Development and implementation of medication-related clinical rules for obstetrics, gynaecology, and paediatric outpatients

Quanyao Chen ⓘ , Luwei Wang, Min Lin, Weida Chen, Wen Wu, Yao Chen

Department of Pharmacy, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, Fujian, China

Correspondence to
Dr Yao Chen, Department of Pharmacy, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, Fujian, China; chenyaoxm@126.com

QC and LW contributed equally.

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ABSTRACT

Objectives Prescription errors can cause serious adverse drug events. Clinical decision support systems prevent prescription errors; however, real-time clinical rules in obstetrics, gynaecology, and paediatric outpatients remain unexplored. We evaluated the effects of localised, real-time clinical rules on alert rates and acceptance rates compared with manual prescription review.

Methods We developed real-time clinical rules that incorporate information systems to obtain characteristic information and laboratory values. We conducted a retrospective cohort study to compare the alert and recommendation acceptance rates of all prescription error types before and after clinical rule implementation in obstetrics, gynaecology, and paediatrics. Clinical rules, prescription error types, and alerts were determined by a prescribing review committee comprising physicians, pharmacists, nurses, and administrators. The difference in alert and acceptance rates between the groups was analysed using relative risk.

Results The number of alerts increased after clinical rules implementation; the number of on-duty pharmacists for review decreased from 10 to 2. Compared with those with manual review, the alert rates for paediatrics and obstetrics and gynaecology increased with the clinical rules by 3.97- and 11.26-fold, respectively, and the alert rates for drug–drug interactions (DDIs) and combined medication errors in obstetrics and gynaecology increased with the clinical rules by 26.10- and 26.54-fold, respectively. In paediatrics, the alert rate for all prescription error types was higher with the clinical rules review than with the manual review; the alert rates for DDI, dosage, and combination medication errors were significantly different between the clinical rules and the manual review. However, there was no difference in the recommendation acceptance rate between the manual review and the clinical rules.

Conclusions Clinical rules can identify prescription errors that manual review cannot detect and ensure real-time review efficiency in high-volume outpatient prescription settings. The high acceptance rate and modification of prescriptions may be relevant to highly customised and localised clinical rules.

INTRODUCTION

Medication errors may lead to patient injury, disability, or even death, and increase medical care costs and wastage of medical care resources.[1][2] Women, especially pregnant women, and children are highly susceptible to adverse drug events caused by prescription errors.[3–5] Prescription errors are associated with medication errors, which can lead to serious adverse drug events and even death.[6–9] The use of information technologies, such as computerised provider order entry (CPOE) and clinical decision support systems (CDSSs), is an effective means of reducing prescription errors.[10][11]

CPOE ensures standardised prescriptions and prevents transcription errors, but without embedding in a CDSS, other patient characteristics, such as indications, biochemical tests, and demographic data, cannot be obtained.[12][13] CPOE embedded in a CDSS can match patient-specific data with a knowledge base to achieve basic functions, such as limited drug–drug interaction (DDI) checking, basic dosage guidance, and drug–allergy interaction checking.[14]

The CDSSs of some medical institutions have more inbuilt complex clinical rules, which can achieve more advanced functions,[15][16] such as DDI checking, dosing support for renal insufficiency and geriatric patients, guidance for medication-related laboratory testing, drug–pregnancy checking, and drug–disease contraindication checking. There have been few studies on large data volume and real-time clinical rules concerning indications, usage and dosage, combination medication, and typographical errors in prescriptions for high-risk groups, such as obstetrics, gynaecology, and paediatric patients.[17][18] In most areas of China, the number of outpatient prescriptions is high. Thus, there is a great risk of prescription errors and serious adverse outcomes. Health management policies require pharmacists to review prescriptions before prescription pricing, and medication dispensing.[19] This requires perfect digital communication, effective data integration, frequent updates, and a high degree of localised customisation.[10][20]

Before 2019, prescription information was subjected to manual review by a pharmacist, without considering other patient characteristics.[21] After 2019, we developed a real-time prescription review system used by pharmacists, with more than 15 000 medication-related clinical rules and visual rule adjustment functions. Clinical rules present prescription error alerts directly to the prescriber during order entry and provide advice for modification. Considering the lack of information regarding the application of real-time clinical rules in obstetrics, gynaecology, and paediatric outpatients, in this study, we aimed to evaluate the effects of localised, real-time clinical rules on alert rates and acceptance rates compared with manual prescription review.

METHODS

Design
This retrospective cohort (before and after) study was approved by the Ethics Council of Human Research in Xiamen Maternal and Child Healthcare Hospital (No. KY-2020–085).

Setting and population
This study was conducted in a grade III tertiary hospital for maternal and child health located in Xiamen, China. The hospital has 1100 employees, 700 beds, and 1.4 million outpatient visits per year. We used data from the hospital information system (HIS) to compare the alert and recommendation acceptance rates before and after clinical rule implementation, including all outpatient prescriptions for 2 years, from 1 January 2018 to 31 December 2019. Clinical rules were introduced in July 2017, and doctors and pharmacists were trained to use the rules which included 15 000 rules when launched.

Classification and definition of prescription errors
We formed prescription review committees, including doctors, pharmacists, nurses, and administrators. Medication prescribing errors were defined as deviations from drug labels and did not include low risk off-label use approved by the prescription review committee in accordance with clinical practice guidelines. According to the Standards for Prescription Reviewing in Medical Institutions issued by the National Health Commission of the People's Republic of China,[19] prescription errors included indication errors (contraindications, wrong diagnosis, and mismatch between diagnosis and medicine), dosage errors (improper prescription involves improper dosage (tolerability over 20%), wrong frequency, wrong administration route, and wrong dosage form), entry errors, DDI errors, and combination medication errors (unreasonable simultaneous or sequential use of two or more drugs for therapeutic purposes, such as treatment of vaginitis with moxifloxacin and metronidazole to addresss anaerobic bacteria). Alerts were divided into five categories based on the above mentioned prescription errors.

Manual review of prescription
The prescribing system requires doctors to enter all content present in the prescription, as well as at least one indication and one drug. The prescribing system only provides basic prescribing services, without mandatory default dosage, frequency, route, and automatic error checking. In a pharmacist team including 20 members, approximately 10 people were on duty every day to review prescriptions. All pharmacists were examined and qualified after a uniform training for error review. Before medication dispensing, prescriptions were reviewed by a pharmacist after drug orders were sent by physicians. Questionable prescriptions were verified and recorded by another pharmacist, who called the prescribing doctor to provide advice or communicate to reach an agreement (figure 1A). To prevent review fatigue, the pharmacists took turns to review the prescriptions every hour. The details of prescription reviewing comprised patient conditions (age, sex, and diagnosis) and therapy regimens (medication selection, dose, frequency, route of administration, and DDI).

System review of prescription
The prescription review system was developed based on the HIS and data integration platforms, including CPOE, laboratory information system, electronic medical records, and other systems (figure 2). In addition to medication-related information, the system integrated patient characteristics and laboratory
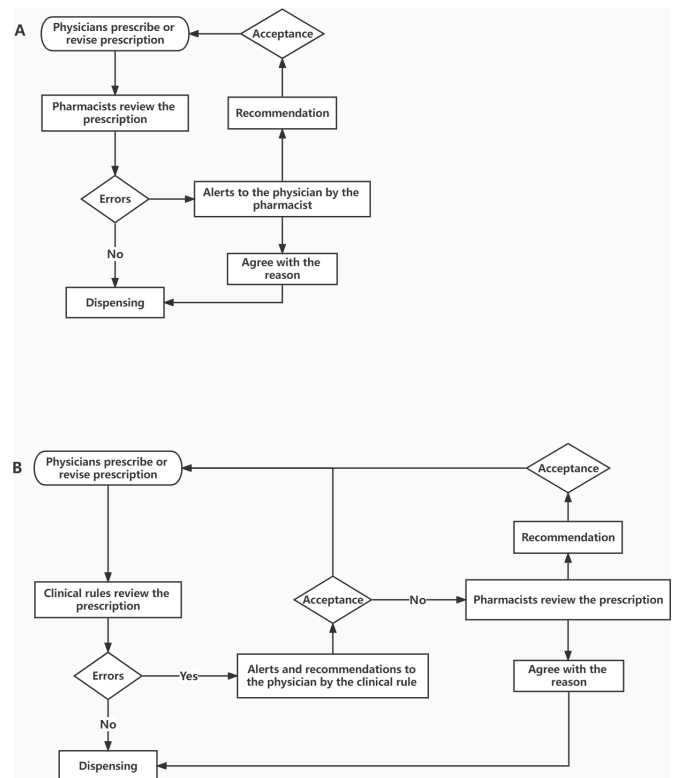

Figure 1 (A) Manual prescription review process. (B) Prescription review process for the system.

values that were included in the algorithms to generate alerts. After a physician sent the prescription order through CPOE, the system determined whether the patient's medication matched all available clinical and demographic information by examining the available structured data in each system database through clinical rules. In the clinical rule service, the pharmacist does not have to check all alerts. The clinical rule directly alerts the doctor on the prescription interface and provides relevant advice if the prescription does not match the clinical rules, implying prescription errors. A doctor who does not accept the recommendation is required to state the reason and communicate with the pharmacist to reach an agreement (figure 1B). For example, for an 8-year-old child of 25 kg weight with *Helicobacter pylori* infection, if a doctor prescribes 400 mg amoxicillin, the rules alert the doctor on the low dose and recommend 625 mg amoxicillin, which is the dosage standard of 50 mg/kg/day for *H. pylori* infection treatment.

Clinical rules are established and revised by prescription review committees, according to labels, professional books, relevant evidence-based guidelines, the latest literature, health management policy requirements, and nearly 30 000 pharmacist review data entries in our hospital over the last 10 years. For each clinical rule, a 'Yes' or 'No' response was displayed. A user-friendly standardised flowchart or decision tree for pharmacists was drawn, and the rules were adjusted as needed (figure 3).

Data analysis
The main outcome indicators included the alert rate and the recommendation acceptance rate of all prescription errors in paediatrics and obstetrics and gynaecology. Secondary outcome indicators included the alert rate of different types of prescription errors in paediatrics and obstetrics and gynaecology. Relative risk (RR) was used to analyse the differences in alert and acceptance
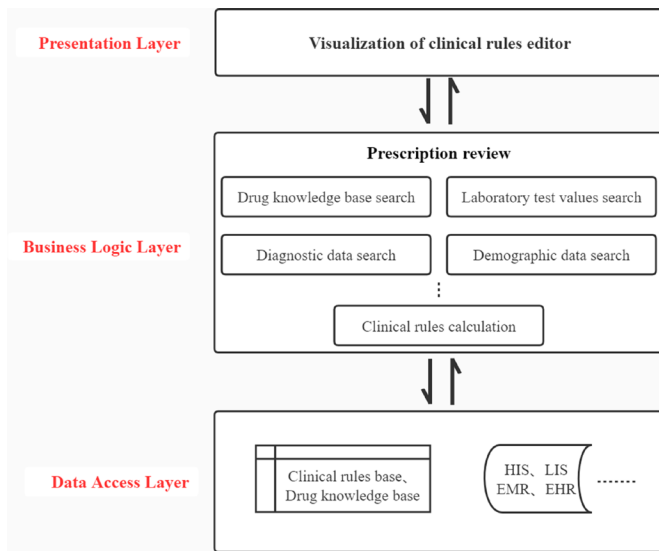
Figure 2 Prescription review system architecture (HIS, Hospital Information System; LIS, Laboratory Information Management System; EMR, Electronic Medical Record; EHR, Electronic Health Record).

rates between the groups. The recommendation acceptance rate was defined as the ratio of the number of prescriptions modified by the prescriber to the number of all recommendations. For a prescription in which the doctor does not accept the recommendation of the rule and uses a manual review, the prescription is included in the number of recommendations during calculation of acceptance rates depending on whether the pharmacist agrees with the reason offered by the doctor or not. To avoid confusion and bias, our study excluded rotation prescriptions. Results with a two-sided p value <0.05 were considered statistically significant. All statistical analyses were performed using R (version 3.6.1).

RESULTS

A total of 1 830 131 prescriptions over 2 years were included in the study. Of these, 735 798 prescriptions were reviewed manually, 3106 alerts were sent, and 2846 recommendations were accepted by doctors (91.6%). The clinical rules reviewed 1 094 333 prescriptions, sent 41 524 alerts, and doctors accepted 38 145 recommendations (91.9%). The on-duty pharmacists for the

system review were adjusted from the original 10 to two persons (table 1).

The alert rate of the system review in obstetrics and gynaecology was higher than that of the manual review (RR 3.97, 95% CI 3.75 to 4.20). The alert rates of DDI errors and combination medication errors in obstetrics and gynaecology significantly increased with the system review (RR 26.10, 95% CI 20.58 to 33.10, and RR 26.54, 95% CI 17.38 to 40.54, respectively) compared with those with the manual review. In paediatrics, all types of prescription error alert rates of the system were higher than those of the manual review (RR 11.26, 95% CI 10.73 to 11.82). The alert rates of DDI, dosage, and combination medication errors significantly increased with the system review (RR 35.49, 95% CI 28.33 to 44.45, RR 36.55, 95% CI 31.61 to 41.49, and RR 18.89, 95% CI 11.30 to 31.58, respectively) compared with those with the manual review. Although the number of alerts was significantly increased, there was no difference in the acceptance rate between the manual reviewer and the system reviewer in obstetrics, gynaecology, and paediatrics (figure 4).

DISCUSSION

In our study, the alert rates for clinical rules review were significantly higher than that for manual review in obstetrics and gynaecology and paediatric outpatients. This may be because clinical rules could obtain structured characteristic data and test values, and could identify many prescription errors that were not detected by the manual review. As expected, although different types of prescription error alert rates have different changes, most prescription error alert rates during the clinical rules review were significantly higher than those during the manual review. The most obvious changes were interactions and combination medications. The built-in knowledge base of drug information in clinical rules makes up for the limitation of pharmacists' manual knowledge. Complicated prescription errors might be ignored by pharmacists during the manual review. For example, supplementing oestrogen and progesterone in menopausal women taking sleeping pills will weaken the effect of hormones. Our rules also solve the problem of a higher possibility of errors when patients have multiple prescriptions, as described by Usha et al.[22] Furthermore, historical prescription information can be obtained based on interaction with other systems in the hospital. For example, if a woman visits department A to receive anticoagulant therapy and is prescribed warfarin, and then visits

Figure 3 Visualisation of clinical rules.

Table 1 Comparison of manual review with the review system

Category	Obstetrics and gynaecology (n, alert or acceptance rate (%))		Paediatrics (n, alert or acceptance rate (%))	
	Manual	Rules	Manual	Rules
All prescriptions	531 827	734 017	203 971	360 316
Per capita	53 182	367 008	20 397	180 158
All alerts	1406	7708	1700	33 816
Entry	473 (0.09)	2884 (0.40)	763 (0.37)	5334 (1.48)
Indication	666 (0.12)	1038 (0.14)	660 (0.32)	11 644 (3.23)
DDI	70 (0.01)	2513 (0.34)	77 (0.04)	4765 (1.32)
Dosage	175 (0.03)	468 (0.06)	185 (0.09)	11 573 (3.21)
Combination	22 (0.004)	805 (0.11)	15 (0.007)	500 (0.14)
Accepted	1288 (91.61)	7133 (92.28)	1588 (93.41)	31 032 (91.77)
DDI, drug–drug interaction.				

department B and is prescribed oestrogen and progesterone, the rule will alert doctors that oestrogen and progesterone will weaken the anticoagulant effect of warfarin. If a patient visits department A and is prescribed amoxicillin granules, and then visits department B, which prescribes amoxicillin and clavulanate potassium, the rule will raise a combination medication error alert.

The results show that the alert rate for paediatric dosage and indication errors is higher with the clinical rules review than with the manual review, but it has a negligible effect on obstetrics and gynaecology. Oral and topical drugs in obstetrics and gynaecology are mostly administered at fixed doses; however, the dosage for children is mostly based on weight and age. Doctors sometimes adjust dosage according to disease severity. Although we set a range of ±20% for some usages based on evidence-based data, most drug dosages are based on labels. The clinical rules require a high degree of matching, without which false positives are prone to occur. For example, when children are prescribed ibuprofen granules, the dosage for a child weighing 21 kg is 210 mg, according to the label. The commercially available packaging specification is 0.2 g. Doctors will usually consider compliance when safety and effectiveness are controllable and prescribe a whole package; however, the rule will raise an alert in this case.

Obstetrics and gynaecology outpatient diseases, such as vaginitis, pelvic inflammatory disease, and metrorrhagia, are diagnosed as common diseases. Many medications do not involve detection values, and the clinical rules have a negligible effect on the alert rate. When manually reviewing paediatric prescriptions, only prescription information can be obtained, and more characteristic information cannot be obtained. Thus, it is difficult to comprehensively judge a variety of physiological information in a short time. The present clinical rules can obtain the patient's characteristic information and test values to review. For example, if methyldopa is prescribed to treat hypertension in pregnancy and the patient's liver function is insufficient, the rule will raise an alert and suggest that labetalol be used instead.

There was no difference in the acceptance rates between the two groups, which were over 90% in both groups. This may be due to the high acceptance rate in the manual review setting and a ceiling effect. Clinical rules do not change the display interface and the operating habits of doctors and display about 13 times as many alerts as that of the manual review. The average processing time for a prescription error was about 1 min for the manual review. The clinical rules automatically screen and obtain multiple data sources on the integrated platform, integrate the specific characteristics of patients and details of drug treatment, and provide personalised recommendations while alerting. It takes an average of 5 s for the clinical rules to deal with a prescription error. In our study, there may have been few doctors who performed the recommended changes without reviewing the alerts properly to save time, which is also the case with the manual review. The actual acceptance rate may be lower. It is necessary to consider false positive alerts; furthermore, alert fatigue caused by frequently occurring alerts that are not clinically relevant tends to be ignored.[23] Eppenga et al[16] demonstrated that when additional patient-related features are included, the clinical relevance of alerts is improved but is still not optimal. The localised system is highly customised to the condition of the implementing agency; thus, it is more likely to have a positive effect on safety and treatment quality.[10 24] Clinical rules are established or revised by prescription review committees,
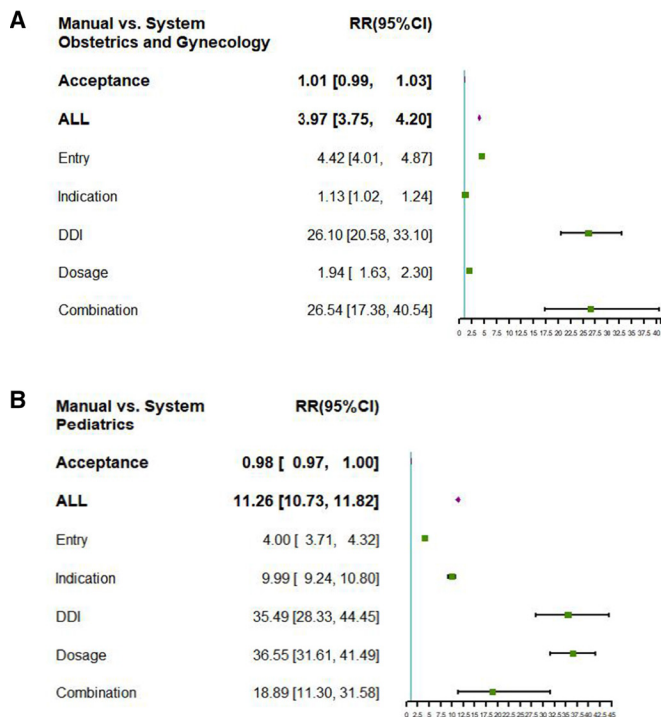
Figure 4 Forest plots of the alert rate and the acceptance rate in obstetrics and gynaecology (A) and paediatrics (B). DDI, drug–drug interaction.

and we used historical prescriptions for testing clinical rules to minimise false positives.

Several studies have described the implementation and evaluation of CPOE and basic and advanced CPOE/CDSS,[22 25] including look-alike/sound-alike and outlier detection.[26 27] However, few studies have described services such as outpatient prescription review systems, especially where pharmacists review outpatient prescriptions in real-time and intervene in cases of incorrect prescriptions. Our clinical rules are similar to the Check of Medication Appropriateness (CMA) system developed by Charlotte et al.[23] The CMA system mainly serves inpatients. It includes a list of comparable clinical rules classified by risk. The generated alerts are sent to the pharmacist instead of directly sending them to the prescribing doctor to prevent the doctor from feeling alarm fatigue. Our rules target outpatient prescriptions for special populations, such as women and children. Most alerts and advice are sent directly to doctors, while pharmacists are responsible for reviewing prescriptions when a doctor does not accept recommendations from clinical rules. This avoids a manual review of errors and review omissions and ensures real-time review efficiency in a large number of outpatient prescription environments.

This study had some limitations.[28 29] As a retrospective single-centre study, we did not assess the actual injury caused by prescription errors and the related cost-effectiveness. False positives alerts can cause frustration and alert fatigue to doctors. Besides, the number of clinically relevant alerts that might have been ignored by the prescribers due to alert fatigue remains unknown, although this scenario may rarely happen.

We plan to promote this service in other healthcare institutions in the region and perform a multicentre study to assess the accessibility of the system. In the subsequent studies, patients' actual injury and doctors' satisfaction will be evaluated, including their general experience with the service, the overall reasons for agreeing or disagreeing with the medication recommendations, and their specific wishes or opinions for future expansion. Although doctors accept most medication-related recommendations, we plan to use more data, frequent updates, and advanced technologies to improve the specificity and sensitivity of this review system, such as identifying and integrating more patient characteristics or parameters, adjusting clinical rules with time, and applying natural language processing.[30]

CONCLUSIONS AND RELEVANCE
Overall, our results show that the prescription review system can be used as an important supplement to the services of a manual reviewer, thereby improving review efficiency and saving human resources. Clinical rules can identify the prescription errors that cannot be detected by manual reviews in real-time based on patient characteristic data, detection values, and flexibly adjustable clinical rules. High acceptance rate and modification of prescriptions may be relevant to highly customised and localised clinical rules. However, some new challenges, such as mechanical reviewing and alert fatigue, may be introduced, and further research is required for optimisation.

ORCID iD
Quanyao Chen http://orcid.org/0000-0003-4408-2565

What this paper adds

What is already known on this subject
⇒ Computerised provider order entry embedded in a clinical decision support system can match patient-specific data with a knowledge base to achieve basic functions, such as limited drug–drug interaction checking, basic dosage guidance, and drug–allergy interaction checking.
⇒ There is a lack of practical information on real-time clinical rules implemented in a large number of obstetrics, gynaecology, and paediatric outpatient prescriptions.

What this study adds
⇒ We developed a real-time prescription review system to prevent prescription errors that has more than 15 000 medication-related clinical rules and can be used as an important aid for a manual reviewer.
⇒ Clinical rules can identify prescription errors that manual review cannot detect and ensure real-time review efficiency in high-volume outpatient prescription settings. The high acceptance rate and modification of prescriptions may be relevant to highly customised and localised clinical rules.

How this study might affect research, practice and/or policy
⇒ Our prescription review system could improve review efficiency and save human resources.

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