ICD-10 codes used to identify adverse drug events in administrative data: a systematic review

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ABSTRACT

Background Adverse drug events, the unintended and harmful effects of medications, are important outcome measures in health services research. Yet no universally accepted set of International Classification of Diseases (ICD) revision 10 codes or coding algorithms exists to ensure their consistent identification in administrative data. Our objective was to synthesize a comprehensive set of ICD-10 codes used to identify adverse drug events.

Methods We developed a systematic search strategy and applied it to five electronic reference databases. We searched relevant medical journals, conference proceedings, electronic grey literature and bibliographies of relevant studies, and contacted content experts for unpublished studies. One author reviewed the titles and abstracts for inclusion and exclusion criteria. Two authors reviewed eligible full-text articles and abstracted data in duplicate. Data were synthesized in a qualitative manner.

Results Of 4241 titles identified, 41 were included. We found a total of 827 ICD-10 codes that have been used in the medical literature to identify adverse drug events. The median number of codes used to search for adverse drug events was 190 (IQR 156–289) with a large degree of variability between studies in the numbers and types of codes used. Authors commonly used external injury (Y40.0–59.9) and disease manifestation codes. Only two papers reported on the sensitivity of their code set.

Conclusions Substantial variability exists in the methods used to identify adverse drug events in administrative data. Our work may serve as a point of reference for future research and consensus building in this area.

INTRODUCTION

The use of prescribed medications has risen dramatically in the past decades.[1] In 2008, over 76% of Americans older than 60 years reported ingesting two or more prescribed medications daily, and 37% used five or more.[1] Patients who use indicated medications appropriately can expect to derive benefit. Yet, a significant proportion will experience adverse drug events, the unintended and harmful effects resulting from medication use that are associated with suboptimal patient outcomes and increased health services utilization.[2–7] Adverse drug reactions alone, a subset of adverse drug events that occur when drugs are used in therapeutic doses,[8] cause 5–10% of acute care hospital admissions,[9–12] prolong hospital stays,[13] and may contribute to more potential years of life lost than all other injuries combined.[14] Efforts to optimize medication use and reduce adverse drug events are therefore a public health priority.[15]

Adverse drug events that are encountered in clinical practice may vary substantially from those observed in pre-market clinical trials.[16] Reasons include differences in patient populations, treatment indications (eg, off-label use), monitoring protocols, duration of drug exposure and compliance between the clinical practice setting and the controlled environment of clinical trials.[6 16 17] Monitoring and evaluating health outcomes that are associated with the way medications are used in clinical practice is difficult, yet essential to understanding the ongoing safety and risk–benefit profiles of medications, and paramount to promoting their optimal use.

Administrative databases, electronic health records and disease registries contain a plethora of health data that can be used to ascertain health outcomes in clinical practice. These data are generally inexpensive, readily accessible and have been collected without interfering in the delivery of care. Thus, data from these sources are more likely to reflect the outcomes experienced by patients in the real-world clinical practice setting than the research setting, provided that the outcomes are appropriately identified and coded.[16]

Administrative databases worldwide, including in the USA, increasingly use the International Classification of Diseases (ICD) revision 10 system to classify diagnostic, health services utilization and death data. The ICD-10 coding dictionary enables coders to document adverse drug events in three ways: (1) by documenting the medication that caused an adverse drug event using 'external injury cause codes' (ie, Y40.0–59.9); (2) by documenting diagnoses that may be caused by a drug using 'disease manifestation codes' (eg, A04.7 *Clostridium difficile* colitis); and (3) by clustering an external injury cause code indicating the drug-related etiology with a disease manifestation code indicating the patient's diagnosis.[18] Because a large number of disease manifestation codes exist that might be adverse drug event related (eg, gastric ulcer), variation exists among health researchers in the code sets and coding algorithms used to identify adverse drug events coded in ICD-10.

Our main objective was to synthesize a comprehensive set of ICD-10 codes used by health researchers to identify adverse drug events. Our secondary objective was to identify studies with ICD-10 coding algorithms for adverse drug events.

METHODS

Data sources and searches

This was a qualitative systematic review of the literature. Ethics approval was not required because it did not involve the use of human subjects or medical records.

A professional librarian (MDW) and study author (CMH) developed a systematic search strategy that was adapted for, and applied to, the following electronic bibliographic databases: MEDLINE (1948–2011), EMBASE (1980–2011), International Pharmaceutical Abstracts ((IPA) 1970–2011), Web of Science (1980–2011), the Cochrane Database of Systematic Reviews (1993–2011) and the Cochrane Central Register of Controlled Trials ((CENTRAL) 1996–2011) (see supplementary appendix A, available online only, for Medline search). Our search strategy combined three concepts: the ICD coding system, adverse drug events, and health outcomes. We reviewed the scope notes for each search term in order to identify and incorporate previous indexing terms, alternative keywords, and appropriate MeSH terms. No language filters were applied.

We hand-searched the following medical journals for relevant studies and conference proceedings from 2000 onwards: the *Milbank Quarterly, Health Technology Assessment Journal*, *Health Affairs*, *Medical Care*, *American Journal of Medical Care*, and *Quality & Safety in Health Care*. We used 2000 as the start date as this was the year that ICD-10 was introduced in Canada. We did not search for any additional conference proceedings not published in the above journals, as we thought it would be unlikely for code sets to be published in abstract format. We conducted an electronic grey literature search using the search engine Google with the same search terms that we used for our electronic bibliographic database searches. We hand-searched the bibliographies of all relevant articles. In 2012, we conducted periodic environmental scans of the literature for newly published studies using auto alerts from MEDLINE, EMBASE and IPA. We contacted content experts and authors of relevant studies for any additional studies and for clarifications about their methodology and code sets.

Study selection

We included all studies reporting the use of the ICD-10 coding system to identify adverse drug events in adult patients. Studies had to report the ICD-10 code set (our outcome measure) or coding algorithms used to search the administrative data. We excluded studies reporting only pediatric data, as common manifestations of adverse drug events vary between adults and children. In addition, pediatric adverse drug events are more commonly the result of dosing errors or unintentional toxic ingestions compared to adult adverse drug events. We also excluded studies using other coding systems, written in languages other than English, French and German, reporting only adverse events to illicit drugs or intentional overdoses, and studies that we could not access.

One study author (AK) screened all titles for potential eligibility using predefined criteria. Any potentially relevant studies were retained for abstract review. Two study authors (AK and CMH) reviewed the abstracts of potentially relevant titles. If either or both of the authors felt the abstract was potentially relevant, the full text article was retrieved and reviewed independently by two authors (AK and CMH) for inclusion and exclusion criteria. All disagreements about study eligibility at the full text review stage were resolved by achieving consensus through discussion.

Data extraction and quality assessment

Two authors (AK and CMH) independently abstracted data from included studies using standardized and piloted abstraction forms. Any disagreements over data abstraction points were resolved by achieving consensus through discussion, after contacting study authors for clarification. Data abstractors were not blinded to authorship or journal.

We are unaware of any validated quality assessment scales to measure the quality of non-comparator, retrospective population-based cohort studies.[19] Therefore, we adapted relevant quality-assessment criteria from the GRACE guidelines and the York Centre for Dissemination and Reviews that were intended for population-based comparative effectiveness studies and reviews of adverse effects (table 1).[19 20]

Table 1 Quality assessment criteria adapted from York Centre of Dissemination Reviews and the GRACE quality assessment checklist for this review of non-comparator cohort studies[19 20]

1. Was the primary outcome(s) defined in a manner that was independent of the code set?	Yes	The primary outcome(s) was defined in a manner that was independent from the code set
	No	The primary outcome(s) was not defined in a manner that was independent from the code set (ie, the definition was based on the ICD-10 codes used for searching)
	NR	Not reported
2. Were methods for identifying the appropriate ICD-10 codes to reflect the primary outcome reported, and was the search comprehensive?	Yes	The methods for identifying the code set were explicit and comprehensive (eg, through literature review or mapping of pharmacovigilance terms to ICD-10 codes). It is unlikely that significant gaps in the code set exist
	No	The methods for identifying the code set was not reported, and the code set is not likely to be comprehensive
	NR	Not reported
3. Did the authors provide data or reference other work to allow the reader to understand how well the primary outcome was ascertained within the same data source(s) using the ICD-10 code set they chose (ie, sensitivity, specificity of the code set)?	Yes	The primary outcome was validated based on medical chart abstraction with clear definitions (eg, a formal medical record review of a sample of charts was done with adjudication of the primary diagnosis by a committee and the code set had reasonable sensitivity and specificity for identifying the primary outcome), or the code set was validated by linking and comparing existing data from various sources to ensure consistency and accuracy (eg, prospective registry compared with administrative data). Alternatively, previous work validated the code set, and the code set was likely to identify the stated primary outcome
	No	No data were reported, and no other work referenced, to suggest that the code set adequately identified the primary outcome
	NR	Not reported
4. Were analyses conducted to test assumptions about the causal link between drug exposure and the disease, and how this uncertainty may have influenced the study results?	Yes	Analyses were reported to evaluate the impact of uncertain causality on the study results (eg, analyses to test the impact of including codes for diagnoses that are likely, but not exclusively drug-induced, ie, *Clostridium difficile* colitis), and may not have been cluster coded with external cause codes
	No	No analysis was done to test the assumptions about the causal link between drug exposure and the disease manifestation

ICD, International Classification of Diseases.

Data synthesis and analysis

We synthesized the data in a qualitative manner, with two authors (CMH and AK) reviewing all data extraction forms and re-reading primary manuscripts. A third author reviewed all tables and figures for accuracy (LR), and all authors subsequently critically reviewed the manuscript for content and accuracy. We adapted causality ratings for individual ICD-10 codes from two previous publications, and modified them by adding the rating 'unlikely' (U) for codes that other authors used to identify adverse drug events in the literature that we felt unlikely to have indicated an adverse drug event (table 2).[21 22] We also added the rating 'vaccine' (V) for codes that were vaccine related. Two study authors (CMH and JS) independently, and blinded to one another's ratings, assigned causality scores to ICD-10 codes without previously assigned causality ratings, and came to consensus through discussion about any disagreement.

Descriptive statistics were provided as averages with 95% CI, or medians with IQR. We calculated the interrater agreement of causality ratings assigned to ICD-10 codes, by collapsing causality ratings into a category indicating that an adverse drug event was very likely (categories A1, A2, B1, B2 and C), and a category in which adverse drugs events were deemed unlikely (categories D, E, U and V) based on the previous literature.[21 22] We calculated κ scores with 95% CI as a measure of agreement beyond chance alone.

RESULTS

Study characteristics and study quality

Our search revealed 4241 titles, of which 41 met our inclusion and exclusion criteria (figure 1). Sixteen studies were conducted in Europe,[21–36] 13 in North America,[14 37–48] nine in Australia,[49–57] and three in Asia (tables 3 and 4).[58–60] The majority of included studies were non-comparator retrospective studies that used administrative data to ascertain the prevalence of adverse drug events in population-based cohorts. Twenty-eight studies examined adverse drug events in general as the main outcome measure,[14 21–26 29 32–40 42 43 49–54 56–58] and 13 examined drug or drug class-specific adverse drug events.[27 28 30 31 41 44–48 55 59 60] Eleven of 28 studies reported explicit methods for identifying the ICD-10 code set they used.[21–23 34–36 38 40 42 53 58]

We found a total of 827 individual ICD-10 codes that have been used in the health literature to identify adverse drug events (see supplementary appendix B, available online only, for the complete list of codes). Of these, 175 were external injury cause codes (Y40.0–59.9), and 652 disease manifestation codes. Only 13 disease manifestation codes only appeared in combination with a clustered code (table 5).[52 61] Among studies examining adverse drug events in general, the median number of codes used was 190 (IQR 156–289). Seven studies used the external injury cause codes Y40.0–59.9 only,[25 26 39 51 54 56 57] five studies used disease manifestation codes only,[23 24 32 33 37] and 16 studies used a combination of both types of codes.[14 21 22 29 34–36 38 40 42 43 49 50 52 53 58] Only one guideline recommended the use of algorithms to search for clustered codes, specifying external injury cause codes that should be clustered with specific disease manifestation codes in order to identify known adverse drug events.[52] This list of clustered codes can be accessed freely online.[61] The most common disease manifestation codes used are listed in table 6. Two authors independently assigned causality ratings to each ICD-10 code that had not previously had a causality rating assigned. The κ statistic as a measure of interrater agreement was 0.88 (95% CI 0.78 to 0.97).

Among studies looking for drug or drug class-specific adverse events, all studies reported the entire code set they used. The median number of codes that was used was three (IQR 1.5–10) (table 4). One study used external injury cause codes only,[44] six studies used disease manifestation codes only,[28 30 31 46 47 59] and six studies used a combination of both types of codes without any requirement for the codes to be clustered.[27 41 45 48 55 60]

Quality assessments

Among the 28 studies looking at adverse drug events in general, 19 reported an explicit definition of their primary outcome measure that was independent of the ICD-10 code

Table 2 Causality rating system adapted with modifications from Stausberg and Hasford[21 22]

Code category	Definition	Examples	
		Code	Code description
A1	The ICD-10 code description includes the phrase 'induced by medication/drug'	J70.2	Acute drug-induced interstitial lung disorders
A2	The ICD-10 code description includes the phrase 'induced by medication or other causes'	142.7 T88.7	Cardiomyopathy due to drugs and other external agents Unspecified adverse event of drug or medicament
B1	The ICD-10 code description includes the phrase 'poisoning by medication'	T36	Poisoning by systemic antibiotics
B2	The ICD-10 code description includes the phrase 'poisoning by or harmful use of medication or other causes'	X44	Accidental poisoning by, and exposure to, other and unspecified drugs, medicaments and biological substances
C	Adverse drug event deemed to be very likely although the ICD-10 code description does not refer to a drug	L51.2	Toxic epidermal necrolysis
D	Adverse drug event deemed to be likely although the ICD-10 code description does not refer to a drug	N17	Acute renal failure with tubular necrosis
E	Adverse drug event deemed to be possible although the ICD-10 code dictionary does not refer to a drug	K25	Gastric ulcer
U	Adverse drug event deemed unlikely	I49.0	Ventricular fibrillation and flutter
V	Vaccine-associated adverse event	A80.0	Acute paralytic poliomyelitis, vaccine-associated

The causality ratings were modified for the purposes of this systematic review. We added category U for ICD-10 codes that have been used by others to identify adverse drug events, but which we felt were unlikely to be adverse drug event related. We also added category V to indicate codes that may be vaccine-related.
ICD, International Classification of Diseases.

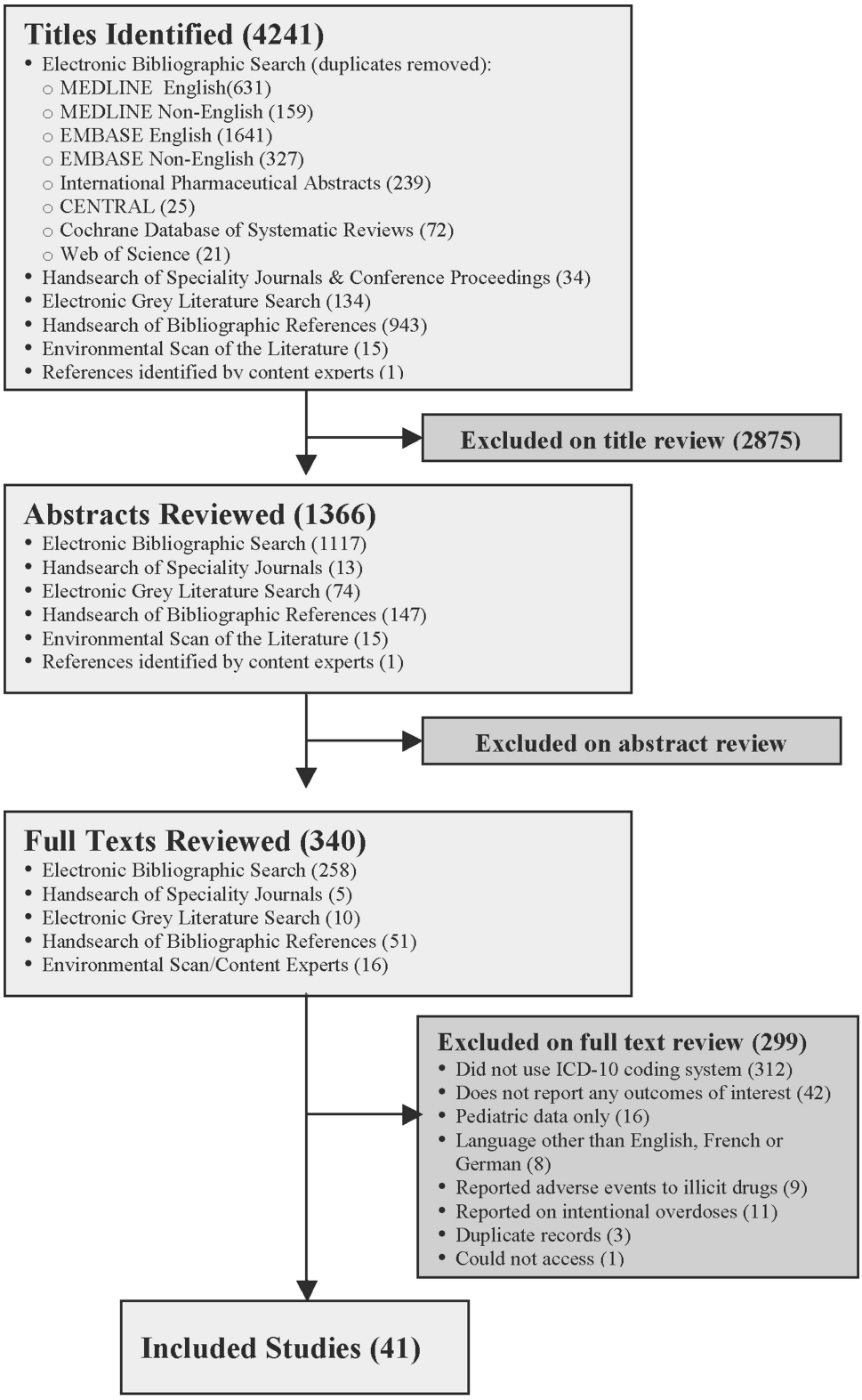

Figure 1 Flow diagram of included studies.

set.[14 21 22 25 29 32 36–40 42 43 49 51 54 56–58] Of these, 9 reported definitions for adverse drug reactions,[29 36 39 40 49 51 56 57 62] 5 definitions for adverse drug events,[14 21 22 38 58] and one explicit definitions for both.[54] Three studies used death as a result of poisoning or prescription drug use as primary outcome.[37 42 43] Among the 13 studies on drug or drug class-specific adverse events, all provided definitions for their primary outcome measure with 4 using drug-induced deaths[41 44 45 47] and 4 hospital admission due to an adverse drug event.[30 46 55 59]

Among the 28 studies looking at adverse drug events in general, 11 provided methods for their selection of ICD-10 codes.[21–23 34–36 38 40 42 53 58] Methods included searching the ICD-10 code dictionary for diagnoses that could be attributable to medications (ie, gastric ulcer) and/or phrases (ie,

Table 3 Characteristics of 28 studies looking at adverse drug events in general, that is, events that were not specific to any drug or disease category

Study	Country	Setting	Design	Data source	Main objective	Main outcome and definition	No. codes	Methods to identify ICD-10 codes	Sample size	Frequency of outcome measure
Malpass *et al*[53]	Australia	NR	Review	NR	To describe an ADE monitoring system	ADE: NR	318[i] AM	Mapped an adverse event classification system to ICD-10.	NR	NR
Cox *et al*[26]	England	Hospital	RS	Admin and PV	To compare ADR reports in administrative and PV data	ADR: NR	175	NR	21 635 records	0.2% of admissions due to ADR
Runciman *et al*[54]	Australia	Hospital	Review	Admin, trial, drug use, chart review and VS	To review information about ADE and medication errors in Australia	ADR: Noxious and unintended response to a drug used at doses for prophylaxis, diagnosis or therapy of disease or modification of function. ADE: ADR, harm from medication errors and underuse	175 AM	NR	NR	▶ ADR: occur in 1% of admissions. ▶ ADE: occur in 2–4% of admissions
Waller *et al*[35]	England	Hospital	RS	Admin	To describe records coded as drug-induced and assess their utility for research	ADR: NR	243	Codes containing 'drug-induced', diagnoses 'due to' a drug, 'clearly implying' an ADR and Y40–59	53.8M records	0.4% of admissions due to ADR
CDC[37]	USA	NR	RS	VS	To describe trends in poisoning deaths	Death from ingestion, inhalation or exposure to pharmaceuticals, illicit drugs and chemicals[37]	137	NR	NR	5.0–7.8 deaths/100 000 population
Wysowski[43]	USA	NR	Letter	VS	To study deaths attributed to therapeutic drug use	Death attributed to drugs used therapeutically	4	NR	604 records	NR
Moneret et al[32]	NR	NR	Review	NR	To review the epidemio-logy of anaphylaxis	Anaphylaxis	6	NR	NR	NR
Burgess *et al*[49]	Australia	Hospital	Case series	Admin data	To examine trends in ADR-related admissions in people ≥60 years	ADR: Noxious and unintended response to a drug that occurs at doses normally used in humans	200 AM	NR	NR	0.8% of admissions associated with ADR
Barrow *et al*[23]	England	Hospital	RS	Admin and PV	To compare ADR in admin data with PV reports	ADR: NR	37	Used codes identified by Waller *et al*[35]	NR	NR
Lugardon *et al*[29]	France	Hospital	RS	Admin and PV	To estimate the incidence of serious ADR in hospital	ADR: Noxious and unintended response to a drug used at doses for prophylaxis, diagnosis, or therapy of disease or modification of physiological function	299	NR	261 records	2.9% of admissions associated with ADR
Wysowski[42]	USA	NR	RS	VS	To identify prescription drugs associated with >1000 deaths/ year	Death due to a prescription drug	NR[ii]	Seven disease manifestation codes and codes listing prescription drugs as cause	NR	NR
Zhang *et al*[57]	Australia	Hospital	RS	Admin, VS and census	To examine trends in repeat ADR causing hospitalization in elderly	Hospitalization for ADR. ADR: Noxious and unintended response to a drug at doses normally used in humans	175 AM	NR	37 296 records	30.3% of ADR-related admissions were repeat events
Patel *et al*[34]	England	Hospital	RS	Admin	To examine trends in hospital admissions associated with ADR	ADR: NR	245	Codes containing 'drug-induced', indicating a diagnosis 'due to' a drug, and codes Y40–59	88M records	0.5% of admissions due to ADR
Phillips *et al*[14]	USA	NA	RS	VS	To describe trends in fatal medication errors	ADE: Preventable deaths resulting from accidental overdose, wrong drug given or taken in error, and other accidents in the use of drugs	180	NR	50M death records	0.4% of deaths due to fatal medication errors
Hwang *et al* [58]	Korea	Hospital	RS	Chart review	To evaluate an electronic ADE monitoring system	ADE: Injury from a medical intervention related to a drug	326	Codes corresponded to ADE described in four previous studies on ADE monitoring systems[73–76]	598 patients	31% of patients admitted to hospital
Benkhaial *et al*[24]	Germany	Hospital	RS	Admin	To assess the value of ICD-10 codes to identify drug allergies	Drug allergy: NR	35 GM	NR	200 records	9% of records indicating an allergy

Continued

Table 3 Continued

Study	Country	Setting	Design	Data source	Main objective	Main outcome and definition	No. codes	Methods to identify ICD-10 codes	Sample size	Frequency of outcome measure
Hodgkin-son *et al*[51]	Australia	Hospital	RS	Admin and PV	To compare ADR identification using coding surveillance with spontaneous reporting	ADR: Noxious and unintended response to a drug that occurs at doses used for prophylaxis, diagnosis, or therapy, or modification of physiological function	175 AM	NR	12 414 records	4.5% of admissions associated with ADR
Wu[40]	Canada	ED	RS	Admin data	To estimate the incidence of ADR-related ED visits and admissions for patients >65 years	ADR: Injury resulting from a medical intervention relating to a drug.	245 CA	Used codes identified by Patel *et al*[34]	966 232 records	0.8% of ED visits were ADR-related
Zhang *et al*[56]	Australia	Hospital	RS	Admin, VS and census	To identify factors that predict repeat hospital admission for ADR in older adults	ADR: Harmful or unpleasant reaction related to a drug that predicts hazard from future use and warrants prevention, treatment, dose change or withdrawal	175 AM	NR	28 548 patients	17.7% of ADR-related admissions were repeat events
Jackson *et al*[52 61]	Australia	Hospital	RS	Admin	To develop a tool to monitor hospital-acquired diagnoses	Hospital acquired diagnosis. ADE: NR	279[iii] AM	Codes Y40–59 and codes with a C prefix, indicating a hospital acquired condition	126 940 records	NR
Wu *et al*[36]	England	Hospital	RS	Admin	To examine trends in hospital admissions associated with ADR	ADR: Undesirable effect of a drug beyond its anticipated therapeutic effects	260	Codes containing 'ADR', 'drug-induced', 'due to drug', 'due to medication', 'drug allergy' and Y40–59	59.7M records	0.9% admissions associated with an ADR
Bergman *et al*[25]	Sweden	Hospital	RS	Admin and PV	To examine trends in the use of the Y57.9 code for ADR reporting	ADR: Unintended effect of therapeutic use of drugs	1	NR	NR	500 ADR reports/million in population
Stausberg and Hasford[21], Stausberg[77]	Germany	Hospital	RS	Admin	To examine the utility of ICD-10 coded diagnoses in admin data to identify ADE among inpatients	ADE: Unfavorable medical event that occurred in association with the use of a medication, and that may be causally related to the medication	502*> GM	Literature search for ADE, identified previously used codes,[78] and applied screening criteria of and data from a PV center. Mapped ADE to ICD-10	12M records	▶ 0.7% admissions due to an ADE ▶ 5.3% admissions possibly due to ADE
Stausberg and Hasford[22]	Germany	Hospital	RS	Admin	To examine the frequency of ADE-related admissions and hospital-acquired ADE	ADE: Injury resulting from a medical intervention related to a drug including errors and ADR	505[iv] GM	Literature search for ADE, identified previously used codes,[78] and applied screening criteria of and data from a PV center. Mapped ADE to ICD-10	48M records	▶ 0.5–0.7% of admissions due to ADE ▶ 5% of admissions possibly due to ADE
Osmont *et al*[33]	France	Hospital	RS	Admin	To evaluate ICD-10 queries to identify serious ADR	ADR: NR	NR	NR	NR	NR
Hauck and Zhao[50]	Australia	Hospital	RS	Admin	To examine the association between ADR and hospital length of stay	ADR: NR	206 AM	NR	206 489 records	3.4% risk of ADR for 2-day admission
Shepherd *et al*[39]	USA	NA	RS	VS	To examine trends in mortality attributed to ADR using US VS data	ADR: Noxious and unintended response to a medication used at doses administered for diagnosis, prophylaxis or treatment	175	NR	NR	0.1 deaths from ADR/ 100 000 in population
Hohl *et al* submitted[38]	Canada	ED	RS	Admin and prospect data	To measure proportion of ADE-related ED visits identifiable in admin data	ADE: Untoward and unintended symptoms, signs or abnormal laboratory values from medication use	650	Adapted previously established code set[21 22] with others found through literature review	1574 records	14.0% of ED visits ADE related

[i]Use of the AM modification likely, although unable to verify with authors.
[ii]Only codes associated with ≥1000 deaths and/or ≥1000 total mentions per year were listed.
[iii]Jackson *et al* describe the CHADx algorithms to identify hospital acquired diagnoses, including adverse drug events (ADE). The CHADx code set and algorithms are published on the Australian Commission on Quality and Safety in Healthcare website. Jackson et al. recommend searching for ADE using disease manifestation codes clustered with external injury cause codes (Y40–59). C-prefixes are codes that were introduced in the Victorian addition of the Australian Modification of ICD-10.
[iv]The difference in the number of codes used by Stausberg *et al*. has to do with the splitting of code E66.1 (in ICD-10-German Modification 2006) into the four codes: E66.10, E66.11, E66.12 and E66.19 (in ICD-10-German Modification 2008).
ADE, adverse drug event; Admin, administrative; ADR, adverse drug reaction; AM, Australian modification; CDC, Centers for Disease Control and Prevention; ED, emergency department; GM, German modification; ICD, International Classification of Diseases; M, million; NR, not reported; pros, prospective; PV, pharmacovigilance; RS, retrospective; VS, vital statistics.

Table 4 Characteristics of 13 studies looking at drug or disease-specific adverse drug events, in order of publication year

Study	Country	Setting	Design	Data source	Main objective	Main outcome and definition	No. codes	Methods to identify ICD-10 codes	Sample size	Frequency of outcome measure reported
Gaus *et al*[28]	Germany	Outpatients	RS case crossover	Admin and drug use	To illustrate case crossover methodology to identify ADR using bleeding complications as an example	Bleeding complications	84	NR	320 644 records	3.5 episodes of bleeding/100 years observation
Wysowski[41]	USA	NR	RS	Drug use and VS	To determine the number, rate and types of deaths attributed to x-ray contrast media	Death from contrast agents	3	NR	NR	1.1–1.2 deaths/million doses
Wysowski[44]	USA	NR	RS	Admin, drug use, PV and VS	To compile and analyze data on the prevalence of bleeding related to warfarin	Warfarin-related deaths	1	NR		0.4–0.5 deaths/100 000 population
Sims *et al*[47]	USA	NR	RS	Admin, drug use and vital stats	To examine the utility of ADR surveillance methods that combine and analyze multiple data sources	Methadone-related death	1	NR	NR	0.8–4.3 deaths/100 000 population
Myers *et al*[46]	Canada	Hospital	RS	Admin and chart review	To validate coding algorithms for acetaminophen overdose and hepatotoxicity	Admission for acetaminophen toxicity	16	NR	1776 cases	NR
Molokhia *et al*[31]	France	Hospital	RS	Admin and PV	To estimate the incidence and reporting rate of nonfatal drug-induced LQTS leading to VT and/or death	Drug-induced LQTS	3	NR	861 cases	10.9 cases/million population/year
Elalamy *et al*[27]	France	Hospital	RS	Admin and laboratory surveillance	To estimate the average cost of one episode of HIT in France	HIT	3	NR	50 958 records	0.9% of admissions
Lyytikainen 2009[30]	Finland	Admin data	RS	Admin and VS	To determine the prevalence of CDAD in hospitalized patients	Admission associated with CDAD	2	NR	NR	16–34 cases/100 000 population
Li *et al*[45]	USA	Hospital	RS	Admin and VS	To examine the epidemiology of anesthesia-related deaths	Anesthesia-related death	46[v]	Lit review and ICD-10 search	NR	8.2 deaths/million surgical discharges
Treeprasertsuk *et al*[60]	Thailand	Hospital	RS	Admin	To examine the incidence and complications of antimicrobial induced liver injury in hospitalized patients	Drug-induced liver injury	4	NR	237 970 records	0.03% of admitted patients
Rhee *et al*[59]	Korea	Hospital	RS case control	Admin	To quantify the risk of digoxin toxicity with concomitant use of diuretics	Admission for digoxin toxicity	1	NR	104 075 records	61.5 cases/100 000 admissions
Sood *et al*[55]	Australia	Hospital	RS	Admin	To examine the epidemiology, outcomes and burden of acetaminophen poisoning	Admission for acetaminophen poisoning	2 AM	NR	NR	39–46 cases/100 000 admissions
Wysowski *et al*[48]	USA	NR	RS	PV, admin, VS, drug use and surveillance	To determine the incidence of serious anaphylactic reactions to parenteral iron	Anaphylaxis due to parenteral iron	2[vi]	NR	NR	0.1–0.3 deaths/million doses sold

[v]Includes one code unrelated to ADE, ADR (eg, Y65.3 Endotracheal tube wrongly placed).
[vi]The authors used surveillance data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) and the Drug Abuse Warning Network (DAWN) *Live!*. Codes indicating anesthesia-related events that were not medication-relation have been omitted.
Admin, administrative; ADR, adverse drug reaction; AM, Australian modification; CDAD, *Clostridium difficile*-associated disease; ED, emergency department; HITS, heparin-induced thrombocytopenia; ICD, International Classification of Diseases; LQTS, long QT syndrome; NR, not reported; PV, pharmacovigilance; RS, retrospective; VS, vital statistics; VT, ventricular tachycardia.

Table 5 Disease manifestation codes that were used only as clustered codes and never as stand-alone codes

ICD-10 code	Description
D68.8	Other specified coagulation defects
F05	Delirium, not induced by alcohol and other psychoactive substances
I95	Hypotension
L21	Seborrhoeic dermatitis
L26	Exfoliative dermatitis
L27	Dermatitis due to substances taken internally
L28	Lichen simplex chronicus and prurigo
L30	Other dermatitis
R20	Disturbances of skin sensation
R23	Other skin changes
R40	Somnolence, stupor and coma
R41	Other symptoms and signs involving cognitive functions and awareness
R44	Other symptoms and signs involving general sensations and perceptions

ICD, International Classification of Diseases.

'drug-induced'), empiric study of existing pharmacovigilance reports and mapping of events to the ICD-10 code dictionary,[21 22 53] and literature review.[21 22 34–36] Others adopted code sets that had previously been established by other authors.[23 38 40 58]

Only two studies estimated the sensitivity with which their code set may have ascertained the desired outcomes.[38 40] Wu *et al*[40] compared records containing adverse drug event-related diagnoses between two administrative databases. The authors' premise was that for patients admitted to hospital through the emergency department for a drug-related diagnosis, the emergency department discharge and hospital admitting diagnoses should be similar. Using an ICD-10 code set containing 245 drug-related codes, including the external injury cause codes, Wu *et al*[40] found that 15% of drug-related emergency department visits leading to hospital admission were coded with a corresponding admitting diagnosis. Wu *et al*[40] estimated the specificity of their code set, and found it to be 99.7%. In comparison, in a study including both admitted and discharged emergency department patients, in which adverse drug events were identified prospectively by pharmacists and physicians, 6.8% of prospectively identified adverse drug events were identifiable using an ICD-10 code set consisting of diagnoses rated as definitely, very likely or likely to be related to medications.[38] When the code set was broadened to include lower likelihood codes, 28.1% were identifiable with little drop in the code set's specificity (98.7–87.7%).

Three studies considered the uncertainty of the causal link between drug exposure and the adverse event, and provided analyses allowing the reader to ascertain the impact that this may have had on the study results.[21 22 38]

Table 6 Top 15 disease manifestation codes used to identify adverse drug events in all studies

ICD-10 code	Description
T88.6	Anaphylactic shock due to the adverse effect of a drug
T88.7	Unspecified adverse effect of a drug
N14.1	Nephropathy induced by drugs, medicaments and biological substances
D59.0	Drug-induced autoimmune hemolytic anemia
D59.2	Drug-induced non-autoimmune hemolytic anemia
D61.1	Drug-induced aplastic anemia
J70.4	Drug-induced interstitial lung disorders
K71	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
L56.1	Drug photoallergic response
N14.2	Nephropathy induced by unspecified drug, medicament or biological substance
T88.3	Malignant hyperthermia due to anesthesia

ICD, International Classification of Diseases.

DISCUSSION

Our objective was to synthesize a comprehensive set of ICD-10 codes and coding algorithms that have been used by health researchers to identify adverse drug events in administrative health data. Among 41 published studies, we found 827 ICD-10 codes that have been used for this purpose. There was a large degree of variability in the number and types of codes used between studies, and only one published guideline recommended the use of algorithms to identify external injury cause codes clustered with disease manifestation codes. Of the reviewed studies, two provided estimates of the code set's sensitivity and specificity.

Adverse drug events represent a growing public health concern.[3] In the USA, adverse drug events represent the fourth to sixth leading cause of death, and are a frequent cause of unplanned hospitalizations, emergency department visits and ambulatory care encounters.[5 10 63–65] The focus of the US$1 billion federal private–public initiative, Partnership for Patients, is to reduce hospital-acquired conditions by 40% and hospital readmissions by 20% by the end of 2013.[66]

In order to accomplish this target, the Partnership for Patients has identified the reduction of in-hospital adverse drug events as a priority. One intervention that the Partnership for Patients is promoting to accomplish this goal is medication reconciliation, a health systems intervention aimed at decreasing adverse drug events that result from the inaccurate transfer of medication information.[67 68] However, to date little research has been conducted to describe and rank possible etiologies of adverse drug events, and as a result, it is largely unknown to what extent inaccurate transfer of medication information contributes to the development of clinically significant adverse drug events. Thus, it is not surprising that a recent systematic review of 26 controlled studies failed to find an effect of medication reconciliation on downstream health services use, mortality or cost.[69] This example underscores the need for further development of innovative, evidence-based and effective patient safety strategies to reduce adverse drug events, and for their evaluation on health outcomes before their implementation outside of the research setting.

In order to inform the development of strategies to reduce preventable adverse drug events, the burden of disease in different healthcare settings and patient populations and their common etiologies need to be understood. This will help to prioritize and rationalize the development and evaluation of emerging strategies to prevent commonly occurring events associated with health services use and cost. Modifiable risk factors that can be targeted in carefully designed health systems

interventions need to be identified. These may be related to medications, medication classes, treatment protocols, prescribing patterns, patient groups, provider groups, healthcare settings, and models of care, some of which may assist in developing successful interventions. Once developed, strategies are likely to benefit from refinement to enhance their feasibility of implementation and their performance. Finally, their impact on health outcomes and cost must be evaluated and compared with that of other health interventions in order to guide rational resource allocation and optimize health value for expenditure.

Population-level administrative health data that can be linked with medication dispensing data may represent a rich source of health information for this type of work. Adverse drug event data from this source may offer accessible and standardized population-level data over long time periods, enabling analysis of time trends, prescribing patterns, and comparisons across healthcare settings.[16 70] However, no consensus presently exists among health researchers on how to identify adverse drug events reliably within such data sources, leading to substantial variability in the methods used for their identification.

Our study is the first systematically to review the health literature to synthesize a comprehensive set of ICD-10 codes previously used to identify adverse drug events. Previous studies have identified code sets by relying on ad hoc reviews of the literature, and mapping of drug-related diagnoses and pharmacovigilance case reports to the ICD-10 code dictionary. Most have adopted and used code sets developed by previous authors without conducting any validation studies to understand their sensitivity or specificity. When examining the code sets, common manifestations of adverse drug events have often been omitted (eg, E16.2 hypoglycemia), while the codes of rare events are commonly used (eg, T88.3 malignant hyperthermia due to anesthesia). This is problematic, as multiple studies relied entirely on disease manifestation codes to identify drug-related diagnoses. The omission of common manifestations of adverse drug events from their code sets based on the assumption that they might be associated with low positive predictive values would probably have dramatically influenced the numbers and types of adverse drug events found.

There is general agreement among health researchers that adverse drug events are underreported in administrative data, and that the effect of coding quality on adverse drug event identification is poorly understood.[23 34 38–40 71] Based on our review, it is also possible that the use of incomplete code sets for adverse drug events may be a contributing factor. We found only two studies that evaluated the sensitivity of their ICD-10 code sets for adverse drug events, and both were low.[38 40] Therefore, validation of a more comprehensive set of adverse drug event-related ICD-10 codes is necessary to try and enhance the sensitivity of the code sets used, while retaining specificity. This work needs to be conducted in a variety of care settings (eg, hospital vs ambulatory care), on a variety of adverse drug event types (eg, adverse drug reactions vs non-adherence), on different grades of adverse drug event severity (eg, severe vs mild), and by syndrome (eg, intracerebral hemorrhage vs epistaxis). Different clinical practice settings may influence the diagnostic performance of the code set(s) that is/are used, and may require refinements of the code sets used. Finally, it may be that administrative data may be well suited to tracking and investigating some consistently coded and identifiable adverse outcomes (eg, bleeding events), but not all manifestations of drug-related events (eg, delirium). Thus, we cannot recommend the adoption of our proposed code set without validation and further refinement. Instead, we present a comprehensive list of codes that we hope will provide the basis for further investigation, debate and consensus building in this area.

Due to the multiple ways in which adverse drug events may be coded (ie, by using external injury cause codes only, disease manifestation codes only, clusters of codes, or a combination of these methods), methodologies need to be developed to avoid double counting. Two of the studies we reviewed concluded that double counting was indeed possible when searching for adverse drug events using a combination of external injury cause codes and disease manifestation codes, and that this occurred in up to 15% of records.[35 36] Similarly, studies need to be conducted to understand to what extent the use of disease manifestation codes (ie, E87.1 hyponatremia), which may indicate an adverse drug event or a non-drug-related event, may influence the sensitivity and specificity of the code set. To date, only one study has compared the sensitivity and specificity of narrower and broader code sets, and compared them to an independent prospective criterion standard in emergency department administrative data.[38] In that study, while the broader code set led to higher sensitivity (6.8% vs 28.1%), broadening the code set had little impact on the code sets' specificity.[38] Unfortunately, the study did not examine coding quality to determine which steps during the patient care and coding trajectory may have contributed most to the under-coding of adverse drug events. Finally, methods to identify and understand the extent to which adverse events related to prescription medication use may be coded using codes that do not distinguish between prescription drugs and drugs of abuse (eg, F11 mental and behavioral disorders due to the use of opioids) need to be developed.

The most widely used definition for adverse drug events is 'harm caused by the use of a drug'.[2 72] In this study, we presented all definitions as reported by the study authors, as these may have led to variability in the code sets used. The existing inconsistency in the operational definition of adverse drug events needs to be addressed before being able to achieve consensus on a common code set(s), and may enhance the consistency with which adverse drug events are identified and reported, and thus comparability between studies. Given this limitation, we provided a comprehensive list of definitions and a corresponding code set that may serve as a point of reference for consensus building.

We did not attempt to meta-analyze data on the prevalence of adverse drug events, as this was not the objective of our study. In addition, significant differences in the ICD-10 code sets used to find adverse drug events are likely to result in significant heterogeneity between studies, and any differences that are found may simply be due to the methods used to identify them.

Ongoing national adaptations of the ICD-10 coding systems have introduced additional variability in the coding of adverse drug events that we were unable to account for. Not all studies described explicitly which national adaptation and versions of the coding dictionary they based their code set on. Some adaptations, for example, the German modification, may use additional two-decimal subcategorizations of individual disease manifestation codes that allow more refined coding than other systems. At present, the USA only uses ICD-10 coding for mortality reporting, explaining why all the US studies reported only on events related to death. Thus, while the majority of code categories are comparable across coding systems, the variability between national adaptations and coding versions used needs to be taken into account before application of any code set.

Additional limitations of our work are that we only reviewed publications in English, French and German. We also did not search extensively for abstracts or conference proceedings, as we

thought we would be unlikely to find code sets published in these formats. We applied the only causality rating system that we are aware of for adverse drug event-related ICD-10 codes.[21 22] While the causality rating system is based on clinical reasoning, and therefore inherently subjective, it may provide health researchers with a framework with which to start incorporating the certainty/uncertainty of drug-related causes to diagnoses identified in ICD-10. Therefore, we applied the previously proposed causality categories to additional ICD-10 codes that we identified through our review.

In conclusion, in this study we have synthesized a set of ICD-10 codes that have been used by health researchers to identify adverse drug events in administrative health data. Our code provides a basis for future work in establishing comprehensive and agreed-upon code sets that can be validated and refined for future work in this area.

Contributors All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: CMH and JS. Acquisition of data: CMH, AK and LR. Analysis and interpretation of data: CMH and AK. Drafting of the manuscript: CMH. Critical revision of the manuscript for important intellectual content: All authors. Administrative, technical or material support: LR. Study supervision: CMH.

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