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**Title:** Clinical rules in hospital pharmacy practice to prevent adverse drug events  
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Evaluation of rule effectiveness and positive predictive value of clinical rules in a Dutch clinical decision support system in daily hospital pharmacy practice

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Abstract

Introduction: Our advanced clinical decision support (CDS) system, entitled ‘adverse drug event alerting system’ (ADEAS), is in daily use in our hospital pharmacy. It is used by hospital pharmacists to select patients at risk of possible adverse drug events (ADEs). The system retrieves data from several information systems, and uses clinical rules to select the patients at risk of ADEs. The clinical rules are all medication related and are formulated using seven risk categories.

Objective: This study’s objectives are to 1) evaluate the use of the CDS system ADEAS in daily hospital pharmacy practice, and 2) assess the rule effectiveness and positive predictive value (PPV) of the clinical rules incorporated in the system.

Setting: Leiden University Medical Center, The Netherlands. All patients admitted on six different internal medicine and cardiology wards were included.

Measures: Outcome measures were total number of alerts, number of patients with alerts and the outcome of these alerts: whether the hospital pharmacist gave advice to prevent a possible ADE or not. Both overall rule effectiveness and PPV and rule effectiveness and PPV per clinical rule risk category were scored.

Study design: During a 5-month study period safety alerts were generated daily by means of ADEAS. All alerts were evaluated by a hospital pharmacist and if necessary, healthcare professionals were subsequently contacted and advice was given in order to prevent possible ADEs.

Results: During the study period ADEAS generated 2650 safety alerts in 931 patients. In 270 alerts (10%) the hospital pharmacist contacted the physician or nurse and in 204 (76%) cases this led to an advice to prevent a possible ADE. The remaining 2380 alerts (90%) were scored as non-relevant. Most alerts were generated with clinical rules linking pharmacy and laboratory data (1685 alerts). The overall rule effectiveness was 0.10 and the overall PPV was 0.08. Combination of rule effectiveness and PPV was highest for clinical rules based upon the risk category ‘basic computerized physician order entry (CPOE) medication safety alerts fine-tuned to high risk patients’ (rule efficiency = 0.17; PPV = 0.14).

Conclusion: ADEAS can effectively be used in daily hospital pharmacy practice to select patients at risk of potential ADEs, but to increase the benefits for routine patient care and to increase efficiency, both rule effectiveness and PPV for the clinical rules should be improved. Furthermore, clinical rules would have to be refined and restricted to those categories that are potentially most promising for clinical relevance, i.e. ‘clinical rules with a combination of pharmacy and laboratory data’ and ‘clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients’.
Introduction

Adverse drug events (ADEs) can occur at any point the medication process, from ordering and prescribing to dispensing, reconstitution and drug administration [1,2]. As advanced information technology plays an important role in the improvement of medication safety, we have opted to use one of the technologies available to prevent ADEs [1]. Different of such technologies are described in literature, for example barcode scanning to identify both drugs and patients, use of computerized physician order entry (CPOE) with or without clinical decision support (CDS) system, smart pumps and the use of robots for drug dispensing [3,4]. Although no randomized control trials were performed, there are investigations showing that a reduction in ADEs can be reached by means of using CPOE in combination with CDS systems [5-7]. CDS systems can range from basic to more advanced [8]. Basic CDS systems, for example, include basic dosing guidance or drug–drug interaction checking only. More advanced CDS systems can include dosing support for renal insufficiency and guidance for medication-related laboratory testing [8].

The information system in use in our hospital is Mirador® with incorporated CPOE system Medicatie/EVS® (Medicator®)(iSOFT Nederland BV, Leiden, The Netherlands), is a basic CDS system which provides online basic medication safety alerts [9]. The safety alerts in our CPOE system are retrieved from a Dutch national drug database (the G-Standard). This database contains safety information on all drugs registered in The Netherlands, and provides drug–drug interactions information, duplicate orders and overdoses alerts [10]. In order to reduce the limitations of a basic CDS system such as Medicator® [11-13], we have developed an advanced CDS system, named ‘adverse drug event alerting system’ (ADEAS). ADEAS is in use in the hospital pharmacy and it is used by hospital pharmacists as medication surveillance tool to select patients at risk of possible ADEs. The system retrieves data from several information systems, and uses clinical rules to select the patients at risk of ADEs. Selection of these patients potentially at risk occurs by combining data from the electronic patient databases (EPD) (laboratory data, patient characteristics), the CPOE (prescribed medication) and the ‘G-standard’ (National Dutch drug database).

In a previous study, we compared ADEAS with our CPOE with basic CDS system and showed that ADEAS has an additional value in selecting different kind of patients at risk of ADEs. This study showed that the basic CDS system generated safety alerts regarding drug–drug interactions and drug-overdosing only, whereas ADEAS also generated alerts regarding declined renal function and other laboratory abnormalities. It was proven that alerts generated by ADEAS led to a larger number of interventions by pharmacists when compared to alerts generated by the basic CDS system [14].
The objectives of this current study were: (1) to evaluate the use of ADEAS in daily practice as a CDS system for hospital pharmacists; (2) to assess the rule effectiveness and positive predictive value (PPV) of the clinical rules incorporated in the ADEAS system.

**Study context**

**Organizational setting**

The study was performed in the Leiden University Medical Center (LUMC), a teaching hospital in Leiden, The Netherlands, forming part of Leiden University. The study was conducted on six clinical wards: haematology (hemat), cardiology (cardio), combined lung/gastrointestinal diseases ward (lung and gastro), short stay internal medicine (short stay) and two combined internal medicine wards, one specializing in endocrinology, nephrology and general internal medicine (called mixed internal 1) and one specializing in infectious diseases, oncology and rheumatology (called mixed internal 2). All patients admitted on these wards during the study period (a 5-month period, from September 2009 up to January 2010) were included in this study, irrespective of their age or the number of different drugs at the time of admission. All included patients were screened on a daily basis by ADEAS throughout their stay in hospital.

**System details and full description of system in use**

**Description of CDS system ADEAS**

ADEAS was composed by means of Gaston (Medecs BV, Eindhoven, The Netherlands), which is a guideline-based decision support framework, consisting of both a guideline development module and a decision support module [15,16]. The guideline development module consists of a task network module [17] which describes the structure (‘logic’ or ‘flow’) of the guideline by means of a set of primitives (such as observations, decisions, and actions) and which provides domain specific knowledge in the form of one or more terminology items. For the guideline development module, we defined the following terminology items: drug, laboratory values, drug–drug interactions and patient characteristics. The data used for ADEAS can be specified as follows. The data for the ‘drug’ and ‘drug–drug interactions’ sections were imported from the national Dutch drug information database (the ‘G-standard’). The data regarding laboratory values and patient characteristics were imported from the hospital information system, Glims® (MIPS Diagnostics Intelligence, Clinisys, UK) and Mirador®. The information about drug use for specific patients was imported from the CPOE, Medicator®.
A decision support module was used to link Gaston with our hospital information system in order to be able to import the required information and to execute the clinical rules. Gaston was originally designed as a CDS system within a CPOE. We, however, preferred to use ADEAS as a pharmacy decision support system, not incorporated in the CPOE. This resulted in technical adaptations to the reporting technology.

The primitives and terminology items were combined and used to create and integrate the clinical rules into the system. The terminology items were moved to the desired field (positive or negative preferences). Per item, sub items such as dosage or administration route for a drug could be added. Most clinical rules consisted of simple observations of one or more positive and/or negative term preferences, for example a drug prescription and the presence of a laboratory value or a drug prescription and the absence of a laboratory value.

More complicated clinical rules were built as a flowchart using the primitives. We started with a set of 121 clinical rules. Figure 7.1 offers the reader insight in ADEAS and gives the reader an example of how clinical rules were formed.

More detailed information about the development and validation of our system including the first set of clinical rules has been described elsewhere [18].

**Description of clinical rules**

The contents of the clinical rules were established with the help of a multidisciplinary team. From a drug perspective seven risk categories were defined which were used to create clinical rules. For each drug or drug class, the seven risk categories were discussed and this, subsequently, resulted in agreement and definition of a clinical rule [18]. The seven risk categories specified by the multidisciplinary team are:

1. Combination of biochemical laboratory values with the initiation of drug use
   
   **Examples of clinical rules:** A) patient start with an aminoglycoside and the estimated glomerular filtration rate (eGFR) < 50 ml/min, B) patient start with lithium and eGFR < 50 ml/min, C) patient start with allopurinol > 200 mg and eGFR < 50 ml/min, and D) no international normalized ratio (INR) 3 days after start phenprocoumon.

2. Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug
   
   **Examples of clinical rules:** A) patient with sotalol > 160 mg and eGFR decline below 50 ml/min, B) INR > 6 during use of coumarin anticoagulant, and C) no therapeutic drug monitoring 2 days after start or dosage change of aminoglycoside or vancomycin.

3. Combination of use of a drug with non-use of a drug, the latter indicated for the prevention of an ADE
Figure 7.1 Example of how the clinical rule no therapeutic drug monitoring 2 days after start vancomycin is created in Gaston-ADEAS.

The terminology item drug-vancomycin is moved to the positive preferences field. A sub item prescribed 3 days ago is added. The terminology item lab result-vancomycin therapeutic drug monitoring is moved to the positive preferences field. A sub item prescribed 3 days ago is added. The terminology item lab result-vancomycin therapeutic drug monitoring is moved to the negative preferences field. A sub item measured 1 time after last prescribed vancomycin is added.
Examples of clinical rules: A) patient with co-trimoxazole and no folic acid, and B) patient with opioid agonist of > 2 days and no laxative.

4. Medication used to treat an ADE
   An example of a clinical rule: A) patient with inhibitor of angiotensin converting enzyme (ACE-inhibitor) and anti-cough medication.

5. Basic CPOE medication safety alerts fine-tuned to high risk patients
   Examples of clinical rules: A) patient with a quinolone antibiotic and interacting co-medications regarding absorption, B) patient with drug-drug interaction between non-steroidal anti-inflammatory drug (NSAID) and ACE-inhibitors or angiotensin receptor blockers (ARBs) and eGFR < 50 ml/min, C) patient with anti-epileptic medication and start a quinolone antibiotic, and D) Patient with start aminoglycoside and prescription of cisplatin in previous 6 months.

6. Safety alerts from inspection authority
   Examples of clinical rules: A) patient with azathioprine in dose > 150 mg/day, and B) patient with methotrexate in non-weekly dose schedule.

7. Medication errors and high risk drug situations
   Examples of clinical rules: A) patient > 80 years of age and Beers-list medication, B) patient with aspirin low dose and co-medication with ulcer risk and no proton pump inhibitor, and C) patient with gastrointestinal tube.

Methods

Study design

The evaluation of ADEAS was investigated in a prospective non-randomized observational study. All patients admitted on one of the six wards used for this study were screened on a daily basis by ADEAS throughout their stay in hospital. ADEAS was used as a CDS system by the hospital pharmacist to select patients at risk of possible ADEs. The system ran every night selecting patients potentially at risk based upon the clinical rules. The output was generated in the pharmacy department every morning. Every day (except during weekends; safety alerts produced during weekends were read on Mondays) all the safety alerts were reviewed in detail by one of the hospital pharmacist. Additional case specific information was subsequently collected for each patient in the EPD to assess the clinical relevance of the alert for that specific patient. Consequently, if necessary, the hospital pharmacist contacted the physician or nurse to give advice or to intervene.
**Outcome measures**

To evaluate the use of the ADEAS system for daily hospital pharmacy practice the following items were scored: 1) the total number of alerts generated by ADEAS, 2) the number of patients with an alert, and 3) the outcome of the alerts; whether the hospital pharmacist gave advice to prevent a possible ADE or not. Of all the advice given by the hospital pharmacist the type of advice was scored. In addition, the percentage of acceptance of the advice by the healthcare professional was scored as well.

The rule effectiveness and PPV of all the rules triggered in ADEAS, and of each rule risk category separately, were calculated.

**Measurement**

To measure the outcome of the alerts, all ADEAS alerts were divided into the following categories:

*Alert category (1) alert considered non-relevant.*

After detailed review by the hospital pharmacist of the alert (for example, after dose check or laboratory value check in the EPD), the alert was considered not clinically relevant for this specific patient.

*Alert category (2) alert resulting in contact with physician or nurse.*

After review of the alert, the hospital pharmacist contacted the healthcare professional (by phone or by means of personal advice, while visiting the ward) in order to discuss the alert and get further clarification about the reasons for prescribing. This contact may or may not lead to an advice to adjust treatment in order to prevent possible ADEs.

*Alert category (3) alert with advice/intervention.*

Category 3 includes all actual advice given after contacting the healthcare professional.

If advice was given by the hospital pharmacist, the following types of advice were distinguished: 1) advice to adjust the dose; 2) advice to discontinue or suspend medication; 3) advice to change medication; 4) advice to continue medication but to monitor side effects; 5) advice to adjust the time drugs are administered; 6) advice to add extra medication; and 7) advice to initiate drug blood level measurement or other laboratory control such as renal function.

To measure the acceptance rate of all advice given, we checked the documented modification in therapy. The hospital pharmacist who gave the advice checked the patient’s EPD the following day in order to ensure that the advice was adhered to.
All generated alerts were specified according to one of the seven risk categories for the clinical rules, described above [18]. Both the overall rule effectiveness and PPV and the rule effectiveness and PPV per rule risk category were scored. A measure of rule effectiveness is the ratio of the number of alerts resulting in contact with healthcare professional to the total number of alerts generated by ADEAS. We used rule effectiveness as a variant of rule efficiency. Rule efficiency is the probability of an alert leading to action by the pharmacist [19]. The PPV is the probability of an alert leading to advice/intervention. The PPV was calculated by the quotient of the number of advice/interventions to prevent a possible ADE and the total number of alerts generated by ADEAS [19].

Results

Results number of alerts and alert outcome

During the 5-month study period (September 2009 – January 2010) ADEAS generated a total of 2650 alerts for 931 patients. This is a mean of 17 alerts per day. The main results are shown in Table 7.1 and Figure 7.2. Most alerts, 2380 (90%) out of 2650, were rated as alerts for category 1 (alert considered non-relevant). In 270 (10%) out of these 2650 alerts, the hospital pharmacist contacted the physician or nurse (alert category 2). In 204 (76%) out of these 270 alerts, the pharmacist gave advice to prevent the possible ADE (alert category 3). For 204 times advice was given, 128 instances were accepted by the healthcare

<table>
<thead>
<tr>
<th>Table 7.1 Main results: number of alerts with ADEAS, alerts outcome and overall rule effectiveness and PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of alerts</td>
</tr>
<tr>
<td>Total number of patients with alerts</td>
</tr>
<tr>
<td>Number of alerts, alerts category 1 (alert considered non-relevant)</td>
</tr>
<tr>
<td>Number of alerts, alert category 2 (alerts resulting in contact with prescriber or nurse)</td>
</tr>
<tr>
<td>Number of alerts, alert category 3 (alert with advice/intervention)</td>
</tr>
<tr>
<td>Number of alerts for which advice was given and adhered to</td>
</tr>
<tr>
<td>Rule effectiveness (overall)</td>
</tr>
<tr>
<td>PPV (overall)</td>
</tr>
</tbody>
</table>
professionals. For the remaining 76 times advice was given, advice was either not adhered to or it is not clear whether advice was adhered to. In total, 128 (4.8%) out of 2650 alerts led to a documented modification in therapy. The alert outcome representing the spread over the study wards is shown in Figure 7.3.

All advice given by the hospital pharmacists is specified in Table 7.2. Sometimes there was more than one type of advice given following an alert, for example, to both add medication and monitor for side effects.

**Results rule effectiveness and PPV**

The overall rule effectiveness of ADEAS was 0.10 (270/2650) and the overall PPV was 0.08 (204/2650) (Table 7.1).
Most alerts, 963 alerts, were generated by clinical rules from risk category 1 ('Combination of biochemical laboratory values with the initiation of a drug'). Clinical rules from risk category 2 ('Combination of biochemical laboratory values or therapeutic drug monitoring values with the ongoing use of a drug') generated 722 alerts. Clinical rules from risk category 5

![Graph showing alerts and advice by ward]

**Figure 7.3** Results number of alerts with ADEAS and alert outcome divided between different wards.

Total alerts: total number of alerts generated by ADEAS (category 1 + category 2)

Alert category 1: number of alerts considered non-relevant

Alert category 2: number of alerts resulting in contact with physician or nurse

Alert category 3: category 3 includes all actual advice given after contacting the healthcare professional

Advice accepted: number of alerts from category 3 for which advice was given by hospital pharmacists and adhered to by the healthcare professionals

<table>
<thead>
<tr>
<th>Wards</th>
<th>Total alerts</th>
<th>Alert category 1</th>
<th>Alert category 2</th>
<th>Alert category 3</th>
<th>Advice accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stay (41 patients)</td>
<td>760</td>
<td>640</td>
<td>120</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Lung &amp; gastro (158 patients)</td>
<td>317</td>
<td>265</td>
<td>88</td>
<td>31</td>
<td>5</td>
</tr>
<tr>
<td>Mixed internal 2 (142 patients)</td>
<td>699</td>
<td>631</td>
<td>68</td>
<td>99</td>
<td>3</td>
</tr>
<tr>
<td>Mixed internal 1 (218 patients)</td>
<td>378</td>
<td>30</td>
<td>17</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Hemat (91 patients)</td>
<td>265</td>
<td>21</td>
<td>43</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Cardio (281 patients)</td>
<td>712</td>
<td>653</td>
<td>68</td>
<td>317</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 7.2** Type of advice given following alerts from ADEAS

<table>
<thead>
<tr>
<th>Type of advice</th>
<th>Number of alerts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose adjustment</td>
<td>67</td>
</tr>
<tr>
<td>Discontinue or suspend medication</td>
<td>12</td>
</tr>
<tr>
<td>Change medication</td>
<td>13</td>
</tr>
<tr>
<td>Monitor side effects</td>
<td>9</td>
</tr>
<tr>
<td>Take drugs separately/adjust administration time</td>
<td>45</td>
</tr>
<tr>
<td>Add medication</td>
<td>37</td>
</tr>
<tr>
<td>Measure drug blood lever or other laboratory control</td>
<td>34</td>
</tr>
</tbody>
</table>
Figure 7.4 Results number of alerts with ADEAS and alert outcome divided per clinical rule risk category.
Total alerts: total number of alerts generated by ADEAS (category 1 + category 2)
Alert category 1: number of alerts considered non-relevant
Alert category 2: number of alerts resulting in contact with physician or nurse
Alert category 3: category 3 includes all actual advice given after contacting the healthcare professional
Advice accepted: number of alerts from category 3 for which advice was given by hospital pharmacists and adhered to by the healthcare professionals

Figure 7.5 Results rule effectiveness and PPV per clinical rule risk category.
Rule effectiveness: the ratio of the number of alerts resulting in contact with physician or nurse to the total number of alerts generated by ADEAS.
PPV (positive predictive value): the quotient of the number of advices/interventions to prevent a possible ADE and the total number of alerts generated by ADEAS.
Rule effectiveness and PPV of clinical rules

('Basic CPOE medication safety alerts fine-tuned to high risk patients') generated 437 alerts. In Figure 7.4, the alert results per clinical rule risk category are shown. The PPV was highest for clinical rules from risk category 5 (0.14). Rules from this category had the second highest rule effectiveness score (0.17). Consequently, this category had the highest combination of rule effectiveness and PPV. Figure 7.5 shows all the results for rule effectiveness and PPV.

An extraordinary result is the high rule effectiveness of 0.29 for rules from category 4 ('Medication used to treat an ADE') together with a PPV of zero. This rule category covered one clinical rule (Patient with an ACE-inhibitor and anti-cough medication) and resulted in 7 alerts during the study period. In two instances, the pharmacist contacted the physician but this never led to an advice. This rule can be considered of low clinical relevance.

Discussion

Answer to study questions

In this study we evaluated the usefulness of the CDS system ADEAS for selecting patients at risk of ADEs in daily hospital pharmacy practice. The main result of this study is that the ADEAS system can be used for this goal, but that both rule effectiveness and PPV would have to be increased in order to use the ADEAS system effectively. The overall rule effectiveness score was 0.10. This means that 10% of the safety alerts generated by means of ADEAS resulted in direct contact by hospital pharmacist and healthcare professional. The overall PPV was 0.08. This means that 7.8% of the alerts resulted in advice or intervention to prevent possible ADEs. In addition, the majority of advice given by the pharmacist was accepted. ADEAS is considered most useful with rules from risk category 1, 2 and 5, because those rules had the highest combination of rule effectiveness and PPV (risk category 5) and the highest number of alerts (risk categories 1 and 2). This is explained in more detail in Section 5.4 of this paper.

A rule effectiveness of 0.10 implicates that a large number of alerts (90%) were scored as non-relevant (alert category 1). The authors feel it is important to comment that all alerts considered in this study could have led to potential ADEs, but that in certain cases, alerts were rated as non-relevant, after detailed review of the patient’s EPD. There are a few of such situations in which an alert was considered non-relevant: 1) one such example is an alert generated by the clinical rule regarding the use of a quinolone antibiotic and a declined renal function (eGFR < 30 ml/min). It could be that the physician in this specific case had already
adjusted the dose himself, taking into consideration the patient’s renal function. In that case, the hospital pharmacist actively checked the patient’s EPD following the alert, but found that the alert was non-relevant because dose adjustment had already taken place; 2) another example is an alert generated by the clinical rule regarding absence of INR laboratory results during phenprocoumon therapy. It could be that the INR laboratory control was ordered the day the pharmacist reviewed the alert, but that the results were not yet known by that time. Because it was clear to the pharmacist that laboratory control of INR had already been ordered, the pharmacist rated the alert as non-relevant; 3) another situation in which the pharmacist considered an alert as non-relevant that can easily be explained occurred on the cardiology ward. Most patients at this ward received an intervention procedure, such as implantation of an implantable cardioverter defibrillator or a percutaneous transluminal coronary angioplasty. These patients often have a short period of declined renal function and high INR values after the procedure but, however, it is known that values improve quickly. In those cases, alerts do not lead to intervention and medication does not need to be adjusted; and 4) a last reason for considering alerts as non-relevant is the fact that alerts reappear for the same patient – the alerts are then counted and included in the total number, but intervention only has to take place once.

All reasons mentioned above are related to the low sensitivity and or low specificity of the created clinical rules in ADEAS. In some cases the clinical rules were adapted during the study, to enlarge their sensitivity or specificity. To lower the number of non-relevant alerts, both rule effectiveness and PPV of ADEAS should be increased in the future. One possible adjustment is to add more sub items to a rule. For example the sub item ‘drug dosage’ can be added in a rule regarding drug use and declined renal function. Or the sub items ‘ward’ or ‘specialty’ can be added in a rule considered not relevant for specific patient categories. In addition, the authors recommend that a technical solution should be found to lower the amount of duplicate alerts. This can be achieved by including a sub item that takes into consideration the previous alerts generated for the same patient. In order to increase the effectiveness of ADEAS for routine patient care, it can be concluded that the clinical rules have to be refined and potentially restricted to those categories that are clinically relevant.

**Strengths and weaknesses of the study**

One of the main strengths of our study is that ADEAS was tested and evaluated in the actual clinical setting it was intended for: in routine daily practice, and not just in a research setting. This makes the evaluation highly clinically valuable and the results very useful and
significant. Actually testing ADEAS in the actual clinical setting meant that the result could be applied directly in clinical practice.

A limitation of our study is that we did not measure ADEs as endpoint. Had we done so, we could have said more about the ability of ADEAS to prevent actual ADEs. In a study not yet published, we investigated the effect of ADEAS on ADEs. Studying a subpopulation consisting of elderly patients with polypharmacy, it was proven that the use of ADEAS resulted in a significantly lower number of preventable ADEs. ADEAS did not have an effect on the total number of ADEs (unpublished data). Our current study is a prospective observational study to evaluate the use of ADEAS in daily practice and measurement did not include ADEs.

Another limitation of our study is that we only based the advice acceptance rate on documented modifications in therapy. The acceptance rate was measured by checking the EPD of the patient the next day to verify if the advice was adhered to. We did not interview the healthcare professional for a complete follow-up, however. We scored a total of 76 (37%) out of 204 advices by the hospital pharmacist, for which advice by the hospital pharmacist was either not adhered to or for which it was unknown whether advice was adhered to. In many cases the acceptance rate could not be verified in the documentation because the patient had already been discharged the following day; this is often the case on the cardiology ward or on the short stay ward, where patient turnover is high. At the cardiology department only 2 out of 30 instances of advice were scored as accepted, and at the short stay ward 4 out of 14. Moreover, the advice ‘monitor side effects’ (given in 9 cases) could not be verified either, because it was not a documented modification in therapy. This could be a possible explanation why the acceptance rate of 63% is rather low compared to other investigations. Two studies in which pharmacists gave dosages advice in case of impaired renal function showed an acceptance rate of 74% (141 of 191 recommendations accepted) and 88% (142 of 162 recommendations accepted) respectively [20,21]. In addition, the study of Silverman et al. reported an acceptance rate of 78.7%, 90.9% and 92.2% in their three different study periods [19].

Finally, another minor limitation of our study is that we did not consider the time element. With time measurement a better judgment can be made whether the found PPV and rule effectiveness is worthwhile for the efforts of the hospital pharmacist. We did measure time for a study that has not yet been published, also mentioned above, regarding a subpopulation consisting of elderly patients with polypharmacy. The amount of time measured required for ADEAS was an acceptable maximum of approximately 1 hour per day per hospital (unpublished data).
Results in relation to other studies

The percentage of safety alerts resulting in advice or intervention by the hospital pharmacist (10%) seems low, but is comparable to or even higher than other international investigations. Jha et al. investigated a commercial computerized surveillance system and found that in 30 (11.3%) out of 266 reviewed alerts the physician was contacted [22]. During a two month period, Kilbridge et al. evaluated 4604 triggers from a computer-based ADE surveillance system with rules of which 206 led to an intervention (4%) [23]. The intervention percentages found by Silverman et al. with their computer-based monitoring system with rules ranged from 5% to 13% [19]. In an earlier study we compared ADEAS with our conventional medication surveillance using only safety alerts from the Dutch national database G-Standard (basic CPOE safety alerts). The percentage of interventions with ADEAS was three times as high [14].

From our study, we can conclude that the variation of rule effectiveness and PPV among the categories of clinical rule was highly variable. However, this is observed in the literature as well. Kilbridge et al. reported a widely varied PPV, ranging from 0.00 to 0.67. The rule efficiency varied between 0.00 and 0.21. The highest PPV values were found for rules detecting ADEs (e.g. antidote order). The rules detecting evolving unsafe situations had lower PPV [23]. We did not use clinical rules triggering on antidote orders. Comparable numbers for PPV are found in the study by Silverman et al. The rule efficiency varied between 0.05 and 0.13. The authors determined that a realistic goal for created rules was a rule efficiency of 0.10 and an idealistic goal a rule efficiency of 0.20 [19]. Our rule effectiveness and PPV of ADEAS were 0.10 and 0.08 respectively. In themselves, these are promising figures indeed, but these figures could be increased if appropriate measures, such as enlarging the sensitivity or specificity of our clinical rules, are taken.

Meaning of the study

The combination of rule effectiveness and PPV was highest for clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients. The safety alerts in the CPOE are retrieved from the Dutch national drug database (the G-Standard). This database is used as a knowledge base for all pharmacy systems and CPOE systems within hospitals in The Netherlands. A problem with the safety alerts (drug–drug interactions, duplicate orders and overdosages) is that they are frequently overridden due to low specificity. The safety alerts also have low sensitivity [12,13]. In our own specifically designed set of clinical rules, we have fine-tuned these safety alerts to patients at risk of ADEs. For example, the safety alert for patients using the combination of a NSAID and ACE-inhibitors or ARBs is
most effective when considered in relation to the kidney function of the individual patient. In the basic CPOE a safety alert is always generated when the combination of the two drugs are prescribed. With ADEAS, the combination only generates an alert if the patient has a declined renal function (eGFR < 50 ml/min). This makes the drug–drug interaction alert more clinically relevant. ADEAS takes into account the renal function of the patient, where the basic CPOE does not. It is clear from this example that using ADEAS is preferred to using a basic CPOE only. Another example is a drug–drug interaction between a NSAID and a corticosteroid. The basic CPOE safety alert is generated always when both drugs are prescribed. ADEAS only generates an alert when a drug for ulcer prevention is absent. ADEAS takes into account the co-medication of the patient, while the CPOE does not. The use of this category of clinical rules improves the specificity of the alerts and therefore may help to decrease alert fatigue. That some other investigators have used this approach as well underlines the importance and usefulness of such an approach [24-26]. For example Seidling et al. suggests refining drug–drug interactions with statin-drugs by using an upper dose limit [25]. And Riedmann et al. searched for context factors, such as patient, prescriber/ward or alert characteristics, to prioritize drug–drug interactions [24].

In our study the highest number of consult and advice were given following alerts from clinical rules related to laboratory values (risk categories 1 and 2). This is in line with the observations in two of our other studies that show that the clinical rules linking laboratory and pharmacy information improve the sensitivity of the medication surveillance [14,27]. Other investigations also show that clinical rules related to laboratory values are suitable clinical rules that offer good results in detecting and preventing ADEs [20,21,28-30]. In our study the clinical rules related to laboratory values generated more than 50% of the alerts. They can be considered as most useful and promising rules. But as mentioned before, for better performance the rule effectiveness and PPV should be increased.

In the future we should focus on clinical rules from the three risk categories 1, 2 and 5 (‘clinical rules with a combination of pharmacy and laboratory data’ and ‘clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients’) to enhance the performance of ADEAS.

**Conclusion**

In conclusion, the CDS system ADEAS can effectively be used in daily hospital pharmacy practice to select patients at risk of potential ADEs, but to increase its benefit for routine patient care and to increase efficiency, both rule effectiveness and PPV for the clinical rules...
should be improved. Furthermore, clinical rules would have to be refined and restricted to those categories that are potentially most promising for clinical relevance, i.e. 'clinical rules with a combination of pharmacy and laboratory data' and 'clinical rules based upon the basic CPOE medication safety alerts fine-tuned to high risk patients'.

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References


