range) percentage of admissions that were preventable and drug-related is 3.73 (1.36–15.42). The scatter plot in Figure 2 shows the relationship between total number of admissions and percentage of preventable drug-related admissions. Two small studies showed a higher than expected proportion of preventable drug-related admissions [21, 23]. These studies included admissions due to problems with patient adherence and, in contrast to the other studies, focused on patients aged ≥65 years rather than adults of all ages.

Drugs associated with preventable hospital admissions
The search identified 11 papers which met the inclusion criteria [7, 9–11, 13, 15, 16, 18–20, 22]. The studies were conducted between 1983 and 2001 and included adults of all ages. Five studies were conducted in Denmark [7, 9–11, 13], three in the UK [15, 16, 18], two in the USA [19, 20] and one in Australia [22]. The five papers from Denmark [7, 9–11, 13] reported the results

Table 1
Details of studies included in the review

Study	Methodology	Unit studied	Age of patients	Type of admission	Method of assessment of causality and preventability	Types of events classified as DRA	Location of study	Period of data collection	Duration of data collection	Number of admissions	Number (%) DRA	Number (%) PDRA
Bigby 1987 [19]	Prospective medical record review with physician and patient interview	All wards in a 700-bed tertiary teaching hospital	Adults	Unscheduled and emergency admissions	Majority clinical judgement of three reviewers	ADR	Massa-chusetts, USA	1983–1984	1 year	686	66 (9.6)	36 (5.2)
Chan 2001 [21]	Prospective medical record review and patient and/or relative interview	Medical wards at a 500-bed public acute care hospital	Adults aged ≥75 years	Acute unplanned admissions	Two reviewers using 'Hallas criteria' for causality, severity and preventability	ADR Under-treatment Over-treatment Non-compliance	Southern Tasmania, Australia	1998	8 weeks	240	45 (18.8)	37 (15.4)
Courtman 1995 [23]	Prospective medical record review by a pharmacist	One acute 32-bed medical ward (including 20 geriatric beds)	Patients aged ≥65 years	All admissions	Unknown number of reviewers used 'amended Hallas criteria' for causality and specific criteria for preventability	ADR Under-treatment Over-treatment Non-compliance	Toronto, Canada	Sep-tember 1992 to February 1993	19 weeks	150	46 (30.7)	18 (12.0)
Cunningham 1997 [14]	Prospective medical record and nursing record review by a pharmacist and patient interview	Care of the elderly wards in a number of hospitals	Patients aged ≥65 years	Admissions to care of the elderly wards over a 4-week period for each hospital	Majority judgement of three independent reviewers using 'Hallas criteria' for causality and preventability	ADR Under-treatment Over-treatment	Tayside, UK	March to December 1992	10 months	1011	54 (5.3)	43 (4.3)

Table 1
Continued

Study	Methodology	Unit studied	Age of patients	Type of admission	Method of assessment of causality and preventability	Types of events classified as DRA	Location of study	Period of data collection	Duration of data collection	Number of admissions	Number (%) DRA	Number (%) PDRA
Dartnell 1996 [22]	Prospective routine pharmacist review of patients, registrar review of computer record, and selected medical records and patient interview	Whole hospital	Adults	Admissions via Emergency Department lasting >24 h	Agreement of two reviewers using modified 'Karch & Lasagna criteria' for causality, and specific criteria for preventability	ADR Under-treatment Over-treatment Non-compliance	Melbourne, Australia	November to December 1994	30 days	965	55 (5.7)	36 (3.7)
Green 2000 [16]	Prospective medical record review and patient and/or GP interview, with follow-up at 5 months	Acute medical admissions units in two hospitals	Adults	Random number selection of 200 acute medical admissions	Agreement of two reviewers using 'Venulet and Ten Hams classification' and 'Naranjo's algorithm' to assess causality. Assessment of preventability unclear	ADR	Liverpool, UK	Unknown	22 weeks	200	15 (7.5)	12 (6.0)
Hallas 1990 [7]	Prospective medical record review and patient, relative, general practitioner, or nurse interview	Department of Cardiology	Adults	All admissions	Majority judgement of four reviewers using 'Hallas criteria' for causality and preventability	ADR Under-treatment Over-treatment Non-compliance	Odense, Denmark	May to June 1988	2 months	NA	NA	NA
Hallas 1990 [9]	As above	General medical ward	As above	As above	As above	As above	As above	March to May 1988	As above	NA	NA	NA

Table 1
Continued

| Study	Methodology	Unit studied	Age of patients	Type of admission	Method of assessment of causality and preventability	Types of events classified as DRA	Location of study	Period of data collection	Duration of data collection	Number of admissions	Number (%) DRA	Number (%) PDRA
Hallas 1992 [10]	As above	Respiratory ward	As above	As above	As above	As above	As above	1989	As above	NA	NA	NA
Hallas 1991 [11]	As above	Geriatric ward	As above	As above	As above	As above	As above	March to June 1998	As above	NA	NA	NA
Hallas 1992 [12]	As above	Six medical wards	As above	As above	As above	As above	As above	March 1988 to May 1989	As above	1999	212 (10.6)	67 (3.4)
Hallas 1993 [13]	As above	General medical and geriatric ward	As above	Unscheduled admissions to medical services from primary care	Judgement of one reviewer using 'Hallas criteria'. Sixty cases randomly selected for review by three reviewers	As above	As above	1989	4 months	703	88 (12.5)	25 (3.6)
Howard 2003 [15]	Prospective routine pharmacist review of patients. Pharmacist review of selected medical records, and patient and GP interview	Medical admissions ward	Adults	Unscheduled admissions from primary care	Majority judgement of three reviewers used 'modified Hallas criteria' for causality and 'Hepler criteria' for preventability	ADR Under-treatment Over-treatment Non-compliance	Nottingham, UK	January to June 2001	6 months	4093	265 (6.5) 178 (4.3)	
Lakshmanan 1986 [20]	Prospective review of all drug charts, discharge sheets and selected medical records	Medical inpatient services of 769-bed general teaching hospital	Adults	All admissions to medical services	Judgement of one reviewer using guideline criteria for causality and preventability	ADR Over-treatment	Ohio, USA	July to August 1984	2 months	834	35 (4.2)	19 (2.3)

Table 1
Continued

Study	Methodology	Unit studied	Age of patients	Type of admission	Method of assessment of causality and preventability	Types of events classified as DRA	Location of study	Period of data collection	Duration of data collection	Number of admissions	Number (%) DRA	Number (%) PDRA
Lindley 1992 [17]	Prospective medical and nursing record review	Acute geriatric, medical and heart care wards in a 677-bed teaching hospital	Patients aged ≥65 years	Emergency and scheduled admissions from primary care (readmissions excluded)	Researcher comparison of symptoms with known ADR profile of drugs, and then verification with consultant, registrar or researcher	ADR	Manchester, UK	Unknown	10 weeks	416	26 (6.3)	13 (3.1)
Pirmohamed 2004 [18]	Prospective routine pharmacist review of patients. Selected medical record review and patient, relative or GP interview by research nurse or pharmacist	Medical and surgical wards in two hospitals (excluding obstetrics and gynaecology)	Adults (over 16 years)	All admissions except obstetric and gynaecology patients	Majority judgement of two or three reviewers using 'Naranjo algorithm' and 'Jones method' for causality and 'Hallas criteria' for preventability	ADR	Liverpool, UK	November 2001 to April 2002	6 months	18 820	975 (5.2)	687 (3.7)
Raschetti 1999 [24]	Prospective nurse review of A&E records and follow-up of medical records of patients admitted	700-bed public hospital	Adults (mean age 54.5 years)	All admissions via the emergency department on the first week of each month	Researcher judgement of causality and preventability	ADR Under-treatment Over-treatment Non-compliance	Milan, Italy	October 1994 to Sep-tember 1995	12 weeks	1833	45 (2.5)	25 (1.4)

DRA, Drug-related admissions; ADR, adverse drug reaction; PDRA, preventable drug-related admission.

Figure 2

Scattergram showing the relationship between the number of patients studied and the proportion of preventable drug-related admissions to hospital
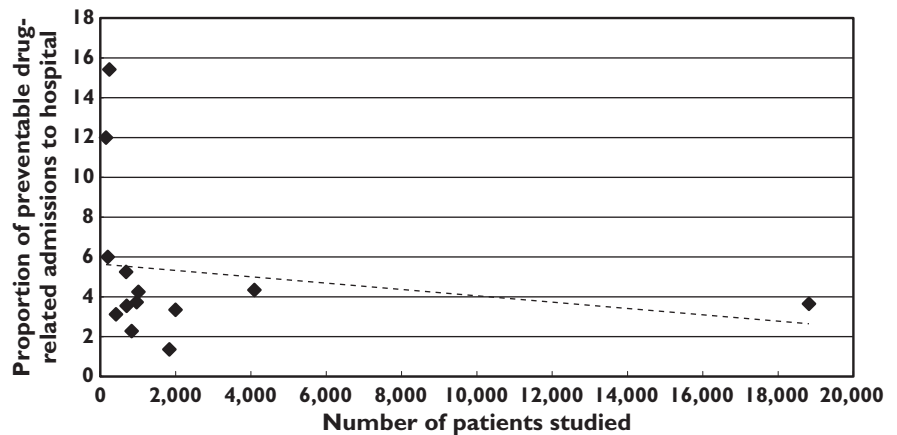
of two studies, four papers reported the detailed results for four units [7, 9–11].

Three studies included admissions caused by adverse drug reactions only [16, 18, 20], whilst the remaining studies reported adverse drug reactions, over- and undertreatment and patient adherence problems. To take account of this, the drugs causing admissions have been broken down into three groups: admissions caused by adverse drug reactions and overtreatment; admissions caused by undertreatment; and admissions caused by problems with patient adherence.

The drug groups most frequently associated with all types of preventable drug-related admissions were antiplatelets, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants (see Table 2). When preventable drug-related admissions were broken down by type of underlying problem, adverse drug reactions and overtreatment were most commonly associated with antiplatelets, diuretics and NSAIDs, undertreatment problems with antiepileptics and patient adherence problems with diuretics, drugs used in diabetes and antiepileptics (see Table 2).

Underlying causes of preventable drug-related admissions
The search identified five papers which met the inclusion criteria [12, 15, 19, 22, 23]. The studies were conducted in the USA [19], Canada [23], Australia [22], Denmark [12] and the UK [15] between 1983 and 2001. One study included only adults aged ≥65 years [23], whilst the remaining studies included adults of all ages. The underlying causes reported in the papers were prescribing problems (assumed to be a problem if admissions were described as preventable adverse drug reactions and not attributed to monitoring problems), monitoring problems and problems with patient adherence. Other categories were reported in some papers

(drug interactions, for example) but could not be applied to all the publications.

Prescribing problems and problems with patient adherence to medication were the most common underlying causes of preventable drug-related admissions [median (range) 30.6% (11.1–41.8) and 33.3% (20.9–41.7), respectively]. Monitoring problems were responsible for a median (range) of 22.2% (0–31.3) preventable drug-related admissions (see Table 3).

Discussion
We found that four drug groups accounted for >50% of preventable drug-related hospital admissions and 12 drug groups accounted for 80% of these admissions. Around one-third of drug-related admissions were associated with prescribing problems, one-third with patient adherence problems and nearly a quarter with inadequate monitoring of medication.

The median of 3.7% of admissions found to be drug related and preventable in our review is slightly lower than that of a previous review [3] because of the inclusion of two recent large UK studies. To our knowledge, only one other review has attempted to detail the drugs most commonly causing patient injury [5]. This review, however, concentrated on adverse drug reactions causing, and occurring during, hospital admission and did not consider whether the admissions were preventable.

We have focused on studies that used prospective medical record review to identify potential drug-related admissions. It is widely accepted that this is the most comprehensive approach to identifying drug-related hospital admissions [25] compared with other methods, such as computer alerts [26] and spontaneous reporting [27]. In addition, the studies included in this review have used either multiple reviewers and/or criteria to assign causality and preventability. The included stud-

Table 2
Drug groups most commonly associated with preventable drug-related admissions relating to adverse drug reactions and overtreatment, undertreatment and problems with patient adherence

Drug group	All preventable drug-related admissions, no. (%) (n = 1406)	Adverse drug reactions and overtreatment no. (%) (n = 1263)	Patient adherence problems no. (%) (n = 98)	Undertreatment no. (%) (n = 45)
Antiplatelets (including aspirin when used as an antiplatelet	225 (16.0))	219 (17.3)	2 (2.0)	4 (8.9)
Diuretics	223 (15.9)	202 (16.0)	20 (20.4)	3 (2.2)
Nonsteroidal anti-inflammatory drugs	155 (11.0)	151 (12.0)	4 (4.1)	0
Anticoagulants	117 (8.3)	113 (8.9)	4 (4.1)	0
Opioid analgesics	69 (4.9)	68 (5.4)	1 (1.0)	0
β-Blockers	65 (4.6)	56 (4.4)	4 (4.1)	5 (11.1)
Drugs affecting the renin–angiotensin system (e.g. angiotensin converting enzyme inhibitors)	62 (4.4)	58 (4.6)	4 (4.1)	0
Drugs used in diabetes	49 (3.5)	40 (3.2)	9 (9.2)	0
Positive inotropes	45 (3.2)	41 (3.2)	3 (3.1)	1 (2.2)
Corticosteroids	44 (3.1)	41 (3.2)	2 (2.0)	1 (2.2)
Antidepressant	42 (3.0)	41 (3.2)	1 (1.0)	0
Calcium channel blockers	39 (2.8)	34 (2.7)	1 (1.0)	4 (8.9)
Antiepileptics	32 (2.3)	11 (0.9)	8 (8.2)	13 (28.9)
Nitrates	24 (1.7)	15 (1.2)	5 (5.1)	4 (8.9)
Inhaled corticosteroids	8 (0.6)	0	7 (7.1)	1 (2.2)
Potassium channel activators	7 (0.5)	1 (0.1)	2 (2.1)	4 (8.9)
Anti-asthmatics*	5 (0.4)	0	5 (5.1)	0
Total	1211 (86.1)	1091 (86.4)	82 (83.7)	40 (88.9)

*Inhaled and oral bronchodilators and corticosteroids and other antiasthmatic drugs.

Table 3
Numbers (percentage) of preventable drug-related admissions associated with prescribing problems, monitoring problems and patient adherence problems

Underlying cause	Number (%) of admissions attributed to different underlying causes					
	Bigby 1987 [19] (n = 36)	Courtman 1995 [23] (n = 18)	Dartnell 1996 [22] (n = 36)	Hallas 1992 [12] (n = 67)	Howard 2003 [15] (n = 178)	Median % (range) for all studies
Prescribing problem	4 (11)	5 (28)	11 (30)	28 (42)	63 (35)	30.6 (11.1–41.8)
Monitoring problem	12 (33)	7 (39)	15 (42)	14 (21)	53 (30)	22.2 (0–31.3)
Patient adherence problem	6 (17)		8 (22)	21 (31)	46 (26)	33.3 (20.9–41.7)
Unclassified	14 (39)	6 (33)	2 (6)	4 (6)	16 (9)	
Total	36 (100)	18 (100)	36 (100)	67 (100)	178 (100)	

ies were conducted over a period of 18 years in several different developed countries, mostly in the western hemisphere. Therefore, the results of this study may not be applicable in all countries. Some of the studies used different definitions of causality and preventability and therefore may not be directly comparable. For example, some studies have included admissions considered to be possibly related to drugs and possibly preventable in their assessments of the prevalence of preventable drug-related admissions. In order to avoid falsely inflat-

ing the prevalence of preventable drug-related admissions we have, wherever possible, excluded these admissions from the estimates reported in our systematic review.

We have focused on medical admissions to hospital from the general population and have included studies with a broad scope of admission types by excluding studies conducted only on specialist units. However, it is possible that the presence of specialist units in some hospitals may have affected the types of admissions seen.

In all of the cases judged to be preventable in the reviewed studies, the innate toxicity of the drug (or failure to prescribe a drug or sufficient dose) was avoidable in some way. The four drug groups most often causing preventable admissions are commonly used in England [28]. Diuretics account for 5.3% of all primary care prescriptions in England, antiplatelets for 4.0%, NSAIDs for 3.0% and oral anticoagulants for 0.8%. These drug groups have a high innate toxicity, with both diuretics and oral anticoagulants requiring close monitoring for their safe use. In addition, all four drug groups are often used in elderly patients who are more susceptible to adverse effects. The ideal solution to this problem would be to have safer drugs, although no drug is ever likely to be completely without risk. In addition, new drugs take many years to reach the market. In the meantime, there are a number of strategies which can be implemented to help reduce the number of preventable drug-related hospital admissions.

NSAIDs are known to increase the risk of gastrointestinal bleeding and renal dysfunction [29, 30]. Co-prescribing a proton pump inhibitor could reduce the risk of gastrointestinal bleeding (and hospital admission) associated with NSAIDs by between 64% (as secondary prophylaxis) and 78% (as primary prophylaxis) [30]. Other options include using alternative analgesia or prescribing the lowest possible dose of NSAIDs.

Low-dose aspirin also increases the risk of gastrointestinal bleeding [30]. Secondary prophylaxis with *Helicobacter pylori* eradication, where necessary, and proton pump inhibitors offers a ninefold reduction in the risk of gastric ulcer bleeding [31].

Close monitoring of patients taking potent diuretics could reduce the number of patients admitted with dehydration and/or renal failure. A nurse-led intervention, which included more frequent monitoring of heart failure patients, reduced hospital admissions due to heart failure by 60% and almost halved the number of days spent in hospital [32].

Ensuring adequate monitoring of patients on oral anticoagulants and avoiding coprescription of drugs which increase the risk of bleeding could reduce the number of patients admitted with bleeding events [33]. More effective computer alerts may help to avoid the coprescription of interacting drugs and to alert to the need for increased monitoring [34].

The strategies detailed above concentrate mostly on avoiding adverse drug reactions, but it is also important to remember that preventable patient injury can be caused by undertreatment. Undertreatment can result from prescribing too low a dose, or patients taking less than the prescribed dose of medication. Prescribers should ensure that patients are treated with the minimum effective dose of drug, but not less, especially when prescribing drugs with a narrow therapeutic range, e.g. antiepileptics or digoxin. In addition, it is important to ensure that patients are given adequate information to enable them to take their medication effectively and safely. However, not all cases associated with adherence problems will be avoidable.

While there are a number of studies that suggest ways in which preventable drug-related injuries could be avoided [30–32, 34], it would be helpful to quantify potential benefits and risks using health economic evaluations and, where necessary, further primary research. For example, a health economic evaluation of combining gastro-prophylaxis with low-dose aspirin would help to clarify the patient groups for which prophylaxis might be justified. In addition, there needs to be greater attention to the evidence base which underpins drug monitoring [35].

Also, despite the large number of studies of preventable drug-related admissions, further studies are needed to provide more information on the underlying causes of these admissions. This may help in the development of interventions aimed at improving the safety of prescribing and drug monitoring, and improving adherence to medication.

Antiplatelets, diuretics, NSAIDs and anticoagulants account for more than half of the drug groups associated with preventable drug-related admissions to hospital. Concentrating interventions on these four drug groups could appreciably reduce the number of preventable drug-related admissions to hospital.

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