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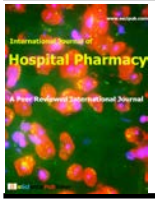

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Assessing the strengths and weaknesses of a computer assisted medication review in hospitalized patients

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ABSTRACT

Introduction: Medication reviews are an essential part of daily routine at a hospital ward but are prone to mistakes. With this study we want to assess the strengths and weaknesses of a Clinical Decision Support System (CDSS) and evaluate the additional value on the reduction of medication errors compared with manual medication reviews. **Materials and Methods:** We gathered all remarks related to (potential) errors in the current medication regime (notifications) regarding medication errors for 332 patients from 12 grand rounds of the internal medicine ward and orthopedic ward at the Maastricht University Medical Centre during four months. Simultaneously, we electronically extracted data regarding the patient's medication list, laboratory data and patient characteristics and entered these data into our CDSS. **Results and Discussion:** One hundred thirty-eight notifications were made during grand rounds. One-hundred and seventy-nine relevant alerts were reported by the CDSS. Only three of the relevant notifications were reported by both. Overall, errors regarding indication without medication and medication without

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indication were most frequently noticed during grand rounds and contraindications or side effects were most frequently noticed by the CDSS. The CDSS may be a relevant addition to the manual performed medication reviews in the hospital. The strength of the present CDSS lies in the detection of errors regarding contraindications and side effects. Future developments include optimizing the cut off values at which the CDSS should provide an alert is an important next step in improving the CDSS. Additionally, in order to increase notifications about indication without medication and medication without indication, the medical history should be incorporated into the CDSS. Finally, relevance on patient outcome should be determined.

KEYWORDS: Clinical decision support system, clinical rules, medication review, medication safety, polypharmacy

INTRODUCTION

Medication management is an essential part of the daily routine at hospital wards. The rising incidence of multi-morbidity and consequently polypharmacy adds to the complexity of the prescribing process. Polypharmacy is one of the main risk factors of medication error and drug-drug interactions,[1-4]. Especially in hospitalized patients, changes in pharmacokinetics, pharmacodynamics and a variability in response to medicines may occur, also contributing to the risk of contra-indications, interactions and side-effects. During hospitalization, medication errors are one of the most common type of adverse events that occur, [5, 6]. They are associated with a prolonged hospital stay, higher mortality rate and increased costs,[7]. A recent nationwide Dutch study showed that adverse events occurred in 21% of patients. Of all adverse events, 15.2% were identified as medication related, and 18% of these were considered preventable,[8]. Aljadhey and colleagues described 30% of adverse drug events as preventable. Even more, they considered 59% as significant, 35% as serious and 6% as life threatening, [9].

A medication review is a widely used method to evaluate a patient's medication list with the intention to support evidence based prescribing and optimize therapy in a structured way. It is a critical evaluation based on the clinical judgment of a physician and/or pharmacist by using available information such as clinical, pharmaceutical and laboratory data [10]. Especially when reviewing complex hospitalized patients and/or patients with polypharmacy these medication reviews are prone to mistakes. Increasing the knowledge about, and availability of laboratory data and patient's medical history improves manual medication reviews. Nevertheless, susceptibility to a significant amount of error remains,[11]. Also, an adequate medication review is a time-consuming process. Physicians indicate that the work load is the most restricting factor in performing a proper medication review,[12]. In addition, medication often changes during hospitalization requiring a continuous monitoring process.

To improve medication safety, several clinical decision support systems (CDSSs) have been developed and implemented,[13, 14]. Studies with these systems have shown promising improvements of the physician's performance and a reduction of medication errors. Decision support systems can help to monitor these errors but can also help to educate professionals by providing links to guidelines when a drug is prescribed. A major challenge in developing a CDSS is the implementation of the system in daily practice,[15, 16]. Factors associated with failure to implement a CDSS are user's dissatisfaction, disruption of workflow, failure to integrate the CDSS with the electronic patient data, low specificity and sensitivity of the alerts given by the CDSS, burden of manual data

entry, incompatibility with guidelines, system immaturity and failure to update,[15, 16].

We have developed a clinical decision support system that takes into account these implementation challenges [17, 18]. The CDSS monitors all prescribed drugs continuously and independently from the prescribing software, while taking into account co-medication, patient characteristics and laboratory data. The aim of this study was to assess the strengths and weaknesses of the CDSS and to evaluate the additional value of our CDSS to manual medication reviews on medication errors in all patients admitted to the internal medicine ward and orthopedic ward.

MATERIALS AND METHODS

The CDSS has not been implemented as standard care in clinical practice yet. In this pilot study, data were gathered by observation of the medication reviews during the weekly grand rounds at the internal medicine and orthopedic ward of the Maastricht University Medical for four months. The grand round is a comprehensive meeting of all medical and paramedical personnel involved in treatment of patients at a specific ward (in contrast to the normal rounds where only the attending resident checks upon patients and performs medication reviews). During these grand rounds, every individual patient was discussed with regard to reason for admission, clinical course, vital signs, laboratory parameters, other diagnostics and medication in order to establish a treatment plan. The medication review was a discussion about the effectiveness, appropriateness, possible side effects, duration of treatment and so on of every individual medicine in all individual patients. Attending physicians were not informed of the purpose of the observation and the observer did not participate in the medication review. Furthermore, other physicians involved in the study did not take part in the grand rounds. The independent observer's purpose was to gather all remarks that identify (potential) medication errors (notifications) and these were classified according to 7 categories, *i.e.* indication without medication, medication without indication, contraindications/ interactions/ side-effects, dosage problems, double medication, wrong medication and therapeutic drug monitoring [19, 20]. For the purpose of this study, up-to-date patient data including medication list, patient characteristics and laboratory data on the morning before the grand rounds were extracted from the electronic patient file and run through and analyzed by the CDSS. This resulted in notifications as explained below. The grand rounds were performed by the attending physicians, unaware of the review by the CDSS (Clinical Rule Reporter, Digitalis Ltd) or the goal of the independent observer. This aimed to maintain an unbiased care as usual performance of the grand rounds. In accordance with the Central Committee on Human Research (CCMO), the Dutch Medical Research in Human Subjects Act (non-WMO) is not applicable for this study.

All notifications obtained during the grand rounds observation and the notifications provided by the CDSS were further classified as relevant or not. The relevance of the notifications was determined by the authors KH and WM, first independently and subsequently in a case by case discussion until consensus was obtained. A notification was considered relevant by the authors when it should result in immediate medication changes. Relevant notifications were used for further analysis. Relevant notifications that were only made by the CDSS were considered to have been of additional value.

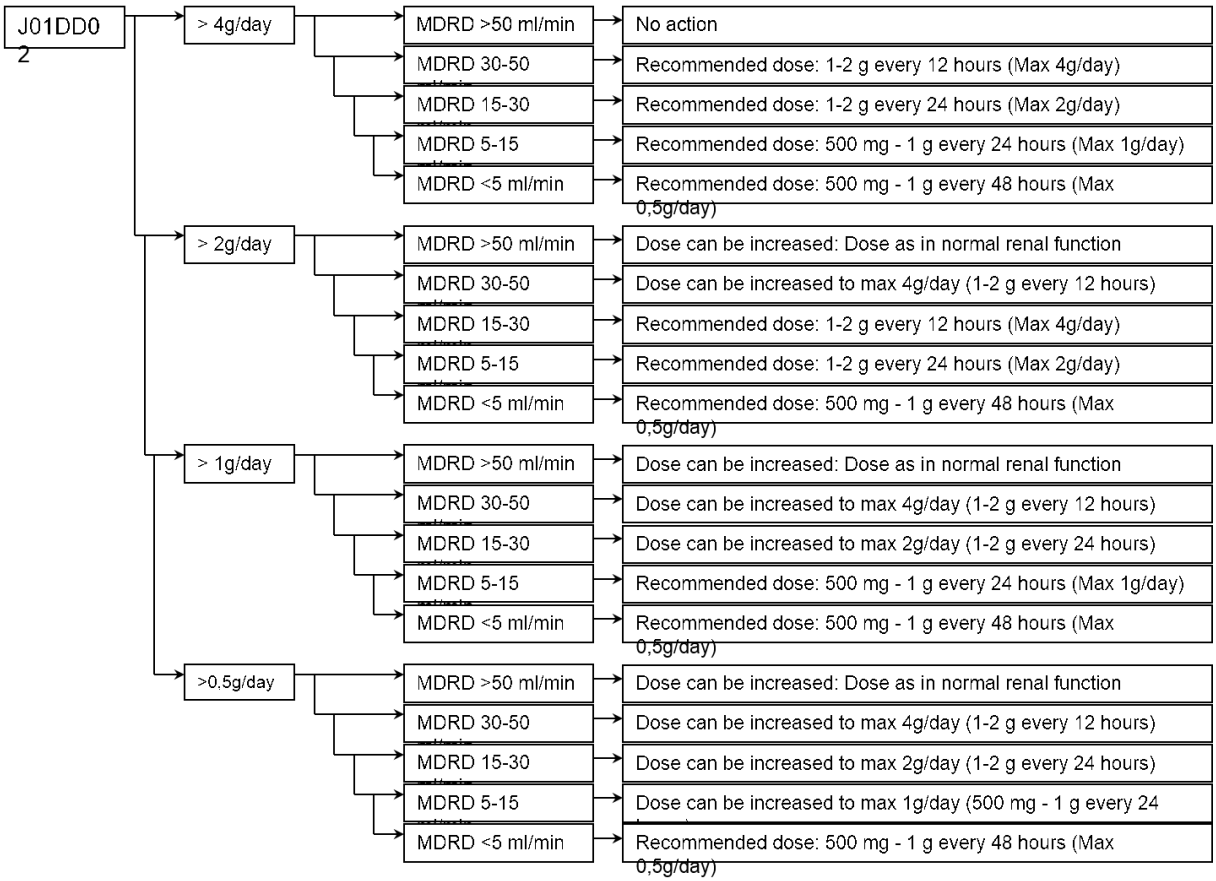
Notifications were subdivided into error types (indication without medication, medication without indication, contraindications/ interactions/ side-effects, dosage problems, double medication, wrong medication and therapeutic drug monitoring). Also, all notifications were subdivided into medication groups (e.g. concerning antibiotics, anticoagulants, diuretics, antidepressants and so on). Next, differences between the results from the grand rounds and the analysis by the

CDSS were compared regarding these error types and medication groups. Finally, we considered possible differences in additional value of the CDSS between the orthopedic ward and internal medicine ward.

The Clinical decision support system

The CDSS has been described in detail previously [17, 18]. In short, a clinical rule is an algorithm that analyses drugs based on the actual risk profile of a patient using current patient data such as laboratory data, age, sex and contraindications. An example of a clinical rule is given in figure 1. The CDSS consists of two separate software items: a clinical rule reporter (CRR) and a clinical rule engine (CRE). The clinical rule reporter is responsible for combining the data for each patient from the extraction files, anonymization and sending it to the CRE. When the CRE returns a reaction, the CRR will display the data in the context of the patient. The CRE is running on a platform and will run through the decision trees. The software has been developed by Digitalis Ltd. The content (decision trees) has been developed by the research group SCREEN. Data from the EHR (laboratory value, weight, age, gender and contra-indications) are converted to a .CSV file which is used by the CDSS.

Figure 1: Example of a Clinical Rule of Ceftazidime**.**



J01DD02= ATC code for ceftazidime, g=grams, mg= milligrams, MDRD= formula to estimate glomerular filtration rate

The clinical rules were developed for an adult population by an expert team consisting of hospital pharmacists, internists, a nursing home physician and a neuropsychiatrist and were based on national guidelines, protocols and important recent studies (Supplementary material A). Emphasis has been put on medication frequently used or contraindicated in older patients. The CDSS consisted of 469 clinical rules developed for both nursing homes and hospitals.

Background process of the CDSS

The CDSS starts from a trigger file containing Anatomic Therapeutic Chemical Classification codes (ATC codes) or the international codes of primary health care (ICPC codes). After the first trigger (e.g. ATC code or ICPC code) the CDSS searches for relevant laboratory data and patient characteristics such as age or weight. For example, when a patient is using cefuroxime and renal function is normal, no notification will be given. However, when there is a mismatch in renal function and the dosage of cefuroxime, the physician will be automatically notified including a dosage advice. As such, the clinical rule is created only to provide a notification when medication and clinical parameters are discordant. The CDSS continuously checks for the use of cefuroxime and renal function. So when the renal function changes during the next days in such a way that dose modification is necessary, a new notification will appear with a new dosage advice. In this way a tailor-made advice per drug per moment per patient is given. The CDSS takes 33 laboratory data into account (figure 2).

Figure 2: Laboratory values incorporated in the CDSS

alkaline phosphatase
alanine aminotransferase
aspartaat aminotransferase
albumin
carbamazepine
cyclosporin
C-reactive protein
creatinine
digoxin
erythrocyte sedimentation rate
estimated glomerular filtration rate
gamma glutamyl transpeptidase
gentamycin peak level
gentamycin trough level
glucose
leukocytes
lithium
phenytoin
phenytoin free fraction
potassium
prothrombin time (International Normalized Ratio)
prothrombin time (seconds)
sodium
tacrolimus
theofylline
thrombocytes
tobramycin peak leve
tobramycin trough level
valproic acid
vancomycin peak level
vancomycin trough level

The CDSS performs automatic and continuous controls of possible medication problems (described also in more detail previously)[21] and alerts the physician when the notification requires action.

Statistical analysis

The statistical analysis was performed with IBM Statistical Products and Service Solutions (SPSS) Statistics 22,[22]. Numerical variables were presented as means (standard deviation, SD). Nominal variables were given as absolute numbers (percentage). Comparison of nominal variables were performed with McNemar's test for paired comparisons (grand rounds versus CDSS) and Chi-squared test for unpaired comparisons (internal medicine versus orthopedics). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Data were obtained from 12 grand rounds at the internal medicine ward and four grand rounds at the orthopedic ward. In total 332 patients were reviewed, 219 at the internal medicine ward and 113 at the orthopedic ward. Mean age of patients on both wards was 67 years (SD 19). Patients used a mean number of nine (SD 5) drugs at the internal medicine ward and ten (SD 4) drugs at the orthopedic ward. One hundred and thirty eight notifications were made during the grand rounds. On the other hand, the CDSS performed 3269 checks. A total of 3030 controls check were performed at the background without reporting an error. However, 239 were reported as notifications, based on the clinical rule algorithm. Overall, 377 notifications were made during the grand rounds and CDSS including four similar notifications (figure 3 and 4).

Figure 3: Number of patients and notifications during grand rounds and from the CDSS

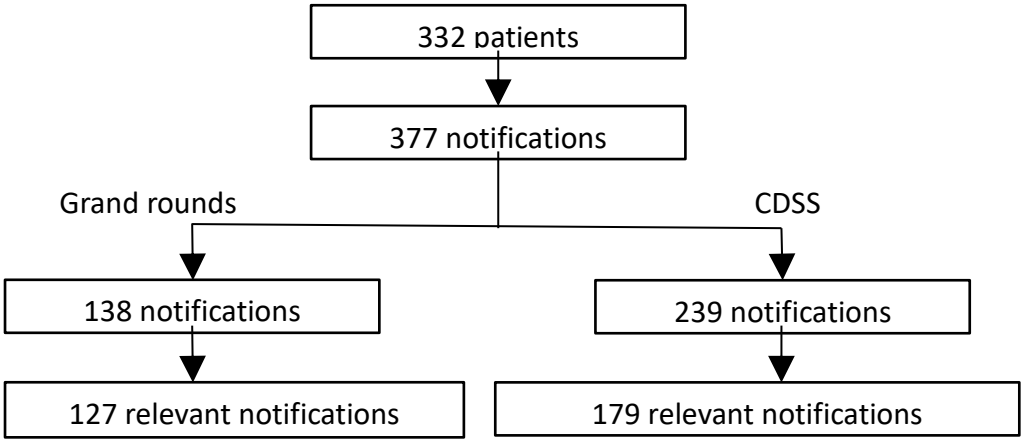
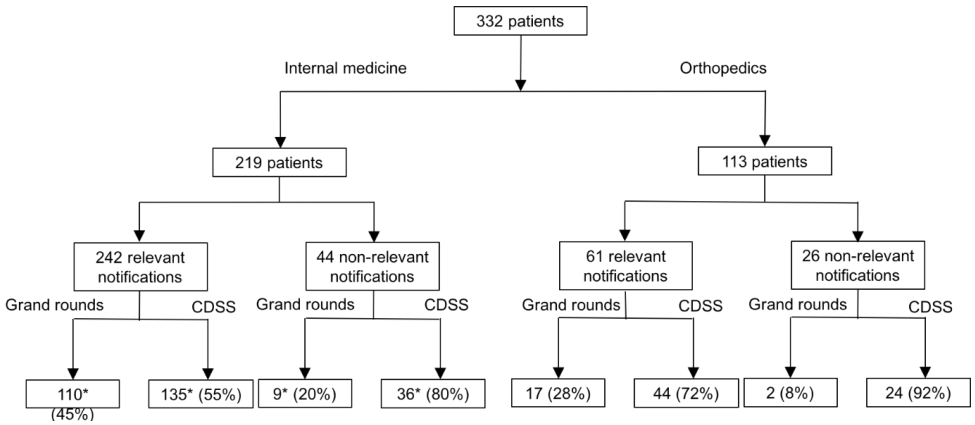


Figure 4: Number of patients and relevant notifications during grand rounds and from the CDSS according to department



*3 relevant notifications made in both grand rounds and by the CDSS *1 non-relevant notification made in both grand rounds and by the CDSS

After analyzing the individual notifications by KH and WM, 303 (81.2%) were considered relevant. The non-relevant notifications of the CDSS mostly resulted from clinical rules that were too strict, often only providing a pre-warning (e.g. the alert that a potassium altering drug was administered whereas the laboratory levels were normal). Ultimately, 179 of 239 (75%) of the notifications of the CDSS were considered relevant and 127 of 138 (92%) of the notifications from the grand rounds (figure 3). Furthermore, 242 (80%) unique notifications were made at the internal medicine ward and 61 (20%) at the orthopedic ward. At the internal ward, 135 (55%) notifications were provided by the CDSS and 110 (45%) obtained during the grand rounds (where three notifications were made by both). At the orthopedic ward, the CDSS reported 44 (72%) of notifications vs 17 (28%) during grand rounds (where no notifications were made by both) (figure 4). Relative to notifications from the grand rounds, the CDSS reported significantly more medication errors at the orthopedic ward than at the internal medicine ward (p=0.020) (table 1).

Table 1: The additional value of the CDSS at the internal medicine and orthopedic ward

Department	Total	Relevant notifications grand rounds (%)	Additional value CDSS (%)
Internal medicine	242 (100)	110 (45.4)	132 (54.5)
Orthopedics	61 (100)	17 (27.9)	44 (72.1)
Total	303 (100)	127 (41.9)	176 (58.1)

Overall, indication without medication (type one medication error) (59 of 303; 19%), medication without indication (type two medication error) (48 of 303; 16%) and contraindications/ interactions/ side effects (type three medication error) (102 of 303; 34%) occurred most frequently. Type one and two medication errors were most frequently noticed during the grand rounds (28 of 127; 22% and 48 of 127; 38% respectively) whereas type three medication errors were most frequently noticed by the CDSS (88 of 176; 50%, p<0.001) (table 2).

Table 2: The additional value of the CDSS with regard to type of medication errors

Type of error	Total	Relevant notifications grand rounds (%)	Additional value CDSS Yes (%)
Indication without medication	59 (100)	28 (47.5)	31 (52.5)
Medication without indication	48 (100)	48 (100)	0 (0)
Contraindications/interactions/side effects	102 (100)	14 (13.7)	88 (86.3)
Dosage problem	44 (100)	14 (31.8)	30 (68.2)
Double medication	6 (100)	3 (50)	3 (50.0)
Wrong medication	10 (100)	10 (100)	0 (0)
Therapeutic drug monitoring	34 (100)	10 (29.4)	24 (70.6)
Total	303 (100)	127 (41.9)	176 (58.1)

The greatest additional value of the CDSS was seen for diuretics and gastric protection whereas suggestions about analgesics were most frequently made during grand rounds (table 3).

Table 3: The additional value of the CDSS with regard to medication groups

Medication group	Total	Relevant notifications grand rounds (%)	Additional value CDSS Yes (%)
Anticoagulants	48 (100)	22 (45.8)	26 (54.2)
Antibiotics	33 (100)	19 (57.6)	14 (42.4)
Gastric protection	29 (100)	7 (24.1)	22 (75.9)
Analgesics	26 (100)	20 (76.9)	6 (23.1)
Diuretics	22 (100)	3 (13.6)	19 (86.4)
Other	145 (100)	56 (38.6)	89 (61.4)
Total	303 (100)	127 (41.9)	176 (58.1)

DISCUSSION

This study provides evidence for the additional value of a CDSS to the medication reviews as currently performed during grand rounds. Although the added value of the CDSS was most prominent for the orthopedic ward, the CDSS was also undeniably important for the internal medicine ward considering the high amount of relevant notifications in addition to the notifications made during grand rounds.

Improving the CDSS

The similarities between relevant notifications made during grand rounds and the CDSS were minimal. This could be explained by the fact that some relevant notifications made by the CDSS may have been considered during the grand rounds but were discarded as not relevant at that moment. For instance, when the patient was using a SSRI and the sodium level was 129 mmol/l, only marginally low, the CDSS would alert the physician while during the grand round this sodium level might have been noticed but did not immediately alarm the physicians. Perhaps a fixed cut-off value is not always significant, but a percentage change in a certain value may be more useful in clinical practice, [23]. On the down-side, relying solely on percent changes of laboratory values may only detect events at a late stage.

The total percentage of relevant notifications from the CDSS for both wards at the time of the study was 75%. Conversely, one quarter of the notifications were ultimately judged irrelevant. When used in clinical practice, a high number of irrelevant remarks may result in physicians and pharmacists being desensitized to alerts and ignoring even clinically relevant remarks, [24]. Furthermore, following the advice of irrelevant alerts may even result in adverse outcome, [25]. It can lead to overriding or ignoring up to 49-96% of all notifications, [26]. This could jeopardize the clinical effectiveness of a CDSS, [27]. The prevention of alert-fatigue is more complex than just using proper clinical rules. It also involves physicians' willingness to use the CDSS, knowledge of drugs, the format in which alerts are given and so on, [26]. These challenges should all be considered before implementing a CDSS.

The CDSS reported more relevant notifications regarding side-effects, contraindications and interactions. Most frequent notifications that were made by the CDSS and not reported during grand rounds were the advice to add a proton pump inhibitor (PPI) when a patient was taking non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid, or the use of diuretics in combination with hyponatraemia, hypokalaemia or decreased kidney function. During the grand rounds relevant notifications concerning medication without indication or indication without medication were made most frequently. For this type of notifications, knowledge about

medical history is needed. The current version of the CDSS is not linked with the patient's medical history. It can be expected that this addition would also enable the CDSS to detect errors concerning medication without indication and indication without medication. To date, to the best of our knowledge this study seems to be the first that makes clear that the CDSS also misses alerts. Whereas present studies focus on the alert fatigue or so called false-positives, not reporting of important alerts may be even more serious. An important reason for not providing insight into underreporting comes from the fact that present studies do not directly compare manual medication surveillance with a CDSS in the same patient population, [28, 29]. Controls usually consist of a different population or a historical cohort. The CDSS relies on the data-input from electronic health records (EHR). Thus the EHR should be kept up to date and readily accessible for the CDSS.

In addition to supporting medication reviews, the CDSS aims to reduce the workload invested in this process. Nevertheless, workload will likely be transferred from the physician performing the manual medication review to the pharmacist, updating and controlling the CDSS. This must be further optimized before implementing the CDSS in clinical practice. An important role seems to be put aside for the suppression of irrelevant remarks, [30]. To guarantee satisfaction of physicians it is also important that the timing of presenting the notifications to the physicians is accurate, e.g. that the notifications are not presented too late,[13, 31, 32].

Manual medication surveillance

This study aimed to focus on the strengths and weaknesses of the CDSS. However, the results also show the importance of the manual medication review. It still remains one of the cornerstones of medication surveillance. This study shows that around half of the medication errors were uniquely detected by manual reviewing, i.e. case based discussions by caretakers. Fully replacing this by computerized surveillance is not the primary goal of the CDSS, since it will lead to a substantial loss in detecting medication errors when taking into account the results of the present study. Additionally, clinical judgement of patients' health status is learned after years of experience, and cannot be taught to a computer. Clinical decision support systems will never replace the manually performed medication review but it is our expectation that such a system will aid the physician in performing higher quality reviews in shorter time. Ultimately both methods should complement each other. The CDSS will work as a continuous program, checking for medication errors at the background. In addition, the manual review can be done periodically (weekly) and has the advantage of including the subtleties of a patient's clinical presentation, a factor that cannot be included into a computer model. Because the CDSS will run day and night many errors will already be excluded. Consequently, fewer errors are needed be discovered during the grand rounds, and it enables the physicians to focus on more detailed and specific patient situations.

Future possibilities and challenges

The CDSS performed an additional 3030 controls that were not reported to the physician (when dosage of a drug is in accordance with renal function, NSAIDs administered in combination with PPIs). The CDSS records which notifications are made, reported to the physician and which notifications prompted medication alterations by the physician making the medication surveillance transparent. The CDSS can check medication lists continuously, enabling the performance of a multitude of checks. When the CDSS performs these processes at the background the manual medication surveillance can become more focused on other specific challenges during drug treatment. Previous studies showed that systems in which the physician had to enter all data manually were less likely to succeed and performed no better than physicians who did not use the CDSS,[13, 15]. Also, manual data entry can cause incomplete and incorrect registration

and consequently lead to an inferior CDSS. Systems that operate automatically and do not have to be activated by physicians have proven to be superior,[14].

For future research, it could be interesting to see whether personalizing the CDSS leads to better medication reviews. One could argue that different kind of physicians require different sets of clinical rules. For example, for an orthopedic surgeon and for an internist, different kinds of medication notifications might be relevant. Also, the setting (hospital versus nursing home) wherein the CDSS is used, plays an important role in the relevance of certain notifications. Finally, the clinical education and experience of the physician could be taken into account in what kind and number of clinical rules are active. An experienced resident or specialist requires less help than a beginning resident. During medical school much is learned about drugs, their uses, adverse events, complications and so on. However, additional insights are continuously renewed and it may be difficult to keep up to date with current knowledge. The present CDSS will also provide links with guidelines, recent studies and so on, which are readily accessible. The CDSS can than go beyond being a passive computerized provider order entry system, giving direct feedback to possible uses and side effects regarding prescribed drugs. As such, the CDSS can be used as a training tool for medical professionals. We believe that this will be especially useful for less experienced physicians. Also an optimal CDSS may stimulate adherence to guidelines and therefore creating uniform care,[33].

The clinical rules in the system were based on national guidelines, protocols and important recent studies. While developing the CDSS, we strived to implement most relevant evidence. Nevertheless, it should be considered that studies can produce conflicting evidence. Thus, the CDSS may report notifications that ultimately are not fully supported by every physician. For example, an important debate revolved around the use of a PPI in combination with acetylsalicylic acid in patients of 60 years and older, where the CDSS encouraged the addition. Indeed there are studies and guidelines that support the addition of PPI when using acetylsalicylic acid but one could argue that the evidence on which these guidelines are based is limited and the effect of PPIs on ulcer complications questionable,[34-36].

The main challenge for the development of the CDSS remains to prove its positive impact on clinical outcome. At present, this has not been proven adequately, [14, 37]. Studies have mainly focused on the medication errors they are able to detect but not on health. A major challenge lies in the relatively low number of preventable adverse drug events, grossly 4% of all adverse events, which even do not all lead to clinical adverse events, [6, 8]. A large study population would be needed and followed thoroughly over a significant period of time.

Limitations

Some limitations of this review should be appreciated. This study did not observe the effect on patient level. The main goal of this pilot study has been to assess the strengths and weaknesses of the CDSS and evaluate the type and amount of medication errors that it detects in addition to the medication errors detected during the grand rounds. To date, it would be important to know whether all relevant alerts resulted in changes in treatment and vice versa if all treatment changes had resulted from relevant notifications. To prove the true value of the CDSS, subsequent studies need to focus on the clinical effects on patient outcome. Moreover, considering the limited amount of patients included in this pilot, a larger patient group should be included to make an adequate assessment of type of medication errors and perform a more in-depth analysis of medication groups. Since the grand rounds were not taped and notifications only scored on paper, some relevant notifications might be missed or fraught to interpretation. Additionally, the study focused on the medication review at the orthopedic and internal medicine ward. This limits the possibility

of extrapolating the results. All in all, the next step should be optimization of the CDSS with subsequent analysis of its value on patient level in larger patient populations.

On average the patients of the internal medicine and orthopedic ward used nine and ten drugs per person, respectively. Because polypharmacy e.g. the chronic use of five or more different drugs on a daily basis, is one of the strongest predictors of medication error, this strongly supports our view that a proper medication review is essential.

CONCLUSIONS

The CDSS may be a relevant addition to the manual performed medication reviews in the hospital. Future developments include adding medical history to the clinical rules, fine-tuning the CDSS and determine relevance on patient outcome. Even when the CDSS is implemented its improvement remains an iterative process.

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The authors declare that they have no competing interests.

All authors have made a substantial contribution to the conception and design of the study, acquisition of the data, analysis and interpretation of data, drafting the article and/or revising it critically for important intellectual content. All approve the final version. All authors accept Non-Disclosure Agreement.

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