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The Pharmacoepidemiology of Medication Errors

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Medications represent the most commonly used form of medical therapy today. For adults, 75% of office visits to general practitioners and internists are associated with the continuation or initiation of a drug [1]. For hospitalized patients, multiple medication orders tend to be written for each patient daily. Theoretically, medication errors can refer to selection of the wrong patient, the wrong drug, the wrong galenic formulation (e.g., tablets with immediate and sustained release), the wrong dosage or route of administration, or wrong time. Medication errors are frequent, but fortunately only a small proportion result in harm [2]. However, given the high prevalence of prescription medication use, preventable adverse drug events are one of the most frequent causes of preventable iatrogenic injuries. The IoM report "To Err is Human" suggested that at least 44 000–98 000 deaths occur in the US from iatrogenic injury [3]. One study estimated that about 7000 deaths are attributed to medication errors [4] and about 1 million injuries might result from medication use in general in the US per year.

Clinical Problems to Be Addressed by Pharmacoepidemiologic Research

Definition and Classification of Medication Errors

While the techniques of pharmacoepidemiology have most often been used to study the risks and benefits of drugs, they can also be used to study medication errors and their attendant adverse drug events. Medication errors have been defined as "any error in the process of ordering, dispensing, or administering a drug" regardless of whether an injury occurred or the potential for injury was present [5]. Mechanistically, medication errors may result from errors in planning actions – for example, not knowing the correct starting dosage for a medication (i.e., knowledge-based mistakes or rule-based mistakes) – or errors in executing correctly planned actions, like picking one sound-alike medication instead of another (i.e., action-based slips or memory-based lapses) [6].

Pharmacoepidemiology, Sixth Edition. Edited by Brian L. Strom, Stephen E. Kimmel and Sean Hennessy.

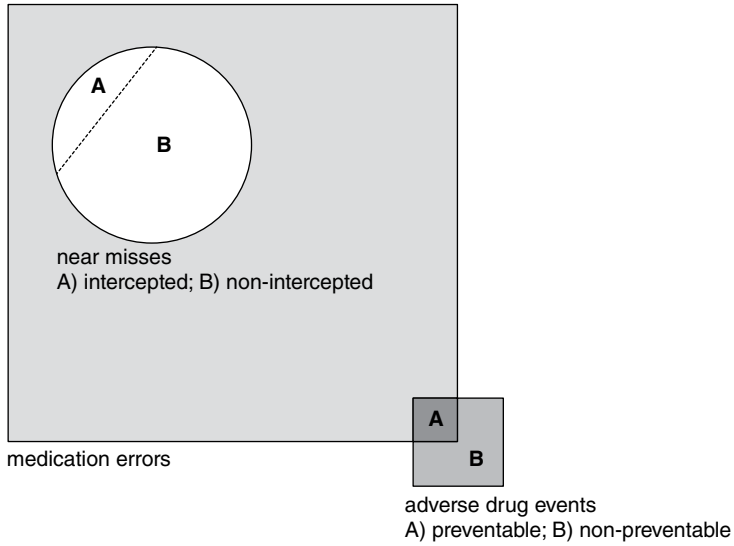

Figure 41.1 Relationship of medication errors and adverse drug events. About 1 in 10 medication errors is likely to result in patient harm [7], whereas about 25% of adverse drug events can be allocated to a medication error [2]. Near misses, both intercepted and nonintercepted, comprise those medication errors with potential for patient harm without resulting in actual harm.

In clinical practice, a medication error may occur at any stage of drug therapy, including drug prescribing, transcribing, manufacturing, dispensing, administering, and monitoring. Medication errors with potential for harm are called near-misses or potential adverse drug events; these errors may be intercepted before they reach the patient, or reach the patient without consequence. However, generally, about one in 10 medication errors results in patient harm [7]. An adverse drug event (ADE) would be considered preventable if a medication error is associated with the ADE (Figure 41.1). While ADEs have been defined as "any injury related to the use of the drug, regardless of whether a therapeutically appropriate dosage is used, although the causality of this relationship may not be proven" [8], an adverse drug reaction (ADR) can be defined as harm which is caused by a drug while appropriately used [9] (see also Chapter 1 for alternative definitions).

Detection of Medication Errors

Approaches for detecting medication errors include manual or automatic screening of claims data, administrative databases, medical records, electronic health records, or incident reports mostly by providers in hospitals, as well as patient monitoring or direct observation often by pharmacists. All approaches have inherent advantages and pitfalls and there is no single approach that is considered the gold standard for detecting medication errors or ADEs. Factors which might influence the identification of medication errors and ADEs include the setting (ambulatory vs inpatients; routine care vs research studies), the expected types of medication errors (prescribing vs administration errors), and the projected costs of detection [10]. In addition, the type of detection method influences which types of medication errors are found (e.g., only those resulting in patient harm) and with which frequency (see Chapters 8 and 10 for further discussions of detecting medication adverse events).

Screening of claims data, administrative databases, medical records, and electronic health records is used to evaluate large datasets, but is generally done retrospectively. The quality of the available information, however, varies between different data sources which limits

opportunities to comprehensively and systematically detect medication errors. Especially in the outpatient setting, claims data can be obtained for very large numbers of individuals. In the US, this represents tens and sometimes hundreds of millions of people, and in many other countries complete data for a population (such as the province of Ontario) may be available. Limitations of using claims data to detect medication errors include uncertainty regarding medication consumption and mischaracterization of the error if not linked to other information sources because clinical detail is often minimal (e.g., information on weight, actual drug dose or renal function might be missing). Since the focus of such data systems is on clinical outcomes and treatment, medication errors will be missed unless they result in patient injury severe enough to come to medical attention. Even then, it is usually not clear whether the injury was due to an error.

In the inpatient setting, manual chart review is a well-established method to detect ADEs and medication errors. With most relevant patient information at hand, the appropriateness of drug prescribing and administration can be assessed, although documentation may still be incomplete, especially for assessing issues such as appropriateness of the medication order. The main limitations with chart reviews are that they are time-consuming and expensive, with the average chart review costing approximately $20 per chart.

If electronic health records are available, the manual screening of paper-based information can be replaced by semi-automated approaches. However, the level of standardization and the extent to which clinical information is stored using controlled vocabulary determine the feasibility and effectiveness of automated, algorithm-based data analyses [11]. If electronic health records include electronic prescribing applications with clinical decision support (i.e., computerized physician order entry – CPOE), data from these applications can readily be used to detect many types of medication errors at the stage of prescribing. However, the specificity of the systems will also depend on the availability of information accessible via the electronic health records [12]. Specific types include overly high dosage, cumulative dose errors, and drug–drug interaction issues, among others.

Screening of incident reports (i.e., reports usually issued by personnel involved in the occurrence of an adverse event or a situation that might have led to an undesirable outcome) and *patient monitoring* (e.g., for specific symptoms) can each reveal medication errors that resulted in patient harm [13]. Screening of incident reports always grossly underestimates the incidence of errors (because of underreporting of events), but is relatively inexpensive because data are collected as a byproduct of routine care delivery. The major barrier for reporting medication errors is staff perception that reporting might be associated with disciplinary actions [14], even if the hospital pursues a nonpunitive policy [15]. One approach to increase reporting would be to only report near misses that help to identify which situations facilitate errors but also which actions might help to detect and prevent errors. These "critical incident reporting systems" typically belong to quality management systems in hospitals and are becoming more prevalent in the primary care setting. Predetermined patient monitoring for adverse drug events, while more time- and cost-intensive, has been successful, and can identify more adverse drug events than chart review [13].

Spontaneous reporting of medication errors (described in Chapter 10) is comparatively easy to implement and to maintain, both in inpatient and outpatient settings. However, both ADEs and medication errors are substantially underreported (see Chapter 10). Nevertheless, spontaneous reporting is useful for obtaining samples of errors. However, this method cannot be used to assess the underlying rate of medication errors in a sample [16].

Direct observation is typically conducted during research studies and offers a comprehensive assessment of medication dispensing and administration errors. While being both cost- and personnel-intensive, direct observation has been successfully and reliably used to classify complex medication errors [17], and is particularly useful at stages that are not sensitive to other detection methods (e.g., drug preparation or drug administration) [18].

Methodologic Problems to Be Addressed by Pharmacoepidemiologic Research

Pitfalls in the Detection of Medication Errors

The reliable and systematic detection of medication errors has many methodologic challenges, including the definition of what constitutes a medication error and the availability and appropriate interpretation of clinical data.

With respect to definition, examples of complexities include whether there was harm or potential for harm, and the decision about whether to include errors that are intercepted before reaching the patient.

Identification of medication errors remains challenging as general standards are lacking. For instance, the detection of "wrong timing errors" (i.e., giving a drug within a timeframe) requires the definition of a threshold value above which the medication is delayed. In the inpatient setting, this threshold value might be two or four hours, depending on the institution. However, sometimes patients are away from their inpatient rooms (e.g., getting diagnostic tests), in which case decisions need to be made about whether to use a singular threshold value.

Using the example of hazardous prescription of interacting drugs, a potential approach to detect a medication error involves the comparison of the prescribed medications with a drug–drug interaction (DDI) knowledge base. However, the content of such knowledge bases varies widely, in terms of both included drug pairs and specific information linked to a drug pair (e.g., severity of the DDI) [19] – see Chapter 40. Especially in the outpatient setting, comprehensive and reliable data on the patient's medication list may be missing. Furthermore, prescribing and dispensing data are seldom jointly available and determining actual patient adherence is even more difficult. Even patient surveys may not give adequate information. While patients might be nonadherent to some prescribed drugs, they might also consume over-the-counter drugs with potential for DDIs (e.g., St John's wort) that they do not report [20].

To evaluate the appropriateness of a medication for a specific patient, knowledge of the patient's characteristics is mandatory. For example, many medications are contraindicated in pregnancy, with notable examples being thalidomide, isotretinoin, and warfarin. In this context, the greatest difficulty lies in assessing whether the patient is pregnant at the time of the exposure. Information on whether a woman is pregnant or not at the time of prescribing is challenging to obtain and most information systems do not have good approaches for tracking this. In retrospective analyses, identification of the date of birth and backward calculation under the assumption of a term pregnancy might be feasible, though this process can still be subject to misclassification (e.g., if the pregnancy was not full term) and can be complex since such information is not readily stored in one location.

Another important piece of clinical information, especially in pediatrics (though also for the administration of chemotherapy and some other situations), is the patient's weight. Most pediatric medications use weight-based dosing. Standardized documentation of this information can be challenging to obtain, hindering not only analyses of pediatric dosing but also actual prescribing by pediatricians. Obtaining accurate

weight is also essential for many oncology patients, as certain intravenous chemotherapy drugs use weight-based dosing. However, this issue is further complicated in obese patients who may require dosing using body surface area (BSA) or ideal body weight (IBW).

Finally, information on the patient's medication allergy status is infrequently and inconsistently available [21,22]. It is important that true allergies (e.g., a rash related to penicillin) be differentiated from medication sensitivities or intolerances (nausea from codeine) through coded information rather than free text. It is particularly important that severe reactions, such as anaphylaxis, are clearly coded and identifiable. The eventual aim is to have one universal medication allergy list in an electronic format for each patient, rather than multiple disparate lists.

Measuring Incidence of Medication Errors

Especially because of the different approaches used in detection of medication errors, the assessment of medication error incidence remains challenging. Comparison of medication error incidence rates among different studies has substantial limitations. This is related to disparate detection approaches and using different methods to ascertain numerators (i.e., the medication errors) and denominators (i.e., the sample from which the medication errors arise). Thus, medication error rates from different studies can be difficult to compare unless the same, or similar, methods were used. Other factors to consider are the setting studied and the patient population. In addition, spontaneous reporting typically lacks information to calculate incidence (see Chapter 10).

Comparing Medication Error Rates Across Settings

Most medication error and ADE studies have been performed in the *hospital* setting. In the inpatient adult setting, patients are vulnerable to medication errors due to their medical acuity, the complexity of their disease process and medication regimens, and their age (e.g., the elderly are particularly susceptible). The medication error rate may differ depending on the type of hospital and may be higher in nonuniversity hospitals. A review from 2007 indicates that medication errors occur in about 5.1% (range 0.038–26%) of medications dispensed in university hospitals and 13.7% (range 3.5–49%) in nonuniversity hospitals [7]. Studies of ADE rates in hospitals have found rates ranging from 2 to 15 per 100 admissions [5,23,24].

In *intensive care units* (ICUs), the rates of medication errors appear higher than on general care units. This may result from the administration or ordering of many more medications that may also be associated with higher levels of toxicity. Beyond the increased incidence of medication errors in ICUs, the nature and causes of medication errors are different and the risk that a medication error will result in patient harm is also higher compared to general inpatient wards [25], with 7.4% of patients experiencing an ADE resulting from a medication error [26].

In *nursing homes* and especially in the *ambulatory setting* [13], assessment of medication error incidence is challenging because the individual steps in the medication process are rarely jointly documented (e.g., administration), and there are often substantial time lags between them. Sometimes estimation of frequency of medication errors has relied on spontaneous reporting of medication errors [27] or documentation of ADEs in charts, which misses both many ADEs and nearly all medication errors. In a recent review of medication errors in nursing homes, medication errors were reported for 16–27% of the residents. Most errors were associated with mild effects and only 0–1% resulted in severe effects [28].

In the ambulatory setting, patients live in their homes and take their medications independently,

which makes detection of medication errors and ADEs challenging. In one review, medication error rates ranged from 12% to 59%, with even higher numbers in elderly patients with complex medication regimes [29]. Thereby, errors can also be committed by a third person such as a caregiver who is also responsible for drug administration [30]. In addition, the incidence of medication error-related ADEs may be estimated by direct patient surveys in the outpatient setting, for example by calling patients or mailing or emailing them a survey. Using this kind of approach, ADE rates ranged from 25% of patients (as self-reported in a survey) [13] to 5% (of hospital admissions) [31]. For medication errors related to the prescription process, the error rate was 7.6% of all prescription orders in one study [32]. Medication error rates stratified for different specializations or dentists have not been studied in detail [33].

Another issue is what happens at the interfaces of care, for example when a patient is discharged home from the hospital. Many studies have shown that discrepancies in drug treatment at transitions of care are frequent and often these discrepancies are unintentional, facilitating substantial risk for patients [34,35]. For example, at the interface between primary and tertiary care [36], and especially in the elderly population, the incidence of problems with the drug prescription regime are frequent after discharge (in about one-third of elderly, discharged patients) and contribute to higher rehospitalization rates [37].

Comparing Medication Error Rates Across Different Patient Populations

Most early studies on medication errors and ADE have been done in *adults*. Medication errors were common, occurring at a rate of 5 per 100 medication orders in inpatients [2]. Seven in 100 medication errors had significant potential for harm, and 1 in 100 actually resulted in an injury [2].

In primarily the inpatient setting, medication error rates in *pediatric patients* have been estimated to be as high as 5–27% of all medication orders [38]. In neonatal intensive care units, error rates have been reported to be in similar ranges [39]. In the outpatient setting in cancer patients, medication error rates were three times higher in pediatric patients (18.8% of patients) than in adult patients (7.1% of patients) [40].

Medication error-related ADE rates have also been reported for the elderly; as many as 35% of elderly outpatients per year may experience an ADE [41], and as much as 30% of hospital admissions are ADE related in the elderly [42]. In elderly patients, many medication error studies have focused on the prescription of inappropriate drugs, especially using the Beers criteria (a list of drugs specified through expert consensus that should be avoided in elderly patients in general or under consideration of specific cofactors including co-morbidity or dosage) [43],although the utility of these criteria has been challenged [44].

Comparing Medication Error Rates Across Detection Methods

The incidence of medication errors may vary as much as 100-fold depending on the detection method. While direct observation is the most cost-intensive approach (about $5 per evaluated medication), it will yield the most accurate estimation of medication error incidence for dispensing and administration errors [45]. When aiming to detect the same set of medication errors by chart review or incident report review, costs substantially decrease but so do numbers of detected events, from the actual incidence rate of 11.7% (direct observation) to 0.7% (chart review) and 0.04% (incident report review). Moreover, the reported incidence will depend on the training and profession of the person who conducts the detection [45].

Medication error incidence rates are grossly underestimated if voluntary reporting methods

are applied [46]. To promote reporting, non-punishment policies as well as anonymous reporting have been established. Moreover, it is especially crucial to invite all individuals in the healthcare system who might be confronted with a medication error to report the error. For example, in the outpatient setting, where patients tend to see several physicians but get their medications from a single pharmacy, medication errors may be discovered in the pharmacy rather than during doctor's consultation. Thus, pharmacists should be invited to report medication errors to improve the systematic collection methodology [47].

Measuring Impact on Health-Related Outcome

As noted earlier, in one study 7 in 100 medication errors had significant potential for harm, and 1 in 100 actually resulted in an injury [2]. More recent literature indicates that in hospitalized patients, even 1 in 10 medication errors might result in an ADE [7]. However, the risk of whether a medication error results in harm varies. For example, the susceptibility to suffer an ADE is higher in geriatric wards as well as ICU patients compared to general care units (12% vs 6%) [25]. On the other hand, in one study pediatric patients had similar rates of ADEs compared to adults but a threefold higher rate of near misses [48]. Incidence rates of ADE in hospitalized patients are reported with a median overall frequency of 6.1% of patients [7]. Again, the detection method used substantially influences the estimation of the incidence, with highest numbers found by patient monitoring [7]. In about 2.9% (range 0.14–5%) of the patients experiencing an ADE, the ADE was fatal [7]. Nonfatal ADEs might prolong the hospital stay or increase the risk of rehospitalization. In another study, 13% of patients experienced an ADE after discharge, and of these 24% were preventable and 38% ameliorable [49]. In addition, ADEs occurring in the outpatient setting can contribute to hospital admissions, with 4.5 preventable ADEs per 1000 person-months [50].

Identifying Risk Factors

The search for risk factors for medication errors has been challenging, as some appear to occur relatively randomly in the medication process. Robust systems need to detect and prevent even errors occurring randomly [51]. Substantial research has been conducted on error nascence (i.e., the origin of the medication error) and it is important to understand and acknowledge the underlying causes on system and workflow or process level facilitating error nascence [52].

To subsequently assess these causes, it can be helpful to determine:

- at what stage of the treatment process medication errors are occurring
- by which person involved in the treatment process (e.g., the physician, the nurse, the pharmacist, the patient, or an informal care person) the error might be committed or potentially intercepted
- what the patient's characteristics are, including age, co-morbidities, and other medications they are taking
- what the clinical setting is.

These factors can be grouped into the categories of system level, patient level, and medication characteristics.

Well-defined factors influencing the risk for medication errors on a *system level* include organization policies or the general safety culture of an institution. On a workflow or process level, risk factors comprise poor communication, heavy workload or inadequate procedures [52]. Also *patient factors* such as renal dysfunction and old age increase error risk. Setting is also important, ICU patients having an especially high risk, because they are more seriously ill and are exposed to large numbers of medications. Settings with only limited monitoring options such as home care appear also risky [53].

In all settings, being administered the wrong dose is the most frequent type of medication error, especially overdosage [54]. Dosage errors may occur at the stage of administration (e.g., accidental intake of two tablets), the stage of manufacturing or dispensing (e.g., misreading the brand name), or, most frequently, at the stage of prescription. To select the appropriate dose for each patient, the physician has to consider a number of *patient characteristics* (age, weight) as well as *drug characteristics*. The individual exposure to a drug is subject to changes in the elimination organ function (e.g., renal or liver disease), pharmacokinetic interacting comedication, and genetic polymorphisms. Moreover, required dosages will depend on age-related pharmacodynamic changes and vary between disease conditions. They might also be higher or lower both at the beginning or the end of the therapy. The physician needs to have all such information at hand once he/she decides to prescribe a certain drug for a specific patient – and a lack of information might result in underdosage or, more often, in overdosage.

Any drug or drug formulation can be associated with a medication error. However, there are *medication characteristics*, including active ingredients, that are associated with an increased risk for medication errors. Predisposing factors include:

- a sophisticated way of prescribing (e.g., complex dosage adjustments), administration (e.g., usage of administration devices), or monitoring (e.g., therapeutic drug monitoring)
- a substantial dose-dependent toxicity which increases the likelihood that a medication error will result in patient harm
- a prescription frequency which is high enough that the error will occur during the study period but low enough that detection can be challenging.

The drug class with the highest prescription frequency is cardiovascular drugs. Consistent with the prevalence of prescribing, cardiovascular drugs have often been associated with an increased risk of medication errors and ADEs [55]. The prescription of antibiotics also has often resulted in ADEs, most often because known allergies were ignored [55]. Medication errors with fatal outcomes, however, are often associated with drugs which are less frequently used but complicated in their mode of administration. For instance, accidental intrathecal injection of vincristine has caused many deaths [56] despite extensive error prevention measures [57]. Similarly, intravenous administration of amphotericin B is complex and carries a high risk of harm; for intravenous administration, amphotericin is used both in an aqueous and a liposomal drug formulation with 3–4-fold higher maximum recommended doses for the liposomal preparation. Erroneous administration of aqueous amphotericin B solution in dosages appropriate only for the liposomal preparation has resulted in a number of cases of renal toxicity and death [58].

Most often, drugs frequently reported in medication error studies have more than one predisposing factor. Examples include warfarin, for which treatment must be closely monitored by adapting dosages to measured INR values to maintain effectiveness and prevent ADEs such as bleeding. In one inpatient study [59], about 30% of reported ADEs were caused by inappropriate anticoagulant use. In elderly patients, drugs associated with medication errors often affect the central nervous system and required dosage adjustments are often neglected [60].

In ambulatory care, specific drug formulations with complex handling requirements promote drug administration errors. For instance, on average, about one in three patients incorrectly self-administers the inhalation device for chronic asthma treatment [61].

Examples by Setting

In adult *inpatients*, administering the wrong dosage is the most frequent medication error. Patients with multiple co-morbidities may

require a dosage adjustment. In pediatric inpatients, wrong dosage often results from dose calculation errors, including 10-fold errors [62]. Moreover, less severe medication errors often result from incomplete drug orders (i.e., not specifying the route of administration if only one route is applicable). However, especially in developed countries, most potential medication errors are intercepted by hospital pharmacists while processing the order.

In the outpatient setting, many medication errors happen at the stage of drug monitoring (e.g., neglecting a required check-up of laboratory values) because patients tend to see their physicians only irregularly. Moreover, they will generally see several physicians concurrently who most often are only partially aware of the actions of their colleagues. Among elderly patients treated in the outpatient setting, the number of physicians seen by a patient was found to be an independent risk factor for a medication error-related ADE [63]. Because patients might often receive drugs from several physicians and additionally purchase over-the-counter drugs, the documentation of an actual and complete medication list is challenging to maintain. Thus, prescription of interacting drugs is frequent and drug–drug interactions contribute to 6% of ADE-related hospital admissions [31]. Compared to the inpatient setting, in the outpatient setting, prescription errors are less likely to be intercepted, so the patient must play a more active role in their medical treatment and assume some degree of responsibility for appropriate drug administration. Two major factors might impede appropriate drug administration: (1) patient nonadherence to prescribed drugs (see also Chapter 38), and (2) inadequate patient knowledge regarding administration, increasing the likelihood of administration errors (e.g., for asthma inhalers).

Moreover, due in part to the fact that information on drug prescription, dispensing, and administration may not be linked, dispensing errors are also important. In a large outpatient study, incidence rates were reported to be about four errors per 10 000 items dispensed [64]. Additionally, inappropriate splitting of tablets was found to be the source of some medication errors [65].

In the *ICU*, critically ill patients are characterized by rapidly changing clinical conditions, receive close and intensive patient monitoring, and require rapid adaptations of their drug therapies. Due to the large number of necessary medications, the frequency of DDIs is particularly high, with about two-thirds of patients having at least one DDI and 44% suffering from a DDI-related ADR in one study [66]. Moreover, a substantial fraction of drugs is given intravenously (IV), potentially using identical IV lines. In one study including 50 ICU patients, 5.8% of concurrently given IV medications were incompatible [67].

In the *long-term care* setting, relatively few data are available [68]. However, medication errors appear to be concentrated in a few different drug classes, most often involving drugs affecting the central nervous system or analgesics [59]. Pharmacotherapy in the elderly occurs in a patient population that is in general multimorbid, polymedicated, and with physiological changes requiring complex dosage adjustment. Therefore, prescribing errors involving inappropriate drug choice as well as inappropriate dosages are frequent [69].

In conclusion, a multitude of different combination of risk factors is possible and these factors must be carefully considered in designing and analyzing pharmacoepidemiology research on medication errors.

Currently Available Solutions

Developing Prevention Strategies

Medication error prevention strategies may address the persons involved in the medication process, the products used, or the process

organization itself. Most often, a prevention strategy might also cover several or all categories; for example, a workflow change will typically include education and training of the staff. Obviously, the best prevention strategies for medication errors will depend on the setting and the nature of the medication errors involved. Slips and lapses in executing correct planned actions can be addressed by workflow changes including skill training and monitoring (e.g., coworker confirmation, checklists) [70]. In contrast, mistakes might be prevented by providing relevant knowledge at the time it is required. Approaches might include educational training as well as provision of paper- or computer-based information at the point of care.

With the majority of errors being knowledge based and occurring during drug prescribing, the implementation of electronic prescribing systems (CPOE) with integrated clinical decision support systems (CDSS) assumes a key role in medication error prevention [71]. Implementation of such systems might eliminate several types of errors, such as transcribing errors [72], and reduce others. Their impact on ADEs in research studies has been less pronounced [73], partly due to the fact that most studies using this approach have been underpowered. However, a metaanalysis from 2014 suggested that implementing CPOE is associated with a greater than 50% decline in the preventable ADE rate [74]. Nearly all CPOE applications in use now were commercially developed, while many of the early studies were done on internally developed systems. In one study, commercial applications in the ICU setting were found in a metaanalysis to be associated with an 85% reduction in the prescribing medication error rates, and a 12% reduction in ICU mortality [75]. Another vulnerable area is intravenous admixture [76]; this is another place where technology is likely to help in the future.

Electronic solutions have been developed to safeguard against drug dispensing or administration errors. For example, barcoding systems are currently used to prevent medication administration to the wrong patient. Electronic medication administration records can be used to electronically monitor drug administration and effectively reduce errors of omission [77]. In the US, CPOE data linked with decision support and barcoding data have become the norm in over 90% of hospitals.

Outcome Assessment

The outcome of prevention strategies is often reported as changes in the frequency of medication errors. However, such information will imperfectly apply as a predictor for health-related outcome. Indeed, in studies assessing both medication errors and patient outcomes, a reduction in medication errors would not necessarily be accompanied by an improvement in patient outcomes. For example, a computer-assisted disease management system might enhance the number of guideline-conformed screenings but the disease severity would not be ameliorated [78]. The assessment of patient outcomes, either by measuring surrogate endpoints (e.g., lab values, disease monitoring parameters) or by assessment of clinical endpoints (e.g., ADE rates, mortality rates), is therefore preferable to estimate the impact of a prevention strategy.

Evaluation of Intervention Strategies

Most prevention strategies are evaluated in a before vs after implementation setting and only scarcely evaluated in randomized trials. Therefore, neglecting of confounding variables can substantially bias the results. In 2005, Han *et al.* reported that the implementation of a CPOE system was an independent factor associated with increasing mortality rates of pediatric inpatients (odds ratio 3.28; 95% confidence interval 1.94–5.55) [79]. However, in this study, the analysis did not control for workflow or policy changes that coincided with the

implementation of the CPOE. Nevertheless, the implementation of prevention strategies might potentially be associated with the introduction of new, "e-iatrogenic" errors [80,81], due to potential changes in workflows. Implementation of CPOE should therefore follow a stepwise roll-out after careful testing and be accompanied by close monitoring [82].

The Future

In the past decades, a multitude of small and several large-scale studies have been conducted in order to assess the frequency and nature of medication errors as well as to evaluate the impact of different prevention strategies. While all studies have found that medication errors happen with considerable frequency during drug therapy, variation in detection approaches makes it hard to narrowly define their incidence and severity. The frequency, best detection approaches, and prevention methods vary by setting and patient population. To allow comparison among study results, careful consideration of the study methodology is especially important. Especially in large-scale studies using only administrative data, information relevant to reliably identifying medication errors is often not systematically available. Key factors in conducting valid research related to medication errors include the consistent use of definitions and classifications of medication errors, and attempts to merge large medication databases with electronic data on patient's clinical information. Another area is refining the decision support in commercial applications.

But perhaps the major current research gap is to develop better approaches for and studies of detection and prevention in the ambulatory care setting – the setting in which the main part of drug treatment takes place. However, additional research is needed in all settings, especially in special populations such as psychiatry and pediatrics.

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