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Research Paper

Better specification of triggers to reduce the number of drug interaction alerts in primary care

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ABSTRACT

Objective: Drug interaction alerts (drug–drug and drug-disease interaction alerts) for chronic medications substantially contribute to alert fatigue in primary care. The aim of this study was to determine which events require (re)assessment of a drug interaction and whether using these events as triggers in clinical decision support systems (CDSSs) would affect the alert rate.

Methods: Two random 5% data samples from the CDSSs of 123 community pharmacies were used: dataset 1 and 2. The top 10 of most frequent drug interaction alerts not involving laboratory values were selected. To reach consensus on events that should trigger alerts (e.g. first time dispensing, dose modification) for these drug interactions, a two-step consensus process was used. An expert panel of community pharmacists participated in an online survey and a subsequent consensus meeting. A CDSS with alerts based on the consensus was simulated in both datasets.

Results: Dataset 1 and 2 together contained 1,672,169 prescriptions which led to 591,073 alerts. Consensus on events requiring alerts was reached for the ten selected drug interactions. The simulation showed a reduction of the alert rate of 93.0% for the ten selected drug interactions (comparable for dataset 1 and 2), corresponding with a 28.3% decrease of the overall drug interaction alert rate.

Conclusion: By consensus-based better specification of the events that trigger drug interaction alerts in primary care, the alert rate for these drug interactions was reduced by over 90%. This promising approach deserves further investigation to assess its consequences and applicability in daily practice.

1. Introduction

The detection and management of drug therapy related problems is important to prevent medication errors. Clinical decision support systems (CDSSs) are widely used to detect drug–drug interactions and drug-disease interactions (hereafter referred to as drug interactions) [1–3]. However, in daily clinical practice most alerts generated by CDSSs do not lead to an intervention: the specificity of alerts is low [4–7].

Up to now, one of the main strategies to improve the specificity of alerts has been the use of advanced clinical decision rules: the incorporation of more clinical characteristics (like renal function and potassium levels) in the algorithms generating alerts or not [7–13]. The results from these advanced clinical decision rules range from limited effect to a 90% decrease in the alert rate for a specific subset of alerts [7,9,11,12]. Most research into advanced clinical decision support has been performed in hospitals, where – unlike in the community – recent clinical values are generally readily available [7,11–15].

Differences between hospitals and primary care can have an important effect on the potential of CDSS improvement strategies. In primary care, the majority of the prescriptions concern chronic medications [16,17]. First time prescriptions and repeat prescriptions often trigger the same alerts. However, many drug interactions are mainly relevant at or immediately after the start of therapy [18–20]. In one study, first drug–drug interaction alerts were eight times more likely to be followed by an action compared with recurrent alerts [21].

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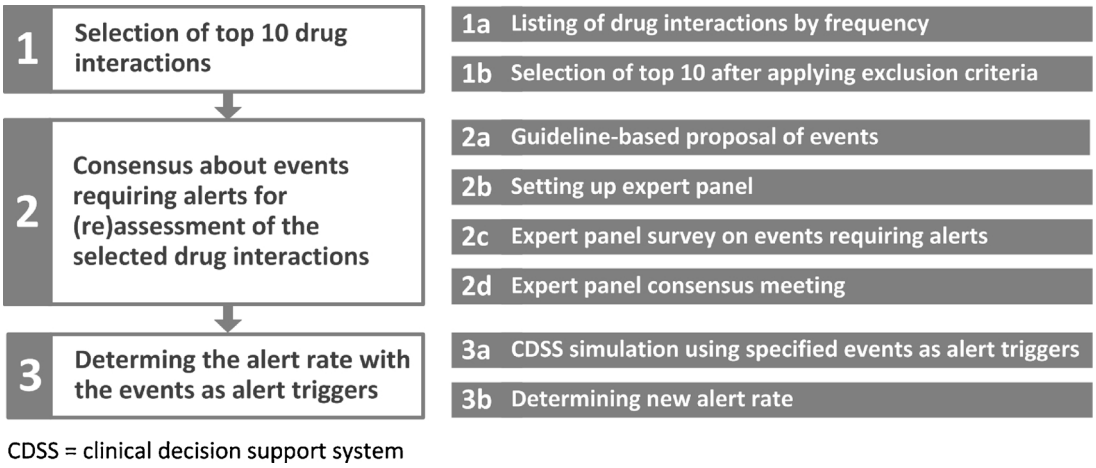

Fig. 1. Research steps.

Moreover, recurrent alerts have been shown to contribute substantially to alert fatigue in primary care [22]. So, for chronic medications, the need for an alert may be different between first time prescriptions and repeat prescriptions. Another difference with hospitals is that outpatients are not continuously monitored, and they are responsible for drug administration themselves. Therefore, health care professionals need to instruct the patients on correct drug use and monitoring. To evaluate whether the patient has understood the advice on a drug interaction and acts accordingly, follow up is needed, which can be supported by CDSS alerts.

Especially in primary care, it can be suboptimal when every repeat prescription without distinction triggers alerts. Alerts should only be triggered in situations requiring (re)assessment of the drug interaction by a health care professional. When it is possible to better specify events indicating this situation (e.g. a change of daily dose) per drug interaction, these events could serve as triggers for alert generation in CDSSs. The objective of this study was to determine which events require (re)assessment of a drug interaction and whether using these events as triggers in CDSSs would affect the drug interaction alert rate.

2. Methods

2.1. Setting

In the Netherlands, over 50% of the community pharmacies use the same pharmacy information system (Pharmacom® by TSS PharmaPartners®) that includes clinical decision support. The system's electronic patient record contains a dispensing history and coded chronic diseases. During processing of prescriptions (including prescriptions both from general practitioners [GP's] and from medical specialists in outpatient clinics), the system generates drug therapy alerts, including drug–drug interaction alerts and drug-disease interaction alerts. First time prescriptions and repeat (renewal) prescriptions trigger identical alerts. Drug interaction alerts are based on the comprehensive drug information database of the Health Base Foundation [18] (which is based on international scientific sources including Stockley's Drug Interactions [19]). Specific management recommendations and background information are available in the pharmacy information system. Identical alerts are generated for regular dispensing (for chronic medications: renewal of prescription every three months) and for multi-dose drug dispensing (generally repeated on a weekly basis) [23]. Pharmacists can suppress an alert manually for a specific patient for a specified period; suppression is lifted in case of changes in the registered patient information, e.g. change of dose, or refill non-adherence.

2.2. Dataset

250 randomly chosen pharmacies from 1080 community pharmacies using the Pharmacom system were asked to provide anonymized patient data over the period August 2012 to July 2014 [16,17]. Extracted data included patient characteristics (age, gender, coded chronic diseases), dispensed medications (including dispensing date, dose, dosing regimen, multi-dose drug dispensing), and all generated drug therapy alerts. The data were analyzed using Microsoft Access 2010 and SPSS (SPSS version 23.0; SPSS Inc. Chicago, IL). Two random non-overlapping samples of five percent of patients per pharmacy to whom at least one drug was dispensed in the period August 2013 to July 2014 were selected (dataset 1 and dataset 2). The dispensing history over the period August 2012 to July 2013 was used to determine first time dispensing and second time dispensing, first time dispensing being defined as the dispensing of a drug which has not been dispensed to the patient in the preceding 12 months, and second time dispensing as the first dispensing thereafter.

2.3. Study design

The investigation consisted of three main steps (Fig. 1):

2.4. Step 1. Selection of drug interactions

Step 1a) In dataset 1, drug interaction alerts were listed by frequency. For this listing only, alerts generated for first time prescriptions were excluded to select drug interactions with recurrent alerts.

Step 1b) Starting from the most frequently generated alerts, drug interactions were excluded when the management guidelines advised monitoring of laboratory values or blood pressure (Appendix A) [18,19]. For these drug interactions, laboratory values should be incorporated in alert generation in addition to the triggers included in this investigation, but availability of laboratory values is not yet commonplace in every community pharmacy [14,15]. The top 10 of remaining alerts were selected.

2.5. Step 2. Two-step consensus process on events requiring an alert

Step 2a) For the selected drug interactions, the management recommendations including background information were examined for information on situations which require (re)assessment of a drug interaction [18–20]. Based on this information, a proposal on events which should serve as alert triggers was drafted. Potential triggers considered for all drug interactions were first dispensing leading to alert, the second dispensing leading to alert, further dispensing of

repeat prescriptions, change of daily dose, change of dosing frequency, discontinuation, refill non-adherence (generating an alert when the patient visits the pharmacy later than expected for a refill, based on the registered daily use – a proxy for non-compliance or intermittent use), and the first dispensing one year after the first alert. Additional triggers were considered depending on the nature of the drug interaction (e.g. new co-medication or new co-morbidity).

Step 2b) An expert panel was set up for conducting a two-step consensus development process consisting of an online survey and a subsequent meeting [24,25]. The aim was to reach consensus on events which require drug interaction (re)assessment, and which therefore should serve as triggers for alert generation, without compromising patient safety.

The ten expert panel members were recruited from the advisory committees from the Health Base Foundation, which consist of practicing community pharmacists who regularly advise on the content of the drug safety alerts and patient counseling information.

Step 2c) The online survey was designed using NETQ (Survalyzer, Utrecht, The Netherlands). For all ten selected alerts, the proposal on triggers from step 2a was presented. The expert panel members were asked to agree or disagree; in the latter case they could suggest alternative events. In addition they were asked to suggest special situations that may need different alert triggers.

Step 2d) A two hour consensus meeting was held with the expert panel and attended by the researchers (AH, MH and MB). The results of the survey were used as input for the discussion, aiming to reach consensus on events that should trigger alerts. Agreement by two third of the panel members was set as threshold for consensus. When for an event no consensus was reached, the event was included as a trigger, to be on the safe side. After the consensus meeting, a report with the results was sent to the expert panel members for information purposes only.

2.6. Step 3. determining the alert rate with the events as triggers

Step 3a) To identify the impact of the consensus on the alert rate, a CDSS using the specified events as alert triggers was simulated. It was assessed which of the original alerts in the current CDSS did match one of the events defined in the consensus meeting (e.g. second time dispensing, change of daily dose). The simulation was performed in dataset 1 and replicated in dataset 2 to check for consistency, and results were compared by a chi-squared test (a p-value < 0.05 was considered statistically significant). The simulation was performed separately on multi-dose drug dispensing and regular dispensing.

Step 3b) The number of alerts generated by the simulation was subtracted from the original number of alerts to calculate the potential reduction of alerts, both in dataset 1 and 2. For the simulated situation, the contribution of each individual trigger (e.g. first time dispensing, change of daily dose) to the total number of alerts was determined.

2.7. Ethics and confidentiality

As this was a retrospective database analysis, the study was exempt of ethical review. To protect the privacy of patients and pharmacists, the data extracted from the pharmacy information system were anonymous. Data could not be used to trace individual patients or pharmacies.

3. Results

Data were extracted from the CDSS of 123 community pharmacies. Dataset 1 and 2 together contained 1,672,169 prescriptions leading to 591,073 drug interactions alerts (Fig. 2), corresponding to an average of 185 drug interaction alerts per pharmacy per day.

Multi-dose drug dispensing accounted for 43.9% of the prescriptions and for 61.6% of the drug interaction alerts. First time prescriptions accounted for 15.3% of the prescriptions and for 8.2% of the alerts. The top 10 of selected alerts – after application of exclusion criteria – accounted for 31.9% of the drug interaction alerts for repeat prescriptions (Table 1).

In the survey, consensus was reached on the majority of proposed triggers; however, additional suggestions were made. Seven pharmacists attended the consensus meeting. In the meeting, consensus was reached for all triggers but one, see Table 2. For 'Obstructive pulmonary disease – beta-blocking agents' no consensus was reached on the need for a reassessment alert at second time dispensing.

The reduction in alert rate for the ten selected drug interactions when comparing the simulation with the original CDSS was 93.0% in dataset 1 and 93.1% in dataset 2. Consistency between results in dataset 1 and dataset 2 was high. Differences in alert rate reduction between the datasets were very small for all 10 drug interactions ($<$ 1% point), and not significantly different for the overall reduction and for 9 of the 10 drug interactions (see Appendix B). Therefore, combined results are presented in Table 3. For regular dispensing, the reduction in alert rate was 81.5%, ranging from 67.5% to 96.4% for the individual drug interactions. The alert rate reduction for multi-dose drug dispensing was 98.4% (range 96.7% to 99.3%). By changing the alert generation for ten selected drug interactions, the overall alert rate for all drug–drug and drug-disease interactions was decreased by 28.3%.

In the simulated situation, 'refill non-adherence' was the most common trigger for alerts (31.5% of the alerts). First and second time dispensing accounted for respectively 27.8% and 14.8% of the alerts, and the alert one year after first dispensing contributed for 16.2%. The other triggers – together accounting for 9.6% of the alerts – were of minor importance.

4. Discussion

This study showed broad consensus of community pharmacists on the events that should trigger alerts for ten common drug interactions. The simulation in a CDSS based on this consensus resulted in a 93% lower alert rate compared with the original CDSS for the ten concerning drug interactions. By reducing the alert rate for this selection only, the overall alert rate for drug interactions was decreased by nearly 30%, corresponding to a reduction of 52 drug interaction alerts per pharmacy per day.

The reduction was most pronounced for multi-dose drug dispensing (98.4%), which can be explained by the high – weekly – dispensing frequency, leading to recurrent alerts in an otherwise unchanged situation. Although the result for multi-dose drug dispensing contributed to the huge overall effect, the data showed also a high reduction of the alert rate for regular (mostly three monthly) dispensing (81.5%). The effect seen in our investigation can be understood from the chronic nature of the therapies involved in the drug interactions that were investigated. For example, when a patient has been instructed on the drug–drug interaction between renin-angiotensin system (RAS) inhibitors and diuretics (precautions during first days of use of the RAS inhibitor, see Table 1), the patient can continue combined use without the need for further instructions.

The study showed that triggering alerts by very specific events rather than by every repeat prescription was an effective approach to reduce the alert rate. The decrease in alert rate was in the upper range compared with other CDSS improvement strategies [7,8,11,12]. An advantage of our approach is the potential for extension to other drug interaction alerts. Based on existing recommendations on drug interaction management, the expert panel relatively easily reached consensus on events that should or should not trigger alerts. Moreover, the consensus suggests that the events can almost completely be derived from the general characteristics of the drug interaction, like the nature, moment of onset and duration of the drug interaction effect. For example: the reached consensus for the drug–drug interaction 'bisphosphonates – polyvalent cations' is applicable to all drug interactions

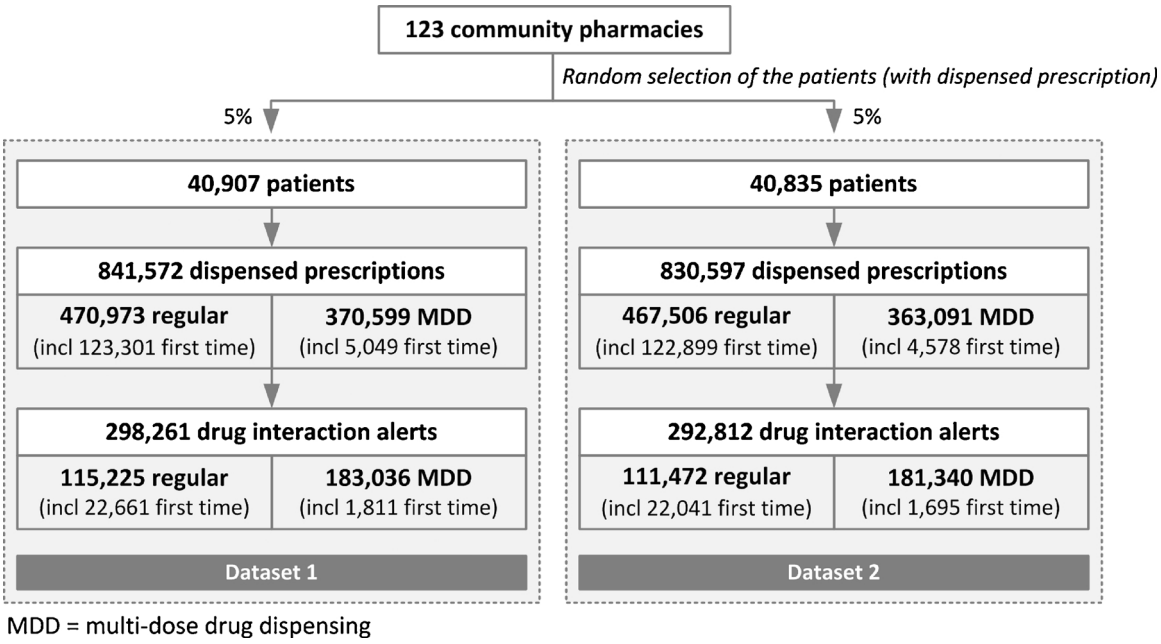

Fig. 2. Dataset characteristics.

Table 1
Characteristics of selected drug interactions.

Drug interaction	% of alerts[a]	Management recommendation [18]
RAS inhibitors – diuretics[b]	8.0	When starting RAS inhibitor: start low, go slow. Instruct patient to take RAS inhibitor at bed time, sitting on the bed.
Diabetes – ACE inhibitors	4.7	Instruct patient to monitor and report symptoms of hypoglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.
Obstructive pulmonary disease – beta-blocking agents	4.4	Instruct patient to monitor symptoms of obstructive pulmonary disease.
Antidiabetics – beta-blocking agents	4.2	Inform patient that symptoms of hypoglycemia may be less prominent.
Bisphosphonates – polyvalent cations	2.3	Instruct patient to take separately.
Heart failure – beta-blocking agents	2.1	Start low; instruct patient to monitor symptoms of edema.
Thyroid drugs – polyvalent cations	1.7	Instruct patient to take separately.
Salicylates (antithrombotic) – SRIs	1.7	Consider gastro-intestinal protection (unless patient is under 60 years or between 60–70 without peptic ulcer in anamnesis), and instruct patient on its use.
Diabetes – thyroid drugs	1.6	Instruct patient to monitor and report symptoms of hypo-/hyperglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.
Diabetes – SRIs	1.3	Instruct patient to monitor and report symptoms of hypoglycemia and (for patients with blood glucose meter) to monitor blood glucose more frequently during first days of use.

ACE = angiotensin converting enzyme; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor.
[a] Percentage of the total number of drug interaction alerts in dataset 1; first time dispensing excluded.
[b] Alert only generated for dispensing of RAS inhibitor.

involving complex formation that should be managed by separation of dosing moments. This potential generalizability can facilitate extension to other drug interactions.

For the implementation of the investigated strategy in CDSSs in daily practice, some prerequisites can be defined. Firstly, for optimal support of the health care professional, the CDSS should provide specific management recommendations for every event that triggers an alert. For example: the management recommendation at first dispensing should guide the instruction on monitoring, while the recommendation for the same drug interaction at second time dispensing should guide evaluation of the interaction effect. However, better specification of management recommendations should not result in a one-size-fits-all protocol without taking into account the situation and preferences of an individual patient. Secondly, even in case of better specification of alert triggers, a CDSS should still offer the possibility to manually overrule the settings. Depending on the individual patient, the need for an alert can be different. For example, when it turns out at second dispensing that a patient has not understood the instructions given at first dispensing, a follow-up at third dispensing can be needed. CDSS alerts are a tool to detect drug therapy related problems, but cannot replace an individualized assessment by the health care professional. Thirdly, when a CDSS uses narrowed down events as alert triggers, these events must be registered on a structural basis. A complete and up-to-date electronic patient record including medication use and chronic conditions is needed [26].

Fourthly, implementation of these triggers should not hamper the performance of the CDSS. In current Dutch CDSSs this technical prerequisite is met.

We expect that our approach is especially useful in primary care settings, where the proportion of repeat prescriptions for chronic medication is high. The approach is applicable to both the CDSSs of prescribers and pharmacists (which are in the Netherlands essentially the same); the decrease in alert rate can be most pronounced in pharmacies where multi-dose drug dispensing often substantially contributes to the alert rate. Our strategy to reduce the alert rate can be easily combined with other available strategies (e.g. restricting alert

Table 2
Consensus on events requiring alerts for drug interaction (re)assessment.

Drug interaction	First dispensing leading to alert	Second dispensing leading to alert	One year after first alert	Event				Additional events	Each dispensing
				Change of daily dose	Change of dosing frequency	Discontinuation	Refill non–adherence		
RAS inhibitors – diuretics	+[a]	–	–	–	–	–	+[a]	–	–
Diabetes – ACE inhibitors	+	+	–	+	–	+	+	–	–
Obstructive pulmonary disease – beta–blocking agents	+	†	+	+	–	–	–	–	–
Antidiabetics – beta–blocking agents	+	+	+	+[d,e]	–	–	+	–	–
Bisphosphonates – polyvalent cations	+	+	–	+[c]	+[c]	–	–	–	–
Heart failure – beta–blocking agents	+	+	–	+[d]	–	–	+	Dose modification loop diuretic[b]	–
Thyroid drugs – polyvalent cations	+	+	–	+[c]	+[c]	–	–	–	–
Salicylates (antithrombotic) – SRIs	According to guideline [18]: no alert for patients under 60 years and for patients between 60 and 70 without peptic ulcer in anamnesis; no alert when gastric protection is already in use (based on dispensing history). In all other cases: alert with each dispensing. Moreover, alert in case of refill non–adherence of the proton pump inhibitor								+
Diabetes – thyroid drugs	+	+	–	+	–	+	+	–	–
Diabetes – SRIs	+	+	–	+	–	+	+	–	–

ACE = angiotensin converting enzyme; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor.
[a] for RAS inhibitor only.
[b] proxy for instable heart failure.
[c] for polyvalent cation only.
[d] dose increase only.
[e] for beta-blocking agent only.
†no consensus reached.

Table 3
Number of alerts for the consensus-based simulation compared with the original CDSS.

Drug interaction	Regular dispensing			Multi-dose drug dispensing			Overall		
	Number of alerts		Change in alert rate	Number of alerts		Change in alert rate	Number of alerts		Change in alert rate
	Original CDSS	Simulation		Original CDSS	Simulation		Original CDSS	Simulation	
RAS inhibitors – diuretics	14,379	2345	− 83.7%	30,420	210	− 99.3%	44,799	2555	− 94.3%
Diabetes – ACE inhibitors	8480	1706	− 79.9%	17,998	249	− 98.6%	26,478	1955	− 92.6%
Obstructive pulmonary disease – beta-blocking agents	7783	2011	− 74.2%	16,607	373	− 97.8%	24,390	2384	− 90.2%
Antidiabetics – beta-blocking agents	8787	1631	− 81.4%	14,481	322	− 97.8%	23,268	1953	− 91.6%
Bisphosphonates – polyvalent cations	5030	693	− 86.2%	9251	112	− 98.8%	14,281	805	− 94.4%
Heart failure – beta-blocking agents	1838	598	− 67.5%	9125	297	− 96.7%	10,963	895	− 91.8%
Thyroid drugs – polyvalent cations	3368	466	− 86.2%	5973	39	− 99.3%	9341	505	− 94.6%
Salicylates (antithrombotic) – SRIs	2956	106	− 96.4%	7586	158	− 97.9%	10,542	264	− 97.5%
Diabetes – thyroid drugs	2584	587	− 77.3%	6041	85	− 98.6%	8625	672	− 92.2%
Diabetes – SRIs	1969	455	− 76.9%	4844	71	− 98.5%	6813	526	− 92.3%
TOTAL	57,174	10,598	− 81.5%	122,326	1916	− 98.4%	179,500	12,514	− 93.0%

ACE = angiotensin converting enzyme; CDSS = clinical decision support system; RAS = renin-angiotensin system; SRI = serotonin reuptake inhibitor

generation to the most severe drug interactions, and context-specific alert generation) [27,28], to reach an approach customized for the specific setting.

By combining our findings with investigations on advanced clinical decision support in hospitals [7,11,29], a general strategy for CDSS improvement emerges. Alerts are only needed when there is a change in the patient's situation, which requires (re)assessment of the drug interaction by a health care professional. Events related to dispensing, for example first time dispensing, can be important triggers indicating a change in the patient's situation. The same holds for events like the registration of a new laboratory value or condition (e.g. to evaluate a patients' medication in case of pregnancy). It is unlikely that repeat prescriptions in an unchanged situation are useful triggers. Not all situations which require an alert for (re)assessment of the drug interaction are directly related to an event like registration of diseases, laboratory values or medications. Actually, sometimes the need for reassessment of a drug interaction is driven by the absence of an event – e.g. when a patient does not show up for a medication refill or for laboratory testing. Or by a change in external circumstances (e.g., a heat wave). Moreover, alerts in primary care should support counseling and follow-up on drug interaction alerts, because patients are not continuously monitored, and patients are responsible for correct drug administration themselves. Research has shown that the most frequent external action performed by community pharmacists in case of a drug–drug interaction alert is communication with the patient (78% of all external actions) [21]. In our investigation, second time dispensing and the evaluation alert after one year accounted for one-third of the alerts. The expert panel incorporated these moments because of the need to evaluate whether the patient has experienced any interaction effect, and whether the patient needs further counseling on the drug interaction. Using standardized, consensus-based events like second time dispensing as trigger to evaluate a drug interaction alert is a first step. Further tailoring these alerts based on patients' (information) needs is an interesting future perspective.

Our study has several limitations. Firstly, we used an expert panel to determine the events requiring an alert. Another group of experts could have reached different conclusions. However, the expert panel consisted of practicing community pharmacists who were experienced in advising on CDSSs and patient counseling.

Secondly, in the original CDSS where our data came from, pharmacists had the possibility to manually suppress alerts for a specific patient and period. Suppressed alerts, however, were included in the database. Pharmacists who already actively used the possibility of suppression will experience less reduction in alert rate by using better specified triggers, but they still have the advantage of a reduced need for time-consuming and error-prone manual suppression of alerts. For every pharmacy and every CDSS the exact reduction of the alert rate will be different. However, the principle of specific triggering alerts can be favorable for nearly every setting, with the highest impact in case of a high dispensing frequency.

Thirdly, our study was a simulation, and real world effects can be different. Further research is needed to assure that no relevant alerts are missed when alerts are only triggered by the specified events. There is a risk that a few of the alerts which are no longer generated, would have led to intervention in current practice. This risk should be weighed against the current risk of overseeing alerts because of alert fatigue. It should also be taken into account that it is possible that recurrent alerts in current daily practice sometimes serve as a safety net for issues which are insufficiently covered otherwise. Therefore, a thorough investigation in daily practice is needed to rule out any unexpected consequences affecting patient safety.

Fourthly, we investigated only a subset of 10 frequent drug interactions, which included mainly drugs that can be combined but only with appropriate counseling or monitoring. This type of advice is especially relevant in primary care, where patients are not subject of continuous monitoring such as in hospital. Because of the nature of the

investigated drug interactions, most – but not all – of the consensus-based triggers were related to dispensing. With other drug interactions, other triggers can be expected to be relevant. However, by focusing on the most frequent drug interactions, we were able to show the potential of the proposed approach in primary care.

In conclusion, this study showed broad consensus on more specific events that should trigger drug interaction alerts in primary care. In a simulation using these specific triggers the alert rate was reduced by more than 90% for the 10 concerned drug interactions. This promising approach to reduce the alert load deserves further investigation to assess its consequences and applicability in daily practice.

Authors' contributions

All authors contributed to the study design. AH and MH collected the data and performed the data analysis. MH drafted the manuscript. All authors critically revised the manuscript. All authors approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest that are directly relevant to the content of this study.

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Summary points

What was already known on the topic

- Clinical decision support systems contribute to the detection and prevention of drug related problems.
- Alert rates in clinical decision support systems are problematically high.
- In primary care, recurrent alerts substantially contribute to alert fatigue.

What this study added to our knowledge

- An expert panel is well able to reach consensus on events that require reassessment of a drug interaction.
- Consensus-based events are suitable to serve as alert trigger in clinical decision support systems (instead of triggering alerts by every repeat prescription).
- Better specification of alert triggers is a promising approach which greatly reduces the alert rate in primary care.

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Appendix A and Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijmedinf.2017.11.005.

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