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A systematic review of hospitalization resulting from medicine-related problems in adult patients

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AIMS
Medicine-related problems (MRPs) represent a major issue leading to hospitalization, especially in adult and elderly patients. The aims of this review are to investigate the prevalence, causes and major risk factors for MRPs leading to hospitalization in adult patients and to identify the main medicine classes involved.

METHODS
Studies were identified through electronic searches of Medline, Embase, Scopus and International Pharmaceutical Abstracts between January 2000 and May 2013. A systematic review was conducted of both retrospective and prospective studies. Studies included were those involving hospitalization resulting from MRPs in adults (≥18 years old), whereas studies excluded were those investigating drug misuse and abuse and studies investigating MRPs in hospitalized patients. Data analysis was performed using SPSS version 20.

RESULTS
Forty-five studies were identified, including 21 that investigated hospitalization resulting from adverse drug reactions, six studies that investigated hospitalization due to adverse drug events and 18 studies that investigated hospitalization due to MRPs. The median prevalence rates of hospitalization resulting from adverse drug reactions, adverse drug events and MRPs were 7% (interquartile range, 2.4–14.9%), 4.6% (interquartile range, 2.85–16.6%) and 12.1% (interquartile range, 6.43–22.2%), respectively. The major causes contributing to MRPs were adverse drug reactions and noncompliance. In addition, the major risk factors associated with MRPs were old age, polypharmacy and comorbidities. Moreover, the main classes of medicines implicated were medicines used to treat cardiovascular diseases and diabetes.

CONCLUSIONS
Hospitalization due to MRPs had a high prevalence, in the range of 4.6–12.1%. Most MRPs encountered were prevalent among adult patients taking medicines for cardiovascular diseases and diabetes.

Introduction

Medical therapy has emerged to improve patients' care in order to achieve optimal healthcare outcomes. However, when medicines are misused (over- or underused), then medicine-related problems (MRPs) can arise [1]. Although MRPs had been used as a term in the scientific literature, they were only defined as a concept in 1990 [2]. Strand *et al*. defined MRPs as 'an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcomes' [3, 4].

Medicine-related problems are classified into the following three subgroups: adverse drug events (ADEs), adverse drug reactions (ADRs) and medication errors (MEs) [5]. An ADE is defined as the injury resulting from appropriate/inappropriate use of a drug [6]. According to the World Health Organization (WHO), an ADR is 'any noxious, undesired and unintended drug effect that

occurs at doses used in human for therapy, diagnosis or prophylaxis' [7]. Medication errors are defined as the problems that arise during the process of medicine use regardless of their associated outcomes [2]. The three subgroups of MRPs (ADEs, ADRs and MEs) may result in hospitalization, which could be preventable [8–11]. However, the prevalence of hospitalization due to MRPs has varied between studies for several reasons, as follows: (i) the definition and method used to identify the MRPs; (ii) the heterogeneity of the reported estimates of prevalence; and (iii) the associated risk factors with these MRPs.

Therefore, the aims of this systematic review are as follows: (i) to investigate prevalence, severity and preventability of hospitalization resulting from MRPs; (ii) to determine the underlying causes and major risk factors contributing to such unplanned hospitalizations; and (iii) to identify the most common medicine classes involved.

Methods

Inclusion criteria

Studies were included in the systematic review if they investigated hospitalization resulting from MRPs (involving ADEs, ADRs and MEs) and had explicit data on adult and elderly populations (≥18 years old). The studies eligible were those published or at least with an abstract written in English.

Exclusion criteria

Two types of studies were excluded from this review. The first type was studies related to drug abuse and misuse, because they did not match the used definition of MRPs [12]. The definition of the MRPs was limited to the 'desired outcomes' of the medical therapy. However, drug abuse/misuse is not part of medical therapy taken by patients to achieve a certain outcome. The second type encompassed studies that only investigated MRPs in hospitalized patients.

Search strategy

We searched the following 14 databases between January 2000 and May 2013: PubMed, Medline, National Electronic Library for Medicines (NeLM), Embase, Scopus, ISI Web of Knowledge, Science Direct, PsycInfo, British Nursing Index, Global health, CINAHL, International Pharmaceutical Abstracts, PsycExtra and Cochrane Library. The search strategy evaluated articles obtained predominantly through databases. Additional articles were retrieved through the bibliography lists of published reviews where applicable.

In addition, we searched different governmental patient safety agencies across the world in order to identify official definitions and different classifications of MRPs; these were the UK Department of Health (DOH), Institute of Medicine (IOM), National Patient Safety Agency (NPSA) and The Pharmaceutical Care Network Europe (PCNE).

We used the following search terms: 'medicine related problems', 'hospital' and 'admission'. The search strategy involved use of the three terms in each database as follows: 'medicine related problem(s)' or 'medicine-related problem(s)' or 'medication related problem(s)' or 'medication-related problem(s)' or 'drug therapy problem(s)' or 'drug-therapy problem(s)' or 'drug-related problem(s)' or 'adverse drug reaction(s)' or 'adverse drug event(s)' or 'medication error(s)' or 'medicines related morbidity(s)' or 'drug-related morbidity(s)' or 'drug-induced problem(s)' AND 'admission(s)' or 'hospitalisation(s)' or 'hospitalization(s)' AND 'hospital(s)' or 'clinic(s)' or 'ward(s)' or 'secondary care(s)' or 'infirmary(s)'.

Data extraction

Data extraction from studies was carried out by the authors and included the following information: study type (retrospective or prospective), country, study settings, population age, definition used, duration, sample size, prevalence, reported severe cases and reported preventability. In this respect, references were screened independently by two reviewers (AAH and MG). The screening process was carried out systematically and included the titles, abstracts and full articles. Where a disagreement was encountered, it was resolved by a discussion. Once the inclusion/exclusion criteria were applied, a third reviewer (ZA) verified the data.

For studies that included all ages in the population, only data for adults and elderly were included. When the definition for MRPs was not used in the study, the criteria used to evaluate MRPs were included. The prevalence of hospitalization due to MRPs was calculated as the number of hospitalizations due to MRPs relative to the sample size in each study. The reported severe cases were calculated as the number of severe cases reported by the study relative to all identified MRPs. The reported preventability was calculated as the number of definite preventable cases of hospitalization due to MRPs.

Data analysis

We carried out data analysis using SPSS version 20 (IBM, Armonk, NY, USA). The summary statistics used included the percentage of each of the reported prevalence rate, severity and preventability, calculated for hospitalization resulting from ADRs, ADEs and MRPs. The reported prevalence rate of hospitalization due to MRPs was calculated as the number of patients admitted to the hospital with at least one MRP (numerator) divided by the total number of patients included in each study (denominator). Reported severity was included from the literature and indicated the percentages of reported severe and/or fatal injuries. Likewise, the reported preventability was measured as the percentage of preventable MRPs relative to the total number of MRPs. Although the prevalence rate was calculated for

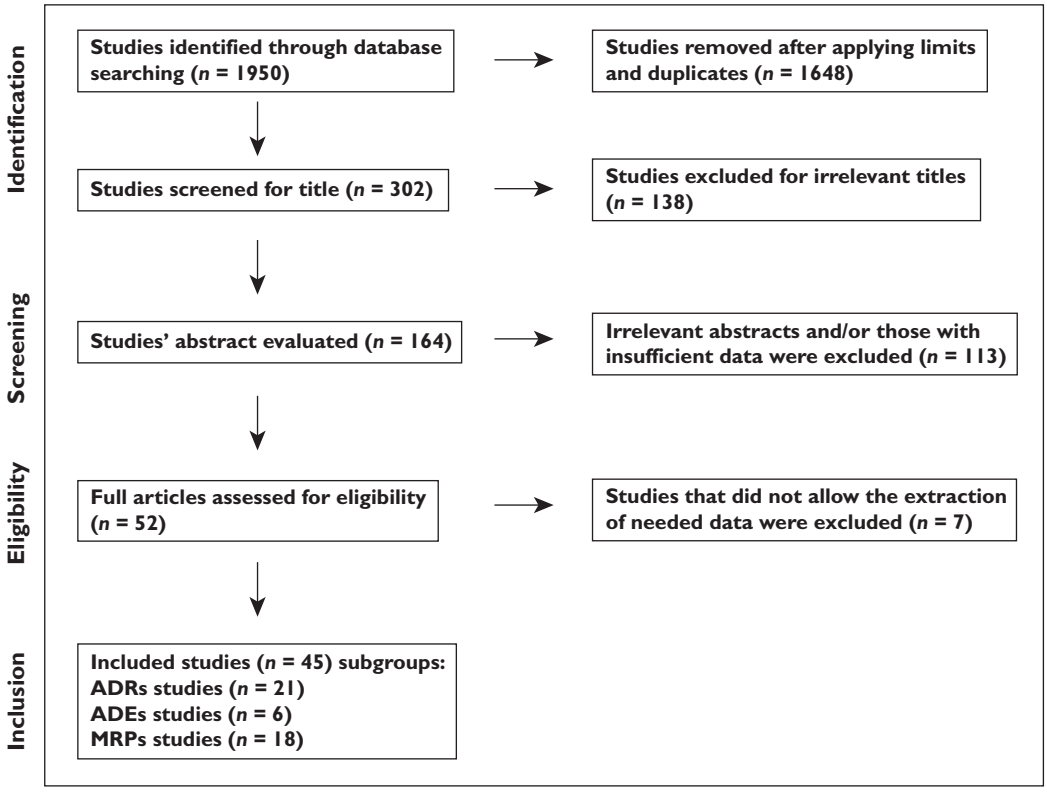

Figure 1

Data extraction and study selection process. Abbreviations are as follows: ADEs, adverse drug events; ADRs, adverse drug reactions; MRPs, medicine-related problems

all the studies, many studies did not report any severity and preventability of medicine-related hospitalization, which affected the results. The heterogeneity of the prevalence rates was calculated based on χ^2 and I^2 tests [13, 14] for each of the studies on ADRs, ADEs and MRPs. A high level of heterogeneity was observed between studies for each of ADRs [χ^2, 390.7; degrees of freedom (d.f.), 20; $P < 0.001$; I^2, 94.9%], ADEs (χ^2, 66.3; d.f., 5; $P < 0.001$; I^2, 92.5%) and MRPs (χ^2, 358.5; d.f., 18; $P < 0.001$; I^2, 94.9%). Consequently, the median and interquartile ranges (IQR) of the prevalence rates were evaluated.

We also identified the main medicine classes associated with hospitalization due to ADR/ADE/MRP. For the purpose of the study and to simplify the comparison, the medicines were grouped into six main categories. The first category included the medicines used in cardiovascular diseases (CVDs), which were as follows: antiarrythmic (amiodarone and cardiac glycosides as digoxin), anti-angina (nitroglycerine, isosorbide mononitrate and isosorbide dinitrate), anticoagulants (warfarin) and antihypertensive [angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), calcium channel blockers (CCB) and diuretics], antiplatelet, antithrombolytic, and cardiotonics. The second category included anti-infectives, which were as follows: antimicrobial, antiparasitic and antiviral. The third category included anticancer medicines (cytostatic and immunosuppressants). The fourth category included antidiabetic medicines, which were insulin and oral hypoglycaemic agents. The fifth category included anti-inflammatory/analgesics, which were aspirin, steroidal/nonsteroidal anti-inflammatories, opioid/non-opioid analgesics, anti-rheumatics and antipyretics. The remaining medicines were less reported than the previous five categories and, consequently, they were grouped as 'others' into a sixth category, which included drugs acting on the central nervous system (CNS), gastrointestinal tract (GIT), respiratory system, blood-forming agents, antihyperlipidaemics and hormone replacement therapy.

Results

In total, 1950 articles were retrieved (Figure 1) before applying the limitations of time (between January 2000 and May 2013), age group (≥18 years old) and language limits (studies published in English). Consequently, 302 studies remained, and their titles and abstracts were investigated. Out of these 302 studies, 138 were excluded because they were not considering 'hospitalization result-

ing from MRPs, ADRs, ADEs and/or MEs'. From the 164 remaining studies, two types of studies were excluded. The first type was the studies that examined MRPs in hospitalized patients rather than upon admission. The second type of studies were excluded because they were letters, comments or editorials and not original research articles. Consequently, the search resulted in 45 relevant studies that were included in this review; 21 studies investigated ADR-related hospitalization, six studies investigated ADE-related hospitalization and 18 studies investigated all types of MRP-related hospitalization. No study specifically investigated hospitalization due to MEs.

Prevalence, severity and preventability of medicine-related problems

The prevalence, severity and preventability of hospitalization resulting from MRPs in both retrospective and prospective studies were evaluated for ADRs, ADEs and MRPs.

For ADR-related admissions, the 21 studies (six retrospective and 15 prospective) identified between the years 2000 and 2013 were carried out in 12 countries (Table 1). The retrospective studies included medical records' review or databases from six different countries. Two of these studies considered all ages in the population; however, the data concerning children (i.e. <18 years) were excluded from the present review. The median prevalence rate of the retrospective studies was 1.47% (IQR, 1–6.26%). Of these studies, only four used the WHO definition [15–18], while the remaining two studies used criteria for evaluation of ADR [19, 20]. Regarding the reported severe cases, only two retrospective studies reported severe ADRs and were 5.64% [15] and 24% [17], which refer to the percentage of reported severe cases in each study out of all the cases. The latter study reported high preventability of 62.3%. However, only one other study reported a preventability rate of 30% [16]. On the other hand, prospective studies investigating ADRs (n = 15) showed higher prevalence rates than retrospective studies reporting ADRs. These prevalence rates had a median of 12% (IQR, 5.89–28.9%). This could be attributed to the fact that prospective studies allowed closer contact with the patients, which permitted more complete and accurate information to be obtained [21]. In addition, the prospective studies used a wide variety of definitions for ADRs, which comprised not only WHO definitions [22–28], but also other definitions based on hazards, harm and poison prediction or classification of ADR types [29–30]. Similar to the retrospective studies, the severity and preventability were underreported. Thus, only seven prospective studies [12, 16, 17, 25, 28, 31] out of the 14 reported severe ADR cases in the range of 0.15–24%, with preventability up to 78%.

For ADE-related hospitalization, six studies (two retrospective and four prospective) were identified from five countries (Table 2). The two retrospective studies were conducted over the same duration (2 months) but used slightly different definitions and had different sample size (6579 and 30 397) [32, 33]. The study with lower sample size had threefold prevalence rate (5%) and reported lower preventability rate. However, the prospective studies [34–38] showed a higher median prevalence rate of 12.4% (IQR, 3.75–22.9%), severe cases (up to 16%) and preventability (up to 60%).

The reported median prevalence rates for MRPs were similar in retrospective [39–44] (n = 5) and prospective studies [5, 27, 31, 45–49] (n = 13; Table 3). The five retrospective studies showed a median prevalence rate of 12.6% (IQR, 10.8–13.3%). The studies had a wide variation in sample size, duration and the definition(s) used. One study used the WHO definition of ADR [42], another used the PCNE definition [44], while the three remaining studies used causality criteria, medicine and disease codes and disease/medicine use assessment. None of these studies assessed the severity of MRPs, and only two studies reported the preventability, which were 20% [38] and 100% [40]. Likewise, the prospective studies investigating MRPs used a diversity of definitions and reported a median prevalence rate of 11.6% (IQR, 6.4–24.1%). Thus, most of these studies used ADR definition and/or Hepler and Strand criteria for classification of drug (medicine)-related problems. The severe cases of MRPs found in these studies ranged from 7.4 to 73% and had a high rate of preventability when reported (up to 78%).

Medicine classes

The main medicine classes involved in hospitalization resulting from ADRs, ADEs and MRPs included medicines used in CVDs, anti-infectives, anticancer, antidiabetics and anti-inflammatory/analgesics (Table 4). Additional classes reported included medicines acting on the GIT, CNS and respiratory system, as well as hormone replacement therapy and antihyperlipidaemics.

For hospitalization resulting from ADRs, each and every study reported CVD medicines, with a median of 33.9% (IQR, 19.9–58.6%). This was followed by anticancer, anti-inflammatories and antidiabetics, which had medians of 18.6% (IQR, 6.96–32.5%), 13.6% (8.21–40.1%) and 9.09% (5.02–21.6%), respectively. Other medicine classes, such as anti-infectives, antihyperlipidaemics, medicines acting on the GIT and medicines acting on the CNS, were less stated, with medians <9%.

In addition, hospitalization resulting from ADE showed more involvement of the CVD medicines, anti-inflammatory medicines, CNS medicines and anti-infectives, which had medians of 42.3% (IQR, 30–72.2%), 24.7% (IQR, 18–27.4%), 23.6% (IQR, 12.2–33.6%) and 13.3% (IQR, 4.9–14.2%), respectively.

In contrast, 10 of the studies investigating hospitalization due to MRPs did not specify the medicine classes involved. The remaining eight studies showed the highest contribution of anticancer medicines (median, 18%), anti-infective medicines (median, 17%) and CVD medicines (median, 14.3%).

Table 1

Characteristics of studies that investigated adverse drug reaction-related hospitalizations

Reference	Country	Setting	Population	Definition used	Duration (months)	Sample size (patients)	Prevalence rate (%)	Reported severe cases (%)	Reported preventability (%)
		Retrospective studies							
Carrasco-Garrido *et al.* [15]	Spain	Hospital data maintained by Ministry of Health and Consumer Affairs	Whole population (mean age, 45 years); only adult population was considered, >18 years old	The WHO definition of ADR	72	350 835	1.63	5.64*	NR
Van Der Hooft *et al.* [25]	The Netherlands	IPCI (Integrated Primary Care Information database)	Whole population; adults and elderly were considered	WHO definition	12	2238	14.9	NR	30.4
McDonnell and Jacobs [17]	USA	Temple University Hospital	Adults of mean age 57 years	WHO definition	11	20 166	0.76	24	62.3
Ruiter *et al.* [18]	The Netherlands	Dutch nationwide registry of hospital discharge (LMR)	Adults and elderly >55 years old	WHO definition	72	2 127 133	1.3	NR	NR
Wawruch *et al.* [20]	Slovak	Department of Internal Medicine of the Hospital in Povazska Bystrica	Adults and elderly >65 years old	A-type ADRs are dose dependant and are a consequence of the drug pharmacological action; B-type ADRs are dose independant and associated with drug pharmacodynamic activity	16	600	7.8	NR	NR
Wu *et al.* [19]	UK	Data from the hospital episode statistics database	Adults and elderly >65 years old	Undesirable effect of a drug beyond its anticipated therapeutic effects occurring during clinical use, and is one of the major causes of iatrogenic disease	120	6 830 067	0.9	NR	NR
		Prospective and observational studies							
Ahren *et al.* [28]	Ireland	Cork University Hospital, Cork, Ireland	Whole population of mean age 68.8 years; adults and elderly were considered	WHO definition	1	856	8.8	NR	5.3
Franceschi *et al.* [56]	Italy	Geriatric Unit of the Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo in Italy	Adults and elderly >65 years; mean age, 76.5 (65–93 years)	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazards from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product	11	1756†	5.8	NR	78
Hopf *et al.* [22]	Scotland	Aberdeen Royal Infirmary (ARI)	Adults and elderly >16 years old	WHO definition	0.5	1101	2.7	NR	13.3
Pérez Menéndez-Conde *et al.* [50]	Spain	Hospital Ramón y Cajal, Madrid	Adult and elderly population of mean age 68.2 years (21–96 years)	Events which can affect the public health of people who consume drugs for therapeutic, diagnostic or prophylactic purposes	12	252	19.4	NR	63.5
Onder *et al.* [57]	Italy	81 academic hospitals across Italy	Adults and elderly, mean age, 70 years (54–96 years)	Any noxious, unintended and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and abuse	120	28 411	5.99	20	NR
Thuermann *et al.* [29]	Germany	Two German pharmacovigilence centres	Adult population	A-type ADRs are dose dependent and are a consequence of the drug pharmacological action; B-type ADRs are dose independent and associated with drug pharmacodynamic activity	48	41 375	2.4	NR	NR

Mjörndal *et al.* [23]	Sweden	Swedish university hospital	Adult population of median age 74 years (21–92 years)	WHO definition	9	681	14.5	NR	NR
Gholami *et al.* [24]	Iran	Cardiovascular clinic at teaching hospital in Tehran	Whole population, but only adults and elderly were considered	WHO definition	8	518	20.3	1.1	1.9
Pirmohamed *et al.* [21]	UK	Two general hospitals in Merseyside, UK	Adults and elderly >16 years old; median age, 76 years (65–83 years)	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product	6	18 825	6.5	0.15	NR
Wasserfallen *et al.* [51]	Switzerland	University hospital at Lusanne	Adults and elderly >16 years old; mean age, 61.4 years (16–93 years)	WHO definition	6	4840	7	9.2	67
Mannesse *et al.* [52]	The Netherlands	University hospital in Rotterdam	Elderly >70 years old	An undesirable clinical manifestation consequent to and caused by the administration of a particular drug or interacting drugs, excluding intentional overdose, substance abuse and therapeutic failure	4	106	12	24	NR
Rodenburg *et al.* [41]	The Netherlands	Dutch National Medical Register	Adults and elderly	An ADR-related hospitalization was defined as a hospitalization with an E-code as secondary diagnosis, indicating an ADR as the mean reason for hospitalization	72	14 207	54	NR	NR
Van Der Hooft *et al.* [25]	The Netherlands	Nationwide computer database for hospital discharge records	Whole population of mean age 48.5 years; only adults and elderly >18 years old were considered	WHO definition	12	668 714	2.03	1	NR
Jayarama *et al.* [27]	India	Jalappa hospital, Kolar emergency department	Adults of mean age 49.5 years (20–79 years)	WHO definition	12	133	37.6	18	18
Varallo *et al.* [26]	Brazil	Private Hospital at São Paulo State	Adults and elderly >60 years old	WHO definition	1	308	54.5	NR	NR

Abbreviations are as follows: ADR, adverse drug reaction; NR, not reported; WHO, World Health Organization. *Patients died. †Geriatric patients. The severity indicated the percentage of reported severe and/or fatal injuries. The WHO definition for an adverse drug reaction is as follows: any noxious, undesired and unattended drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis.

Table 2

Characteristics of studies that investigated adverse drug event-related hospitalizations

Reference	Country	Study settings	Population age (years)	Definition used	Duration (months)	Sample size (patients)	Prevalence rate (%)	Severe cases (%)	Preventability (%)
		Retrospective studies							
Briant *et al.* [33]	New Zealand	Medical records from 13 public hospitals	Adults and elderly of mean age 58.6 years	Unintended injury, resulting in disability and caused by healthcare management rather than the underlying disease process	12	6579	1.99	NR	100*
Gurwitz *et al.* [32]	USA	Medical enrollees	Elderly >65 years old	An injury resulting from the use of a drug	12	30 397	5	38†	27.6
		Prospective and observational studies							
Peyriere *et al.* [36]	France	Internal Medicine Unit A of the Saint-Eloi University Hospital, Montpellier	Adults and elderly of mean age 66.5 years (19–79 years)	An injury resulting from the use of a drug	2	156	20.5	NR	57.9
Chan *et al.* [37]	Australia	Royal Hobart Hospital	Elderly patients >75 years old; mean age, 81.8 years	Ocurring if one drug caused one or more adverse manifestations or if two or more drugs contributed to one adverse manifestation	2	240	30.4	15.7	53.4
Edwards *et al.* [34]	USA	Banner Desert Medical Center, Mesa	Adults and elderly >17 years old; mean age, 66.3 years	An injury resulting from the use of a drug	24‡	62 064	2.4	4.2§	NR
Benkirane *et al.* [35]	Morocco	General Teaching Hospital, Rabat	Adult population of mean age 44.3 years (18.9–59.7 years)	When a patient is unintentionally harmed as a result of drug use, including preventable and nonpreventable events	0.24	1390	4.2	2	13.2

Abbreviation is as follows: NR, not reported. *The study by Briant *et al.* investigated preventable adverse drug events in particular. †Considered as fatal, serious and life threatening. ‡The incidence rate has been estimated to be in the range of 19–29% and its mean (24%) has been considered. §Only 4.2% (63 patients) were considered severe, of whom 49 patients died.

Table 3

Characteristics of studies that investigated medicine-related problem-related hospitalizations

Reference	Country	Study settings	Population size	Definition used	Duration (months)	Sample size (patients)	Prevalence rate (%)	Severe cases (%)	Preventability (%)
		Retrospective studies							
Claydon-Platt *et al.* [39]	Australia	Inner-city Australian teaching hospital	Adults and elderly >18 years old	Medication errors due to hypoglycaemia, poisoning and accidental poisoning and adverse drug reactions*	24	5205	7.2	NR	NR
Kalisch *et al.* [38]	Australia	Australian veteran population	Elderly of median age 81 years	MRH defined by the clinical indicator (ATC for medicines and ICD-10 codes for diseases)	60	10 904	13.3	NR	20.3
Koh *et al.* [40]	Singapore	Alexandra Hospital	Adults and elderly 16–97 years old	Hallas criteria for causality	2	347	10.8	NR	100
Yee *et al.* [42]	USA	Veterans Affairs Hospital	Adults and elderly >18 years old; mean age, 60.2 years	WHO definition of ADR	12	2169	12.6	NR	NR
Zaman Huri and Fun Wee [44]	Malaysia	Malaysia's premier teaching hospital at the University of Malaya Medical Centre (UMMC)	Adult patients >18 years old	An event or circumstance that actually or potentially interferes with desired health outcome	12	200	90.5	NR	NR
		Prospective and observational studies							
Andreazze *et al.* [54]	Brazil	Hospital de Clinicas de Porto Alegre	Adult population of mean age 44.9 years (23.7–54.1 years)	Classification of the Brazilian Pharmaceutical Care Consensus: classified by evaluating three distinct criteria of pharmacotherapy, i.e. indication, effectiveness and safety. Suspected ADRs were classified according to Naranjo's algorithm	1	350	31.6	NR	NR
Baena *et al.* [58]	Spain	University Hospital Virgen de las Nieves in Granada	Adult population of mean age 41.92 years	Pharmacotherapy negative clinical outcome prevalence (MRP); represents a broad concept, including safety, necessity and effectiveness resulting from pharmacotherapy as a process of care	12	2261	33.17	73	NR
Howard *et al.* [45]	UK	Teaching Hospital in Nottingham	Adult population (mean age, 62 years)	Hallas criteria for causality and Helper criteria for preventability	6	4039	6.5	NR	67
Malhotra *et al.* [53]	India	Medical emergency department of tertiary care referral hospital in North India	Elderly >65 years old; mean age, 72.5 years (65–91 years)	WHO definition	7	578	14.4	NR	NR
Santamaria-Pablos *et al.* [43]	Spain	Department of University Hospital, Cantabria	Adult population (mean age, 65.6 years)	Negative results related to drugs based on five criteria to assess the causality of ADR: literature, chronology, evolution, reappearance of tests and alternative cause	3	163	16.6	10.4†	23

Table 3
Continued

Reference	Country	Study settings	Population size	Definition used	Duration (months)	Sample size (patients)	Prevalence rate (%)	Severe cases (%)	Preventability (%)
Leendertse *et al.* [5]	The Netherlands	21 Dutch Hospitals	Adults and elderly >18 years old	MRHs were defined as hospitalization due to ADEs: harm due to adverse effects of medication use or due to medication errors	1.3	13 000	5.6	NR	2.55
Koneri *et al.* [31]	India	Kempegowda Institute of Medical Sciences, Bangalore	Adult patients between 18 and 80 years old	WHO definition for ADR. ADR and DTF were used. The criteria for rating DTF were made using Naranjo classification	6	2340	6.4	NR	64
Juntti-Patinen and Neuvonen [46]	Finland	Helsinki University Central Hospital	Adult population who died in the hospital; mean age, 65 years (24–93 years)	WHO definition for ADR	12	1511	5	NR	NR
Repp *et al.* [30]	USA	St Luke's Hospital	Adults and elderly >18 years old; mean age, 53.1 years	Helper and Strand criteria for DRP, Harvard Medical Practice scale to assess DRP and Naranjo scale to assess ADR	36	48‡	40	NR	58
Singh *et al.* [47]	India	Department of Internal Medicine at the Government Medical College, Jagdalpur	Adult population of mean age 49.1 years	WHO definition of ADR; Helper and Strand criteria	72	3560	3.31	6.78	78
Samoy *et al.* [48]	Canada	Internal Medicine Unit: Vancouver General	Adult and elderly population of mean age 69.3 years	WHO definition of ADR; Helper and Strand criteria	3	565	24.1	7.4	72.1
Rogers *et al.* [59]	UK	North London Hospital	Adult population >65 years old	WHO definition of ADR; Helper and Strand criteria	3	409	6.4	NR	69.1
Zed *et al.* [55]	Canada	Emergency department at University of British Columbia teaching hospital	Whole population; only adult population >18 years old were considered	WHO definition; Helper and Strand criteria	3	1017	11.55	9.8	83

Abbreviations are as follows: ATC, WHO anatomical and therapeutic classification of diseases; DTF, dose-related therapeutic failure; ICD-10, WHO international statistical classification of diseases and related problems; NR, not reported; MRH, medicine-related hospitalization; WHO, World Health Organization. The WHO definition for an adverse drug reaction is as follows: any response to a drug which is noxious and unintended, and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. *This definition was used due to the purpose of the study. †Out of the 10.4%, there were 17 moderate, eight serious and one death. ‡Transplant patients.

Table 4

Medicine classes associated with medicine-related problems leading to hospital admission

Study	No. of patients	No. of MRPs	Cardiovascular disease Number (%)	Anti-infective Number (%)	Anticancer Number (%)	Antidiabetic Number (%)	Anti-inflammatory/analgesic Number (%)	Others Number (%)
Adverse drug reactions								
Ahren *et al*. [28]	856	75	CVD drugs, 73 (46.5); diuretics, 22 (14); ACEI/antihypertension/ anticoagulants	NR	Chemotherapy, 10 (6.37)	Insulin, 1 (0.64); oral hypoglycaemic, 1 (0.64)	NR	CNS drugs, 50 (31.8)
Carrasco-Garrido *et al*. [15]	350 835	350 835	Anticoagulants, 26 546 (7.57)	Antibiotics, 22 144 (6.31)	Antineoplastic/immunosuppressant, 75 760 (21.6)	NR	Adrenal corticosteroids, 47 539 (13.6)	NR
Van der Hooft *et al*. [16].	2238	115	CVD drugs, 32 (27.8)	Anti-infectives, 6 (5.22); antimalarials, 1 (0.87)	Antineoplastic/immunosuppressant, 22 (31.3)	NR	NSAIDs, 9 (7.83)	GIT drugs, 3 (2.61); CNS drugs, 19 (16.5); blood-forming organs, 40 (34.8); hormones, 11 (9.57); respiratory, 1 (0.87)
McDonnell and Jacobs [17]	20 166	158	Anticoagulants/cardiotonics/ antihypertensives/diuretics, 54 (34.2)	Antibiotics, 10 (0.87)	Anticancer/immunosuppressant, 36 (22.8)	Antidiabetics, 17 (11.04)	Opiates, 4 (2.59); NSAIDs, 9 (5.84)	Anti-epileptics/antidepressants/ antipsychotics, 21 (13.6); antihyperlipidaemics, 3 (1.95)
Ruiter *et al*. [18]	2 127 133	27 653	Anticoagulants	NR	NR	Antidiabetics	Salicylates/antirheumatics	
Wawruch *et al*. [20]	600	47	ACEI/β-blocker/CCB/digoxin/ amiodarone/potassium-sparing diuretics/warfarin/ATB, 35 (74.4)	NR	NR	NR	Opioid, 1 (2.1); NSAIDs/corticosteroids, 3 (6.4)	Propulsive/atypical antipsychotic, 2 (4.25); statin, 2 (4.25)
Wu *et al*. [19]	6 830 067	557 978	CVD drugs, 851 (0.15)	Systemic antibiotics/ anti-infective/ antiparasitic, 8314 (1.49)	NR	NR	Analgesics/antipyretics/anti-inflammatory, 877 (0.16)	CNS drugs/anti-epileptics/ antiparkinson/sedative/hypnotic/ anti-anxiety/psychotropic, 7061 (1.26); GIT drugs, 857 (0.15)
Franceschi *et al*. [56]	1756	102	Antiplatelets/CVD disorders/warfarin/digoxin/ amiodarone/ACEI, 75 (73.4)	Antibiotics, 30 (2.9)	NR	NR	Analgesics, 30 (2.9); NSAID, 24 (23.5); aspirin, 14 (13.7)	GIT drugs, 48 (47.1)
Hopf *et al*. [22]	1101	30	CVD drugs, 16 (53.3)	NR	Cytotoxic, 2 (6.67)	NR	Opioid, 5 (16.7); NSAID, 9 (30)	Antipsychotic, 3 (0.1)
Pérez Menéndez-Conde *et al*. [50]	252	49	CVD drugs, 7 (14)	NR	Antineoplastic/immunosuppressant, 19 (38)	NR	NR	Hormone therapy, 15 (30.6); thyroid drugs, 12 (23.5)
Onder *et al*. [57]	28 411	1704	Diuretics/CCB/ digoxin/anticoagulants/ACEI/ antiplatelet, 497 (29.2)	Antibiotics, 63 (3.69)	Antineoplastic, 30 (1.76)	NR	NSAIDs, 81 (4.75); corticosteroids, 40 (2.34)	Antipsychotic, 40 (2.35); benzodiazepines, 33 (1.94)
Thuermann *et al*. [29]	41 375	993	Antithrombotic, 267 (26.9); CCB/β-blocker/digitalis, 50–80 (5–8)	NR	NR	Oral antidiabetic, 63 (6.3); insulin, 152 (15.3)	NSAIDs, 153 (15.4)	NR
Mjörndal *et al*. [23]	681	99	Amlodipine/atenolol/cholestyramine/ cilazapril/digoxin/diltiazem/enalapril/ felodipine/furosemide/glyceryl trinitrate/hydrochlorothiazide/ irbesartan/isosorbide/metholazone/ metoprolol/nifedipine/ramipril/sotalol/ verapamil/aspirin/dipyridamole/ticlopidine/ warfarin, 59 (59.6)	Ceftriaxone/ciprofloxacin/ influenza vaccine/ metronidazole, 5 (5.05)	Amsaparine/azathioprine/ chlorambucil/cyclophosphamide/ doxorubicin/tamoxifen, 7 (7.05)	Glibenclamide, 2 (2.02); human insulin, 6 (6.06); metformin, 1 (1.01)	Dextropropoxyphene/naproxen/ paracetamol, 4 (4.04); betamethasone/budesonide/ cortisone/methyl prednisolone/ ketobemidone, 10 (10.1)	Antiparkinson, 16 (16.2); flunitrazepam, 2 (2.02); nefazodone, 1 (1.01), oxazepam, 2 (2.02); paroxetine, 1 (1.01); risperidone, 1 (1.01); venlafaxine, 2 (2.02); amsacrine, 1 (1.01); azathioprine, 2 (2.02); chlorambucil, 1 (1.01); antiparkinson, 4 (4.04); GIT drugs, 12 (12.1); hormone replacement therapy, 10 (10.1)

Table 4

Continued

Study	No. of patients	No. of MRPs	Cardiovascular disease Number (%)	Anti-infective Number (%)	Anticancer Number (%)	Antidiabetic Number (%)	Anti-inflammatory/analgesic Number (%)	Others Number (%)
Gholami *et al.* [24]	518	105	Diltiazem, 25 (23.5); atenolol, 3 (3)	NR	NR	NR	NR	NR
Pirmohamed *et al.* [21]	18 820	1225	Diuretics, 334 (27.3); warfarin, 129 (10.5); ACEI and ATB, 94 (7.7); β-blocker, 83 (6.8); digoxin, 36 (2.9); clopidogrel, 29 (2.4)	NR	NR	NR	Opioid, 73 (6); NSAID, 363 (29.6); aspirin, 218 (17.8); prednisolone, 31 (2.5)	Antidepressants, 87 (7.1)
Wasserfallen *et al.* [51]	4840	339	CVD, 107 (31.6); anticoagulant, 31 (9.14); cardiotonic, 21 (6.19); hypotensive, 27 (7.96); diuretic, 23 (6.79); β-blocker, 5 (1.49)	Antibiotics, 16 (4.72)	Cytostatic, 84 (24.78)	Antidiabetic, 17 (5.02)	NSAIDs, 30 (8.85); corticosteroids, 14 (4.13)	Psychotropic, 18 (5.31); psycholeptic, 13 (3.83)
Mannesse *et al.* [52]	106	13	CVD drugs	NR	NR	NR	NR	CNS drugs; GIT drugs
Van Der Hooft *et al.* [25]	668 714	12 238	Anticoagulants, 2185 (17.9); diuretics, 979 (7.99)	NR	Cytostatic/immunosuppressive, 1809 (14.8)	Insulin/other antidiabetics, 541 (4.42)	Salicylates, 509 (4.16); antirheumatic, 496 (4.05)	NR
Varallo *et al.* [26]	308	168	CVD drugs, 63 (37.7)	NR	NR	NR	NR	CNS drugs, 58 (34.6); GIT drugs, 34 (20); respiratory, 10 (5.7)
Malhotra *et al.* [53]	578	32 (ADR)	Digoxin, 2 (6.25)	Antituberculosis, 5 (15.6); penicillins, 2 (6.25)	Cancer chemotherapy, 5 (15.6)	Oral hypoglycaemic, 12 (37.5)	NSAIDs, 6 (18.8)	Phenytoin, 2 (6.25)
Jayarama *et al.* [27]	133	50	Fluoroquinolones, 4 (8%); cotrimoxazole, 1 (2); rifampicin/isoniazide, 2 (4)	NR	NR	Insulin, 8 (6)	NSAIDs, 16 (32); glucocorticoids, 10 (20)	Phenytoin, 2 (4); domeperidone, 1 (2); lignocaine, 1 (2); esomeprazole, 1 (2); flunarizine, 1 (2); prochloperazine, 1 (2); iron sucrose, 1 (2); pyrazinamide, 1 (2)
Adverse drug events								
Briant *et al.* [33]	6579	131	ACEI/diuretics, anticoagulants, warfarin, 7 (0.76); amiodarone, CCB, digoxin, β-blocker, 59 (45.1)	Antibiotics, 18 (13.7)	NR	NR	NSAIDS, 9 (6.9); aspirin, 8 (6.11)	Centrally acting, 23 (17.5); opiates, 8 (6.11)
Gurwitz *et al.* [32]	30 397	1520	CVD drugs, 720 (47.2); diuretics, 203 (13.3); anticoagulants, 121 (7.9)	Antibiotics, 224 (14.7)	NR	Hypoglycaemic, 103 (6.8)	Opioid, 74 (5.9); non-opioid analgesics, 180 (11.8); steroids, 80 (5.3)	Neuropsychiatric, 131 (8.6); GIT drugs, 321 (21.1); metabolic/endocrine, 210 (13.8)
Peyriere *et al.* [36]	156	32	CVD, 13 (39.5)	Anti-infective, 4 (13.2)	Antineoplastic, 3 (7.9)	NR	NR	Psychotropic, 10 (31.6)
Chan *et al.* [37]	240	73	ACEI/diuretics/β-blocker/calcium antagonist/digoxin/nitrates/warfarin, 61 (83.6)	NR	NR	NR	Aspirin, 5 (6.85); corticosteroids, 7 (9.59); NSAIDs, 6 (8.22)	Benzodiazepines, 6 (8.22); phenothiazines, 6 (8.22); antidepressants, 1 (1.36); SSRI, 5 (6.85); tricyclics, 4 (5.47); antiparkinsonian, 3 (4.1); anti-epileptics, 1 (1.36)
Edwards *et al.* [34]	62 064	1495	Anticoagulant/antiplatelet/ACEI and ATB/diuretics/β-blocker/CCB/ anti-arrhythmic/antihypertensive, 572 (38.3)	Antimicrobial, 47 (3.14)	Antineoplastic, 15 (1)	Antidiabetic, 121 (8.29)	Opioid, 136 (9.1); NSAID/acetaminophen, 250 (16.7)	Antidepressant, 60 (4.01); antipsychotic, 11 (11.73)
Benkirane *et al.* [35]	1390	76	Anticoagulants, 4 (5.2)	Antibiotics, 5 (6.6)	NR	NR	Analgesics, 13 (17.1); anti-inflammatory, 9 (11.8)	GIT, 20 (26.3)

Medicine-related problem								
Claydon-Platt *et al.* [39]	5205	686	NR	NR	NR	Antidiabetic, 6 (0.87)	Analgesics, 5 (0.73)	Benzodiazepines, 5 (0.73)
Rodenburg *et al.* [41]	41 785	14 207	CVD, 7690 (54); anticoagulants and salicylates, 8988 (63.3); high- and low-ceiling diuretics, 2242 (15.8); cardiotonic glycosides, 932 (6.56)	NR	NR	NR	NR	NR
Yee *et al.* [42]	2169	274	Anticoagulants, 10 (3.64); diuretic, 4 (1.45); ACEI, 3 (1.09); β-blocker, 3 (1.09); CCB, 3 (1.09); α-blocker, 3 (1.09)	Anti-infective, 6 (2.18)	Chemotherapy, 6 (2.18)	NR	Narcotic analgesic, 3 (1.09); aspirin and NSAIDs, 4 (1.45)	Antipsychotic, 2 (30.73)
Howard *et al.* [45]	4039	263	Aspirin, β-blocker, anti-epileptic, diuretic, digoxin, nitrates	NR	NR	Sulfonyl urea, insulin	NSAID	NR
Santamaria-Pablos *et al.* [43]	163	53	CVD: nitroglycerine, furosemide, digoxin, diltiazem, quinapril	Systemic anti-infective	NR	NR	NR	CNS, locomotive system, GIT drugs, hormonal, 4%
Leendertse *et al.* [5]	13 000	714	Antiplatelet, 29 (4.06); oral anticoagulants, 21 (2.94)	NR	NR	Antidiabetic, 41 (5.74)	NSAID, 17 (2.38)	CNS, 17 (2.38)
Koneri *et al.* [31]	2340	150	CVD, antihypertensive	Antibiotic, antituberculosis, antiretroviral	NR	Antidiabetic	NSAID, steroid	Anticonvulsant, respiratory drug, H_1 antagonist
Jutti-Patinen and Neuvonen [46]	1511	76	Warfarin, 15 (19.7); heparin, 5 (6.58); alteptase/streptase, 2 (2.64); anticoagulants, 20 (26.4); antihypertensive, 1 (1.32)	Antibiotic, 2 (2.64)	Cytostatic/immunosuppressant, 23 (30)		Corticosteroids, 4 (5.26); NSAIDs, 12 (15.8)	Antipsychotic, 2 (2.64)
Repp *et al.* [30]	48	19	Anticoagulants	Antimicrobial	Immunosuppressant	NR	NR	NR
Singh *et al.* [47]	3560	118	Antihypertensive	NR	Chemotherapy	Insulin; hypoglycaemic agents	NR	NR
Samoy *et al.* [48]	565	136	CVD, anticoagulants, furosemide, warfarin, ramipril, spironolactone	Antibiotics	NR	Hypoglycaemics	NSAIDs, aspirin	CNS
Rogers *et al.* [59]	409	57	CVD, 11 (19.3)	NR	NR	NR	NR	NR
Zed *et al.* [55]	1071	122	NR	Antimicrobial, 20 (16.4)	NR	NR	Opioid-containing analgesics, 20 (16.4)	Antipsychotic, 17 (13.9); benzodiazepines, 11 (9.02)
Andreazza *et al.* [54]	350	123	CVD, 17 (14); captopril, 6 (5.14)	NR	NR	NR	NR	CNS, 16 (13.2); lithium, 6 (4.87)

Abbreviations are as follows: ACEI, angiotensin-converting enzyme inhibitor; ATB, angiotensin receptor blocker; CCB, calcium channel blocker; CNS, central nervous system; CVD, cardiovascular disease; GIT, gastrointestinal tract; MRP, medicine-related problem; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; SSRI, selective serotonin reuptake inhibitor. The number and percentage of medicines associated with MRPs is calculated in reference to the number of MRPs reported in the study.

Causes of medicine-related problems

The underlying causes identified were reported in only 20 of the 45 studies [5, 16, 21, 23, 31–33, 35, 37, 40, 42, 45, 47, 48, 50–55], as follows: seven ADR studies [15, 23, 50–53], four ADE studies [32, 33, 35, 37] and nine MRP studies [5, 31, 40, 42, 45, 47, 48, 54, 55]. In all these studies, ADR and noncompliance were the main causes leading to hospitalization. Additional causes included the following: treatment effectiveness [16, 44, 50], intoxication [23], undertreatment and inadequate instructions [33, 35, 37, 40, 42, 45, 48, 50, 53–55], cost [53], insufficient laboratory test monitoring [16], polypharmacy [37], drug–drug interaction [37, 42, 44, 48], toxicity [37], comorbidities [5], impaired cognition [5], patient's insufficient awareness of health and disease [44] and drug allergy [42].

Risk factors

Nine risk factors were reported in the studies and contributed to MRPs either through direct correlation with the MRP itself or indirectly by affecting the causes of MRPs.

Old age [15–20, 24–26, 33, 36, 37, 39–41, 44, 50–52, 55–58] and polypharmacy [15, 17, 18, 20, 23, 24, 26, 31, 36, 37, 40, 44, 49, 50, 52–54, 56–59] were the main risk factors reported in most studies. Furthermore, some studies reported gender as a risk factor; females were more likely to develop MRPs [16, 18, 19, 24, 34, 39–41, 53, 55, 57]. Fewer studies reported depression (three studies) [5, 20, 39], education (two studies) [54, 56], cohabitation (two studies) [5, 39, 56] and immobilization (one study) [20] as risk factors.

Discussion

The findings of this systematic review suggested that hospitalization due to ADR/ADE/MRP had a high prevalence that had a rate of more than 50% in some studies. However, the median prevalence rates varied between 4.6 and 12.1% for the three types of studies. More specifically, ADRs had a median prevalence rate of 7% (IQR, 2.4–14.9%), which was higher than the prevalence rates reported by three former systematic reviews [10, 13, 60]; these three reviews reported prevalence rates ranging between 3.1 and 5.3%. The difference in the result could be attributed to two main reasons. The first is that the present review included and compared retrospective with prospective studies. The second reason is that the present review focused on MRPs leading to hospitalization in adult/elderly patients and excluded the paediatric population. Adults and elderly patients have a higher prevalence of ADRs due to a high number of comorbidities and polypharmacy [15, 17, 18]. For instance, Van der Hooft *et al*. [16] found that adults had more than 10-fold prevalence rate (9.8%) of ADRs compared with younger populations (0.4%).

In addition, the median prevalence rate of hospitalization due to ADEs found in the present systematic review was 4.6% (IQR, 2.85–16.6%). This was different from the three previous systematic reviews investigating hospitalization due to ADEs. These reviews reported a wide variation in the prevalence rates, which were 1.46% [61], 20.1% [62] and 30% [63]. Those three reviews investigated more than 20 studies relating to ADEs, whereas in our systematic review only six studies were investigated.

On the other hand, our review studies investigating hospitalization due to MRPs revealed a much higher median prevalence rate of 12.1% (IQR, 6.43–22.2%) compared with the only former review, which showed a prevalence rate of 3.7% [8]. However, the wide difference between the results of the two reviews could be attributed to the fact that the previous systematic review included only observational studies and excluded studies conducted in an emergency setting, which was not the case in the present review.

Severe cases and preventability were under-reported in the studies assessed in the present systematic review. Only few studies reported severe cases, whether investigating hospitalization resulting from ADRs, ADEs or MRPs. The highest number of severe cases reported was 24% for ADRs, 38% for ADEs and 73% for MRPs. Moreover, the highest preventability rates reported for hospitalization leading to ADRs, ADEs and MRPs were 78, 57.9 and 100%, respectively. However, the study reporting 100% preventability rate [40] was a pilot study with a small sample size (n = 347). The preventability, along with an understanding of the causes, is crucial in constructing interventions to minimize/eliminate MRPs [62]. Additionally, the causes help in understanding why the problem has occurred [61]. The present systematic review identified the two major causes as ADRs and noncompliance, which was consistent with the result identified by Howard *et al*. [8]. In addition, old age and polypharmacy were over-represented as risk factors among patients admitted to hospitals with ADRs, ADEs and MRPs. Thus, older people have altered pharmacodynamics/pharmacokinetic parameters and underlying comorbidities, which could influence the effect of the medicines in the body [13, 15] and result in an alteration of the metabolism and excretion of medicines. This was found by Chan *et al*. [37] and Zaman Huri and Fun Wee [44], who found that elderly age along with CVDs increased the prevalence of MRPs. This was because approximately 60% of the elderly patients with MRPs in the latter study were suffering from CVDs. In addition, Taché *et al*. [62] found that age-related differences influence the disease and prescription, thus affecting MRPs.

The present review identified the major classes of medicines associated with MRPs as CVD, anti-infective, anticancer, antidiabetic and anti-inflammatory medicines. This was similar to previous systemic reviews, in which CVD medicines were reported as the main class of medicines leading to ADRs [13], ADEs [61, 62] and MRPs [8,

10, 32, 34, 64, 65]. These studies also reported medicines treating the CNS and nonsteroidal anti-inflammatory drugs, antidiabetics, anti-infectives and analgesics. The CVDs comprised chronic conditions, which required multiple medicine regimens (or polypharmacy), and this contributed to MRPs.

Strengths and limitation of the study

This systematic review involved investigation of data from previous studies by two independent reviewers. After studies were identified, a third reviewer verified the results in order to avoid bias. Moreover, the articles were investigated manually and then inclusion/exclusion criteria were applied to meet the research objectives, to identify the prevalence rate, causes, risk factors and main medicine classes of hospitalization resulting from MRPs in adult patients. However, the systematic review still suffered from some limitations. First, due to the heterogeneity in the data, it was not possible to take a meta-analytical approach. Instead, the median and IQR were used to compare ADR/ADE/MRP prevalence rates. The heterogeneity in the data was mainly encountered due to differences in the country, study settings, sample size and study duration. The studies were obtained from 19 countries, so it might not be possible to make a conclusive judgment for all countries. Moreover, the review was not able to obtain decisive data regarding severe cases and preventability, which were not reported in many studies.

Conclusion

Hospitalization resulting from MRPs represented a major issue in both prospective and retrospective studies. The hospitalization rate had a higher prevalence in patients admitted due to MRPs (12.1%) than patients admitted due to ADRs (7%) and ADEs (4.6%). Most MRPs were encountered among adult patients admitted with CVDs and diabetes. The main causes of hospitalization due to MRPs were ADRs and noncompliance. In addition, old age and polypharmacy were highly represented among patients admitted to hospitals due to MRPs.

Competing Interests

All authors have completed the Unified Competing Interest Form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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