

Reliability of the assessment of preventable adverse drug events in daily clinical practice[†]

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SUMMARY

Purpose To determine the reliability of the assessment of preventable adverse drug events (ADEs) in daily practice and to explore the impact of the assessors' professional background and the case characteristics on reliability.

Methods We used a combination of the simplified Yale algorithm and the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) scheme to assess on the one hand the causal relationship between medication errors (MEs) and adverse events in hospitalised patients and on the other hand the severity of the clinical consequence of MEs. Five pharmacists and five physicians applied this algorithm to 30 potential MEs. After individual assessment, the pharmacists reached consensus and so did the physicians. Outcome was both MEs' severity (ordinal scale, NCC MERP categories A–I) and the occurrence of preventable harm (binary outcome, NCC MERP categories A–D vs. E–I). Kappa statistics was used to assess agreement.

Results The overall agreement on MEs' severity was fair for the pharmacists ($\kappa = 0.34$) as well as for the physicians ($\kappa = 0.25$). Overall agreement for the 10 raters was fair ($\kappa = 0.25$) as well as the agreement between both consensus outcomes ($\kappa = 0.30$). Agreement on the occurrence of preventable harm was higher, ranging from $\kappa = 0.36$ for the physicians through $\kappa = 0.49$ for the pharmacists. Overall agreement for the 10 raters was fair ($\kappa = 0.36$). The agreement between both consensus outcomes was moderate ($\kappa = 0.47$). None of the included case characteristics had a significant impact on agreement.

Conclusions Individual assessment of preventable ADEs in real patients is difficult, possibly because of the difficult assessment of contextual information. Best approach seems to be a consensus method including both pharmacists and physicians. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS—reliability; adverse drug events; assessment

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INTRODUCTION

Drugs have undoubtedly contributed to a better disease control. However, besides their obvious benefits they have untoward harmful effects, i.e.

adverse drug events (ADEs). These events can occur as either adverse drug reactions (non-preventable) or as harm due to medication errors (MEs) (preventable).¹ Historically, the focus has been on 'idiosyncratic' adverse drug reactions (ADRs) especially since the thalidomide disaster in the 1960s. Lately, the focus has been shifting towards preventable ADEs.² Minimising this type of events makes health care safer, for which various risk reduction strategies (e.g. computerised physician order entry) have been developed. However, to critically assess the strategies' impact on patient safety, reliable instruments are needed to identify preventable ADEs. These instruments should not only be applicable for scientific purposes, but also in daily clinical practice.

Various instruments have been developed and are being used to assess in a systematic way the causality between a drug and an adverse event.³⁻⁷ The structure of these instruments varies from sets of questions to complex algorithms. Their focus usually is the assessment of ADRs (non-preventable) and not specifically the assessment of preventable ADEs. Specific instruments for assessing the drug causality of preventable ADEs are to our knowledge not available. Nevertheless, the underlying principle of assessing ADRs and preventable ADEs is the same. Therefore the aforementioned instruments can in our view be applied to preventable ADEs as well.

If there is a causal relationship, the severity of the consequence of the error can be classified. For classification of the severity of an error the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) index⁸ is widely used. This index was recently found to be reliable based on the substantial agreement between the assessors.⁹ In this study the assessment was based on centrally extracted data pertaining to the occurrence of a specific event and presented in a standardised format to experienced assessors who were mainly pharmacists. This leaves open the question about the reliability and the generalisability to everyday practice, in which MEs and related ADEs are not assessed by specialised pharmacists on extracted data, but have to be made based on data from medical charts with a variety of clinical information and by professionals, who are not specifically trained as assessors. Nevertheless, it is important to know this reliability. Only if both physicians and pharmacists agree on the presence or absence of preventable ADEs, useful strategies for reduction of these events in daily practice can be developed and implemented in a successful way, and only on this condition, a positive effect of these strategies can be expected.

The aim of this study is to determine the reliability of the assessment of preventable ADEs in daily practice (i.e. assessment by practicing physicians and pharmacists using complete clinical information), and to explore the impact of the assessors' professional background and the case characteristics on reliability.

METHODS

Setting

This study was part of a larger study on the effect of a computerised Physician Order Entry system on Medication Safety and costs (the POEMS study), which collected data in three internal medicine wards (two general internal medicine wards and one gastroenterology/rheumatology ward) of the 1300 bed University Medical Center Groningen and in two internal medicine wards (one geriatric and one general internal medicine ward) of the 600 bed teaching hospital 'TweeSteden' in Tilburg, The Netherlands.

A waiver of the Medical Ethical Committee was obtained for this study, as the study fell within the boundaries of normal hospital routine of quality improvement and assurance. However, to protect patient privacy, patients were informed of the study and could object to inclusion of the study.

Study population and data collection

In the POEMS study, patients admitted to the study wards were included from July 2005 through November 2005. Patients received a letter with information about the study and they could object to inclusion. During daily ward visits, data on patients' characteristics, diseases, medication, laboratory values and adverse events were prospectively extracted by chart review. Two research pharmacists initially reviewed the medication and identified potential prescribing and transcribing errors according to the classification scheme for MEs of The Netherlands Association of Hospital Pharmacists.¹⁰ Prescribing errors were defined as errors in the process of prescribing drugs and were subdivided into administrative (e.g. errors on readability, drug name or route of administration), dosing (e.g. errors on dosage, frequency or length of therapy) and therapeutic errors (e.g. interactions, contraindications or duplicate therapy). Transcribing errors were defined as errors in the process of interpreting, verifying and transcribing of medication orders (MOs). For the current study, 30 patients were randomly selected, for whom in the

initial medication review at least one potential ME was detected by one of the two research pharmacists.

Assessment tool

To standardise the assessment procedure for POEMS, we combined the NCC MERP scheme with the simplified Yale algorithm³ (Figure 1). The NCC MERP scheme categorises MEs into nine categories (A–I) based on severity of related patient outcomes; our first primary outcome (Table 1). Categories A–D are associated with the absence of a preventable ADE, and Categories E–I are associated with the presence of a preventable ADE. These collapsed categories, A–D and E–I, form our secondary outcome. The Yale algorithm assesses the causality of the association between a drug and an adverse event.³ We adopted the first three items of the Yale algorithm (knowledge about the relation between this drug and the event, influence of other clinical conditions and the time relation between drug and event). The causal relationship could be assessed as unlikely (score < 0), possible (score ≥ 0 and ≤ 3) and probable (score = 4). Combining these algorithms, an event was defined as a preventable adverse drug event when it was possible or probable related to an ME.

Assessment procedure

The reliability of the assessment tool (combination of the NCC MERP scheme and the simplified Yale algorithm) was tested using the following procedure. All patients' clinical information, including the identified potential MEs in the initial medication review by one of the two research pharmacists, was given to two panels. The first panel consisted of five pharmacists of whom two were specialised as hospital pharmacists. Two of them were connected to the TweeSteden hospital, the others to the University Medical Center Groningen. Three pharmacists had experience in clinical practice for more than 5 years. The other two were involved in the POEMS study as members of the research team. The second panel consisted of five physicians who were all specialised in internal medicine. Three of them were geriatricians and four of them were registered as clinical pharmacologists. One of the physicians was connected to the TweeSteden hospital, two to the University Medical Center Groningen and two to other Dutch hospitals (in Utrecht and Helmond). All physicians had experience in clinical practice for more than 5 years.

Before assessing the 30 cases, the raters were individually instructed how to use the assessment tool by one of the two researchers.

These panels performed a detailed medication review. The clinical information available to these assessors consisted of patients' characteristics, diseases, all medication used (home- and hospital-initiated), adverse events, laboratory data and discharge letters. The panel members assessed individually the same potential MEs. After individual assessment of all 30 cases, the five pharmacists (panel 1) reached consensus on all cases in one plenary meeting and so did the five physicians (panel 2) in their own plenary meeting after individual assessment.

Outcome variable

Two outcome variables were defined; (a) the severity of an ME (NCC MERP categories A–I) and (b) a dichotomised version of this severity score, namely presence (NCC MERP categories E–I) or absence (NCC MERP categories A–D) of a preventable ADE as assessed by the panel.

Determinants

The assessors' professional background (pharmacist vs. physician) was studied as determinant for agreement. The case characteristics included as determinants were patients' age (≥ 75 years vs. < 75 years), patients' length of hospital stay on the study ward (≥ 20 days vs. < 20 days), number of MOs per case (≥ 15 MOs vs. < 15 MOs), the medical ward's specialism to which patients were admitted (geriatrics vs. internal medicine including gastroenterology/rheumatology and general internal medicine patients), and the type of ME (dosing errors vs. therapeutic errors). Cut-off points were based on the mean observed results. We chose as determinants those characteristics of which we thought that they could have an influence on agreement.

Data analysis

Agreement was calculated by using kappa statistics. For this calculation, the software program, AGREE[®] version 7 (ProGAMMA[™], The Netherlands) was used.

Kappa values less than 0.20 were considered as poor agreement, between 0.21 and 0.40 as fair agreement, between 0.41 and 0.60 as moderate agreement, between 0.61 and 0.80 as good agreement and between 0.81 and 1.00 as very good agreement.¹¹

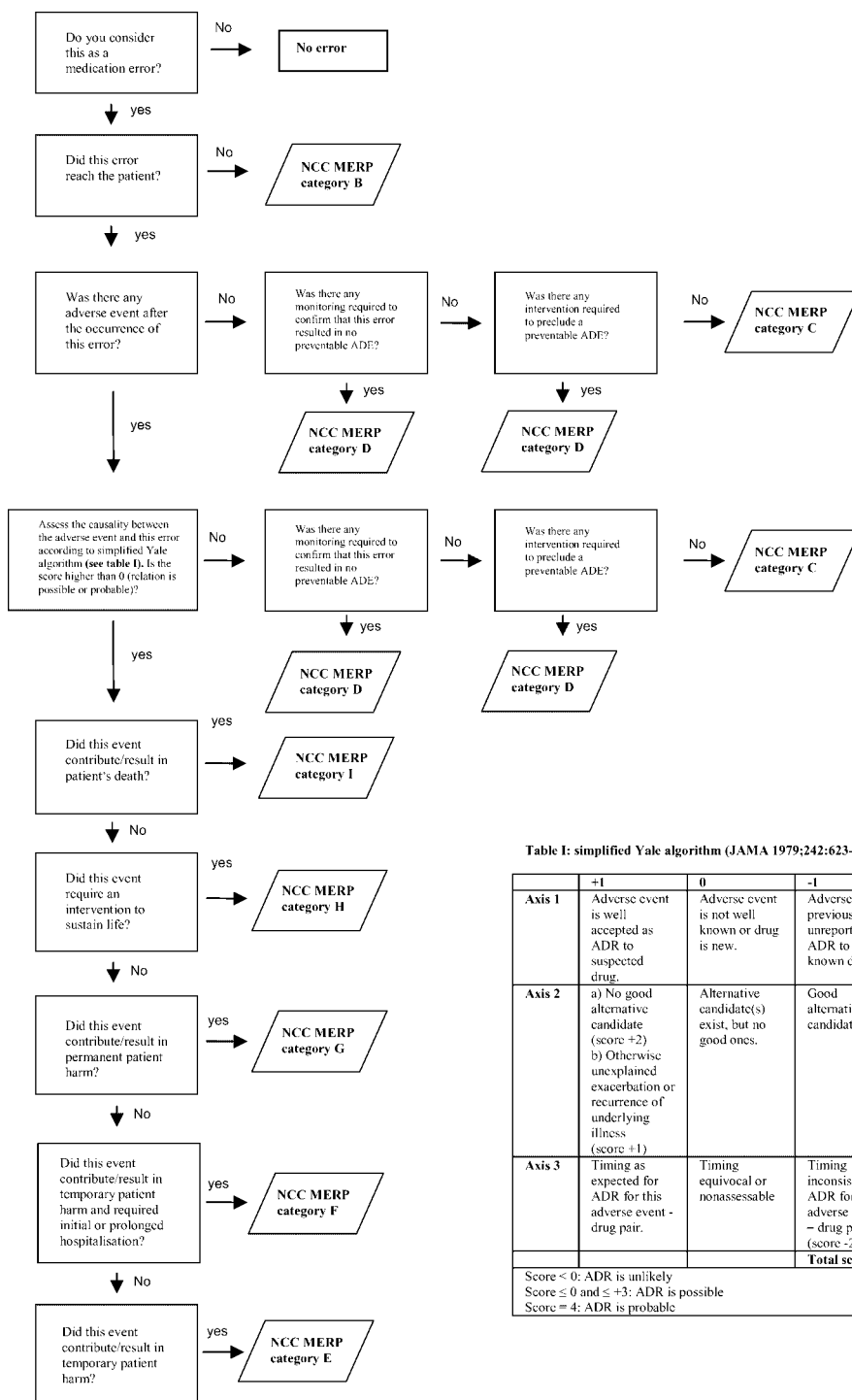


Table I: simplified Yale algorithm (JAMA 1979;242:623-632)

	+1	0	-1	Score
Axis 1	Adverse event is well accepted as ADR to suspected drug.	Adverse event is not well known or drug is new.	Adverse event previously unreported as ADR to well-known drug	
Axis 2	a) No good alternative candidate (score +2) b) Otherwise unexplained exacerbation or recurrence of underlying illness (score +1)	Alternative candidate(s) exist, but no good ones.	Good alternative candidate.	
Axis 3	Timing as expected for ADR for this adverse event - drug pair.	Timing equivocal or nonassessable	Timing inconsistent for ADR for this adverse event - drug pair (score -2)	
			Total score	
Score < 0: ADR is unlikely Score ≤ 0 and ≤ +3: ADR is possible Score = 4: ADR is probable				

Figure 1. Combination of the NCC MERP scheme and the simplified version of the Yale algorithm.

Table 1. NCC MERP Categories

Category	Content
A	Circumstances or events that have the capacity to cause error
B	An error occurred but the error did not reach the patient
C	An error occurred that reached the patient but did not cause patient harm
D	An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm
E	An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention
F	An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalisation
G	An error occurred that may have contributed to or resulted in permanent patient harm
H	An error occurred that required intervention necessary to sustain life
I	An error occurred that may have contributed to or resulted in the patient's death

Agreement was calculated for both outcomes; the severity of MEs (expressed as an ordinal scale from NCC MERP index categories A–I) as well as the presence/absence of a preventable ADE expressed as a binary outcome (presence; NCC MERP index categories A–D, vs. absence; categories E–I).

The impact of assessors' professional background on agreement was assessed by calculating the overall agreement for all 30 cases within the total group of assessors, within the group of pharmacists and within the group of physicians. To determine the impact of reaching consensus within both expert panels on reliability, agreement between both consensus outcomes (pharmacists vs. physicians) was calculated.

To explore the impact of case characteristics on agreement, the cases were divided into groups with specific case characteristics. Agreement within the total group of assessors was calculated for these groups.

The significance of the differences between kappa values was determined, using AGREE[®], version 7. A

p-value of less than 0.05 was considered statistically significant.

The selected 30 cases had a power of 80% to detect a kappa difference of 0.25 ($\alpha = 0.05$). This was based on an initial estimation of the distribution of ME's severity (NCC MERP).

RESULTS

Study population

The mean age of the study population was 77 ± 15 years. They received 17 ± 9 MOs during their hospital stays on the study wards, which lasted on average 20 ± 9 days. Nineteen patients were admitted to the geriatric ward, seven patients to the general internal medicine ward and four patients to the gastroenterology/rheumatology ward (Table 2).

Potential MEs included 14 dosing errors, 11 therapeutic errors, 5 transcribing errors and no administrative errors.

Table 2. Patient characteristics of study population ($n = 30$)

Female ($n, \%$)	13 (43%)
Age (years)	77 ± 15
Length of stay on ward (days)	20 ± 9
MOs per patient (mean \pm SD)	17 ± 9
Geriatric patients ($n = 19$)	
Primary discharge diagnoses	Delirium (4), mobility problems (4), mental disorders (3), cancer (2), pneumonia (2), hyponatremia based on medication use,* myocardial infarction, urinary tract infection, pulmonary embolism
General internal medicine ($n = 7$)	
Primary discharge diagnoses	Cancer (2), sepsis, deregulated diabetes mellitus, gastroenteritis, cellulites, ileus
Gastroenterology/rheumatology ward ($n = 4$)	
Primary discharge diagnoses	Cancer (2), cholangitis, cholestasis

*This adverse drug event was the reason for admission and did not occur during admission.

Table 3. Agreement between assessors

Raters	Severity of MEs	Presence/absence of a preventable ADE
	Kappa (95% CI)	Kappa (95% CI)
<i>Agreement for individual assessment</i>		
Within total group of assessors ($n = 10$)	0.25 (0.18–0.32)*	0.36 (0.23–0.49)*
Within group of pharmacists ($n = 5$)	0.34 (0.21–0.47) [†]	0.49 (0.29–0.68) [‡]
Within group of physicians ($n = 5$)	0.25 (0.14–0.35) [†]	0.36 (0.23–0.49) [‡]
<i>Consensus</i>		
Between pharm. and phys. ($n = 2$)	0.30 (0.09–0.50) [§]	0.47 (0.15–0.78) [§]

No significant difference between:

*the severity of MEs and the presence/absence of a preventable ADE: $p = 0.73$.

[†]pharmacists and physicians: $p = 0.28$.

[‡]pharmacists and physicians: $p = 0.30$.

[§]the severity of MEs and the presence/absence of a preventable ADE: $p = 0.74$.

Agreement between assessors

The agreement between the 10 raters was fair for both outcomes: the severity of MEs (0.25) as well as the presence/absence of a preventable ADE (0.36).

The agreement on the severity of MEs was fair within the group of pharmacists (0.34) and within the group of physicians (0.25) (Table 3). The agreement between the consensus outcomes was also fair (0.30).

The agreement on the presence/absence of a preventable ADE was slightly higher; moderate for the pharmacists (0.49) and fair for the physicians

(0.36) (Table 3). The agreement between both consensus outcomes was moderate (0.47).

For pharmacists, the agreement on both the severity of MEs and presence/absence of a preventable ADE seemed to be higher than for the physicians. However, these differences were not significant. In the consensus procedure, the physicians assessed nine potential MEs as no error while the pharmacists considered all cases as an error (Figure 2). Pharmacists as well as physicians did not assess MEs more severe than classification F; i.e. errors leading to prolonged hospitalisation. MEs in these 30 cases were not assessed

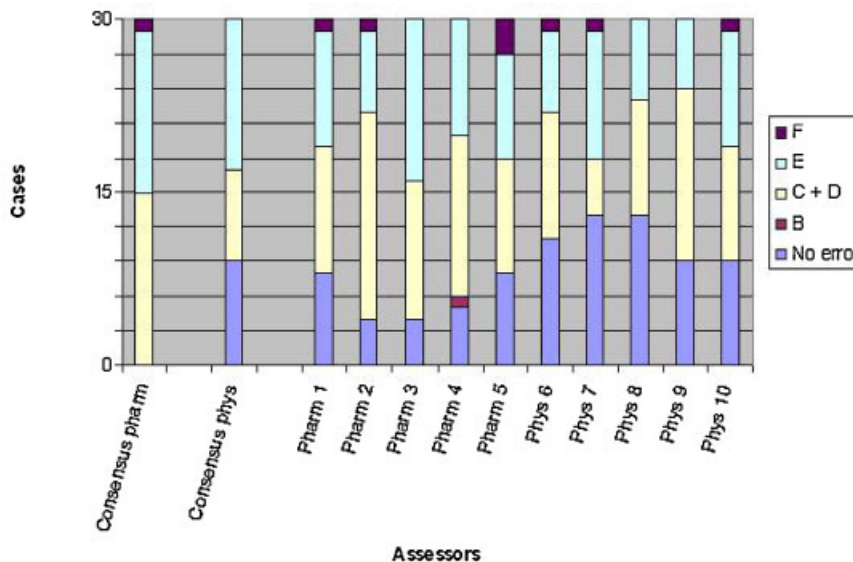


Figure 2. Outcomes of the 10 assessors.

to be associated with permanent patient harm, needing interventions to sustain life, or with patient's death.

Impact of case characteristics on agreement

Of the different types of MEs, only dosing errors and therapeutic errors were included as determinant because of the small number of transcribing errors ($n = 5$). None of the included case characteristics had a significant impact on agreement (data not shown).

Cases

The cases are described in more detail in the Appendix, both for cases with agreement (Table A1) and for cases with disagreement (Table A2).

DISCUSSION

Only in two cases the level of agreement between raters was higher than fair, i.e. the agreement on the presence of a preventable ADE within the pharmacists panel and between the two consensus assessments. As is already known from studies into the assessment of ADRs (non-preventable), it is difficult to reach good agreement between raters whether there is a standardised procedure or not.¹²⁻¹⁴ Our findings underline it is the same for assessing preventable ADEs and their severity from medical charts in everyday practice. This is in line with the recently published study of Haynes *et al.*¹⁵ but surprisingly is in contrast with high inter-rater agreement found by Forrey *et al.*⁹ and Snyder *et al.*¹⁶ So, why do some studies find such poor agreement while others do not?

First, the level of detail of case information given to the assessors differs. Instead of extracted information associated with an adverse drug event or ME only,^{9,16} we used an overview of all available clinical information during hospital admission. Yet, this overview reflects the reality of clinical situations, in which individual patients have various diseases, use many different medications and experience several symptoms that can be ADEs or are caused by the normal disease process.

Secondly, in our study we made use of professionals, not specialised in assessing ADEs. This is not in line with most other studies, where judgements were made by specialised assessors. For example, in the study of Forrey *et al.*⁹ the health care professionals were regular MEDMARX users and the researchers could not exclude that they were more experienced in assessing MEs. However, when implementing strategies to improve medication safety in everyday practice, specialised assessors are not always available

in sufficient numbers in individual hospitals. Moreover, even such specialised assessors have been shown to disagree significantly possibly because of variations in subjective weighing of causality arguments.^{13,14} This affects mainly arguments that are not factual (i.e. other risk factors or comorbidities which could have been the actual reason for the event).

Thirdly, a learning curve could explain higher levels of agreement. In the study by Snyder *et al.*¹⁶ each case was assessed, then classified after discussion by the individual raters before moving to the next case. This is in contrast to both the study of Haynes *et al.*¹⁵ (in which raters individually classified only without discussion) and our study, in which only after all cases were classified individually, consensus was reached in a subsequent meeting. We chose for this method, because our goal was to determine agreement between individual assessors prior to consensus building in order to evaluate the 'average' healthcare professional opinion on preventable ADEs. In our study, discussion could not have influenced the individual ratings in contrast to the approach by Snyder *et al.*¹⁶ that could have resulted in a learning curve and finally higher agreement.

A potential barrier for implementing strategies to increase medication safety is the rather low agreement between pharmacists and physicians when assessing preventable ADEs. The physicians in our study considered nearly a third of all potential MEs not to be a real error. In contrast, the pharmacists rated all potential MEs as real errors. We cannot exclude that the difference in clinical experience between the physicians and the pharmacists had an impact on this result. Besides, physicians will probably assess medication safety issues from another perspective than pharmacists do, because of differences in education, specialisation and experiences. Furthermore, it could be hypothesised that physicians look at the patient and his disease first and will then consider the relevance of an error, while pharmacists in their daily routine are focused on the medication process (how this could be improved) and on pharmacological aspects from a more drug related view. This may have influenced the group process and outcome of the classification. Still, the different professional groups were in moderate agreement on the presence/absence of a preventable ADE after the consensus procedure. However, agreement within the group of physicians remained fair only. Overall, we may conclude that the impact of profession is not unambiguously clear neither in our study nor in that of Dean and Barber¹⁷, who also found that reliability was not affected by profession (comparing pharmacists, physicians and nurses).

KEY POINTS

- There is only fair agreement on the assessment of an adverse event being actually preventable harm.
- A consensus method including both pharmacists and physicians seems to be the best practical solution.

A remarkable finding is that in the consensus ratings of the pharmacists there were no 'no error' ratings while each pharmacist individually had rated some MEs as 'no error'. A possible explanation could be that one of the raters was leading in the consensus meeting. Therefore, we determined the agreement between the individual raters and the consensus outcomes for both pharmacists and physicians (data not shown). Based on these results, we draw the conclusion that none of the pharmacists was particularly dominant. The same applies to the physicians. Unfortunately, we are not able to further explain the reason for the difference between individual and consensus ratings other than that this may have been a chance occurrence.

Our findings did not indicate an effect of the studied case characteristics, but can also not completely rule out they did not. Decision making by the individual assessors does not seem to be influenced by the case characteristics investigated. The results may however not extend to other specialities than internal medicine, as only patients from these departments were included in this study. Specific population characteristics, e.g. children, may have a different effect on agreement. However, internal medicine patients use in general relatively many drugs and are therefore a relevant population for evaluating the reliability of assessing medication safety.

This study shows that there is only fair agreement on the assessment of an adverse event being actually preventable harm. Our conclusion is the same as Haynes *et al.*,¹⁵ it is still a challenge to assess ADEs in a reliable way. As long as the reliability is low, it will be difficult to determine the absolute number of preventable ADEs. This problem has to be addressed when developing useful strategies to improve medication safety in everyday practice. Although consensus methods have their limitations, the best practical solution seems to be the consensus method including both pharmacists and physicians because it will increase the acceptability in the field which is necessary when implementing change.

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APPENDIX

Table A1. Cases with agreement

Sixteen cases with agreement (between both consensus outcomes)	Type of ME
Agreement on the occurrence of a preventable ADE ($n = 10$)	<ul style="list-style-type: none"> • Hypotension → Overdose of Perindopril • Rash → A prescription of Flucloxacillin for a patient with a known allergy for this drug • Unrest → Stop of administration of Strumazol[®] (antithyroid drug) because of a transcribing error • Agitation → Prescription of high dose of OxyContin[®] (opioid) at once instead of increasing gradually • Hypoglycemia → Gliclazide administered on wrong moment because of a transcribing error • Bleeding nose → Continuation of Clopidogrel instead of stopping • Edema → Interaction between Clarithromycin and Nifedipine • Dizziness → Overdose of Ipratropium • Hyperkalemia → Duplicate therapy of Perindopril and Irbesartan • Decrease of INR → Stop of administration of Acenocoumarol because of a transcribing error
Agreement on the occurrence of an ME without a preventable ADE ($n = 6$)	<ul style="list-style-type: none"> • Pravastatin 20 mg → Prescribed to administer it in the morning instead of in the evening • Albumin 100 cc → No indication for this drug • Isosorbide mononitrate 50 mg → Prescribed twice a day instead of once a day (nitrate free interval is required because of nitrate tolerance) • Nitrofurantoin 100 mg → wrong scheme of administration: 100 mg twice a day instead of 50 mg four times a day (mistaken for the capsule with extended release) • Nitrofurantoin 100 mg → Prophylaxis: prescribed to administer in the morning instead of in the evening • Rifampicin 600 mg → Interacts with midazolam (may decrease the level of midazolam)

Table A2. Cases with disagreement

Fourteen cases with disagreement (between both consensus outcomes)	Type of ME
Agreement on the occurrence of an ME, disagreement on the occurrence of a preventable ADE ($n = 5$)	<p>Preventable harm, only according to pharmacists</p> <ul style="list-style-type: none"> • <i>Clostridium difficile</i> infection → Overdose of ceftazidime • Decrease of INR → Stop of administration of Acenocoumarol because of a transcribing error <p>Preventable harm, only according to physicians</p> <ul style="list-style-type: none"> • Haematuria, diarrhea, vomiting → Overdose of cotrimoxazole prescribed for a patient with renal impairment

(Continues)

Table A2. (Continued)

Fourteen cases with disagreement (between both consensus outcomes)	Type of ME
Disagreement on the occurrence of an ME ($n = 9$)	<ul style="list-style-type: none"> • Rectal prolapse → No administration of microlax[®], an enema (a laxative), because of an omission of the nurses to transcribe this drug on the administration chart. • Increase of alkaline phosphatase → Overdose of acetaminophen <p>MEs only according to pharmacists:</p> <ul style="list-style-type: none"> • Ferrous fumarate 200 mg once a day: an underdose. • Prescriptions of both aspirin and dexamethasone. No prescription of a proton pump inhibitor. • Acenocoumarol prescribed to a patient with a history of duodenal ulcer. No prescription of a proton pump inhibitor. • Duplicate therapy of lactulose and magnesium hydroxide (both laxatives). • Hydroxocobalamin 1 mg/3 months: underdose • Nitrofurantoin prescribed to a patient with a creatinine clearance probably of 50 mL/min. Patient's weight was not known. • Various switches of antibiotics: indication not clear. • Domperidone 60 mg three times a day (suppository): an overdose. • Allopurinol 300 mg once a day prescribed to a patient with a creatinine clearance lower than 60 mL/minute: an overdose.