Ambulatory Care

Systematic Review of the Incidence and Characteristics of Preventable Adverse Drug Events in Ambulatory Care

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OBJECTIVE: To estimate the incidence and describe characteristics of preventable adverse drug events (pADEs) in ambulatory care.

DATA SOURCES: Studies were searched in PubMed (1966–March 2007), *International Pharmaceutical Abstracts* (1970–December 2006), the Cochrane database of systematic reviews (1993–March 2007), EMBASE (1980–February 2007), and Web of Science (1945–March 2007). Key words included medication error, adverse drug reaction, iatrogenic disease, outpatient, ambulatory care, primary health care, general practice, patient admission, hospitalization, observational study, retrospective studies, health services research, and follow-up studies. Additional articles were found in the reference sections of retrieved articles.

STUDY SELECTION AND DATA EXTRACTION: Peer-reviewed articles assessing pADEs in ambulatory care, with detailed descriptions/frequency distributions of (1) ADE/pADE incidence, (2) clinical outcomes, (3) associated drug groups, and/or (4) underlying medication errors were included. Study country, year and design, sample size, follow-up time, ADE/pADE identification method, proportion of ADEs/pADEs and ADEs/pADEs requiring hospital admission, and frequency distribution of adverse outcome, associated drug groups, or medication errors were extracted.

DATA SYNTHESIS: Twenty-nine studies met inclusion criteria: 14 were ambulatory-based and 15 were hospital-based. Seven studies enrolled only elderly patients. The median ADE incidence was 14.9 (range 4.0–91.3) per 1000 person-months, and the pADE incidence was 5.6 per 1000 person-months (1.1–10.1). The median ADE preventability rate was 21% (11–38%). The median incidence of ADEs requiring hospital admission was 0.45 (0.10–13.1) per 1000 person-months, and the median incidence of pADEs requiring hospital admission was 4.5 per 1000 person-months. Cardiovascular drugs, analgesics, and hypoglycemic agents together accounted for 86.5% of pADEs, and 77.2% of pADEs resulted in symptoms of the central nervous system, electrolyte/renal system, and gastrointestinal tract. Medication errors resulting in pADEs occurred in the prescribing and monitoring stages. The most frequent drug therapy problem and error of commission reported in ambulatory-based studies on pADEs was the use of inappropriate drugs (42.7%; 40.4–45%). For pADEs requiring hospital admission, the most frequent drug therapy problem and error of omission reported was inadequate monitoring (45.4%; range 22.2–69.8%). Failure to prescribe prophylaxis to patients taking nonsteroidal antiinflammatory drugs or antiplatelet drugs frequently caused gastrointestinal toxicity, whereas lack of monitoring of diuretic, hypoglycemic, and anticoagulant use caused over- or under-diuresis, hyper- or hypoglycemia, and bleeding.

CONCLUSIONS: ADEs in ambulatory care are common, with many being preventable and many resulting in hospitalization. Quality improvement programs should target errors in prescribing and monitoring, especially for patients using cardiovascular, analgesic, and hypoglycemic agents.

KEY WORDS: ambulatory care, medication errors, preventable adverse drug events.

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The seminal Institute of Medicine (IOM) report on patient safety from 1999 estimated that medical error is the eighth leading cause of death in the US.[1] While the report provided extensive detail on the epidemiology of medication errors and their sequelae, as well as data on preventable adverse drug events (pADEs) in acute care, it concluded that little is known about the ambulatory care settings. Some studies have reported frequency estimates of preventable drug-related hospital admissions, but a substantial part of pADEs may occur in ambulatory care. While many of these do not require hospital admission, they present serious implications for patients and strain healthcare resources.[2-8] No previous systematic review that provides a comprehensive assessment of the frequency of pADEs occurring in ambulatory care is available.

A second gap in the available information on pADEs in ambulatory care is a systematic assessment of their frequency and characteristics. Such an assessment would identify the most prevalent and serious types of pADEs, which in turn could assist in focusing quality improvement programs.

This review aims to estimate the incidence of pADEs in ambulatory care and describe their characteristics, defined by type of clinical outcome, type of medication error causing pADEs, and drug categories most frequently associated with these pADEs.

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Methods

TERMINOLOGY

The following definitions were used in accordance with the IOM report on medical errors. An adverse event is an injury resulting from a medical intervention, with an adverse drug event (ADE) being the result of drug therapy.[1] A pADE is an ADE attributable to a medication error. An error is defined as the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. Medication errors include errors of commission (taking the wrong action) and errors of omission (failing to take action). Applied to drug therapy, errors of commission are direct consequences of drug therapy, such as toxicity caused by inappropriate use of contraindicated or interacting drugs or overdosing. Errors of omission are indirect consequences of drug therapy, such as therapeutic failure caused by failure to prescribe an indicated medication, ignoring available clinical results, or failure to provide adequate drug monitoring.

LITERATURE SEARCH

Studies of pADEs in the ambulatory setting were searched in March 2007 in the following bibliographic databases: PubMed (1966–March 2007), *International Pharmaceutical Abstracts* (IPA) (1970–December 2006), the Cochrane database of systematic reviews (1993–March 2007), EMBASE (1980–February 2007), and Web of Science (1945–March 2007). The searched key words were based on the index system used by each database. The MeSH terms searched in PubMed were (medication errors or adverse drug reaction reporting systems or drug therapy/adverse effects or iatrogenic disease/drug therapy) and (emergency medical services or primary health care or patient admission or hospitalization or outpatients or ambulatory care) and (retrospective studies or health services research or follow-up studies or cohort studies). The keywords searched in IPA and Web of Science were (medication error or iatrogenic disease or adverse drug reaction or ADR or adverse drug event) and (outpatient or ambulatory or hospitalization or emergency or primary care). The MeSH term searched in the Cochrane database was medication errors. The EMTREE key words searched in EMBASE were (adverse drug reaction or medication error or iatrogenic disease) and (hospital admission or hospitalization or ambulatory care or outpatient care or primary medical care or emergency care). References were reviewed manually and, if the abstract was found to be relevant, the full article was retrieved. Additional articles were found in the reference section of retrieved articles and through manual search.

Articles published in English in peer-reviewed journals from any country were included provided they fulfilled a set of predetermined criteria. First, the articles had to provide an overall assessment of the epidemiology of pADEs in the ambulatory setting, that is, studies that addressed only particular pADEs or pADEs in patients with a particular disease were excluded, as were studies solely on children. Furthermore, the studies had to give detailed descriptions or frequency distributions of at least one of the following: (1) the incidence of ADE or pADE, (2) the types of clinical outcomes, (3) the types of drugs/drug groups associated, and/or (4) the types of medication errors that caused ADEs or pADEs.

Studies either followed a cohort of patients in ambulatory care (incidence or ambulatory-based studies) or reviewed hospital admissions and determined the proportion attributable to pADEs acquired in ambulatory care (prevalence or hospital-based studies). Only incidence studies were used to estimate the incidence of pADEs, whereas both incidence and prevalence studies were used to describe characteristics of pADEs.

DATA EXTRACTION

A data extraction form was used to extract the following information: study country and year, study design, methods used to identify ADEs and pADEs, sample size, follow-up time, proportion of persons with ADEs and pADEs, proportion of ADEs and pADEs requiring hospital admission, frequency distribution of type of adverse outcome, and drug groups associated with or type of medication error that caused the event.

DATA ANALYSIS

Although the aim of this article is to characterize pADEs in ambulatory care, characteristics of ADEs in ambulatory care are reported throughout the article for comparative reasons, as they often differ in nature from pADEs.

The individual studies used different measures to report the frequency of pADEs. Only incidence estimates were extracted for summative analysis. In this study, incidence was expressed either as number of patients with one or more ADEs per total number of patients at risk per time unit, or as total number of ADEs per total number of patients at risk per time unit. Thus, the total number of events or persons with events is reported per total follow-up time of the patient cohort (ie, events per 1000 person-months). Both types of incidences were calculated if possible. Incidence estimates were expressed using the smallest time unit common to all studies (person-months) to avoid extrapolations beyond the follow-up period of each study. The preventability rate of ADEs (ie, the percentage of ADEs deemed preventable) was calculated by dividing the total number of pADEs by the total number of ADEs multiplied by 100, using studies that provided information on

both types of ADEs. Results across studies were summarized using median and range. Definitions of an ADE and preventability varied considerably among studies. Therefore, we included ADEs and preventability rates reported in the individual studies without attempting to adjust these according to a common criterion.

We analyzed pADEs on 3 levels according to an approach by Kanjanarat et al.[9] on the nature of inpatient pADEs: types of outcomes associated with pADEs, drug categories involved, and the types of medication errors that cause the pADE. Proportions of ADEs or pADEs by type of error, drug, or outcome are reported using median and range. If this information was available, medication errors were described according to (1) the stage in the drug use process when the error occurred, (2) the type of drug-therapy problem, and (3) whether they were errors of commission or omission.[9]

To be able to compare findings across studies, it was sometimes necessary to collapse subcategories of drugs, outcomes, or errors to accommodate broader categories used by another study. Therefore, information from more detailed subgroups was lost. For example, not every study distinguished between nonsteroidal antiinflammatory drugs (NSAIDs) and opioids, and all analgesics were collapsed into one category.

As some studies reported only the drugs/drug groups most frequently associated with ADEs/pADEs, and because one ADE/pADE could be associated with more than one drug group, reported percentages do not always total 100%. Most investigations reported just the most frequent errors, drugs, and outcomes associated with ADEs or pADEs and placed the residual cases in categories named "miscellaneous" or "other." We therefore treated studies that did not report data on a specific category as missing those data and included only available data in the statistical analysis.

Lastly, some studies provided detail on combinations of types of outcomes, errors, and associated drugs. The most frequently mentioned combinations are explicitly described.

Results

Twenty-nine studies published between 1977 and 2003 met the inclusion criteria (Table 1),[2-8,10-36] with one study described in 6 separate articles.[28-33] Twenty studies were conducted in North America, 7 in Western Europe, and 2 in Australia. Fifteen studies were conducted in hospitals and were used only to analyze the nature of pADEs, and 14 cohort studies were conducted in ambulatory care, which allowed retrieval of incidence estimates as well as analysis of the nature of pADEs. The studies used a wide variety of methods to identify ADEs and pADEs, including expert review of charts, hospital discharge summaries, emergency department notes, face sheets, or adverse drug reaction reports; analysis of computer-generated signals; patient/patient representative or physician/nurse interview; solicited report by healthcare providers; and pharmacist clinical intervention documentation. Ten of the ambulatory-based studies enrolled adults in all age groups,[10,12,14,16,18-23] one study reported an average age of 71.6 years,[18] and 4 enrolled patients 65 years or older.[11,13,15,17] The hospital-based studies were conducted in a wide range of hospital departments; 3 studies enrolled patients 65 years or older,[5,24,27] and 12 studies enrolled patients in all age groups.[2-4,6-8,25,26,28-36]

INCIDENCE ESTIMATES

Eight studies were available from which to calculate incidence estimates.[10-15,17,23] The remaining 6 ambulatory-based studies were excluded because the sample size was not reported[16] or because follow-up time was less than one month, not defined,[18,19,22] or impossible to determine.[20,21] The median incidence of ADEs was 14.9 (range 4.0–91.3) per 1000 person-months,[10-15,17,23] or 16.7 (range 4.9–81.7) persons with an ADE per 1000 person-months.[10,13-15,17,23] The highest ADE incidence (91.3 ADEs per 1000 person-months) was found in the study with the shortest follow-up time (3 mo),[10] and the second highest ADE incidence was estimated in a study on elderly patients with polypharmacy.[13] The 2 studies reporting the lowest ADE incidence rates (range 4.0–5.6 per 1000 person-months) had the largest sample sizes and did not use patient interviews to identify ADEs.[11,12]

Two studies were available to estimate a pADE incidence at 5.6 (range 1.1–10.1) per 1000 person-months.[10,11] The median ADE preventability rate based on 4 studies was 21% (range 11–38%).[10-12,14] Eight studies also reported the proportion of ADEs requiring hospital admission, with an incidence of 0.45 (range 0.10–13.1) per 1000 person-months.[10-15,17,23] One study reported the proportion of pADEs requiring hospital admission, with an incidence of 4.5 per 1000 person-months.[10]

ADES, PADEs, AND PADEs REQUIRING HOSPITAL ADMISSION

Fourteen ambulatory-based studies reported detail on the drug groups associated with ADEs,[10-23] and 2 studies reported detail on drugs responsible for pADEs.[10,11] These ambulatory-based studies did not differentiate between drug groups associated with ADEs resolved in ambulatory and hospital care. In addition, 12 hospital-based studies reported the drug groups most frequently associated with pADEs resolved in hospital care (Table 2).[2-4,6-8,24-26,28-30,32,35,36] Cardiovascular drugs were the most frequently associated with ADEs (33.3%; range 1.1–73.6%), pADEs (47.0%; range 35–59.0%), and pADEs that required hospital admission (46.6%; range 6–80.0%).

Table 1. Characteristics of Included Studies

Reference	Country	Study Setting	Methods of ADE Identification	Inclusion/Exclusion Criteria	Pts., N	Time of Follow-Up	Definition and Assessment Criteria of ADE	Definition and Assessment Criteria of pADE
Bigby (1987)[25]	US	hospital	physician and pt. interview/ questionnaire, expert chart review	admissions through ED or primary care clinic; pts. not attending the hospital's primary care clinic excluded	686	9 mo	events due to ADRs[a]; structured implicit assessment criteria	NA
Campbell (1977)[20]	US	ambulatory	review of medical care contacts, morbidity codes, physician interview	5% sample of health plan members	22 992 person-years	36 mo	undesirable effect of a drug used for disease treatment, cure, prevention, or diagnosis	NA
Campbell (1978)[21]	US	ambulatory	review of medical care contacts, morbidity codes, physician interview	sample of poor families in prepaid medical care program	26 497 person-years	48 mo	undesirable effect of a drug used for disease treatment, cure, prevention, or diagnosis	NA
Cannon (1997)[24]	Northern Ireland	hospital	pt. medical notes, interview with pt. or pt. surrogate	nonelective admissions of elderly pts. (aged >65 y); transferals from other hospitals and pts. admitted >1 time during study period excluded	87	6 wk	NA; Karch and Lasagna causality criteria[37]	event that could have been avoided by more appropriate prescribing or by appropriate measure; Hallas et al. assessment criteria[29]
Chan (2001)[5]	Australia	hospital	expert chart review	emergency admissions to medical wards of pts. aged ≥75 y	219	8 wk	ADRs[38]; nonadherence, drug interaction, dosage decrease or cessation, overdose, omission of indicated treatment, inadequate medication, multiple drugs causing ADEs[39]; Hallas et al. causality criteria[29]	NA, Hallas et al. assessment criteria[29]
Chrischilles (1992)[15]	US	ambulatory	pt. interview	noninstitutionalized persons aged ≥65 y from 2 rural counties	3170	1 y	pt.-reported ADRs, unwanted reactions or problems from medications	NA
Darchy (1999)[4]	France	hospital	expert chart review	admissions to medicosurgical intensive care unit	623	1 y	unintended or noxious event caused by medical management carried out according to the best of medical science; Karch and Lasagna causality criteria[37]	event that should not occur if management is the best that medical science can provide
Darnell (1986)[18]	US	ambulatory	pt. interview	poor tenants in subsidized housing unit	155	NA	NA	NA
Dartnell (1996)[26]	Australia	hospital	expert chart review, pt. interview	admissions through ED; admissions <24 h or due to intentional drug overdose excluded	965	30 days	suspected cause was some aspect of drug therapy and not likely a result of disease progression; modified Karch and Lasagna causality criteria[37]	admission could have been avoided if appropriate measures had been taken by health workers; own assessment criteria
Finn (1995)[16]	US	ambulatory	adverse drug reactions report	pts. attending general medicines clinic	>12 000	9 mo	NA	NA
Forster (2003)[34]	Canada	hospital	pt. interview or pt. surrogate, expert chart review	discharged pts; non–English-speaking and pts. without telephone excluded	400	81 days	an injury resulting from medical management rather than the underlying disease	an injury judged to probably be the result of an error or a system design flaw

ADE = adverse drug event; ADR = adverse drug reaction; ED = emergency department; NA = not available; pADE = preventable adverse drug event.

[a]Hospital admissions categorized as iatrogenic, due to nonadherence or to natural history of disease. Iatrogenic disease was subdivided into failure to follow-up abnormal symptoms, signs, or laboratory test results, ADRs, complication from a procedure, or misdiagnosis. Only ADRs were included in this study to ensure that the event was related to drug therapy; however, subcategories were not mutually exclusive and other categories could be drug-related.

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Table 1. Characteristics of Included Studies (continued)

Reference	Country	Study Setting	Methods of ADE Identification	Inclusion/Exclusion Criteria	Pts., N	Time of Follow-Up	Definition and Assessment Criteria of ADE	Definition and Assessment Criteria of pADE
Gandhi (2000)[14]	US	ambulatory	pt. interview, expert chart review	pts. aged 20–75 y attending 11 ambulatory clinics; very ill, hearing impaired, non–English-/non–Spanish-speaking pts. excluded	2248	1 y	injuries due to drugs	NA
Gandhi (2003)[10]	US	ambulatory	pt. interview, expert chart review	pts. aged >18 y attending 4 primary care clinics; very ill, hearing impaired, non–English-/non-Russian-speaking pts. excluded	661	3 mo	injuries due to drugs	due to errors that could have been entirely avoided
Gurwitz (2003)[11]	US	ambulatory	provider report, expert chart review, computer screen incident reports	Medicare enrollees aged ≥65 y attending multispecialty group practice; long-term care facility residents excluded	30 397 person-years	1 y or 30 397 person-years	injury resulting from use of a drug; eg, medication errors (ie, errors in prescribing, dispensing, adherence, monitoring) or from ADRs	if due to an error and preventable by any means available; Bates assessment criteria[40]
Hallas (1990–1992)[28-33]	Denmark	hospital	expert chart review, blood samples, interview with pt. or relatives, family physicians, or home nurses	admissions to 6 medical departments: general and infectious medicine, geriatrics, general medicine and endocrinology, cardiology, respiratory medicine, gastroenterology	1999	2[28,29] or 3 1/2[31] mo[b]	ADRs[38] or dose-related therapeutic failures (absence of therapeutic response that could be linked causally either to a prescribed dose that was too low, drug nonadherence, recent dose reduction/discontinuation, interaction or inadequate monitoring; Hallas et al. causality criteria[29]	event could have been avoided by appropriate measures taken by health service personnel; Hallas et al. assessment criteria[29]
Hanlon (1997)[13]	US	ambulatory	pt. interview	pts. aged ≥65 y, taking ≥5 medications, attending general medicines clinic at Veterans Affairs Medical Center	167	1 y	pt.-reported ADRs, unwanted reactions, or other problems with medications	NA
Honigman (2001)[12]	US	ambulatory	computer screen, expert chart review	pts. attending primary care clinics with electronic records	15 665	1 y	injury resulting from an intervention related to a drug[40]	an identifiable error in the medication process; Bates assessment criteria[40]
Howard (2003)[8]	UK	hospital	review of case summaries based on medical notes, physician and pt. interview	admissions to medical admissions unit	4093	6 mo	ADRs,[38] failure to optimize treatment, unintentional overdose, and adherence problems; amended Hallas et al. causality criteria[29]	NA, Hepler assessment criteria[41,c]
Hutchinson (1986)[23]	Canada	ambulatory	pt. interview	pts. attending internal medicines unit	1026	299 days[d]	NA; pt.-reported health complaints and responses to a check-list of 25 symptoms of ADRs; Kramer causality criteria[42]	NA

ADE = adverse drug event; ADR = adverse drug reaction; NA = not available; pADE = preventable adverse drug event.

[b]The studies from a department of respiratory medicine and from a geriatric department did not specify exact follow-up times.

[c]The following 4 criteria had to be fulfilled to confirm preventability: (1) ADE was preceded by a recognizable drug therapy problem, (2) given the drug therapy problem, the ADE would have been foreseeable, (3) the cause of ADE would have been identifiable with a reasonable probability (Hallas criteria probable or definite for causality), (4) the cause of the ADE could have been reasonably controllable within the context and objectives of treatment.

[d]Average follow-up time of included persons.

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Table 1. Characteristics of Included Studies (continued)

Reference	Country	Study Setting	Methods of ADE Identification	Inclusion/Exclusion Criteria	Pts., N	Time of Follow-Up	Definition and Assessment Criteria of ADE	Definition and Assessment Criteria of pADE
Jha (2001)[36]	US	hospital	computer screens, expert chart review	adults admitted to 2 medical and 1 surgical intensive care units, and 4 medical and 2 surgical general care units	3238	8 mo	injury resulting from an intervention related to a drug[40]	an event due to an error or that could have been averted by any means currently available
Klein (1984)[19]	US	ambulatory	pt. interview	pts. (one-third ≥65 y) visiting general medicines clinics	299	NA	pt.-reported medication ADRs[e]	NA
Lakshmanan (1986)[3]	US	hospital	expert chart review	admissions to hospital medical service; admissions to specialty units excluded	834	2 mo	adverse reactions to medical therapy, surgery or diagnostic procedures; own causality criteria	no specific definition, but examples given[f]; own assessment criteria
Lindley (1992)[27]	UK	hospital	medical notes and medication cards	admissions of pts. aged ≥65 y to acute geriatric and medical wards; transferals and readmissions excluded	416	10 wk	NA; structured implicit causality criteria	NA
Martys (1979)[22]	UK	ambulatory	pt. interview	general practice pts. prescribed a new medication	817	1 wk[g]	pt.-reported events, symptoms or signs occurring during the course of treatment that were not usual components of the pt.'s illness and not intended in the course of treatment	NA
McDonnell (2002)[7]	US	hospital	expert chart review	hospital ADE reports	437	11 mo	noxious, unintended, and undesired effect of a drug after doses used in humans for prophylaxis, diagnosis, or therapy[43]; Naranjo causality criteria[43]	NA, adapted Schumock and Thornton assessment criteria[44]
Schneider (1992)[17]	US	ambulatory	medical chart review	pts. aged ≥70 y attending geriatric or medical clinic	463	1 y	ADRs[38]; Naranjo causality criteria[43]	NA
Senst (2001)[6]	US	hospital	computer screens, clinical intervention documentation, adverse drug reaction codes, incident reports, expert chart review	admissions to tertiary care facility, mental health center, psychiatric hospital for children, and facility for children with disabilities	3187	53 days	an injury, large or small, caused by the use (including nonuse) of a drug; ADEs caused by errors or occur despite proper usage[45]	an ADE caused by an error or preventable by means currently available

ADE = adverse drug event; ADR = adverse drug reaction; NA = not available; pADE = preventable adverse drug event.

[e]Patients were asked if they had experienced the following: mood or sleep disturbances, gastrointestinal tract difficulties, equilibrium problems, head or chest discomfort, muscular aches, incontinence or excessive urination, sexual dysfunction, skin eruptions or pruritus, or other problems.

[f]Examples of pADE were: toxic effect where levels could have been checked or were available but ignored; complications caused by a contraindicated drug or a drug used in a manner not recommended; failure of physician to detect or patient to report ADE that was present prior to admission.

[g]Follow-up time was one week except for contraceptive pills with a follow-up time of one month.

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Table 1. Characteristics of Included Studies (continued)

Reference	Country	Study Setting	Methods of ADE Identification	Inclusion/Exclusion Criteria	Pts., N	Time of Follow-Up	Definition and Assessment Criteria of ADE	Definition and Assessment Criteria of pADE
Tafreshi (1999)[35]	US	hospital	interview with pt. or pt. representative	ED visits; visits due to illicit drug use, alcohol, trauma or minor injuries excluded	253	35 days	undesirable, unintended, and unexpected event that requires discontinuing a drug, modifying a dose, prolonging hospitalization, or providing supportive treatment; Hepler and Strand categorization[41]; Naranjo causality criteria[43]	NA; own assessment criteria[h]
Trunet (1980)[2]	France	hospital	expert chart review	admissions to multidisciplinary intensive care unit	325	12 mo	noxious and unintended effect of a drug occurring at recommended doses[37] and therapeutic errors (overdosage, therapeutic contraindication, therapeutic antagonism, or inappropriate route of administration); Karch and Lasagna causality criteria[37]	NA

ADE = adverse drug event; ED = emergency department; NA = not available; pADE = preventable adverse drug event.
[h]Examples of pADE were: history of allergy or previous reaction to the drug; drug interaction; poor patient adherence; drug not appropriate for the patient's clinical condition; dosage, route, or frequency of use not appropriate for the patient's age, weight, or renal function; therapeutic drug monitoring or other necessary laboratory tests not performed; prescribing, dispensing, and administration errors.

The drug groups most frequently associated with ADEs identified in ambulatory-based studies were cardiovascular agents 33.3% (1.1–73.6%), oral contraceptives 22.5% (19.1–25.8%), and central nervous system (CNS)-active drugs 10.1% (6.9–49.7%). The drug groups most frequently associated with pADE-related hospital admissions identified in hospital-based studies were cardiovascular drugs 46.6% (range 6–80.0%), CNS-active drugs 14.9% (range 5–44%), and respiratory drugs 12.2% (range 5.3–14%). Interestingly, only 3 drug categories (cardiovascular drugs, analgesics, hypoglycemic agents) were responsible for 86.5% of pADEs identified in ambulatory-based studies. Oral contraceptives and first-generation antihistamines were reported only in studies from the 1970s. Apart from these 2 drug groups, no longitudinal trend was identified. Cardiovascular drugs, analgesics, and hypoglycemic agents were more frequently associated with pADEs than with ADEs, whereas CNS-active drugs, antiinfectives, and corticosteroids were more frequently associated with ADEs.

TYPES OF CLINICAL OUTCOMES

Table 3 shows the 10 ambulatory-based studies that reported the organ systems affected by ADEs and pADEs.[10-16,19,22,23] According to these investigations, ADEs resulted most frequently in CNS symptoms such as dizziness, sleep disturbances, or mood changes (25.1%; range 9.6–44.2%), followed by gastrointestinal symptoms such as nausea, diarrhea, or anorexia (22.7%; range 5.8–30.0%), electrolyte/renal symptoms such as urinary problems, increased serum creatinine, or metabolic acidosis/alkalosis (12.4%; range 2–16.8%), hematologic symptoms such as over-anticoagulation (11.5%; range 7–13.6%), and skin symptoms such as rash, itching, or edema (6.8%; range 3–38.5%). Symptoms involving the CNS, electrolyte/renal, and gastrointestinal systems occurred in 77.2% of pADEs. Furthermore, electrolyte/renal, cardiovascular, hematologic, and metabolic/endocrine symptoms were more frequently associated with pADEs than with ADEs.

TYPES OF MEDICATION ERRORS

Two studies in ambulatory care[10,11] and 11 hospital-based studies reporting ambulatory medication errors that resulted in hospital admission[2-5,7,8,26,27,33-35] investigated the types of medication errors that caused pADEs (Table 4). The largest proportion of errors originated in the prescribing stage—64.7% of all pADEs and 56.0% of pADEs causing hospital admission. The proportion of errors occurring in the monitoring stage of the medication use process was retrieved by collapsing errors due to inadequate monitoring and ignoring clinical/laboratory results. This resulted in a proportion of monitoring errors associated with pADEs of 72.7% and a proportion of monitoring errors causing pADE-related hospital admission of 61.2%.

Table 2. Drug Groups Frequently Associated with Ambulatory ADEs and pADEs[a]

Reference	Cardio-vascular[b]	Contra-ceptives	CNS[c]	Anti-infectives	Analgesics[d]	Hypo-glycemics[e]	Endocrine/ Metabolic	Respiratory	Immune System[f]	GI Tract	Allergy/ Antiemetics	Anti-neoplastics	Other
Ambulatory-based studies on ADEs, % of all ADEs													
Campbell (1977)[20]	8.3	19.1	9.1	7.9	4.5	1.3	NA	NA	NA	NA	1.0	NA	48.8
Campbell (1978)[21]	1.1	25.8	10.1	12.6	8.1	NA	NA	NA	NA	NA	1.4	NA	40.9
Chrischilles (1992)[15]	32.4	NA	8.1	8.1	22.2	NA	9.2	7.8	NA	5.3	NA	NA	7.2
Darnell (1986)[18]	NA	NA	NA	NA	13	NA	NA	NA	NA	NA	NA	NA	NA
Finn (1995)[16]	49.9	NA	15.4	9.6	5.8	7.7	NA	NA	NA	NA	NA	NA	9.6
Gandhi (2000)[14]	NA	NA	13.0	21.0	6.0	NA	NA	NA	NA	NA	NA	NA	NA
Gandhi (2003)[10]	24.0	NA	10.0	4.0	11.0	NA	NA	NA	4.0	NA	NA	NA	NA
Gurwitz (2003)[11]	49.2	NA	6.9	14.7	16.7	6.8	NA	0.8	5.3	1.3	NA	NA	14.3
Hanlon (1997)[13]	33.3	NA	27.8	NA	NA	NA	4.2	5.6	NA	2.8	NA	NA	16.4
Honigman (2001)[12]	73.6	NA	9.9	8.3	5.0	NA	NA	NA	NA	5.0	NA	NA	NA
Hutchinson (1986)[23,g]	40.7	NA	23.7	5.1	NA	NA	NA	NA	NA	1.7	NA	NA	5.1
Klein (1984)[19]	58.9	NA	NA	NA	NA	10.0	NA	5.6	NA	NA	NA	NA	NA
Martys (1979)[22]	NA	NA	49.7	31.1	NA	NA	NA	NA	NA	3.3	4.5	NA	12.0
Schneider (1992)[17]	31	NA	10	NA	10	NA	NA	NA	NA	NA	NA	NA	NA
Median (range)	33.3 (1.1–73.6.)	22.5 (19.1–25.8)	10.1 (6.9–49.7)	9.0 (4.0–31.1)	9.1 (4.5–22.2)	7.3 (1.3–7.7)	6.7 (4.2–9.2)	5.6 (0.8–7.8)	4.7 (4.0–5.3)	3.1 (1.3–5.3)	1.4 (1.0–4.5)	NA	13.2 (5.1–48.8)

ADE = adverse drug event; CNS = central nervous system; GI = gastrointestinal; NA = not applicable; pADE = preventable adverse drug event.

[a]Some events were associated with drugs in more than one category; therefore, frequencies total more than 100%.

[b]Includes antihypertensives, diuretics, anticoagulants, lipid-lowering drugs. and digoxin.

[c]Includes antidepressants, antiseizure, anti-Parkinson's disease and Alzheimer's disease medications, antipsychotics, hypnotics, and sedatives.

[d]Includes opioids, aspirin, and nonsteroidal antiinflammatory drugs.

[e]Includes insulin and sulfonylureas.

[f]Includes corticosteroids and other immunosuppressants.

[g]The study only included ADEs associated with newly started drugs.

(continued on page xxx)

Table 2. Drug Groups Frequently Associated with Ambulatory ADEs and pADEs[a] (continued)

Reference	Cardio-vascular[b]	Contra-ceptives	CNS[c]	Anti-infectives	Analgesics[d]	Hypo-glycemics[e]	Endocrine/ Metabolic	Respiratory	Immune System[f]	GI Tract	Allergy/ Antiemetics	Anti-neoplastics	Other
Hospital-based studies on pADEs requiring hospital admission, % of all pADEs													
Bigby (1987)[25]	66.6	NA	12.5	NA	12.5	8.3	NA	NA	NA	NA	NA	NA	8.3
Cannon (1997)[24]	66.7	NA	NA	NA	33.3	NA	NA	NA	33.3	NA	NA	NA	NA
Darchy (1999)[4]	50.0	NA	NA	3.3	6.7	NA	NA	NA	NA	NA	NA	3.3	46.7
Dartnell (1996)[26,h]	47.3	NA	13.9	NA	8.3	5.6	NA	13.9	2.8	NA	NA	NA	NA
Hallas (1990)[28] (1990)[29] (1991)[30] (1992)[32,i]	52.3	NA	15.8	10.5	10.5	5.3	NA	5.3	NA	NA	NA	NA	NA
Howard (2003)[8]	26.0	NA	10.1	NA	12.4	8.4	NA	NA	3.9	NA	NA	NA	56.2
Jha (2001)[36]	42.9	NA	19.0	9.5	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lakshmanan (1986)[3]	36.8	NA	10.5	NA	NA	10.5	NA	10.5	10.5	NA	NA	10.5	NA
McDonnell (2002)[7]	45.9	NA	12.5	10.4	11.4	16.7	NA	NA	12.5	NA	NA	5.2	NA
Senst (2001)[6]	6	NA	44	6	9	NA	NA	NA	NA	NA	NA	NA	34
Tafreshi (1999)[35]	16.0	NA	26.0	8.0	18.0	NA	NA	14.0	NA	NA	NA	NA	28.0
Trunet (1980)[2]	80.0	NA	20.0	20.0	20.0	NA	NA	NA	NA	NA	NA	NA	NA
Median (range)	46.6 (6–80.0)	NA	14.9 (5–44)	9.5 (3.3–20.0)	11.9 (6.7–33.3)	8.4 (5.3–16.7)	NA	12.2 (5.3–14)	10.5 (2.8–33.3)	NA	NA	5.2 (3.3–10.5)	34.0 (8.3–56.2)

ADE = adverse drug event; CNS = central nervous system; GI = gastrointestinal; NA = not applicable; pADE = preventable adverse drug event.

[a]Some events were associated with drugs in more than one category; therefore, frequencies total more than 100%.

[b]Includes antihypertensives, diuretics, anticoagulants, lipid-lowering drugs. and digoxin.

[c]Includes antidepressants, antiseizure, anti-Parkinson's disease and Alzheimer's disease medications, antipsychotics, hypnotics, and sedatives.

[d]Includes opioids, aspirin, and nonsteroidal antiinflammatory drugs.

[e]Includes insulin and sulfonylureas.

[f]Includes corticosteroids and other immunosuppressants.

[h]The pADEs include 3 definitely avoidable and 33 possibly avoidable cases.

[i]Only studies on admissions to departments of respiratory medicine, general and infectious medicine, cardiology, and geriatrics had data on drugs associated with pADEs; no such data could be identified for studies on admissions to a department of medical gastroenterology, general medicine, and endocrinology. Only drugs associated with definite pADEs are included.

Table 3. Organ Systems Affected by ADEs and pADEs in Ambulatory Care Patients[a]

Reference	Organ system affected, % of all ADEs (pADEs)										
	CNS[b]	GI Tract[c]	Electrolyte/ Renal Function[d]	Hemato-logic[e]	Skin[f]	Metabolic/ Endocrine[g]	Cardio-vascular[h]	Respiratory	Musculo-skeletal	Hepatic	Other
Chrischilles (1992)[15]	26.2	31.2	NA	NA	11.0	2.9	5.0	2.1	6.0	NA	15.6
Finn (1995)[16]	9.6	5.8	11.5	11.5	38.5	NA	3.8	1.9	1.9	1.9	11.5
Gandhi (2000)[14]	17	7	2	NA	3	NA	NA	NA	3	NA	4
Gandhi (2003)[10]	33 (35)	22 (25)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gurwitz (2003)[11]	12.4 (18.2)	23.3 (23.0)	16.8 (26.6)	13.6 (16.1)	12.6 (3.5)	9.5 (13.8)	4.3 (5.9)	5.4 (2.9)	0.3 (0.2)	1.5 (0.7)	6.8 (1.7)
Hanlon (1997)[13]	28.8	30.0	NA	NA	3.8	6.2	15.0	6.2	NA	NA	10.0
Honigman (2001)[12]	24	18	NA	7	26	NA	4	16	NA	NA	4
Hutchinson (1986)[23]	44.2	28.1	NA	NA	6.8	NA	NA	NA	NA	NA	17.5
Klein (1984)[19]	9.6	9.6	13.3	NA	4.4	NA	NA	NA	2.6	NA	20.4
Martys (1979)[22]	33.8	29.9	NA	NA	5.6	NA	1.7	0.5	NA	NA	8.5
Median (range) of ADEs	25.1 (9.6–44.2)	22.7 (5.8–30.0)	12.4 (2–16.8)	11.5 (7–13.6)	6.8 (3–38.5)	6.2 (2.9–9.5)	4.3 (4–18)	3.8 (0.5–16)	2.6 (0.3–6.0)	1.7 (1.5–1.9)	9.3 (1.7–20.4)
Median (range) of pADEs	26.6 (18.2–35)	24 (23–25)	26.6	16.1	3.5	13.8	12.0 (5.9–18)	2.9	0.2	0.7	1.7

ADE = adverse drug event; CNS = central nervous system; GI = gastrointestinal; NA = not applicable; pADE = preventable adverse drug event.

[a]Numbers do not always total 100%; some studies only reported the most frequent types of events, and some adverse events caused more than one type of event.

[b]Includes dizziness, fatigue, sleep disturbances, mood changes, headache, ataxia, tardive dyskinesia.

[c]Includes nausea, diarrhea, anorexia, weight change.

[d]Includes urinary problems, increased serum creatinine, hyper- or hyponatremia, metabolic acidosis or alkalosis.

[e]Includes over-anticoagulation with and without hemorrhage.

[f]Includes rash, edema, itching.

[g]Includes hypotension, tachycardia.

[h]Includes cough, shortness of breath.

Table 4. Types of Medication Errors Related to Ambulatory pADEs and Ambulatory pADEs Requiring Hospital Admission[a]

Type of Error	% (n) of pADEs			% (n) of pADEs Requiring Hospital Admission										
	Median (range)	Gandhi (2003)[10]	Gurwitz (2003)[11]	Median (range)	Chan (2001)[5]	Darchy (1999)[4]	Dartnell (1996)[26]	Forster (2003)[34]	Hallas (1992)[33]	Howard (2003)[8]	Lakshmanan (1986)[3]	Lindley (1992)[27]	McDonnell (2002)[7]	Tafreshi (1999)[35]	Trunet (1980)[2]
Omission															
Inadequate drug monitoring	36.1	NA	36.1 (152)	45.4 (22.2–69.8)	NA	46.7 (14)	22.2 (8)	50 (7)	23.9 (16)	22.5 (40)	57.9 (12)	NA	69.8 (67)	44 (22)	NA
Inadequate pt. education	18	NA	18 (75)	18.3 (8–28.6)	NA	NA	NA	28.6 (4)	NA	NA	NA	NA	NA	8 (4)	NA
Ignoring clinical/ laboratory result[b]	36.6	NA	36.6 (154)	15.8 (7.5–83.3)	NA	NA	NA	NA	7.5 (5)	NA	15.8 (3)	NA	83.3 (80)b	NA	NA
No prescribing of indicated drug	NA	NA	NA	12.5 (6.7–23.6)	17.9 (7)	6.7 (2)	NA	7.1 (1)	NA	23.6 (42)	NA	NA	NA	NA	NA
Commission															
Pt. nonadherence[c]	21.1	NA	21.1 (89)	36.6 (20.9–46)	23.1 (9)	NA	41.2 (15)	NA	20.9 (14)	38.8 (69)	NA	NA	34.4 (33)	46 (23)	NA
Prescribing inappropriate drug[d]	42.7 (40.4–45)	45 (9)	40.4 (170)	16.7 (3.9–100)	NA	20.0 (6)	16.7 (6)	NA	10.5 (7)	3.9 (7)	5.2 (1)	100 (13)	32.3 (31)	44 (22)	60.0 (3)
Inappropriate dose/frequency	22 (20–24)	20 (4)	24 (101)	26.8 (1.1–53.1)	NA	26.7 (8)	22.2 (8)	42.9 (6)	26.9 (18)	1.1 (2)	5.2 (1)	NA	53.1 (51)	NA	40.0 (2)
Administration error	NA	NA	NA	3.5 (2–5)	NA	NA	NA	NA	NA	5 (9)	NA	NA	NA	2 (1)	NA

NA = not applicable; pADEs = preventable adverse drug events.
[a]Columns do not total 100%; some events were results of more than one type of medication error, and some studies only reported the most frequent medication errors.
[b]Defined as toxic/abnormal laboratory values being available to the treating physician.
[c]Can be result of both errors of commission (using the drug differently from prescribed) or errors of omission (not taking the drug). It was not possible to determine whether reported cases of nonadherence were errors of commission or omission and they were therefore collapsed as errors of commission.
[d]Comprises prescribing of contraindicated, interacting, or unnecessary drugs; drugs to which the patient previously reacted; or choosing the wrong drug.

The drug therapy problems most frequently associated with pADEs were use of inappropriate drugs in 42.7% (40.4–45%) of cases, ignoring clinical or laboratory results in 36.6% (1 study), and inadequate monitoring in 36.1% (1 study). The drug therapy problems most frequently associated with pADEs requiring hospital admissions were inadequate monitoring in 45.4% (22.2–69.8%), followed by patient nonadherence in 36.6% (20.9–46%), and dosing/frequency errors in 26.8% (1.1–53.1%).

ERRORS OF COMMISSION OR OMISSION

One of the 2 ambulatory-based studies that reported ADE-related medication errors described only details on errors of commission,[10] whereas the other study reported errors of both commission and omission.[11] Two of the 11 hospital-based studies that reported pADE-related medication errors did not report errors of omission.[2,27] Inadequate monitoring and ignoring clinical/laboratory results were the most frequently reported errors of omission associated with pADEs in ambulatory-based studies: 36.1% (1 study) and 36.6% (1 study), respectively. Furthermore, inadequate monitoring was the most frequently reported error of omission associated with pADE-related hospital admission in hospital-based studies (45.4%; 22.2–69.8%). Use of inappropriate drugs was the most frequently reported error of commission associated with pADEs in ambulatory-based studies (42.7%; 40.4–45%), whereas patient nonadherence was the most frequently reported error of commission associated with pADE-related hospital admission in hospital-based studies (36.6%; 20.9–46%).

EXPLICIT COMBINATIONS OF MEDICATION ERROR, ASSOCIATED DRUG, AND ADVERSE OUTCOME

Explicit descriptions of frequent combinations of medication error, associated drug, and adverse outcome from 10 studies are presented in Table 5.[2,3,8,24-26,28-30,34] Gastrointestinal toxicity resulting from failure to prescribe prophylaxis to pa-

tients taking NSAIDs or antiplatelet drugs was a frequent problem. Lack of monitoring was a frequent problem with diuretics, hypoglycemics, and anticoagulants, resulting in over- or under-diuresis, hyper- or hypoglycemia, and increased risk of or manifest bleeding, respectively. Underdosed or unmonitored antiepileptics resulting in either seizures or toxicity were also frequent, as was overdosed or unmonitored digoxin, resulting in digoxin toxicity. Lastly, one study found several cases of patient nonadherence to corticosteroids, resulting in exacerbation of asthma.[8]

Discussion

Frequency estimates determined in this study reveal that ambulatory care patients run a significant risk of experiencing ADEs. A large proportion of these ADEs are preventable, and nearly half of the preventable ADEs require hospital admission. Incidence estimates across the included studies varied considerably, potentially due to differences in study methodology, setting, or sample characteristics, leaving doubts as to whether our ADE incidence estimate of 14.9 per 1000 person-months is representative. Our ADE incidence estimate appears to be lower than the estimate reported by Nolan and O'Malley[46] in their review from 1988, despite their ADE definition being restricted to adverse drug reactions. They reported that an average of 30% of outpatients experience an ADE within an unspecified period.

We determined an ADE preventability rate of 21% and, notwithstanding difficulties in comparing preventability rates across different study settings, it is of interest that the preventability rate in the ambulatory setting appears to be lower than preventability rates found in other settings. For example, a review on inpatient pADEs reported a preventability rate of 35.2%,[9] a study in a long-term care facility reported a preventability rate of 42%,[47] and a nursing home study reported a preventability rate of 51%.[48] In addition, reviews on the prevalence of pADEs in ambulatory care that require hospital admission have reported preventability rates between 24% and 75%.[49-51] These results suggest that a smaller proportion of ADEs in ambulatory care settings are amenable to preventive interventions than are ADEs that occur in settings where patients are more likely to be fragile and receive more complex medication regimens than the general ambulatory population does.

We found that the incidence of ADEs resolved in ambulatory care was substantially higher than the incidence of ADEs requiring hospitalization. Some investigators in the studies reviewed here proposed that the largest proportion of ADEs in ambulatory care are mild or transient.[10,11] In contrast, the incidence of pADEs requiring hospitalization was

Table 5. Explicit Descriptions of the Most Frequent Combinations of Drugs, Medication Errors, and Clinical Outcomes Reported in Studies on Ambulatory pADEs Requiring Hospital Admission

Drug Group	Medication Error	Clinical Outcome	Cases, n
Antiepileptics[8,26,29]	inadequate monitoring of drug concentrations, underdosage, inappropriate cessation, nonadherence	seizure	15
	inadequate monitoring of drug concentrations, inappropriate continuation[8]	toxicity	6
Antiplatelet drugs[24-26,34]	no GI prophylaxis despite risk factors	GI toxicity	14
	failure to prescribe secondary prevention[8,25,28]	thrombotic event	4
β-blockers[8]	underdosing despite symptoms, inappropriate cessation, interaction	congestive heart failure, tachycardia, chest pain, cerebral edema	6
Calcium antagonists[8,29]	interaction	congestive heart failure, postural hypotension	3
Corticosteroids[8]	nonadherence	exacerbation of asthma	7
Digoxin[8,28,30]	inadequate monitoring of renal function or digoxin concentrations, overdosage	digoxin toxicity	8
Diuretics[2,8,24,26,28,30]	inadequate monitoring of fluid balance, renal function, or electrolytes, overdosage, no reasonable indication, nonadherence	dehydration, constipation, electrolyte imbalance, renal failure, hypotension	30
	inadequate monitoring, ignoring symptoms of congestive heart failure, nonadherence[8]	congestive heart failure or pulmonary edema	15
Insulin[3,8,29,34]	ignoring symptoms, overdosage, nonadherence	hypoglycemia	5
	inadequate monitoring of blood glucose, nonadherence	hyperglycemia	6
Nitrates[3,8]	nonadherence	chest pain	5
NSAIDs[8]	no GI prophylaxis despite risk factors	GI toxicity	21
Opioids, benzodiazepines, promazine[29,34]	no coprescription of stool softener, failure to teach pain management, overdosage, contraindication	constipation, vomiting, pain, stupor, allergic shock, unconsciousness	5
Polypharmacy[8,26,30]	unnecessary polypharmacy	dizziness, uncharacteristic malaise	3
Sulfonylureas[3,8,26,29]	inadequate monitoring of blood glucose, prescribing unnecessary or contraindicated drug, nonadherence	hypoglycemia	8
	inadequate monitoring of blood glucose[8]	hyperglycemia	3
Warfarin[2,8,30,34]	inadequate monitoring of INR, interaction	bleeding, INR imbalance	10

GI = gastrointestinal; INR = international normalized ratio; NSAIDs = nonsteroidal antiinflammatory drugs; pADEs = preventable adverse drug events.

close to the incidence of pADEs resolved in ambulatory care. This observation is based on just one study but may suggest that a larger proportion of pADEs than ADEs is serious enough to require hospital admission. This is consistent with the finding by Gurwitz et al.[11] that severe ADEs are more likely to be preventable than are less severe events.

We found that the drug groups most often involved in ADEs have not changed much over time and include drugs with large prescribing prevalence (eg, cardiovascular agents, analgesics) and those with a narrow therapeutic range (eg, hypoglycemic agents, digoxin). This finding has been confirmed by a large number of studies that have focused on these categories.[52-57] Studies on ADE-associated mortality report cardiovascular drugs as being associated with a substantial proportion of drug-related deaths.[58-60] From a quality improvement perspective, it is important to note that only 3 drug groups were responsible for more than 86% of pADEs. Thus, patients with cardiovascular diseases or diabetes and patients who require chronic pain management are important target groups when planning future quality improvement interventions aimed at preventing pADEs.

More than 75% of pADEs resulted in symptoms of the CNS, electrolyte/renal system, and gastrointestinal tract, as found in hospital-based studies on pADEs.[52,55,61] Many of these clinical outcomes are readily detectable with appropriate monitoring of electrolytes, international normalized ratio, glucose levels, renal function, and hematology panel, and the reported explicit descriptions of combinations of medication errors, associated drugs, and outcomes support the evidence that improved monitoring of such outcomes is likely to prevent a substantial number of pADEs.

We found that medication errors resulting in pADEs occur frequently in the prescribing and monitoring stage of the medication use process, and optimization of drug prescribing and patient monitoring is therefore critical for medication safety interventions in the ambulatory setting. Furthermore, patient nonadherence was a frequent cause of error and also deserves more attention. Patient safety interventions, with their focus on hospital settings, have largely focused on errors in prescribing, dispensing, and monitoring of drugs. Nonadherence has received very little attention, probably because it is likely to be a minor problem in hospitalized patients under close surveillance by medical staff. However, in ambulatory care, where patients have greater responsibility for their drug therapy, improved adherence may offer an important means to reduce medication errors.

We conclude that analysis of the causes of medication errors is an important contributor to an understanding of why errors occur and how they can be avoided. Extensive analysis of the causes of medication errors in hospital settings is ongoing, but further study in the ambulatory setting is needed.

Our study had limitations. Incidence estimates are affected by 4 factors: the methods used to identify ADEs, the employed definition of an ADE, the criteria used to determine manifestation of an ADE, and the source population and setting. The studies included in this review reported highly varying frequency estimates. For example, high-sample studies that did not use patient interviews reported the lowest incidence rates, potentially because smaller studies were able to employ more comprehensive pADE ascertainment methods such as interviews, which have been found to identify more errors than do chart reviews, computer-based triggers, or self-reports from health professionals.[62] Studies comparing various methods agree that ascertainment methods are largely complementary and that the true incidence may be higher than previously reported.[62,63] Likewise, the ADE definition and criteria for manifestation, while reported by only some, varied greatly across studies. For example, some studies used a narrow ADE definition including only outcomes caused by adverse drug reactions, whereas other studies expanded their definition toward errors of omission. In summary, the reported frequency estimates are heterogeneous due to a variety of factors and do not allow calculating a meta-analytic summary estimate. The reported medians are only provided for descriptive purposes and should be interpreted in the context of the individual studies and their methodological differences.

Another important limitation is the variation in the way that findings were reported in the reviewed studies. Different categorization schemes were used and it was often impossible to determine whether a study did not identify certain drug groups, outcomes, or medication errors, or whether the authors chose not to report them. Also, very few studies provided a comprehensive assessment of the nature of pADEs including all components reviewed here; results should be interpreted with this in mind. In addition, unpublished data were not pursued, which could bias results, and 8 of the included studies were retrospective, which introduces the risk of recall bias and problems related to incomplete documentation. Lastly, studies mainly investigated ADEs in the elderly and all were conducted in industrialized countries.

Since the majority of health care occurs outside the hospital, the ambulatory setting provides a tremendous opportunity for research. This systematic review on pADEs in ambulatory care has identified new opportunities for studies on drug utilization and patient safety in the ambulatory setting. First, further studies investigating all the components of ambulatory pADEs reviewed here are needed to make the information available at present more comprehensive. Subsequently, quality improvement programs should target errors in prescribing and monitoring, especially for patient groups using cardiovascular drugs, analgesics, and hypoglycemic agents. Studies should further investigate the root causes of medication errors in ambulatory care to guide quality improvement initiatives and provide solid estimates of the impact of pADEs on healthcare expenditures and patients' health-related quality of life to inform public health action.

Summary

Many of the ADEs that occur in ambulatory care are preventable. Nonetheless, they are common, with many resulting in hospitalization. Quality improvement programs should target errors in prescribing and monitoring, especially for patient groups using cardiovascular drugs, analgesics, and hypoglycemic agents.

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Revisión Sistemática de la Incidencia y Características de Eventos Adversos Prevenibles en Escenarios de Atención Ambulatoria

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EXTRACTO

OBJETIVO: Estimar la incidencia y describir las características de eventos adversos prevenibles (pADEs) en escenarios de atención ambulatoria.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en la literatura en PubMed (1966–marzo 2007), *International Pharmaceutical Abstracts* (1970–diciembre 2006), el banco de datos de revisiones sistemáticas de Cochrane (1993–marzo 2007), EMBASE (1980–febrero 2007), y Web of Science (1945–marzo 2007). Las palabras claves incluyeron error en medicación, reacción adversa a medicamentos, enfermedad iatrogénica, paciente ambulatorio, atención ambulatoria, atención de salud primaria, práctica general, admisión de pacientes, hospitalización, estudio observacional, estudios retrospectivos, investigación de servicios de salud, y estudios de seguimiento. Se identificaron artículos adicionales en la sección de referencia de los artículos seleccionados en la búsqueda bibliográfica.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se incluyeron artículos revisados por pares donde se identificaron pADEs con descripciones detalladas y distribuciones de frecuencia de (1) incidencia de ADE/pADE, (2) resultados clínicos, (3) grupos de medicamentos asociados con los ADE/pADEs, y/o (4) errores médicos subyacentes. Se extrajo información relacionada con el país donde se realizó el estudio, el año y diseño del estudio, tamaño de muestra, tiempo de seguimiento, método de identificación de ADE/pADE, proporción de ADEs/pADEs y de ADEs/pADEs que requirieron admisión al hospital, y distribución de frecuencia de eventos adversos, grupos de medicamentos asociados, a los eventos o errores médicos.

SÍNTESIS: Veintinueve estudios cumplieron con los criterios de inclusión, 14 de escenarios ambulatorios, y 15 de escenarios hospitalarios. Siete estudios solamente reclutaron pacientes de edad avanzada. La mediana de incidencia de ADE fue 14.9 (rango 4.0–91.3) por 100 000 personas-mes, y de pADE fue de 5.6 por 1000 personas-mes (rango 1.1-10.1). La mediana de la tasa de prevención de ADE fue de 21% (rango 11–38%). La mediana de incidencia de ADEs y pADEs que requirieron admisión al hospital fue de 0.45 (0.10–13.1) por 1000 personas-mes y 4.5 por 1000 personas-mes, respectivamente. Medicamentos cardiovasculares, analgésicos, y agentes hipoglicémicos estuvieron asociados con 86.5% de los pADEs. Setenta y siete por ciento de los pADEs resultaron en síntomas del sistema nervioso central, el sistema de electrolitos/renal, y el trayecto gastrointestinal. Errores en medicación que resultaron en pADEs ocurrieron en las etapas de prescripción y monitoreo. El problema de terapia de medicamentos y error de cometido más frecuentemente reportado en estudios realizados en escenarios ambulatorios fue el uso no apropiado de medicamentos (42.7%; rango 40.4–45%). En el caso de los pADEs que requirieron hospitalización, el problema de terapia de medicamentos y error de omisión más frecuentemente reportado fue seguimiento no adecuado (45.4%; rango

22.2–69.8%). La falta de prescripciones profilácticas para pacientes tomando antiinflamatorios no esteroidales (NSAIDs, por sus siglas en inglés) o agentes antiplaquetarios frecuentemente ocasionó toxicidad gastrointestinal, mientras que la falta de de seguimiento en el uso de diuréticos, agentes hipoglicémicos, y anticoagulantes causó sobre- o subdiúresis, hipo- o hiperglicemia, y sangrado.

CONCLUSIONES: Los eventos adversos a medicamentos en escenarios de atención ambulatoria son comunes, siendo muchos de estos prevenibles y resultando en hospitalizaciones. Los programas de mejoramiento de calidad deben enfocar los errores en la prescripción y seguimiento, especialmente en pacientes usando agentes cardiovasculares, analgésicos, e hipoglicémicos.

Traducido por Homero A Monsanto

Une Revue Systématique de l'Incidence et des Caractéristiques des Effets Indésirables Évitables en Milieu Ambulatoire

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RÉSUMÉ

OBJECTIF: Estimer l'incidence et décrire les caractéristiques des effets indésirables évitables (EIE) en milieu ambulatoire.

SOURCES DES DONNÉES: Les études ont été recherchées dans PubMed (1966–mars 2007), *International Pharmaceutical Abstracts* (1970–décembre 2006), EMBASE (1980–février 2007) et Web of Science (1945–mars 2007) avec les mots-clés suivants : medication error, adverse drug reaction, iatrogenic disease, outpatient, ambulatory care, primary health care, general practice, patient admission, hospitalization, observational study, retrospective studies, health services research, et follow-up studies. Des références additionnelles ont été identifiées à l'aide des références des articles retenus.

SÉLECTION DES ÉTUDES ET EXTRACTIONS DES DONNÉES: Les articles révisés par les pairs évaluant les EIE en milieu ambulatoire avec des descriptions détaillées et des fréquences de distribution de (1) l'incidence des EI/EIE, (2) les résultats de santé, (3) les classes de médicaments, et/ou (4) les erreurs de médicaments sous-jacentes ont été examinés. Le pays, le devis clinique, l'année de l'étude, la taille de l'échantillon, la période de suivi, la méthode d'identification des EI/EIE, la proportion des EI/EIE et de ceux nécessitant une hospitalisation, ainsi que la fréquence de distribution des résultats de santé, des classes de médicament, et des erreurs de médicament ont été extraites.

SYNTHÈSE DES DONNÉES: Vingt-neuf études ont rencontré les critères d'inclusion, 14 en milieu ambulatoire, 15 en milieu hospitalier. Sept études incluaient uniquement des patients âgés. L'incidence médiane des EI était de 14.9 (4.0–91.3) cas par 1000 personnes-mois alors que l'incidence des EIE était de 5.6 (1.1–10.1) cas par 1000 personnes-mois. Le taux médian de prévention des EI était de 21% (11–38%). L'incidence médiane des EI nécessitant une hospitalisation était de 0.45 (0.10–13.1) par 1000 personnes-mois et l'incidence des EIE nécessitant une hospitalisation était de 4.5 par 1000 personnes-mois. Les médicaments cardiovasculaires, analgésiques, et agents hypoglycémiants étaient en cause dans 86.5% des EIE; 77.2% des EIE ont résulté en des symptômes au niveau des systèmes nerveux central, rénal/électrolytes, et gastro-intestinal. Les erreurs médicamenteuses causant des EIE ont été notées durant la période de prescription et de suivi. Le problème le plus fréquent rapporté dans les études en milieu ambulatoire était l'usage inapproprié d'un médicament (42.7% [40.4–45%]). Pour les EIE en milieu hospitalier, le problème le plus fréquent était le suivi inapproprié (45.4% [22.2–69.8%]). L'omission de prescrire une thérapie prophylactique chez des patients prenant des AINS ou des anti-plaquettaires a causé des problèmes gastro-intestinaux, alors que le manque de suivi au niveau des diurétiques, hypoglycémiants, et anticoagulants a causé des problèmes de diurèse, de glycémie, et de saignements.

CONCLUSIONS: Les EI en milieu ambulatoire sont communs et plusieurs peut être évités afin de prévenir une hospitalisation. Les programmes de gestion de la qualité devaient porter attention aux erreurs de prescription et de suivi, notamment pour les patients recevant des agents cardiovasculaires, analgésiques, et hypoglycémiants.

Traduit par Nicolas Paquette-Lamontagne