Methods for assessing the preventability of adverse drug events: A systematic review.

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Katja Marja Hakkarainen, Karolina Andersson Sundell, Max Petzold and Staffan Hägg, Methods for assessing the preventability of adverse drug events: A systematic review, 2012, Drug Safety, (35), 2, 105-26.

<http://dx.doi.org/10.2165/11596570-0000000000-00000>

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Postprint available at: Linköping University Electronic Press

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-74228>

A. Title page

Methods for Assessing the Preventability of Adverse Drug Events
– A Systematic Review

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Running title: Preventability assessment of adverse drug events

Word count: 4856

B. Acknowledgements

We would like to acknowledge Dr Anna K Jönsson for her contribution on the planning of the study and NHV's librarian Susanne Tidblom-Kjellberger for her advice in conducting the database searches. The research is funded through an unrestricted grant from The National Corporation of Swedish Pharmacies (Apoteket AB). The funder had no role in the design or conduct of the study nor in the preparation of the manuscript. The authors have no conflicts of interest that are directly relevant to the content of this review.

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F. Abstract

Background

Preventable adverse drug events (ADEs) have been reported to be common in both outpatient and inpatient settings. However, the proportion of preventable ADEs varies considerably in different studies, even when conducted in the same settings, and methods for assessing the preventability of ADEs are diverse.

Objective

To identify and systematically evaluate methods for assessing the preventability of ADEs.

Data sources

Seven databases (Cochrane, CINAHL, EMBASE, IPA, Medline, PsycINFO and Web of Science) were searched in September 2010 utilising the databases' index terms and other common terminology on preventable ADEs. No limits for the years of publication were set. Reference lists of included original articles and relevant review articles were also screened.

Study selection

Applying predetermined inclusion and exclusion criteria on 4161 unique citations, 142 (3.4%) original research articles were included in the review. One additional article was included from reference lists. Outcome measures of included studies had to include the frequency of ADEs and the assessment of their preventability. Studies were excluded if they focused on individuals with one specific type of a treatment, medical condition, medical procedure or ADE.

Data extraction

Measurement instruments for determining the preventability of ADEs in each article were extracted and unique instruments were compared. The process of assessing the preventability of ADEs was described based on reported actions taken to standardise and conducting the assessment and information on the reliability and validity of the assessment.

Data synthesis

Eighteen unique instruments for determining the preventability of ADEs were identified. They fell under four groups: instruments using a definition of preventability only (n=3), instruments with a definition of preventability and an assessment scale for determining preventability (n=5), instruments with specific criteria for each preventability category (n=3) and instruments with an algorithm for determining preventability (n=7). Of actions to standardise the assessment process, performing a pilot study was reported in 21 (15%) and the use of a standardised protocol in 18 (13%) of the included 143 articles. In 86 (60%) articles, the preventability was assessed by physicians, and in 41 (29%) articles by pharmacists. In 29 (20%) articles, persons conducting the assessment were described trained for or experienced in preventability assessment. In 94 (66%) articles, more than one person assessed the preventability of each

case. Among these 94 articles, the assessment was done independently in 73 (51%) articles. Procedures for managing conflicting assessments were diverse. The reliability of the preventability assessment was tested in 39 (27%) articles and 16 (11%) articles referred to a previous reliability assessment. Reliability ranged from poor to excellent (kappa 0.19-0.98; overall agreement 26-97%). Four (3%) articles mentioned assessing validity but no sensitivity or specificity analyses or negative or positive predictive values were presented.

Conclusions

Instruments for assessing the preventability of ADEs vary from implicit instruments to explicit algorithms. There is limited evidence for the validity of the identified instruments and the instruments' reliability varied significantly. The process of assessing the preventability of ADEs is also commonly imprecisely described which hinders the interpretation and comparison of the studies. For measuring the preventability of ADEs more accurately and precisely in the future, we believe that the existing instruments should be further studied and developed or one or more new instruments should be developed and their validity and reliability established.

G. Text pages

1 BACKGROUND

Adverse events resulting from medication therapy are common causes of morbidity and mortality in health care (1,2). These events are referred to as adverse drug events (ADEs) in this review. According to one definition, ADEs that occur as a result of a medication error, a failure in the medication use process, such as prescribing, dispensing or administration of medicines, are considered to have been preventable(3).

Preventable ADEs occur in both outpatient and inpatient settings (4-7). The estimated frequencies of preventable ADEs and the supposed preventability rates of ADEs vary considerably in different studies. A systematic review of preventable ADEs in ambulatory care found that per 1000 patient-months the median incidence of ADEs was 14.9 and the median ADE preventability rate was 21%, ranging from 11 to 38% (5). Another review study on drug-related hospital admissions concluded that the median percentage of preventable drug-related hospital admissions was 3.7%, ranging from 1.4 to 15.4% (4). In a review of ADEs in hospitalised patients, the preventability rate ranged from 15 to 90% (6). Also an older review reported that the preventability rate of ADEs in hospital settings ranged from 19 to 73%, with the median of 35%, and the median frequency of preventable ADEs was 1,8%, ranging from 1.3 to 7.8% (7).

In systematic reviews, the heterogeneity between studies assessing preventable ADEs has been described as a barrier for conducting a meta-analysis on preventable ADEs (4,5). Using different definitions for adverse outcomes and preventability has been suggested to decrease the comparability of different studies (6,7). While some research groups have repeatedly assessed the preventability of ADEs reliably (8,9), some have found only fair agreement on the assessment of preventable ADEs and criticised the lack of reliable methods for assessing preventable ADEs (10). A recent narrative systematic review outlining and discussing how preventable adverse drug reactions (ADRs) and preventability of ADRs are defined found that several definitions are used and existing approaches are limited (11). Thus, better understanding of methods to assess the preventability of ADEs is required. We are not aware of a systematic review study that has explicitly focused on evaluating methods for assessing the preventability of ADEs in both inpatient and outpatient settings and systematically compared the applied methods against the same criteria. Therefore, this review was undertaken to identify and systematically evaluate different methods for assessing the preventability of ADEs, excluding methods on investigating potential ADEs and their potential preventability.

2 LITERATURE REVIEW METHODS

Terminology

As described in earlier, an ADE is defined as “an injury resulting from medical intervention related to a drug” (8). In this review, ADEs include ADRs and other adverse health outcomes associated with medication therapy, such as adverse drug events due to drug intoxications, drug dependence, under-treatment and therapeutic failure. When we refer to ADEs in this review, the relationship between a negative health outcome and medication therapy has been assessed. Studies on medication errors, drug-related problems (DRPs) and potentially inappropriate medicines were considered in this review only if actual adverse health outcomes were investigated. Without the assessment of “injury resulting from medical intervention related to a drug”, studies on for example potentially inappropriate medicines according to the Beers criteria (12) would not meet the definition of an ADE in our study.

As there is no universally accepted definition for the preventability of ADEs, we considered all studies that investigated the preventability of ADEs, regardless of how this was defined. With preventability assessment of ADEs we refer to a case-by-case assessment. Studies in which potential preventability of ADEs was investigated were not considered. We did not include studies in which the occurrence of medication errors was assessed first, then whether they caused harm and which concluded that errors with harm represent preventable ADEs, as the preventability of ADEs is not assessed in such studies.

Data sources

Seven databases, the Cochrane database of systematic reviews, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), International Pharmaceutical Abstract (IPA), MEDLINE, PsycINFO and Web of Science (–September 2010), were searched by one researcher (KMH). Databases’ index terms and other commonly utilised terminology on ADEs and preventability were used (Appendix 1). The search was limited to publications in English. No limits for the years of publication were set. References of included original articles and relevant review studies identified in the database search or through other sources were also retrieved. Citations that were not available through the databases, library or the internet were retrieved through contacting corresponding authors or research institutes.

Study selection

Original peer-reviewed research articles were included into the review according to predetermined inclusion and exclusion criteria. Commentaries, editorials, letters, guidelines, reports, conference proceedings, case reports, conceptual papers and other non-original research articles were excluded.

Studies on chemical compounds other than medicines and studies on pharmacodynamic, pharmacokinetic and pharmacogenetic measures were also excluded. Outcome measures of included studies had to include the frequency of ADEs or synonymous concepts and the assessment of their preventability. Thus, studies on errors or potential adverse events without information on actual adverse events were excluded. The required outcome measures had to be reported in the results sections of the studies. Articles summarising previous results without original assessment of the preventability of ADEs were excluded. Studies were also excluded if they focused on specific treatments or other health intervention (e.g. patients on antidepressants), diagnostic procedures (e.g. patients having colonoscopy), types of ADE (e.g. renal failure), disease areas or medical conditions (e.g. depression patients) and if the settings or the sampling frame of the study represented one or two specific disease areas (e.g. cardiac intensive care unit). Original studies published in other languages than English were excluded.

A total of 5770 citations were found in the database search (Figure 1). After removal of duplicate records, the above mentioned inclusion and exclusion criteria were applied on titles of 4161 unique citations. Subsequently 1751 abstracts were reviewed against the same criteria. Based on the abstract review, the inclusion and exclusion criteria were applied on 386 articles' full texts. Out of the 4161 unique citations, 142 articles (3.4%) fulfilled the inclusion criteria. As one additional article was included from reference lists, in total 143 articles were included in the review. The screening and selection of articles was done by one researcher (KMH). Two articles that fulfilled the inclusion criteria based on the abstract could not be retrieved through several libraries internationally or through contacting the authors and research institutes and thus, were excluded from the review (13,14).

Data extraction

Data extraction from the included articles was performed utilising a pilot tested data collection template. Extracted characteristics of the articles included information on study design, data source, setting, sampling frame, characteristics of the study population and outcome measures. The utilised measurement instruments for defining the preventability of ADEs in the included articles were identified and, when referenced, original publications on the measurement instruments were retrieved. These publications could include scientific articles as well as gray literature, such as professional publications, in any language.

Unique measurement instruments that were used in at least one included article, in addition to the original publication, were classified and compared. A measurement instrument was considered unique when it was not introduced in previous articles and when it had a new way of categorising or defining preventability. When evaluating uniqueness of an instrument, the functional meaning of the wording was evaluated and

small changes in wording were overlooked. When an introduced instrument did not appear unique but was reported as unique and was not referenced, the introduced instrument was analysed as unique.

Figure 1. Flow diagram of study selection of eligible studies.

The process of assessing the preventability of ADEs in each article was assessed based on reported actions that may influence the validity and reliability of the measurement (15-17). Firstly, information on standardising the assessment process through performing a pilot or using an operational manual was extracted. Secondly, data on persons conducting the assessment was extracted, including the assessors' profession, training for or experience in preventability assessment, the number of assessors per case and whether multiple assessors' assessment was independent of each other, and procedures for managing conflicting assessments. Thirdly, reported reliability and validity of the preventability assessments was extracted from each article. The extracted data was based on data reported in the included articles.

Authors were not contacted when information was missing. One researcher (KMH) conducted the data extraction.

3 RESULTS

The characteristics of the 143 included studies are presented in Table I. Thirty-eight (27%) articles investigated the preventability of ADRs, excluding other types of ADEs. The preventability of ADEs was studied in 65 (45%) articles. Fifteen (10%) articles examined the preventability of all medical adverse events (AEs), not only drug-related outcomes. The remaining 25 (17%) articles studied the preventability of otherwise defined drug-related morbidity, such as drug-related hospital admissions.

Among the 143 included studies, 18 unique instruments for determining the preventability of ADEs were identified (Table II; Figure 2). The instruments fell under four groups, with different degree of structure. The preventability instruments in the first group are the most implicit and in the fourth group the most explicit.

The first group, instruments using only a definition of preventability, included three instruments (8,18,19) (Table II, Figure 2). All three instruments shared the same preventability categories and no specific criteria for determining the type of a preventability category, apart from the definition for preventability, were mentioned. The oldest instrument by Dubois and colleagues (18) was originally developed for analysing the preventability of deaths. The two other instruments, developed to assess specifically the preventability of ADEs, originated from Dubois' instrument.

In the second group, instruments with a definition of preventability and a scale for determining preventability category, five unique instruments were identified (20-24) (Table II, Figure 2). In these instruments, the preventability of adverse events was determined utilising a confidence scale from 0 to 6 (20-23) or a five-point Likert scale (24). Apart from Kaushal's instrument (24), these instruments were developed to assess the preventability of adverse events (AEs), not only ADEs, and they derived from the first instrument by Hiatt and colleagues (20).

The third group included three instruments with specific criteria for each preventability category (25-27) (Table II, Figure 2). Two instruments had more than one category for preventable events and each category had own criteria (25,27). In one instrument, preventability was categories dichotomously and preventable events had to fulfil three criteria (26). All three instruments in this group were developed for drug-related adverse events. The instruments were not derived from each other. However, a six-point confidence scale in the instrument by Gandhi and colleagues (27) originated from the confidence scale first published by Hiatt and colleagues (20).

Figure 2. Utilised unique instruments for assessing the preventability of adverse drug events (ADEs) and their development in relation to each other (n=18).

In the instrument of Hallas and colleagues (25), a case was *definitely avoidable* when “the drug event was due to a drug treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account”, *possibly avoidable* when “the prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands” and *not avoidable* when “the drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice”. Unlike any other identified instrument, Hallas and colleagues’ instrument included a category *unevaluable* for cases in which data for rating was not available or evidence was conflicting. According to Hepler and Strand (26), a case was *preventable* when the undesirable clinical outcome was foreseeable, the cause of the outcome were identifiable and controllable. Out of included unique instruments, Gandhi and colleagues’ instrument (27) was the only one considering *ameliorable* adverse drug events as a preventability category.

Seven instruments fell under the fourth group, instruments with algorithm for determining preventability category (28-34)(Table II, Figure 2). All seven instruments were developed for drug-related adverse events. The instruments by Winterstein and colleagues (32), Baena and colleagues (31), and Lau and colleagues (33) were modified from the one by Schumock and colleagues (28), while the instrument by Livio and colleagues (30) appeared to originate from Schumock’s instrument. The instrument by Olivier and colleagues (34) derived from the one by Imbs and colleagues (29). In all seven instruments, the preventability was assessed using an explicit algorithm consisting of statements indicating that an error was present. A case was categorised in an appropriate preventability category based on the number of valid statements. In the instrument of Schumock and colleagues (28), for example, preventability was categorised dichotomously (preventable/ not preventable) based on seven statements concerning possible contraindications, inappropriate dose, inappropriate therapeutic drug monitoring, not considering previous allergic reactions to the drug, drug interactions, toxic serum drug concentration and compliance. If at least one statement was valid, the case was judged preventable.

Actions taken to standardise the process of assessing preventability were rarely described (Table III). Performing a pilot study, where the preventability assessment is evaluated, and adjusting the method according to feedback was reported in 21 (15%) articles. Eighteen (13%) articles described the use of an operation manual, guidelines or other standardised protocol for the assessment of preventability.

In 86 (60%) articles, the preventability assessments were made by physicians, and in 41 (29%) articles by pharmacists, often in combination of both. In 50 (35%) articles, the profession of the assessors was unclear or not reported. In 29 (20%) articles, the assessors were described trained for or experienced in such

preventability assessment. Among the 94 (66%) articles with more than one person assessing the preventability of each case, an independent assessment was reported in 73 (51%) articles. Procedures for managing conflicting assessments were diverse.

The reliability of the preventability assessment was reported in 39 (27%) articles and 16 (11%) articles referred to a previous reliability assessment (Table III). The results of the reliability assessments reported in the included articles are summarised in Table IV. Although no definite guidelines for determining sufficient reliability exist, reliability is commonly considered good when the kappa value is 0.61-0.80 and very good when it is 0.81-1.00 (35). Lower kappa indicates moderate (0.41-0.60), fair (0.21-0.40) or poor (<0.20) reliability. Thus, inter-rater reliabilities ranged from poor to excellent (kappa 0.19-0.98; overall agreement 26-97%). Of the 24 (17%) articles that reported excellent reliability of the preventability assessment (kappa >0.81), one study used an explicit algorithm in the fourth group (36) and 23 used more implicit methods (8,9,22,37-56). In four (3%) articles, reliability assessments were mentioned, but as no exact figures for the reliability of the preventability assessment were presented, the articles are not presented in Table IV (24,57,58). In addition, two (1%) articles reported the reliability of the preventability assessment in a non-comparable manner and are thus not presented in Table IV (59,60).

Four (3%) articles mentioned assessing the validity of the preventability assessment (56,61-63). In one (1%) article (62), an assessment method introduced by the authors was compared with a previously introduced method and the number of identified cases by the two methods was reported. However, no sensitivity or specificity analysis or negative or positive predictive values were not reported. Three articles (2%) mentioned previous validity assessments (56,61,63), but no results of the validity assessments were presented.

4 DISCUSSION

We identified 18 unique instruments for assessing the preventability of ADEs varying from implicit instruments that define preventability loosely to explicit algorithms in which criteria for preventability is clearly expressed. In the most implicit instruments, the reviewers of a case used only the definition of preventability for determining whether an ADE is preventable. In explicit algorithms, the reviewers assessed preventability applying an explicit list of statements. While the level of structure and wording in defining preventability were diverse, all instruments shared the same basis for defining preventability: whether an error or sub-standard care had resulted in an ADE.

There is conflicting evidence on which instruments have the highest reliability for assessing the preventability of ADEs. We found that reliability was not reported in most articles and when reported, it varied markedly across studies. A previous study demonstrated that intra- and inter-rater reliabilities of the preventability judgements of ADEs was poorer when using implicit instruments compared to an explicit algorithm (64), perhaps due to the larger impact of the individual reviewers' clinical judgement in implicit instruments. The poor reliability of assessing the preventability of deaths using implicit methods has also been criticised (65), and the need for developing more explicit methods for assessing the preventability of adverse events and the appropriateness care has been recognised by several authors (65,66). However, we did not find evidence on better reliability when explicit algorithms were used. In the contrary, implicit methods appeared to result in excellent reliability more commonly (although this review does not allow pooling reliabilities). A study on medication-related events among paediatric inpatients also found that the inter-rater reliability of assessing preventability was poor when a highly structured algorithm was used (68). The lack of practice standards and the common, often justified, use of unlicensed medicines in paediatrics may cause difficulty in interpreting a highly structured algorithm and lead to misclassification of preventable cases and poor reliability. It has also been argued that when the aim of a study is to assess all adverse events, not only drug-specific ones, creating explicit criteria for preventability is impossible and therefore implicit judgement is required (69). The external and internal reliability may also differ for the identified instruments. The internal reliability, i.e. the same assessors coming to the same conclusion when cases are re-assessed, may be excellent when the assessors are competent and experienced in a well-established research groups. If other assessors who assess the same cases using the same instrument do not come to the same conclusion, the assessment lacks external reliability. Zegers and colleagues using implicit methods found that inter-rater reliability within pairs of assessors was higher than between assessors (70), indicating poor external reliability. As the assessors' clinical judgement is crucial when using implicit instruments, implicit instruments may be sensitive to variations of external reliability, even though their internal reliability was good. Considering the scattered evidence on the external and internal

reliability of measuring the preventability of ADEs, the reliability of the preventability assessment should be described in published articles. Comparing the reliability of different measurement instruments, for example algorithms and implicit judgements (64), in different settings and in a single dataset would also provide important evidence on the potential to improve reliability. As reliability is an important indicator of the potential of a measurement to be valid (17), reliability should be assessed in conjunction with testing validity.

The validity of the preventability assessment was rarely mentioned in the included articles and there is little evidence on the validity of the methods. As there is no gold standard for assessing ADEs or AEs (71,72), some argue that validity can not be studied (71). A gold standard is required for assessing criterion validity when a new instrument is developed to improve the feasibility of the measurement compared to a previous instrument (17). However, in the absence of a gold standard, other types of validity could be explored. Convergent and discriminant validity, for example, could be assessed by comparing the measurement using an instrument to known variables that are known to correlate or not to correlate with the new measurement. For example, preventability should correlate to whether a patient has been compensated due to an error in the care process. It would be an indication of validity if these are found somewhat correlated. Recently, a descriptive scheme for assessing the theoretical preventability of ADRs was introduced by Aronson and Ferner (73). Its explicit flowchart for determining preventability, based on previously introduced classification systems of ADRs, could be assessed for representation validity using for example an expert group, i.e. investigate how well the operational definitions translate into measurable outcomes. Even though investigating the validity of preventability assessments is challenging, it is essential for measuring the preventability of ADEs more accurately and scientifically more rigorously in the future.

In the identified measurement instruments, the preventability categories varied from dichotomous (Yes/No) to four-point ordinal categories. In dichotomous categorisation, in general, the continuous nature of the studied phenomenon is disregarded and there is a risk of error if reviewers have different perceptions of the boundary of a positive and negative response (74). In addition, fewer categories than the reviewers' capability to discriminate may cause in loss of information which may lead to reduction of reliability. Thus, allowing reviewers to be insecure about their preventability assessment through the inclusion of categories such as *possibly preventable* is likely to be advantageous. A confidence scale used in the second group of instruments, where only cases with certain confidence are categorised as preventable, has also been reported to increase the reliability of the assessment (75). Optimal categorisation should be studied in the future as there is little evidence on which preventability categories would produce the most reliable and valid results.

Descriptors such as *definite*, *probable* and *possible* were used to label different categories of preventability in the assessed instruments. In the literature on measuring health outcomes the use of imprecise, verbal terms for probability is discouraged because different reviewers may interpret such terms differently (74). In one study, the inter-reviewer agreement between clinicians was poor when clinicians assigned values to verbally described probabilities, for example estimates for *highly probable* ranged between 60% and 99% (76). The challenge of interpreting verbally described probabilities may, however, be less problematic when using these instruments in the second group, where preventability was determined according to an estimated, numerical level of evidence or confidence that the event was preventable. As the reliability of preventability assessments of ADEs with current methods varies, investigating the use of more precise, numerical categories for preventability would be justified.

In addition to the diversity of instruments used for assessing the preventability of ADEs, the imprecisely described process of assessing the preventability hinders the interpretation and comparison of the studies. Assessing the preventability of ADEs is considered challenging and standardising the assessment process improves the reliability of a measurement (15). However, only the limited number of articles reported on pilot studies or using operational manuals. This may be due to space constraints in publications or that it has been done in previous studies in similar settings when a new pilot is not always necessary. The assessors' profession and training for or experience in assessing preventability were diverse and also commonly not reported, as were the number of assessors and procedures for managing conflicting assessments. Even though there is little evidence on by whom and how the preventability of ADEs could be assessed in the most valid and reliable manner, the profession and competences of the assessors (15,77,78), the number of assessors (71), and the procedures for managing conflicting assessments (79,80) may influence the validity and reliability of the measurement. Thus, in accordance with recently published guidelines (81,82), we recommend authors of future studies to describe the reliability and validity of the preventability measurement, actions taken to standardise the measurement, assessors' profession and their training for or experience in assessing preventability, the number of assessors, whether they assessed each case independently and how conflicting assessments were managed.

The varying pharmacological nature of different types of ADEs, such as ADRs, drug intoxications from overdose and therapeutic failures, has to be considered when assessing their preventability. Some ADEs can be prevented pharmacologically, for example by increasing the dose slowly when there is a risk for an early ADR associated with tolerance (73). Also, therapeutic failure due to under treatment may be prevented when the response is observable by increasing the dose against the response. Other ADEs, such as drug intoxications from overdose, may not be prevented pharmacologically. Instead, other measures may prevent them, such as education to patients. Thus, some pharmacologically non-preventable ADEs

may be preventable in practice and some pharmacologically predictable ADEs may not be preventable in practice settings. To clarify what is meant by the preventability of ADEs in future research, different scenarios for the preventability of different types of ADEs should be described. Based on the scenarios, a clear, shared definition for preventability and its relationship to medication errors and predictability should be established, as currently multiple definitions are used (83).

Due to the limitations and diversity of the used instruments, it is unknown whether variation in the preventability rates in different settings and populations depends on the methodology or actual differences in the preventability of ADEs. Assessing the preventability rate accurately requires more evidence on the methodology of the measurement. Although modifying previous measurement instruments or developing new ones is challenging and time-consuming (74), we believe that the existing instruments should be further investigated in collaboration with several research groups working in the field. Based on thorough investigation, either one or more existing instruments should be further developed or one or more new instruments for assessing the preventability of ADEs in different settings should be developed. A starting point for developing a new instrument could be creating a clear definition of the preventability for different types of ADEs. The possibility of assessing all ADEs using a single instrument should be investigated, as the diversity of possible scenarios may hinder assessing them together. Suitable preventability categories, potentially numerical ones to improve reliability, and different structures for facilitating the assessors' decision making could then be investigated in different settings. In addition, the feasibility of the assessment in research settings has to be considered. Any new instruments should also be compared with the existing ones. It is of importance that one or more measurement instruments gained rigorous evidence and became a gold standard enabling the comparability of different studies.

Improving the methodology for assessing the preventability of ADEs is also in the interest decision makers in health care. Patient and medication safety are in the agendas of the World Health Organization (84), the Council of Europe (85), the European Medicines Agency (86), as well as national health authorities. As identified by the World Health Organization (87), research in patient safety includes measuring harm, understanding causes, identifying solutions, evaluating impact and translating evidence into safer care. In medication safety research, assessing the preventability of ADEs is required in all of these stages, for example for evaluating interventions to decrease ADEs and preventable ADEs. Evidence from such research can be used by decision makers for improving patient safety practices.

The inconsistent terminology used to study ADE was a limitation for investigating methods for assessing their preventability in this review. We used the term ADE in order to include not only ADRs, but also other adverse events related to medication therapy. ADEs have been described to consist of medication errors,

which are by definition preventable, and ADRs, which are not preventable (3). According to this definition, assessing the preventability of ADRs would not be necessary as they are never preventable. However, as others have defined ADRs differently (88), elaborated on their preventability (11), and found part of them preventable (89), studies investigating the preventability of ADRs were considered in this review.

This review included articles published in English in scientific journals. Thus, some relevant original studies may have been overlooked because we excluded unpublished studies or studies published in other languages than English. However, we believe that the most widely used and accepted methods have been published in scientific journals in English. Further, no language limitations were set when evaluating unique measurement instruments in the included studies. The use of seven databases and a wide range of search terms increased the likelihood of capturing relevant articles, but as study selection was done by one researcher and the reliability of the selection was not assessed, some relevant articles may not have been selected. A major limitation of this study is that only reported information in each article was extracted and authors were not contacted for complementary information. Some of the evaluated aspects of preventability assessment, such as performing a pilot or use of an operational manual, may have been performed but not be described in the published articles. Thus, our findings may not reflect how the preventability assessment was actually conducted. Furthermore, methods for assessing the preventability of ADEs were not assessed separately for different settings and study designs which must be considered when the results are interpreted. As data extraction and analysis were also conducted by one researcher, the results represent this researcher's interpretation of the included articles. However, we believe that the systematic data extraction procedure improved the objectivity of the review.

H. Conclusion

Instruments for assessing the preventability of ADEs vary from implicit instruments to explicit algorithms. The level of structure differs in the identified instruments, but they share the same basis for defining preventability: whether an error or sub-standard care had resulted in an ADE. However, there is scattered evidence for the instruments, as the reliability of the preventability assessments varies markedly, validity is rarely assessed and the categorisation of preventability appears suboptimal. In addition, the process of assessing the preventability of ADE is commonly imprecisely described which hinders the interpretation and comparison of the studies. For measuring the preventability of ADEs more accurately and precisely in the future, we believe that the existing instruments should be further studied and developed or one or more new instruments should be developed and their validity and reliability established.

I. Footnotes

Table I.

a Wording as in the original publications.

Table I.

a Reference describing the instrument most comprehensively.

b Categories named as in the original publications.

c Expressed as 50%, 75% or 90% likelihood for preventability based on number of valid statements.

d Expressed as 0% likelihood for preventability based on no valid statements.

Table III.

a Some articles using multiple strategies fell under several categories.

Table IV.

a References that report the reliability of the same study are in the same column.

b Original unpublished manuscript (Peterson LA. Clinical and management variables as risk factors for potentially preventable adverse events on a medical service. 1993) could not be accessed.

K. Tables

Table I. Characteristics of included articles (n=143)

Reference	Country	Study design	Setting ^a	Study population	Data source
<i>Preventability of ADRs as outcome measure</i>					
Calderon-Ospina et al. 2010 (90)	Colombia	Cross-sectional, observational	University hospital	F+M, ≥18 years	Case records, interviews
Farcas et al. 2010 (91)	Romania	Prospective, observational	Teaching hospital	F+M, 25-92 years	Case records, interviews, reports
Jönsson et al. 2010 (92)	Sweden	Retrospective, observational	No setting restrictions	F+M, no age limitation	Case records
Lopez et al. 2010 (93)	Colombia	Prospective, observational	University hospital	F+M, ≥18 years	Case records, interviews
Davies et al. 2009 (94)	United Kingdom	Prospective, observational	Teaching hospital	F+M, no age limitation	Case records, reports
Pourseyed et al. 2009 (95)	Iran	Prospective, observational	University hospital	F+M, 13-91 years	Case records, observation, survey
Alexopoulou et al. 2008 (96)	Greece	Prospective, observational	University hospital	F+M, 15-100 years	Reports
Al-Malaq et al. 2008 (97)	Saudi-Arabia	Retrospective, observational	University hospital	F+M, no age limitation	Case records
Baniasadi et al. 2008 (98)	Iran	Prospective, observational	University hospital	F+M, no age limitation	Reports
Franceschi et al. 2008 (99)	Italy	Prospective, observational	Hospital	F+M, ≥65 years	Case records, interviews
Hopf et al. 2008 (100)	United Kingdom	Prospective, observational	Teaching hospital	F+M, >16 years	Case records
Joshua et al. 2008 (101)	India	Prospective, observational	Teaching hospital	F+M, no age limitation	Case records, observation
Mehta et al. 2008 (102)	South Africa	Prospective, observational	Teaching hospital	F+M, >16 years	Case records, reports
Ruiz et al. 2008 (103)	Spain	Prospective, observational	Hospital	F+M, no age limitation but excluding “paediatrics”	Case records, interviews/questionnaire
Subish et al. 2008 (104)	Nepal	Retrospective, observational	Teaching hospital	F+M, no age limitation	Reports
Van der Hooft et al. 2008 (58)	Netherlands	Retrospective, observational	General practice	F+M, no age limitation	Case records
Grenouillet-Delacre et al. 2007(105)	France	Prospective, observational	Teaching hospital	F+M, >15 years	Case records, interview, survey
Patel et al. 2007 (106)	India	Prospective, observational	Hospital	F+M, >18 years	Observation
Rivkin 2007 (107)	United States	Prospective, observational	Teaching hospital	Not reported	Case records
Davies et al. 2006 (108)	United Kingdom	Prospective, observational	Teaching hospital	F+M, no age limitation	Case records, reports
Hanlon et al. 2006 (109)	United States	Prospective, intervention	Veterans Affairs Medical Center	M, >65 years	Case records, interviews, survey
Jose et al. 2006 (110)	India	Retrospective, observational	Teaching hospital	F+M, no age limitation	Case records, interviews, reports
Dormann et al. 2004 (111)	Germany	Prospective, observational	University hospital	F+M, 18-97 years	Case records

Pirmohamed et al. 2004 (112)	United Kingdom	Prospective, observational	Teaching hospital and general hospital	F+M, >16 years	Case records, interviews, information from GPs
Temple et al. 2004 (113)	United States	Retrospective, observational	Hospital	F+M, “paediatric”	Case records, interviews, reports, communication with staff
Dormann et al. 2003 (114)	Germany	Prospective, observational	University hospital	F+M, 17-97 years	Case records
Easton-Carter et al. 2003a (115)	Australia	Retrospective, observational	Teaching hospital	F+M, “paediatric”	Case records, reports
Easton-Carter et al. 2003b (116)	Australia	Prospective, observational	Teaching hospital	F+M, 0-17 years	Case records
McDonnell et al. 2002 (117)	United States	Retrospective, observational	University hospital	F+M, no age limitation	Case records, reports
Olivier et al. 2002 (62)	France	Prospective, observational	University hospital	F+M, >15 years	Case records
Letrilliart et al. 2001 (72)	France	Prospective, observational	General practices	F+M, 0-99 years	Case records, interviews, reports
Wasserfallen et al. 2001 (118)	Switzerland	Prospective, observational	University hospital	F+M, 16-93 years	Case records, interviews
Lagnaoui et al. 2000 (119)	France	Prospective, observational	University hospital	F+M, 15-94 years	Case records
Gholami et al. 1999 (120)	Iran	Prospective, observational	University hospital	“All patients” (appears to exclude children <10 years)	Case records, interviews
Schumock et al. 1995 (121)	United States	Prospective, observational	University hospital	Not reported	Reports
Pearson et al. 1994 (122)	United States	Prospective, observational	Hospital	F+M, no age limitation	Case records, interviews, reports
Kramer et al. 1985 (123)	Canada	Prospective, observational	Private group practice, combination of primary and secondary care	F+M, 0-18 years	Case records, interviews
Choonara et al. 1984 (124)	United Kingdom	Prospective, observational	Hospital	F+M, “paediatric”	Case records, interviews, observation, survey
<i>Preventability of ADEs as outcome measure</i>					
Franklin et al. 2010 (125)	United Kingdom	Retrospective, observational	Teaching hospital	Not reported	Case records
Hug et al. 2010 (126)	United States	Retrospective, observational	Hospital	F+M, ≥18 years	Case records
Benkirane et al. 2009a (127)	Morocco	Cross-sectional observational	Teaching hospital	F+M, no age limitation	Case records, interviews
Benkirane et al. 2009b (128)	Morocco	Prospective, intervention/observational	Teaching hospital	F+M, “adults and paediatric”	Case records, observation, reports
Kunac et al. 2009 (129)	New Zealand	Prospective, observational	University-affiliated hospital	F+M, 0-17 years	Case records, interviews, observation,

					reports
Gurwitz et al. 2008 (130)	Canada	Retrospective, interventional	Academic long-term care facility	F+M, no age limitation	Case records, reports
Hwang et al. 2008 (131)	Korea	Retrospective, observational	Teaching hospital	F+M, “adults”	Case records
Jha et al. 2008 (132)	United States	Prospective, interventional/observational	Teaching hospital	F+M, “adults”	Case records
Kaushal et al. 2008 (133)	United States	Prospective, intervention	Teaching hospital	F+M, “paediatric”	Case records, reports
Koneri et al. 2008 (134)	India	Prospective, observational	Teaching hospital	F+M, 18-80 years	Case records, interviews
Kunac et al. 2008 (135)	New Zealand	Prospective, observational	University-affiliated hospital	F+M, 0-17 years	Case records, interviews, observation, reports
Saha et al. 2008 (136)	India	Prospective, observational	Hospital	F+M, 18-80 years	Case records, interviews
Takata et al. 2008a (137)	United States	Retrospective, observational	Hospital	F+M, “paediatric”	Case records, reports
Takata et al. 2008b (57)	United States	Retrospective, observational	Teaching hospital	F+M, <18 years	Case records, reports
Tam et al. 2008 (138)	Hong Kong	Prospective, observational	Primary care clinic	F+M, <18 years	Case records, reports, survey
Zandieh et al. 2008 (56)	United States	Prospective, intervention	Ambulatory practices, community and hospital based	F+M, <21 years	Case records, survey
Field et al. 2007 (52)	United States	Prospective, intervention	Ambulatory practice	F+M, ≥65 years	Case records, reports
Glassman et al. 2007 (139)	United States	Retrospective, intervention	Outpatient clinic, ambulatory care centre	M, “veterans”	Case records
Holdsworth et al. 2007 (140)	United States	Prospective, intervention	Hospital	F+M, “paediatric”	Case records, interviews
Kaushal et al. 2007 (53)	United States	Prospective, intervention	Office practices, in teaching hospital, health centre or affluent	F+M, <21 years	Case records, survey
Queneau et al. 2007 (141)	France	Retrospective, observational	University hospitals, general hospitals	F+M, ≥18 years	Case records, interviews
Seger et al. 2007 (142)	United States	Retrospective, observational	Teaching hospital	F+M, ≥24 years	Case records
Wang et al. 2007 (54)	United States	Prospective, observational	Academic community hospital	Sex not mentioned, “paediatric”	Case records, reports
Kane-Gill et al. 2006 (143)	United States	Retrospective, observational	Academic medical centre	F+M, >18 years	Case records
Kopp et al. 2006 (50)	United States	Prospective, observational	Academic medical centre	F+M, “adult”	Case records, observation, reports

Miller et al. 2006 (144)	Australia	Cross-sectional, observational	General practices	F+M, no age limitation	Case records, interviews
Schade et al. 2006 (145)	United States	Prospective, observational	Hospital	F+M, >18 years	Case records
Schnipper et al. 2006 (146)	United States	Prospective, intervention	Teaching hospital	F+M, no age limitation	Case records, interviews
Walsh et al. 2006 (147)	United States	Retrospective, intervention	Teaching hospital	Sex not mentioned, “paediatric”	Case records, reports
Al-Tajir et al. 2005 (148)	United Arab Emirates	Prospective, observational	Hospital	F+M, no age limitation	Case records, reports
Field et al. 2005 (49)	United States	Retrospective, observational	Ambulatory clinics	F+M, ≥65 years	Case records, reports
Forster et al. 2005 (149)	United States	Prospective, observational	Academic health sciences centre	F+M, 43–71 years	Case records, interviews
Gurwitz et al. 2005 (150)	Canada	Prospective, observational	Academic long-term care facilities	F+M, mean 86 years (SD ±8)	Case records, reports
Mycyk et al. 2005 (151)	United States	Retrospective, intervention	Academic hospital	F+M, “adults”	Case records, reports
Weingart et al. 2005 (152)	United States	Prospective, observational	Primary care practices (affiliated with an academic medical centre)	F+M, ≥18 years	Case records, interviews, survey
Field et al. 2004a (47)	United States	Prospective, observational	Multispecialty group practice, ambulatory	F+M, ≥65 years	Case records, reports
Field et al. 2004b (48)	United States	Prospective, observational	Multispecialty group practice, ambulatory	F+M, ≥65 years	Case records, reports
Forster et al. 2004 (61)	Canada	Prospective, observational	Teaching hospital	F+M, “adults”	Case records, interviews, reports
Hardmeier et al. 2004 (153)	Switzerland	Prospective, observational	University hospital	F+M, no age limitation	Case records
Gandhi et al. 2003 (27)	United States	Prospective, observational	Primary care practice at academic medical centre	F+M, >18 years	Case records, survey
Gurwitz et al. 2003 (46)	United States	Prospective, observational	Multispecialty group practice, ambulatory	F+M, ≥65 years	Case records, reports
Holdsworth et al. 2003 (154)	United States	Prospective, observational	Hospital	F+M, “paediatric”	Case records, interviews
Peyriere et al. 2003 (155)	France	Prospective, observational	University hospital	F+M, 19-97 years	Case records
Winterstein et al. 2002 (32)	United States	Retrospective, observational	Teaching hospital	F+M, no age limitation	Case records, reports
Chan et al. 2001 (156)	Australia	Cross-sectional, observational	Hospital	F+M, ≥75 years	Case records, interviews

Honigman et al. 2001 (45)	United States	Retrospective, observational	Primary care practice	F+M, no age limitation	Case records
Jha et al. 2001 (157)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records
Kaushal et al. 2001 (24)	United States	Prospective, observational	Teaching hospital	F+M, “paediatric”	Case records, reports
Malhotra et al. 2001 (158)	India	Prospective, observational	Hospital	F+M, no age limitation	Case records, interviews
Senst et al. 2001 (159)	United States	Prospective, observational	Hospitals (affiliated with a university)	Not reported	Case records, interviews, reports
Gurwitz et al. 2000 (160)	United States	Prospective, observational	Nursing homes	F+M, no age limitation mentioned	Case records, interviews, reports
Bates et al. 1999a (42)	United States	Prospective, observational	Hospital	F+M, “adult”	Case records, interviews, reports
Bates et al. 1999b (43)	United States	Prospective, observational, interventional	Academic hospital	“all patients”	Case records, interviews, reports
Leape et al. 1999 (44)	United States	Retrospective, interventional	Teaching hospital	A sample of “all patients”	Case records
Raschetti et al. 1999 (161)	Italy	Prospective, observational	Hospital	F+M, no age limitation	Case records
Bates et al. 1998 (40)	United States	Prospective, observational, interventional	Hospital	F+M, “adult”	Case records, interviews, reports
Gray et al. 1998 (36)	United States	Prospective, observational	Hospital	F+M, ≥ 70 years	Case records, interviews
Jha et al. 1998 (41)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, reports
Bates et al. 1997 (38)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, interviews, reports
Cullen et al. 1997 (39)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, interviews, reports
Bates et al. 1995a (162)	United States	Prospective, observational	Teaching hospital	Not reported	Case records, interviews, reports
Bates et al. 1995b (8)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, interviews, reports
Cullen et al. 1995 (9)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, interviews, reports
Leape et al. 1995 (37)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, interviews, reports
Bates et al. 1993 (19)	United States	Prospective, observational	Teaching hospital	F+M, “adult”	Case records, reports, observation
<i>Preventability of AEs as outcome measure</i>					
Agarwal et al. 2010 (163)	United States	Retrospective, cross-sectional observational	Hospital	F+M, “paediatric”, mean 6.3 years	Case records
Mercier et al. 2010 (164)	France	Prospective, observational	Teaching hospital	F+M, “all patients”	Case records

Aranaz-Anders et al. 2008 (165)	Spain	Retrospective, observational	Hospital	F+M, no age limitation	Case records
Ligi et al. 2008(55)	France	Prospective, observational	University hospital	F+M, “neonates”	Reports
Buckley et al. 2007 (51)	United States	Prospective, observational	Academic medical centre	F+M, <18 years	Case records, observation
Michel et al. 2007 (166)	France	Prospective, observational	University, private and public hospitals	F+M, no age limitation	Case records, interviews
Sari et al. 2007 (167)	United Kingdom	Retrospective, observational	Hospital	Not reported	Case records
Woods et al. 2006 (168)	United States	Retrospective, observational	Hospital	F+M, 13-21 years	Case records
Rothschild et al. 2005 (169)	United States	Prospective, observational	Academic hospital	F+M, “adult”	Case records, observation, reports
Woods et al. 2005 (170)	United States	Retrospective, observational	Hospital	F+M, 0-20 years	Case records
Davis et al. 2003 (171)	New Zealand	Retrospective, observational	Hospital	F+M, no age limitation	Case records
Forster et al. 2003 (69)	United States	Prospective, observational	Academic hospital	F+M, no age limitation	Case records, interviews
Thomas et al. 2000 (22)	United States	Prospective, observational	Teaching and non-teaching hospital	F+M, no age limitation	Case records
Darchy et al. 1999 (172)	France	Retrospective, observational	Hospital	F+M, “adult”	Case records
Leape et al. 1993 (63)	United States	Prospective, observational	Teaching and non-teaching hospital	F+M, no age limitation	Case records
<i>Preventability of otherwise defined drug-related morbidity as outcome measure</i>					
Hoonhout et al. 2010 (173)	Netherlands	Retrospective, observational	Hospital, university and general	F+M, no age limitation	Case records
Pattanaik et al. 2009 (174)	India	Retrospective, observational	Hospital	F+M, ≥ 12 years	Case records, reports
Rogers et al. 2009 (175)	United Kingdom	Cross-sectional, observational	Hospital	F+M, ≥ 65 years	Case records
Al-Olah et al. 2008 (176)	Saudi-Arabia	Prospective, observational	Hospital	F+M, no age limitation	Unclear
Leendertse et al. 2008 (177)	Netherlands	Prospective, observational	Hospital, university and general	F+M, ≥ 18 years	Case records, reports
Witherington et al. 2008 (178)	United Kingdom	Retrospective, observational	Teaching hospital	F+M, ≥ 75 years	Case records
Zed et al. 2008 (179)	Canada	Prospective, observational	Teaching hospital	F+M, “adults”	Case records, interviews
Zargarzadeh et al. 2007 (180)	Iran	Prospective, observational	Teaching hospital	F+M, ≥ 21 years	Unclear

Baena et al. 2006 (181)	Spain	Prospective, observational	University Hospital	F+M, no age limitation	Case records, interviews
Samoy et al. 2006 (182)	Canada	Prospective, observational	Teaching hospital	F+M, “adults”	Case records, interviews
Easton et al. 2004 (183)	Australia	Prospective, observational	Teaching hospital	F+M, ≤17	Case records, interviews
Howard et al. 2003 (184)	United Kingdom	Prospective, observational	Teaching hospital	F+M, no age limitation	Case records, interviews
Koh et al. 2003 (185)	Singapore	Retrospective, cross-sectional, observational	Hospital	F+M, 16-97 years	Case records
Ng et al. 1999 (186)	Australia	Prospective, observational	Teaching hospital	F+M, no age limitation (but population elderly)	Case records, interviews
Tafreshi et al. 1999 (187)	United States	Prospective, observational	Hospital	F+M, 0-95 years	Interviews, survey
Easton et al. 1998 (188)	Australia	Prospective, observational	University-affiliated hospital	F+M, 0-18 years	Case records, interviews
Cunningham et al. 1997 (189)	United Kingdom	Prospective, observational, interventional	Hospital	F+M, ≥65 years	Case records, interviews
Dartnell et al. 1996 (190)	Australia	Prospective, observational	Teaching hospital	F+M, 15-91 years	Case records, interviews, reports
Dennehy et al. 1996 (191)	United States	Retrospective, observational	University teaching hospital	F+M, no age limitation	Case records
Nelson et al. 1996 (192)	United States	Prospective, observational	University-affiliated hospital	F+M, no age limitation	Case records, interviews
Courtman et al. 1995(193)	Canada	Prospective, observational	Teaching hospital	F+M, ≥65 years	Case records
Hallas et al. 1993 (59)	Denmark	Prospective, observational, interventional	University hospital	F+M, no age limitation	Case records, interviews
Hallas et al. 1992 (60)	Denmark	Prospective, observational	University hospital	F+M, no age limitation	Case records, interviews
Hallas et al. 1991 (194)	Denmark	Prospective, observational	University hospital	F+M, “elderly”	Case records, interviews
Hallas et al. 1990 (25)	Denmark	Prospective, observational	University hospital	F+M, 0-94 years	Case records, interviews

a Wording as in the original publications.

ADE = adverse drug event; **AE** = adverse event; **ADR** = adverse drug reaction; **CPOE** = computerised physician/provider order entry; **ME** = medication error; **F** = ≥75% female; **M** = ≥75% male; **F+M** = <25% male or female

Table II. Utilised unique instruments for assessing the preventability of adverse drug events (ADEs) and their characteristics (n=18).

Instrument ^a	Settings	Assessed cases	Definition of /criteria for preventability	Preventability categories ^b												
				Definitely preventable/ avoidable	High preventability	Preventable	Probably preventable	Possibly/ potentially avoidable	Low preventability	Ameliorable	Probably not preventable	Not preventable/ avoidable	Definitely not preventable	Negligence present	Negligence not present	Unevaluable
<i>Instruments with only definition of preventability for determining preventability category</i>																
Dubois et al. 1988 (18)	Hospital	Deaths	Poor care resulted in death	√			√				√		√			
Bates et al. 1993 (19)	Hospital	ADEs	-	√			√				√		√			
Bates et al. 1995 (8)	Hospital	ADEs	Due to error or preventable by any means currently available	√			√				√		√			
<i>Instruments with definition of preventability and a scale for determining preventability category</i>																
Hiatt et al. 1989 (20)	Hospital	AEs	Failure to meet standards											√	√	
Wilson et al. 1995 (21)	Hospital	AEs	Failure to follow accepted practice		√				√			√				
Thomas et al. 2000 (22)	Hospital	AEs	Avoidable using any means considered standard care			√						√				
Davis et al. 2001 (23)	Hospital	AEs	Failure to follow accepted practice		√	√						√				
Kaushal et al. 2001 (24)	Hospital	ADEs	Associated with medication errors, 5-point Likert scale			√						√				
<i>Instruments with specific criteria for each preventability category</i>																
Hallas et al. 1990 (25)	Hospital	DRHs	Separate criteria for each category	√				√				√				√
Hepler and Strand. 1990 (26)	-	DRM	3 criteria that all must be fulfilled to grant preventability			√						√				
Gandhi et al. 2003 (27)	Ambulatory	ADEs	Separate criteria for each category, 6-point confidence scale			√				√		√				
<i>Instruments with algorithm for determining preventability category</i>																

Schumock and Thornton 1992 (28)	-	ADRs	≥1 of 7 statements valid			√						√				
Imbs et al. 1998 (29)	Pharmaco-vigilance	ADRs	Score based on valid statements			√						√				
Livio et al. 1998 (30)	Hospital	DRHs	Likelihood based on valid statements			√ ^c						√ ^d				
Baena et al. 2002 (31)	Hospital	DRPs	≥1 of 13 statements valid			√						√				
Winterstein et al. 2002 (32)	Hospital	ADEs/ADRs	≥1 of 8 statements valid			√						√				
Lau et al. 2003 (33)	Hospital	ADRs	≥1 of 8 statements valid	√			√					√				
Olivier et al. 2005 (34)	Pharmaco-vigilance	ADRs	Score based on valid statements			√		√				√				√

a Reference describing the instrument most comprehensively.

b Categories named as in the original publications.

c Expressed as 50%, 75% or 90% likelihood for preventability based on number of valid statements.

d Expressed as 0% likelihood for preventability based on no valid statements.

ADE = adverse drug event; **ADR** = adverse drug reaction; **AE** = adverse event; **DRH** = drug-related hospitalisation; **DRM** = drug-related morbidity; **DRP** = drug-related problem

Table III. Characteristics of the process of assessing the preventability of ADEs in the included studies (n=143).

Characteristic	Category	Number of studies (%)	References
<i>Standardising the assessment process</i>			
Performing pilot	Yes	21 (15%)	(8,9,37-43,55,57,63,129,138,163,165,173,175,179,181,184)
	No	122 (85%)	(19,22,24,25,27,32,36,44-54,56,58-62,69,72,90-128,130-137,139-162,164,166-172,174,176-178,180,182,183,185-194)
Use of operational manual/guidelines/protocol	Yes	18 (13%)	(49,57,63,102,128,129,135,137,138,159,163,165,166,171,173,177,180,181)
	No	125 (87%)	(8,9,19,22,24,25,27,32,36-48,50-56,58-62,69,72,90-101,103-127,130-134,136,139-158,160-162,164,167-170,172,174-176,178,179,182-194)
<i>Assessors</i>			
Profession ^a	Pharmacist(s)	41 (29%)	(50,51,57,61,62,92,98,100,102,107-109,111,114-116,119,120,122,129,131,133,137-140,143,151,154,159,163,175-177,179,182-184,186,190,191)
	Physician(s)	86 (60%)	(8,9,24,27,37-44,46-58,60-63,69,90,92,98,100,102,105,108,109,111,112,114,116,119,123,126,129,130,132,133,135,137,138,140,141,143,144,146-154,156,159,160,162-167,169,171-173,175,176,179,183,184,186,190,194)
	Nurse(s)	8 (6%)	(57,116,137,138,143,145,159,183)
	Other(s)	4 (3%)	(92,141,143,159)
	Not reported	50 (35%)	(19,22,25,32,36,45,59,62,72,90,91,93-97,99,101,103,104,106,110,113,117,118,121,123-125,127,128,134,136,142,155,157,158,161,168,170,174,178,180,181,185,187-189,192,193)
Training for/ experienced in assessment	Yes	29 (20%)	(54,55,57,58,63,105,107,112,113,129,131,132,135,137,138,140,145,153,159,163-167,171,173,177,179,182)
	No	114 (80%)	(8,9,19,22,24,25,27,32,36-53,56,59-62,69,72,90-104,106,108-111,114-128,130,133,134,136,139,141-144,146-152,154-158,160-162,168-170,172,174-176,178,180,181,183-194)
Number of assessors per case	1	13 (9%)	(57,106,112,120,131,132,139,144,145,156,182,191,192)
	≥2	94 (66%)	(8,9,19,22,24,27,36-44,46-56,58,60-63,69,90,92,94,100,102,105,107-109,111,113-117,119,122,123,125,126,128-130,133,135,137,138,140,143,146-150,152-154,159-173,175-179,183,184,186,190,194)
	Not reported	36 (25%)	(25,32,45,59,72,91,93,95-99,101,103,104,110,118,121,124,127,134,136,141,142,151,155,157,158,174,180,181,185,187-189,193)

Independent assessment ^a (if category ≥ 2 from above)	Yes	73 (51%)	(8,9,19,22,24,27,36-44,46-56,58,61-63,69,90,92,94,100,107,109,113,114,122,123,125,126,128-130,133,135,137,138,140,146-150,152-154,160,162-164,166,167,169,173,177-179,183,184,186)
	No	22 (15%)	(60,62,102,105,108,111,115-117,119,143,159,161,165,168,170-172,175,176,190,194)
Managing conflicting assessments ^a (if category ≥ 2 from above)	Discussion until consensus	35 (24%)	(19,22,24,27,36,46-50,52,54,56,61,90,100,102,108,109,111,125,130,133,138,140,147,150,152,154,160,162,169,175,177,179)
	Additional assessor(s)	29 (20%)	(8,9,37-44,51,55,58,63,69,94,107,122,126,127,146,148,149,165,173,178,179,183,190)
	Another method	11 (8%)	(51,62,92,114,137,163,164,172,176,184,186)
	Not reported	22 (15%)	(53,60,62,105,113,115-117,119,123,129,135,143,153,159,161,166-168,170,171,194)
<i>Reliability and validity of assessment</i>			
Reliability of preventability assessments	Yes, in same article	39 (27%)	(8,9,19,22,24,27,36,46-58,62,69,113,123,126,131,146-150,152,153,160,162,166,167,177,184)
	Yes, reference to another article	16 (11%)	(37-45,63,129,135,162,166,170,173)
	No	90 (63%)	(25,32,59-61,72,90-112,114-122,124,125,127,128,130,132-134,136-145,151,154-159,161,163-165,168,169,171,172,174-176,178-183,185-194)

^a Some articles using multiple strategies fell under several categories.

Table IV. Reported reliability of the preventability assessments.

Reference ^a	Description of assessment	Kappa (and CI when reported)	Agreement
<i>Reliability assessment reported in an included article</i>			
Hug et al. 2010 (126)	Inter-rater reliability between two reviewers	0.44 (95% CI 0.25- 0.62)	80.5%
Hwang et al. 2008 (131)	Inter-rater reliability between original reviewers and a panel	0.26	-
Leendertse et al. 2008 (177)	Percentage of agreement between two reviewers	-	26%
Ligi 2008 et al. (55)	Inter-rater reliability between two reviewers	0.84	-
Zandieh et al. 2008 (56)	Inter-rater reliability between two reviewers	0.95	-
Kaushal et al. 2007 (53)			
Buckley et al. 2007 (51)	Inter-rater reliability and agreement between two reviewers	Prevalence and bias-adjusted kappa 0.93	97%, average positive agreement 0.8, average negative agreement 0.98
Field et al. 2007 (52)	Inter-rater reliability between two reviewers	0.67	-
Field et al. 2005 (49)			
Field et al. 2004a (47)			
Field et al. 2004b (48)			
Gurwitz et al. 2003 (46)			
Michel et al. 2007 (166)	Inter-rater reliability and agreement between two reviewers	0.31 (95% CI 0.05- 0.57)	67.8%
Sari et al. 2007 (167)	Inter-rater reliability and agreement between two reviewers	0.44	83%
Wang et al. 2007 (54)	Inter-rater reliability between two reviewers	0.89 (95% CI 0.84- 0.95)	-
Kopp et al. 2006 (50)	Inter-rater reliability and agreement between two reviewers	0.32, prevalence-adjusted and bias-adjusted kappa 0.84	91.9, average positive agreement 0.96, average negative agreement 0.35
Schnipper et al. 2006 (146)	Inter-rater reliability between two reviewers	0.59	-
Walsh 2006 et al. (147)	Inter-rater reliability between two reviewers	0.80 (95% CI 0.67-0.82)	-
Al-Tajir et al. 2005 (148)	Inter-rater reliability and agreement between two reviewers	0.74	86.9%
Forster et al. 2005 (149)	Inter-rater reliability and agreement between two reviewers	0.60	82%
Gurwitz et al. 2005 (150)	Inter-rater reliability between two reviewers	0.49	-
Weingart et al. 2005 (152)	Inter-rater reliability between two reviewers	0.70	-
Hardmeier et al. 2004 (153)	Inter-rater reliability and agreement between two reviewers	For incident ADEs: 0.5; For ADEs at admission: 0.9	For incident ADEs: agreement 0.97, positive agreement 0.5 and negative agreement 0.99;

			For ADEs at admission: agreement 0.96, positive agreement 0.93 and negative agreement 0.97
Temple et al. 2004 (113)	Inter-rater reliability between two reviewers	0.620	-
Forster et al. 2003 (69)	Inter-rater reliability and agreement between two reviewers	Preventability : 0.60 Ameliorability: 0.51	Preventability : 82% Ameliorability: 78%
Gandhi et al. 2003 (184)	Inter-rater reliability between two reviewers	0.70 (95% CI 0.62-0.78)	-
Howard 2003 (184)	Inter-rater reliability between three reviewers	Between the three reviewers: 0.77, 0.77 and 0.74; intraclass correlation coefficient 0.74 (95% CI 0.70-0.78)	-
Olivier et al. 2002 (62)	Inter-rater reliability between four reviewers	0.14-0.58	-
Gurwitz et al. 2000 (160)	Inter-rater reliability between two reviewers	0.73	-
Thomas et al. 2000 (22)	Inter-rater reliability and agreement between original reviewers' and investigators	0.81	91%
Gray et al. 1998 (36)	Inter-rater reliability between two reviewers	0.84	-
Bates et al. 1995b (8), referenced by (37-45)	Inter-rater reliability and agreement between two reviewers	0.92	96%
Cullen et al. 1995 (9)	Inter-rater reliability between two reviewers	0.98	-
Bates et al. 1993 (19), referenced by (129,162)	Inter-rater reliability between two reviewers	0.71	-
Kramer et al. 1985 (123)	Inter-rater reliability between two reviewers	Weighted kappa +0.379	-
<i>Reliability assessment reported in another cited article</i>			
Zegers et al. 2010 (70), referenced by (173)	Inter-rater reliability within and between pairs of reviewers	Within pairs 0.72 (95% CI 0.66-0.79); between pairs 0.40 (95% CI 0.07-0.73)	Within pairs 86.1; between pairs 70.4
Kunac et al. 2006 (68), referenced by (129,135)	Inter- and intra-rater reliability between three reviewers	Overall inter-rater reliability 0.37 (95% CI 0.33-0.41), for not preventable events 0.47 (95% CI 0.43-0.51); Intra-rater reliabilities for preventability (yes/no) 0.31(95% CI 0.25-0.37), 0.30 (95% CI 0.24-0.36) and 0.50 (95% CI 0.42-0.58)	-
Michel et al. 2004 (195), referenced by (166)	Inter-rater reliability and agreement between three reviewers	0.31 (CI 0.05-0.57)	67.8%
Thomas et al. 2002	Inter-rater reliability between three assessment methods	0.19-0.24 (lowest bound of 95% CI 0.05 and	-

(71), referenced by (170)		highest 0.37)	
Peterson 1993 ^b , referenced by (63)	Inter-rater reliability between two reviewers	0.60	-

a References that report the reliability of the same study are in the same column.

b Original unpublished manuscript (Peterson LA. Clinical and management variables as risk factors for potentially preventable adverse events on a medical service. 1993) could not be accessed.

CI = confidence interval

Appendix 1. Search strategy

#1 Abstract, title and index term search with exact phrase:

adverse drug effect
adverse drug effects
adverse drug event
adverse drug events
adverse drug reaction*
adverse drug reactions*
drug induced disease
drug induced diseases
drug related morbidity
drug related problem
drug related problems
medication error
medication errors

OR

*used only for title and abstract in EMBASE

#2 Abstract, title and index term search with exact phrase:

avoidable
avoidability
preventability
preventable
prevention
preventive

OR

#3 #1 AND #2

J. Reference list

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