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Part IV
Clinical utility
Preventing adverse drug events in the elderly patient with polypharmacy by use of clinical rules and interventions by hospital pharmacists

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Submitted
Abstract

Introduction: The computerized tool Adverse Drug Event Alerting System (ADEAS) is a clinical decision support system for the pharmacy and is developed as a method for performing more sophisticated medication surveillance. ADEAS applies clinical rules and can be used to select patients at risk of an adverse drug event (ADE).

Objective: This study investigates the extent in which ADEAS based interventions by hospital pharmacists prevent ADEs.

Setting: Leiden University Medical Center (LUMC) on five different internal medicine and cardiology wards.

Design: Frequencies of ADEs were estimated at baseline period and during a period after implementation of ADEAS (intervention period). ADEs were identified by chart review using a trigger list. Patients 65 years of age or older and using five or more different medications at admission were included. During the baseline period only conventional medication surveillance was performed. During the intervention period conventional medication surveillance and ADEAS were used. Hospital pharmacist made preventive interventions based upon alerts generated by ADEAS.

Measurement: Primary endpoint was the number of preventable ADEs compared in both study periods.

Results: In the baseline period, 223 patients were included during 240 admissions. In the intervention period 236 patients were included during 248 admissions. In the baseline period 42 preventable ADEs (0.18 preventable ADEs per admission) were found compared to 27 ADEs (0.11 preventable ADEs per admission) in the intervention period (P < 0.01, Chi square test).

Conclusion: Use of ADEAS and subsequent interventions by the hospital pharmacists showed a significant reduction of preventable ADEs in our hospital.
Introduction

Patient safety remains an important issue and consequently preventing patient harm in health care settings is crucial. Prescribing drugs to cure patients or to relieve symptoms represent the most common medical intervention but Adverse Drug Events (ADE) also attribute considerably to patient harm. Different methods to prevent ADEs are described in the literature, such as barcode scanning of drugs and patients, clinical pharmacist interventions on ward rounds, use of computerized physician order entry (CPOE) with or without clinical decision support systems (CDSS) and the use of robots for drug dispensing [1]. It is suggested that computerized tools, such as CDSS, are one of the important tools to prevent ADEs [1-3]. With this aim we have developed the computerized tool Adverse Drug Event Alerting System (ADEAS) for selecting patients at risk of an ADE [4]. ADEAS is a clinical decision support system for the pharmacy and is meant as a sophisticated medication surveillance system. It applies clinical rules combining information from multiple electronic sources. ADEAS is more sophisticated than our conventional medication surveillance because it selects through the use of algorithms, the so-called clinical rules, the patients at risk of an ADE. In this way the hospital pharmacist can pay attention to the medication of that patient who needs it the most and make preventive interventions. The development of this expert system including the first set of clinical rules is described in detail elsewhere [4]. Briefly, ADEAS was composed in Gaston (Medecs BV, Eindhoven, The Netherlands), a guideline-based decision support framework, consisting of both a guideline development module and a decision support module. Selection of the potential patients at risk of an ADE occurs by combining data from the electronic patient file (EPF) (laboratory data, patient characteristics), the CPOE (prescribed medication) and the ‘G-standard’ (National drug data and drug-drug interaction database). The guideline development module in Gaston is used to create and support the clinical rules. The decision support module is used to link Gaston with our hospital information system for the required patient related information and to execute the clinical rules. The clinical rules were formulated in a multidisciplinary team using seven drug related risk categories [4].

In a previous study we compared ADEAS with our conventional medication surveillance procedures and showed that ADEAS has an additional value specifically in selecting patients at risk of an ADE and lead to more interventions by the hospital pharmacist [5]. The aim of the current study is to investigate the extent in which ADEAS based interventions by the hospital pharmacist actually prevent ADEs in elderly patients with polypharmacy in the clinical setting.
Methods

Setting and patients

The study was performed in Leiden University Medical Center (LUMC), a university hospital in Leiden, The Netherlands. The study was conducted on five wards: haematology, cardiology, combined lung/gastrointestinal diseases ward, and two combined internal medicine wards covering the specialism’s endocrinology, nephrology, infectious diseases, oncology, rheumatology and general internal medicine. Patients admitted to the five wards were included in the current study if they were 65 years of age or older and had five or more different medications at admission (polypharmacy). Exclusion criteria were admission less than 24 hours, scheduled admission for chemotherapy or Internal Cardiac Device (ICD) implantation. The study included 2 time spans: a 4-month baseline period, and a 3-month intervention period (see Figure 6.1). The length of the period was determined by the time it lasted until 250 consecutive patients were included in each period. During the baseline and intervention period the ADE measurements were performed. The hospital pharmacist made ADEAS-based intervention during the intervention period, and not during the baseline period. The period between the baseline and intervention period, the run-in period, was needed to get used to the ADEAS system and to update the system. During the entire study period all patients received standard pharmaceutical care which included conventional medication surveillance as described below.

The research protocol was submitted for consideration to the Medical Ethics Committee of the LUMC before start of the study. This Committee judged the protocol as not needing medical ethical approval. All data were collected anonymously.

<table>
<thead>
<tr>
<th>Baseline period</th>
<th>Implementation period (Run-in period)</th>
<th>Intervention period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard pharmaceutical care</td>
<td>Standard pharmaceutical care Testing and introduction of ADEAS</td>
<td>Standard pharmaceutical care Routine ADEAS + interventions hospital pharmacist</td>
</tr>
<tr>
<td><strong>Baseline measurement:</strong></td>
<td><strong>Intervention measurement:</strong></td>
<td></td>
</tr>
<tr>
<td>ADE collection by chart review</td>
<td>ADE collection by chart review</td>
<td></td>
</tr>
</tbody>
</table>

Figure 6.1 Outline study.
Standard pharmaceutical care

During the entire study period standard pharmaceutical care was given to all admitted patients in the hospital including those participating in this study. Standard pharmaceutical care is the same as our conventional medication surveillance and consists of daily retrospective checks by the hospital pharmacist of the drug-drug interaction and drug-overdosing alerts overridden during electronic prescribing by the physician. All the ignored and overridden alerts are collected in a Microsoft Access® database in the central pharmacy and the hospital pharmacists review these alerts the following day (except for the weekend, when the alerts are seen on Monday). If necessary, the hospital pharmacist checks laboratory values or co-medications, and selects potentially clinically relevant alerts to discuss with the prescribing physician. In addition, advices are given following therapeutic drug monitoring results.

Our hospital information system, Mirador® (iSOFT Nederland BV, Leiden, The Netherlands), includes integrated patient-specific data with demographics, laboratory results, discharge letters, medical diagnosis code, surgery reports, radiology reports and pharmacy orders. The CPOE system, Medicatie/EVS® (Medicator®) (iSOFT Nederland BV, Leiden, The Netherlands), is incorporated in Mirador and is described in detail elsewhere [6]. Briefly, Medicator provides online drug-drug interaction checks and drug-overdosing checks, but is not integrated with a sophisticated CDSS. The drug information on which the safety alerts are based is retrieved from a national drug information database the ‘G-standard’ (Z-Index BV, The Hague, The Netherlands). The ‘G-standard’ contains information about drugs available in The Netherlands and the majority of Dutch pharmacy information systems use this database to support medication surveillance, prescribing, dispensing, and pharmacy logistics.

Study design

The study is a prospective, non-randomized intervention study. During baseline and intervention period chart review was used to collect the number of ADEs during admission. An independent research pharmacist (YH for baseline period and MBJ for intervention period) manually reviewed the paper and electronic chart of all included patients using a paper trigger list. This list consists of clinical symptoms and laboratory abnormalities which may be an indicator of the presence of a drug-related ADE. This list was composed using information from the Dutch POEMS study, Dutch HARM investigation, the national drug information database the ‘G-standard’ and other literature references [7-9]. With this list ADEs were searched in the chart and if possible linked to the drug use by the patient.
For both baseline and intervention period all charts were evaluated independently by a second reviewer, an internal medicine specialist (HA) and all ADEs found by the research pharmacist were discussed. All ADEs were classified by the two reviewers (research pharmacist and internal medicine specialist) to the following criteria: causality, severity and preventability. Causality assessment was done using a simplified Yale algorithm, also used in the Dutch POEMS study [10]. Severity scaling was done using the Common Terminology Criteria for Adverse Events (CTCAE) system [11]. Preventability was independently judged by the clinical knowledge of the two reviewers. ADEs are considered preventable if they were due to an error. When there were disagreements that affected classification of an event, the two reviewers met and reached consensus. If consensus could not be reached, a third reviewer, a hospital pharmacist (MR or IT), evaluated the event.

**ADEAS based interventions**

ADEAS was introduced on the five study wards during a run-in period while no changes were made regarding performance of standard pharmaceutical care (see Figure 6.1). ADEAS was run every night selecting potential patients at risk based upon the clinical rules and output was generated in the pharmacy department every morning. In the weekends, the retrieved patients and alerts were collected on Monday. During run-in and intervention period 121 clinical rules were implemented into the system [5]. Additional case specific information was subsequently collected for each patient by the hospital pharmacist and used to assess the clinical relevance of the alert for the specific patient. Consequently, if necessary, interventions were made by the hospital pharmacist following alerts from ADEAS. ADEAS alerts were categorized as follows:

1. the alert needed no intervention because the alert was false positive or the alert was considered not clinically relevant for this specific patient (for example after dose check or laboratory control);

2. the hospital pharmacist consulted the physician or nurse (by phone or by ward visit) to discuss the alert, for clarification, which did not result in an advice to alter therapy or treatment;

3. the hospital pharmacist consulted the physician or nurse and they agreed that the patient was at risk of a possible ADE. This resulted in an advice aimed to prevent the possible ADE.

For the intervention period, the total number of alerts following ADEAS, the number of patients with an alert and the number of alerts in each category was calculated. Following alerts with advice the percentage of acceptance by the healthcare professional was scored.
Measurements

The primary endpoint was the number of preventable ADEs found in the baseline period compared to the number of preventable ADEs in the intervention period. As secondary endpoints the total number of ADEs (including causality and severity assessment), the number of alerts generated by ADEAS and number interventions by the hospital pharmacist were evaluated.

Statistics

Comparison of number of preventable ADEs between baseline and intervention group was made using chi-square test with 1 degree of freedom (df).

We expected an average of 15 preventable ADEs per 100 admissions, based upon results of the Dutch POEMS study [9,12]. Approximately 50% of ADEs in hospitalized patients were assumed to be preventable [13]. To detect a 50% reduction in ADEs (80% power at a 0.05 significance level) a sample size of 496 admissions equally distributed over baseline and intervention periods was needed.

Results

In the baseline period, 223 patients were included during 240 admissions (10 patients were excluded because retrospectively they did not meet the inclusion criteria). Sixteen patients were admitted twice and one patient was admitted three times during the baseline period. In the intervention period, 236 patients were included during 248 admissions (2 patients were excluded because retrospectively they did not meet the inclusion criteria). Thirteen patients were admitted twice during the intervention period. The patient characteristics are shown in Table 6.1. All patients were 65 years of age or older and had five or more different drugs at admission and stayed in the hospital more than 24 hours.

Table 6.2 shows the primary endpoint, number of preventable ADEs per admission. A total of 88 ADEs were collected in the baseline period in 70 out of 240 admissions (mean 0.37 per admission), compared to 97 ADEs in the intervention period in 70 out of 248 admissions (mean 0.39 per admission). In the baseline period 42 preventable ADEs (0.18 preventable ADEs per admission) were found compared to 27 ADEs (0.11 preventable ADEs per admission) in the intervention period (P < 0.01, Chi square test 1 df); a significant difference. Examples of preventable ADEs are constipation due to codeine and other opioids, worsening
of Parkinson disease symptoms due to start promethazine, hypokalemia during diuretic use and orthostatic hypotension due to levodopa-carbidopa overdosing.

Table 6.3 shows the number of ADEs divided per specialism. The causality, severity and preventability assessment of the ADEs are shown in Table 6.4.

**Results interventions ADEAS**

During the intervention period ADEAS generated in total 521 alerts. Most alerts (474, 91%) needed no intervention; after dose check or lab control the alerts were considered not clinically relevant for the specific patient (category 1). In 47 (9%) alerts (in 33 different
Table 6.3 Number of ADEs found with chart review per specialism

<table>
<thead>
<tr>
<th>Specialism’s wards</th>
<th>Baseline period: ADEs = 88 (0.37/admission)</th>
<th>Intervention period: ADEs = 97 (0.39/admission)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>36 (0.27/adm; 41%)</td>
<td>26 (0.18/adm; 27%)</td>
</tr>
<tr>
<td>Lung</td>
<td>19 (0.48/adm; 22%)</td>
<td>20 (0.74/adm; 21%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5 (0.42/adm; 6%)</td>
<td>4 (1.00/adm; 4%)</td>
</tr>
<tr>
<td>Hematology</td>
<td>3 (0.38/adm; 3%)</td>
<td>6 (0.60/adm; 6%)</td>
</tr>
<tr>
<td>General internal medicine*</td>
<td>--</td>
<td>12 (0.57/adm; 12%)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>3 (0.23/adm; 3%)</td>
<td>0</td>
</tr>
<tr>
<td>Nephrology</td>
<td>8 (0.89/adm; 9%)</td>
<td>27 (0.93/adm; 28%)</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>3 (0.50/adm; 3%)</td>
<td>0</td>
</tr>
<tr>
<td>Oncology</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>11 (0.73/adm; 13%)</td>
<td>2 (0.28/adm; 2%)</td>
</tr>
</tbody>
</table>

* Not included during baseline due to another pilot study.

Table 6.4 Causality, severity and preventability assessment of ADEs

<table>
<thead>
<tr>
<th>ADE criteria</th>
<th>Baseline period (N = 88)</th>
<th>Intervention period (N = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ -3 and &lt; 0 (unlikely)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>≥ 0 and ≤ +3 (possible)</td>
<td>15 (17%)</td>
<td>25 (26%)</td>
</tr>
<tr>
<td>+ 4 (probable)</td>
<td>73 (83%)</td>
<td>72 (74%)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – mild</td>
<td>13 (15%)</td>
<td>24 (25%)</td>
</tr>
<tr>
<td>2 – moderate</td>
<td>46 (52%)</td>
<td>41 (42%)</td>
</tr>
<tr>
<td>3 – severe</td>
<td>24 (27%)</td>
<td>20 (21%)</td>
</tr>
<tr>
<td>4 – life-treating or disabling</td>
<td>5 (6%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>5 – death related</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Preventability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not preventable</td>
<td>46 (52%)</td>
<td>70 (72%)</td>
</tr>
<tr>
<td>Possible preventable</td>
<td>18 (21%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Definitely preventable</td>
<td>24 (27%)</td>
<td>22 (23%)</td>
</tr>
</tbody>
</table>

patients) the hospital pharmacist consulted the physician (category 2 & 3). In 39 out of 47 consults the pharmacist gave additional advice to prevent the possible ADE (category 3). Sixteen advices were accepted by the nurse or physician (41%) and the remaining 23 advices were not accepted or it was unknown if they were accepted. The flowchart of the results with ADEAS is shown in Figure 6.2. The different types of advice given by the hospital pharmacist are shown in Table 6.5.
Table 6.5 Types of advices following alerts from ADEAS during intervention period

<table>
<thead>
<tr>
<th>Type of advice</th>
<th>Number of alerts with advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose adjustment</td>
<td>16</td>
</tr>
<tr>
<td>Stop medication</td>
<td>1</td>
</tr>
<tr>
<td>Change medication</td>
<td>4</td>
</tr>
<tr>
<td>Monitoring side effects</td>
<td>2</td>
</tr>
<tr>
<td>Take drugs separately</td>
<td>8</td>
</tr>
<tr>
<td>Add medication</td>
<td>8</td>
</tr>
<tr>
<td>Therapeutic drug monitoring</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>41*</td>
</tr>
</tbody>
</table>

* 2 patients had two advices: dose adjustment or stop medication and dose adjustment and monitoring side effects.

Figure 6.2 Results alerts with ADEAS during intervention period.
Discussion

This study shows that the ADEAS based interventions by the hospital pharmacist were effective in reducing the number of possible and definitely preventable ADEs. The number of preventable ADEs was significantly lower in the intervention period compared to the baseline period. However, the total number of ADEs before and after implementation of ADEAS remained constant.

The finding that the number of preventable ADEs is lower in the intervention period, is in line with our expectations. In the intervention period ADEAS was used, and ADEAS is designed to select patients with a potential ADE. Alerts generated by ADEAS lead to an action by the hospital pharmacist regarding the patient at risk, which could have prevented the ADE. Potential ADEs, in contrast to actual ADEs, are medication errors with the potential to cause injury but which do not necessarily cause any injury [8,14]. Medication errors, or extrinsic harm, are related to the manner the drugs used and can be prevented by interventions more easily. In particular, ADEs due to error or negligence are preventable [15]. Indeed, the alert system ADEAS contains clinical rules that search for these situations, such as medication dosages not adapted to a declined renal function, an opioid agonist prescribed without a laxative or a drug-drug interaction between cyclosporine and voriconazol without therapeutic drug monitoring.

In contrast to the number of preventable ADEs, the total number of ADEs was equal in the baseline and intervention period, caused by a higher number of non-preventable ADEs in the intervention period. Non preventable ADEs, also referred to as intrinsic harm or adverse drug reactions, are the result of the pharmacological properties of the drug itself [3]. An explanation for this can be the non-equal distribution of specialisms between baseline and intervention period. The inclusion of all consecutively admitted patients who met the inclusion criteria resulted in this non equal distribution of specialisms. In the intervention period more patients were admitted at the nephrology and general internal medicine department. The fact that more patients were admitted at the nephrology department in the intervention period could have had an influence on the relatively large proportion non-preventable ADEs in the intervention period. Indeed in the intervention period 27 ADEs were found in patients admitted to the nephrology department compared to 8 in the baseline period. At the nephrology department mostly kidney transplant patient are admitted which use immunosuppressive medication causing frequently adverse drug reactions which are by definition unpreventable. For example in the intervention period 8 non-preventable ADEs were found regarding hyperglycaemia and deregulation of diabetes mellitus due to
prednisolone. The median length of stay and the study population, the elderly patient with polypharmacy, was equal in baseline and intervention period.

The number of ADEs per admission in the baseline period and the percentage considered preventable in our study is comparable with ADE rates found in the literature [13]. The Dutch POEMS study found 15 preventable ADEs per 100 admissions [9,12]. We found a comparable number of 17.5 possible or definitely preventable ADEs per 100 admissions in the baseline period. Due to our ADEAS based interventions this number declined to 11 possible or definitely preventable ADEs per 100 admissions, a 37% reduction.

This study does not allow to indirectly compare ADEAS to the effects of other interventions aimed at reducing medication errors or ADEs. Most studies investigating the effect of CPOE and CDSS on medication errors and ADEs differ substantially in their setting, design, quality and thus, their results [16]. However, it seems that the use of CPOE and CDSS can reduce ADEs [2,16,17]. For example, implementation of CPOE with basic CDSS in two Dutch hospitals reduced the incidence of medications errors but did not demonstrate a direct effect on actual patient harm [9]. In addition, a computerized reminder system that used rules to alert physicians of using four preventive therapies (pneumococcal vaccination, influenza vaccination, subcutaneous heparin and aspirin at discharge) showed a significant increase in the rate of delivery of such therapies [18].

A limitation in our study is the use of chart review to search and detect ADEs. The incidence rates of ADEs have shown to be dependent on the method of detection used [19]. However, we choose chart review because it is a well-known and classical way of adverse (drug) event detection [15,20]. More importantly, studies comparing different methods of ADE detection found that chart review was more effective in detecting events manifested primarily by symptoms, such as change in mental status, nausea and vomiting, rigors and hypotension and less effective in detecting changes in laboratory values [19,21]. Clearly, most ADEs will be found with a combination of methods. For that reason, we used a paper trigger list with symptoms and laboratory abnormalities in combination with review of paper and electronic charts.

Another limitation of our study is that we used two different research pharmacists to perform chart review for the baseline and the intervention period. This may have attributed to the difference in number of ADE between the two periods. But both persons used the same trigger list, same clinical research form and same instruction and the second reviewer, the internal medicine specialist, was the same in both periods. We also did not estimate interrater scores for ADE, causality, severity and preventability assessments. Indeed, the Dutch POEMS
study showed that there was only fair agreement on the assessment of preventable ADEs, and it was suggested that the best practical solution is a combination of a pharmacist and a physician for scoring, like we used in our study [10]. We agree with Haynes et al. that it is still a challenge to assess ADEs incidence in a reliable way [22]. Despite the fact that many other variables such as patient characteristics and setting, may influence ADE rates, we found comparable numbers as reported in the literature. Therefore, we believe that inter observer variability may have played only a minor role in our current study.

In our study confounding bias cannot be ruled out since the performance of the study may have led to more awareness related to medication safety.

A relatively small number of the clinical rules active in the system ADEAS resulted in alerts, and the “potential ADE capture rate” of some clinical rules was not high. Only 9% of the alerts resulted in an action by the hospital pharmacist. The other 91% of the alerts needed no intervention, but frequently dose checks and lab control were performed by the hospital pharmacist. For example a rule regarding the combination of a drug and a declined renal function can result in no intervention when the dosage of the drug is already correctly adapted. But still it is a useful clinical rule with alert that leads to a check by the pharmacist. Maybe our set of clinical rules needs some adaptations and modifications in order to further enlarge the amount of positive alerts, for example special clinical rules for elderly patients or transplantation patients. Adapting the content of the rules during use is an acceptable way to enlarge the positive predictive value for the clinical rules [23]. With smarter clinical rules, the added value of ADEAS in detecting patients at risk can even be increased.

Overall we can conclude that the use of the clinical decision support system ADEAS for the pharmacy which combines patient data and drug information available from multiple sources, helps to reduce preventable ADEs and to improve patient safety.

Acknowledgements

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References


