Classification of drugs with different risk profiles

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ABSTRACT

INTRODUCTION: A risk stratification approach is needed to identify patients at high risk of medication errors and a resulting high need of medication review. The aim of this study was to perform risk stratification (distinguishing between low-risk, medium-risk and high-risk drugs) for drugs found to cause serious adverse reactions due to medication errors. The study employed a modified Delphi technique.

METHODS: Drugs from a systematic literature search were included into two rounds of a Delphi process. A panel of experts was asked to evaluate each identified drug's potential for harm and for clinically relevant drug-drug interactions on a scale from 1 (low risk) to 9 (high risk).

RESULTS: A total of 36 experts were appointed to serve on the panel. Consensus was reached for 29/57 (51%) drugs or drug classes that cause harm, and for 32/57 (56%) of the drugs or drug classes that cause interactions. For the remaining drugs, a decision was made based on the median score. Two lists, one stating the drugs' potential for causing harm and the other stating clinically relevant drug-drug interactions, were stratified into low-risk, medium-risk and high-risk drugs.

CONCLUSIONS: Based on a modified Delphi technique, we created two lists of drugs stratified into a low-risk, a medium-risk and a high-risk group of clinically relevant interactions or risk of harm to patients. The lists could be incorporated into a risk-scoring tool that stratifies the performance of medication reviews according to patients' risk of experiencing adverse reactions.

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An adverse reaction (AR) is defined as a response to a medicinal product, which is noxious and unintended, and the definition includes medication errors (MEs) [1, 2] (**Table 1**).

One way to potentially avoid MEs related to prescribing is by systematic medication reviews. So far, no commonly accepted definition of medication reviews exists. However, a medication review can be defined as a structured evaluation of a patient's medication aimed at optimising the drug effect and at minimising the number of inappropriate drugs, thereby also minimising the number of MEs. A systematic review confirmed that medication reviews improve the quality of prescribing [3]. However, a recent Cochrane review did not find that medication review had an effect on all-cause mortality or number of hospital readmissions [4].

The lack of effect of medication reviews may be due to the fact that all patients are receiving the same intervention despite varying ME risks. We hypothesise that important, variable factors are the number of drugs and the risk associated with drugs that cause serious MEs. In order to stratify patients according to their ME risk, we therefore performed a literature search of drugs causing serious MEs [5]. However, as underreporting of ARs is considerable and fatal MEs are more likely to be reported than non-fatal MEs, risk stratification of harmful drugs based on a literature search alone may not yield a reliable portrait of high-risk drugs [6]. Due to publication bias, some drugs and some MEs may be published more frequently than others. We therefore chose to have data from the literature confirmed and further qualified by adding clinical experience from an expert panel.

A modified Delphi process performed by clinical experts could be an important approach to achieve a clinically relevant risk stratification of the drugs that were revealed as harmful in the literature. Therefore, the aim of this study was to perform a clinically relevant risk stratification of the drugs that were identified as harmful in the existing scientific literature.

METHODS

The modified Delphi method

The Delphi method is a consensus process originally developed by Helmer and Dalkey [7, 8]. In the modified version used in the present study, participants were asked to evaluate every drug relative to its potential for harm and its potential for interactions on a scale of 1-9 [9, 10]. The panelists were allowed to consult professional reference books as needed. The interval of 1-3 indicated a "low risk", 4-6 a "medium risk" and 7-9 a "high risk", and the evaluation allowed panelists to add comments. Consensus was present if the median and interquartile range of the responses fell within 1-3, 4-6 or 7-9.

Only drugs for which no consensus was reached in the first round were included in the second Delphi round. Prior to the second round, changes were made if comments from the experts required adaptation. In this round, experts were asked to reconsider their scores based on the panel's written responses. They were informed about the median and interquartile ranges of the panel's scores for each drug and about any additional comments made by other experts and reminded of their own personal scores from the first round. If dis-

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TABLE 1

Term definitions.

Term	Definition
Adverse reaction	Response to a medicinal product which is noxious and unintended; this includes adverse reactions which arise from: Use of a medicinal product within the terms of the marketing authorisation Use outside the terms of the marketing authorisation, including overdose, misuse, abuse and medication errors Occupational exposure [1, 2]
Medication error	Error in the stages of the medication process – ordering, dispensing, administering and monitoring of the effect – causing harm or implying a risk of harming the patient [9]
Seriousness	A serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect [1, 2]

TABLE 2

Drugs included in the Delphi process.

Drugs from literature		
Allopurinol	Calcium antagonists	Opioids
Alpha-blockers	COX2-inhibitors	Paracetamol (acetaminophen)
Amiodarone	Cyclophosphamide	Potassium
Anticoagulants, oral other	Digoxin	Potassium sparing diuretics
Antidepressants, other	Glucocorticoids	Protease inhibitors
Antidiabetics, oral	Insulin	Renin-angiotensin system inhibitors
Antiepileptics	Loop diuretics	SSRI
Antimycotics	Low molecular heparins	Statins
Antineoplastic agents	MAO-inhibitors	TCA
Antipsychotics	Macrolides	Thiazides
Antithrombotics	Metoclopramide	Warfarin
Azathioprin	Methotrexate	Xanthines
Benzodiazepines	Nitrofurantoin	
Beta-blockers	NSAIDs, non-selective	
Added		
Ondansetron	Sildenafil	Isoniazide
Propafenone	Fluoroquinolones	Calcineurine inhibitors
Flecainide	Rifamycins	Disulfiram
Fibrates		
Removed		
Adrenaline	Levothyroxine	Naltrexone
Nitrates	Carbimazole	Pentamidine
Adenosin	Vincristine	Salbutamol
Ferrioxidesaccharate	Daunorubicine	Terbutaline
Magnesium sulphate	Carboplatin	Promethazine
Laxatives	Colchicine	Protonpump inhibitors
Levonorgestrel	Lidocaine	Trimethoprim
Desmopressine		

COX = cyclooxygenase; MAO = monoamine oxidase; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

agreement still existed after the second round, the final decision relating to the drug's risk was based on the location of the median, i.e. a drug having a median in the interval 1-3 was categorised as "low risk"; 4-6: "medium risk"; and 7-9: "high risk".

The expert panel received a link to the questionnaire generated in Survey Xact, Rambøll Management Consulting, Aarhus, Denmark, by e-mail [11]. Furthermore, two reminders were sent by e-mail. The panelists were blinded to each other's assessments during the consensus process.

The expert panel

The expert panel consisted of physicians primarily specialised in internal medicine and pharmacists preferably with clinical experience. Danish Medical Societies, the Danish Health and Medical Agency and the Danish Society of Pharmacists were invited to appoint members to the panel. Prior experience with risk evaluation was not mandatory.

The list of drugs

In a recent paper, we described a systematic literature search for drugs that have caused serious MEs, where seriousness was defined using the World Health Organization (WHO) criteria [1, 5, 12] (Table 1). We found 40 different drugs or drug classes that had caused serious MEs (**Table 2**).

The purpose of making lists of drugs for the present study is to stratify patients according to their risk of serious MEs at admission, prior to discharge or in out-patients. Drugs were therefore removed from the list if they were administered intravenously or subcutaneously by health-care professionals during hospitalisation (i.e. adrenaline or cytostatics). Furthermore, underprescribing of drugs causing serious MEs in the literature (i.e. omission of a laxative during opioid treatment) and drugs approved for compassionate use only were removed. Finally, ten drugs were added by the study group due to pharmacological issues (i.e. narrow therapeutic index, known serious adverse effects, problematic metabolic pathways) (Table 2).

The expert panel was informed that the drugs in the questionnaire had caused a serious ME due to prescribing or lack of monitoring of effect.

Trial registration: not relevant.

RESULTS

A total of 36 experts were appointed to serve on the panel. Among these, 30 (83%) completed the first round and 27/36 (75%) completed the second round. In total, 23 medical doctors and four pharmacists completed the second round.

In the first round of the Delphi process, consensus was reached for anticoagulants, loop diuretics and beta-blockers. For 13 other drugs or drug classes, consensus for either potential of harm or interaction was reached.

After the first round, the questionnaire was revised in concordance with the comments from the experts, i.e. one expert did not agree that selective serotonin reuptake inhibitors (SSRIs) as a class had the same risk as the single drugs fluoxetine and fluvoxamine. Therefore,

TABLE 3

The final lists of drugs with a risk of causing harm and drugs with a risk of causing interactions. Consensus was reached for 51% of drugs or drug classes causing harm and for 56% of drugs or drug classes causing interactionsa.

Drugs with risks of causing harm			Drugs with risks of causing interactions		
low risk	**medium risk**	**high risk**	**low risk**	**medium risk**	**high risk**
Metoclopramide	Oral antidiabetics	Insulin	Metoclopramide	Low molecular heparins	Rifamycin
Fibrates	Xanthines	Other oral anticoagulants	Insulin[a]	Digoxin	Lithium
Calciumantagonists excl. verapamil	Potassium	Propafenone	Nitrofurantoin[a]	Propafenone	Erythromycin
Statins	Low molecular heparines	Flecainide	Paracetamol[a]	Alpha-blockers	Calcineurin inhibitors
Ondansetron[a]	Renin-angiotensin system inhibitors	Calcineurin inhibitors	Ondansetron[a]	Thiazides	TCA
	Viagra	Azathioprine		Verapamil	MAO-inhibitors[a]
	Nitrofurantoin	NSAID		Statins	Antiepileptics[a]
	Antimycotics	COX-inhibitors		Viagra	Vitamin K antagonists[a]
	Paracetamol	Opioids		Macrolides excl. erythromycin	Amiodarone[a]
	SSRI, excl. fluvoxamine, fluoxetine	Antipsychotics		Ciprofloxacin	
	MAO-inhibitors	Lithium		Antimycotics	
	Erythromycin[a]	Benzodiazepines		NSAID	
	Ciprofloxacin[a]	TCA[a]		Antipsychotics excl. lithium	
	Rifamycins[a]	Vitamin K antagonists[a]		Benzodiazepines	
	Isoniazide[a]			Fluvoxamine	
	Protease inhibitors[a]			Fluoxetine	
	Allopurinol[a]			Opioids	
	Antiepileptics[a]			Fibrates[a]	
	Fluvoxamine[a]			Loop diuretics[a]	
	Fluoxetine[a]			Glucocorticoids[a]	
	Other antidepressant[a]			Potassium sparing diuretics[a]	
	Antithrombotics[a]			Beta-blockers[a]	
	Alpha-blockers[a]			Calcium antagonists excl. verapamil[a]	
	Thiazides[a]			Isoniazide[a]	
	Loop diuretics[a]			Protease inhibitors[a]	
	Potassium sparing diuretics[a]			Cyclophosphamide[a]	
	Beta-blockers[a]			Methotrexate[a]	
	Verapamil[a]			Azathioprin[a]	
				Potassiuma	
				COX-2 inhibitors[a]	
				Allopurinol[a]	
				Other oral anticoagulants[a]	
				Antitrombotics[a]	
				SSRI, excl. fluvoxamine and fluoxetine[a]	
				Renin-angiotensin system inhibitors[a]	
				Flecainide[a]	
				Other antidepressants[a]	
				Disulfiram[a]	
				Xanthines[a]	
				Oral antidiabetics[a]	

COX = cyclooxygenase; MAO = monoamine oxidase; NSAID = non-steroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
a) Consensus was reached by the experts.

SSRIs were divided into SSRIs except for fluvoxamine, fluoxetine and a separate group consisting of only fluvoxamine and fluoxetine.

The resulting list of drugs increased from 49 drugs or drug classes in the first round to 54 drugs or drug classes in the second round of the Delphi process. Drugs and drug classes for which consensus had not been reached were resubmitted for the second round along with the aforementioned drug groups.

After the second round, consensus still had not been reached for 29 drugs concerning harm and 25 drugs concerning interactions. Most categories, however, showed a trend towards agreement and a decision of risk strata for these drugs was based on the median. In total, consensus was reached for 29/57 (51%) drugs or drug classes that cause harm and for 32/57 (56%) of drugs or drug classes that cause interactions (**Table 3**).

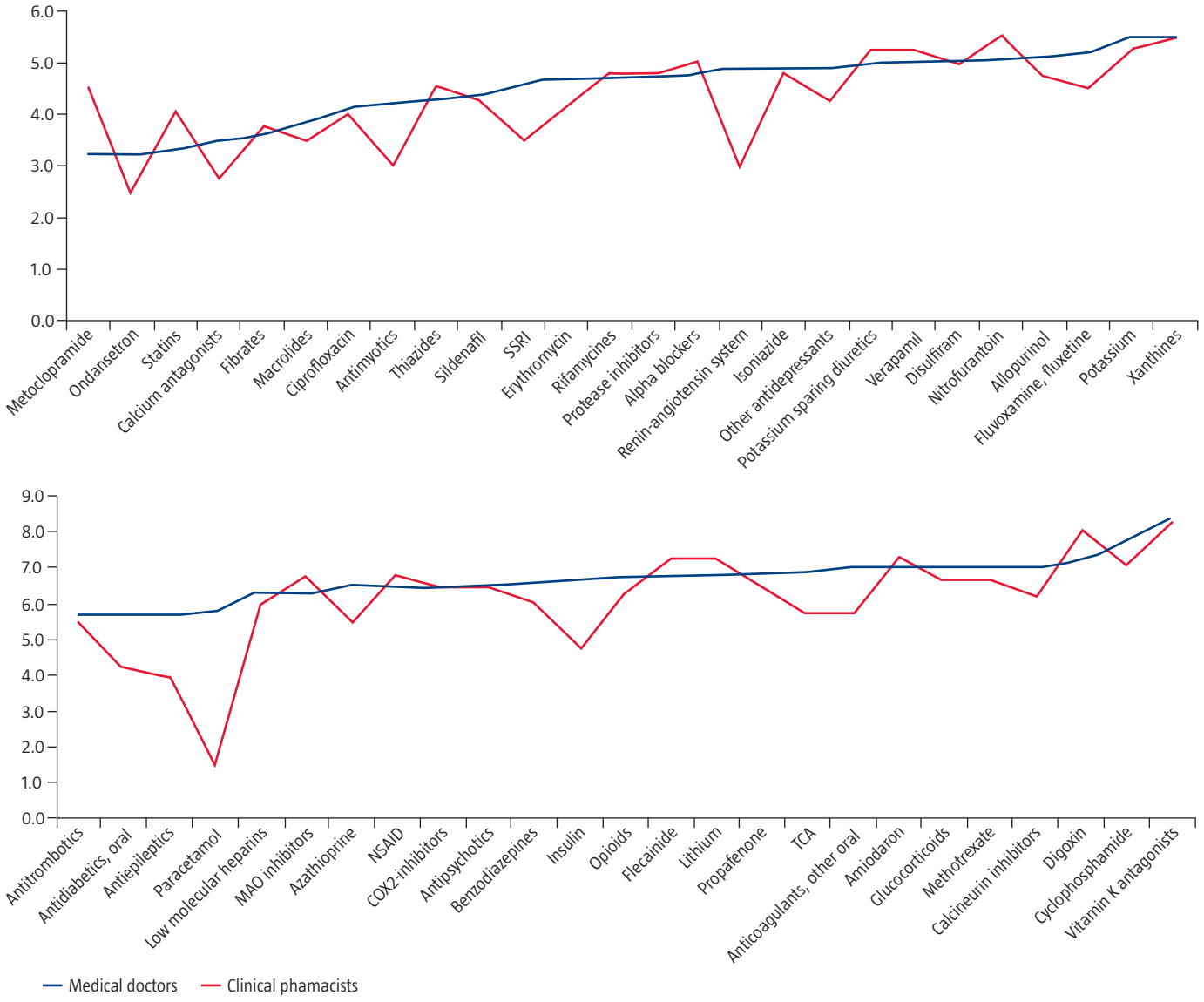
Additionally, we investigated trends in risk scoring between different professions comparing the mean scores of medical doctors with pharmacists. As can be seen in **Figure 1**, there was a tendency towards pharmacists scoring the potential risk of drugs slightly lower than the medical doctors. The pharmacists' scores were lower in 32 instances; four scores were completely in line with the physicians; and in 15 instances, they scored the drug higher than the medical doctors did.

DISCUSSION

Based on the Delphi technique, we created two lists of drugs with low, medium and high risk of causing either

FIGURE 1

Mean evaluations of the potential for harm divided into medical doctors and pharmacists.



COX = cyclooxygenase; MAO = monoamine oxidase; NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants.

adverse interactions or harm to patients, respectively. Seven drugs were involved in half of all serious MEs found in the systematic literature review [5]. These were methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, digoxin, opioids, beta-blockers and acetylic salicylic acid. The experts evaluated that the beta-blockers and acetylic salicylic acid were medium-risk drugs in terms of harm, while the remaining five drugs kept their position as high-risk drugs. Thus, the clinical evaluation was in line with that reported in the literature, despite the fact that the experts were not introduced to the results from the literature.

For drugs causing adverse interactions, the experts agreed on only one drug class from the previous literature review, namely vitamin K antagonists (e.g. warfarin) [5]. In fact, only nine drugs were present in the high-risk group of interactions. We compared the drugs in the low-risk, medium-risk and high-risk groups, respectively, with the recommendations in the Danish public Database of Interactions [13] and found that high-risk drugs are in concordance with the drugs that have red warnings (critical interactions), medium-risk drugs are in accordance with the yellow warnings (potentially problematic interactions) and low-risk drugs are in accordance

with green warnings (unproblematic interactions). This could either be because the Delphi panel consulted this database prior to scoring each drug, or it could be so because the interactions mentioned in the database were based on clinically available data and, thus, considered clinically relevant by the experts.

Consensus in the Delphi process was reached for 51% of drugs or drug classes causing harm and for 56% of drugs or drug classes causing interactions. Studies have found that facts are easier to agree upon than problems that require an element of judgment [14-17]. Examples of facts are laboratory tests and drug levels, whereas clinical judgment is required when evaluating questions like "is the risk low, medium or high for a patient to suffer from death, life-threatening events, hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity if an error occurs with this drug?"

The Delphi panel consisted of physicians from various medical fields, general practitioners, clinical pharmacologists and employees of the health authorities. Various fields of expertise were represented in the panel in order to ensure that there were at least a few experts with in-depth knowledge of all drugs/drugs classes in the panel. This meant that some experts did not have experience with drugs outside their medical specialty and therefore tended to score these drugs as medium-risk (score 5) drugs for both harm and interaction when this was the case. This causes the evaluation to regress towards the mean, and this may also explain why the group of medium risk is, by far, the largest in the list of drugs that cause patients harm as well as the list of drugs that cause interactions . Additionally, four pharmacists were included. The pharmacists should preferably have clinical experience; however, only one of them worked in clinic practice. Interestingly, the pharmacists' scores were lower in 32 instances, and in only 15 instances they scored the drugs higher than the medical doctors did. This is assumed to be a chance finding since no studies have previously published similar results.

There is no consensus in the literature concerning the definition of high-risk drugs, also called high-alert medication. The American Institute for Safe Medication Practices (ISMP) uses the definition: "Medications that bear a heightened risk of causing significant patient harm when they are used in error [18]". This definition includes all kinds of errors, but when we studied the list of drugs, we found that many of these represent highly specialised drugs like chemotherapeutics or anesthetics. Likewise, the National Agency for Patients' Rights and Complaints in Denmark created a list of medicines [19]. Their definition includes risk of MEs in all stages of the medication process and therefore includes administration errors and dispensing errors, contrary to our study. Furthermore, this list includes drugs handled by healthcare professionals, whereas we only included drugs for self-administration. Apart from this difference, the lists of drugs concerning self-administration are very similar.

The lists of high risk-drugs presented in this paper are different from the aforementioned lists, primarily because only drugs allowed for self-administration were included, and only drugs due to prescribing errors and errors from lack of monitoring of therapeutic efficacy were considered [5]. Consequently, this may imply that the risk of fatality for many of the drugs on our lists is lower; however, the overall consumption of these drugs is much higher and they are often used for long-term chronic conditions and therefore pose a more frequent and potentially harmful impact on patients health (e.g. antihypertensives) [5].

The risk stratification of drugs according to harm that was created in this Delphi process could be incorporated into an electronic risk score. Consequently, patients treated with several high-risk drugs would have a high score, which ideally should increase the physician's attention to these patients.

Consensus in the Delphi process could have been increased by adding a third round; however, the number of participants was likely to decline even more and cause a decrease in accuracy due to a higher level of random error [20]. Furthermore, several studies have shown that the main part of improvement in consensus and the main effect of feedback concerning accuracy takes place between round one and two [20].

CONCLUSIONS

Using a modified Delphi process, we created two lists of drugs with a low, a medium and a high risk of causing either interactions or harm to patients. The lists confirm a previous literature search concerning evaluation of the drugs with the highest risk and furthermore extend this knowledge underpinning the clinical relevance of the findings. These lists could ideally be challenged in a tool that stratifies individual patient risk from drug therapy to facilitate resource allocation for patients who are at a high risk of serious MEs.

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