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Determination of risk factors for drug-related problems:

A multidisciplinary triangulation process

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ABSTRACT

Introduction

Drug-related problems (DRPs) constitute a frequent safety issue among hospitalised patients leading to patient harm and to increased healthcare costs. Because many DRPs are preventable, the specific risk factors that facilitate their occurrence are of considerable interest. Identifying patients at risk for DRPs will enable clinical pharmacists to guide and target preventive measures in patients where they are needed most.

Methods

We conducted an expert panel, using the nominal group technique (NGT) and a qualitative analysis, to gather risk factors for DRPs. The expert panel consisted of two senior hospital physicians (internal medicine and geriatrics), one emergency physician, one general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse and two community pharmacists. The literature was searched for additional risk factors. Gathered factors from the literature search and the NGT were assembled and validated in a Delphi questionnaire.

Results

The NGT resulted in the identification of 33 items with an additional 13 risk factors from the qualitative analysis of the discussions. The literature search delivered another 39 risk factors. The 85 risk factors were refined to produce 42 statements for the Delphi online questionnaire. Of these, 27 risk factors were judged to be “important” or “rather important”.

Conclusion

The gathered risk factors will help to characterise and identify patients at risk for DRPs and will enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. As a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Strengths and limitations of this study:

- This research project followed a comprehensive triangulation method to gather risk factors for drug related problems integrating experts’ opinion and literature data, which represents – to our knowledge a new approach in this topic.
- Participating experts represented a wide variety of settings of patient care and steps in the medication process. This allowed a broad view on the topic of DRPs.
- Inviting actively practising healthcare professionals as experts ensures the practical relevance of gathered risk factors.

- The restricted number of participants in the NGT may have limited the diversity of risk factors.

INTRODUCTION

Drug-related problems (DRPs), defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”,[1] constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. The term DRP embraces medication errors (MEs), adverse drug events (ADEs), and adverse drug reactions (ADRs). A medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer“.[2] An adverse drug event can be defined as “an injury – whether or not causally related to the use of a drug”.[3] Adverse drug reactions include “any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological functions”.[4] In a systematic review of the years from 1991 to 2001, Krähenbühl et al. found that approximately 8% of hospitalised patients experience an ADE, and 5-10% of all drug prescriptions or drug applications are erroneous.[5] In general internal medicine, about 15% of hospitalised patients and 12% to 17% of patients after discharge experience ADEs.[6, 7] In a group of 435 patients with discharge prescriptions from six different European countries, Paulino et al. found a DRP in at least 63% of cases.[8] In a Swiss study, 89 of 264 (34%) discharge prescriptions contained qualitative deficiencies and 72 (27%) showed DRPs.[9] Thus, unplanned medication-related readmissions within a short time after discharge are frequent. In a multicentre, observational study with a prospective follow up, 5.6% of 12,793 unplanned admissions were medication-related and of these, 46.5% were potentially preventable.[10]

Because DRPs are an important problem and many of them are preventable, the specific risk factors that facilitate the occurrence of DRPs are of considerable interest. Previous studies have determined numerous risk factors for DRPs. In a literature review, female sex, polypharmacy, administration of drugs with a narrow therapeutic range, renal elimination, age over 65 years, and the use of oral anticoagulants and diuretics were identified as relevant risk factors for ADEs and ADRs.[5] Leendertse and colleagues considered risk factors, such as four or more comorbidities, polypharmacy, dependent living situation, impaired cognition, impaired renal function, and non-adherence to medication regimen as independent and significant risk factors potentially responsible for preventable hospital admission.[10]

These publications mostly rely on retrospective data and often focus on specific points in the whole care process of a patient, e.g. hospital admission or discharge. Thus, data from the literature might not fully reflect the current problems of practising healthcare providers, especially when the information comes from another country with a completely different health care system. Few studies used a qualitative approach and attempted to reflect real-life situations by interviewing patients and healthcare providers. Risk factors reported in such studies differed from those found in quantitative studies. Howard et al. conducted qualitative interviews with patients, general practitioners, and community pharmacists and concluded that communication failures and knowledge gaps at multiple stages in the medication process are important risk factors for preventable drug-related admissions.[11] A combination of both a qualitative and a quantitative approach in gathering risk factors for DRPs has not been very prevalent in the current literature.

The aim of our study was to determine the individual risk factors for DRPs by combining current evidence from the literature with the professional experience of healthcare providers throughout the entire medication process. A triangulation process with quantitative and qualitative research methods in combination with consensus techniques served as a comprehensive approach to bridge the gap between research results and professional experience. It is hoped that this will lead to a list of risk factors for DRPs that accurately reflects the reality of daily practice. Risk factors collected will help to characterise and identify patients at risk for DRPs and will enable clinical pharmacists to guide and target preventive measures in order to minimise the occurrence of DRPs.

METHODS

Nominal group technique

As method for eliciting risk factors we used the nominal group technique (NGT).[12-14] We set up an expert panel consisting of two senior hospital physicians (internal medicine and geriatrics), one emergency physician, one general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse, and two community pharmacists. The selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience.

The moderator (CK) started the NGT meeting with a short introduction to the topic with the aim of communicating the goal of the meeting and bringing everybody's knowledge about drug-related problems up to the same level. The participants were then asked to write down as many risk factors for DRPs as they could spontaneously think of. To avoid double-nominations, synonyms, and very closely related terms (e.g. "dementia" and "cognitive impairment"), two clinical pharmacists (ML, DS) and a community pharmacist (KH) grouped the gathered risk factors while retaining each individual factor in the list. Subsequently, we presented the collected risk factors to the participants and invited them to rank each risk factor by its relevance. Each expert allocated 50 points (1.5 times the number of risk factors [=33]). Experts could assign as many points to as many of the risk factors as they wanted until all points were used. After the first ranking, we collected the ranking sheets and summarised the points to create a first ranking list. We discussed the ranking list with the expert panel, paying special attention to high and low scoring and discrepancies in the ranking among participants. In the second round of the ranking process, panellists had only as many points as the number of available risk factors, forcing them to fine-tune their previous ranking and to reach a consensus. We collected the rerated lists, created the new ranking, and then returned the resulting ranking list to all participants for final comments.

We audiotaped the entire discussion session of the expert panel and transcribed it into a written text for qualitative analysis. Two of the authors (CK, DS) split the transcript in fragments and rearranged them by grouping the fragments treating related subjects. We labelled every fragment with a unique index number to assure transparency.

Literature search

In addition to the results of the expert panel we conducted a non-systematic literature search. Our goal was to gain an impression of the current state of research in the field of risk factors leading to drug-related problems. We wanted to know which risk factors for drug-related problems were described in current literature and which ones were most mentioned. We conducted our search on PubMed and Embase. Language was restricted to German and English. The following search terms were used in Embase: ‘drug related problems' AND 'risk'/exp AND factors AND [systematic review]/lim AND ([english]/lim OR [german]/lim) AND [humans]/lim.; 'Triage'/exp OR 'triage'/syn AND ('risk'/exp OR 'risk'/syn) AND assessment AND ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([meta-analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim).; 'Adverse drug reaction'/exp AND 'screening'/exp AND 'high risk patient'/exp AND [humans]/lim AND [english]/lim

The following search terms were used in PubMed:

"Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Drug Toxicity"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; (("Drug Toxicity"[Mesh]) OR "Medication Errors"[Mesh]) AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Medication Errors"[Mesh] AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; ("Risk Factors"[MeSH Terms]) AND "Hospitalization/statistics and numerical data"[MAJR]

"Risk Assessment/methods"[MeSH Terms] AND "Medication Errors"[Mesh]

Titles and abstracts were screened for relevance. Abstracts needed to mention the terms “risk factors”, “predictors”, or “high risk” in combination with “drug related problems” or subterms of its definition. The study design had to be a controlled trial, a cohort study, or a case-control study.

We checked the reference list of each paper selected for further possible hits. Besides this literature search, we reviewed different tools focusing on the assessment of inappropriate prescribing which we identified in a previous systematic review.[15] Inappropriate prescribing is a known source of DRPs, ADEs, and ADRs. Original publications of these tools were screened for risk factors associated with inappropriate prescribing that are connected with negative outcomes, e.g. DRPs, ADEs, ADRs, and rehospitalisation. PubMed and Embase were searched for validation studies using the name of the tool and if necessary “outcome” or “assessment” as MeSH terms or by checking publications which cited the original paper.

Delphi process

We validated the risk factors collected from the literature search and the NGT by using the Delphi technique.[16] Before integrating the risk factors in the questionnaire, we condensed them by using the following exclusion criteria:

- The risk factor is mentioned in only one of the relevant publications.
- The risk factor, set in the lowermost quartile of our nominal group technique's ranking list, is not mentioned anywhere else.
- The risk factor is categorised as an issue of seamless care (e.g. lack of communication between healthcare professionals, patient information, and discharge management).
- The risk factor represents a hardly predictable event or circumstance (e.g. unscheduled discharge, confusion of drug names by professionals).

We excluded seamless care issues, because they are not individual risk factors, but instead reflect system failures; they are, therefore, not assessable for an individual patient.

In a two-round online Delphi survey (Flexi Form, In. 2.0 ed.) the NGT participants rated each risk factor on a four-item Likert scale (1 = "unimportant", 2= "rather unimportant", 3= "rather important", 4 = "important") according to its potential to cause DRPs.

The questionnaire for the second rating included the same questions as the first one, but the sequence represented the ranking list of the first round. We presented the median score and the inter-quartile range (*IQR)* of each question to the participants to give them the possibility to consider the group's rating for their own re-rating. Below the Likert scale of each question, the number of participants, who rated for the respective relevance, was shown. After the second rating, the median scores and IQRs were calculated and a final ranking list of risk factors collected was established.

RESULTS

NGT rating and literature search (see figure 1):

The ranking process of the NGT resulted in 33 items. We extracted 13 additional risk factors from the qualitative analysis of the discussion. The literature search resulted in additional 39 factors, which were not mentioned in the NGT.

Delphi questionnaire:

In total, we gathered a preliminary list of 85 risk factors. Of these, we excluded 38 risk factors because they fulfilled our exclusion criteria (see table 1). Twice, we split a risk factor into two parts, and we eliminated seven synonyms. Ultimately, we used 42 risk factors in the Delphi questionnaire.

In table 2a&b, the results of the Delphi technique are shown. They are arranged by median score of the second round. In the second round, 10 risk factors were assessed as “important” (Likert scale: 4) concerning their contribution to the occurrence of DRPs, 17 risk factors as “rather important” (Likert scale: 3), 15 risk factors as “rather unimportant” (Likert scale: 2), and none as “unimportant” (Likert scale: 1). The sum of the IQRs changed from 30 in the first round to 20 in the second round representing a stronger consensus between the participants. Finally, we created a list of 27 risk factors, rated as important or rather important for the occurrence of drug-related problems.

Table 1: Risk factors excluded from the Delphi questionnaire

Exclusion category	Risk factors
Mentioned in only one of the selected publications	heart failure; liver disease (not hepatic impairment); problems with "water works"; antidepressant; drugs with positive inotrope effects, potassium channel activators; antibacterial drugs; laxatives; corticosteroids for inhalation, loperamide; statins; cephalosporins; compound analgesics (with opioids); low molecular weight heparins; macrolide antibiotics; penicillin; aspirin; salbutamol; antihypertensives; bladder antimuscarinic drugs; cerebral vasodilators; nitroglycerine; ranitidine; 1st generation antihistamines
Lowermost quartile of the NGT ranking list and not mentioned elsewhere	money; Morbus Parkinson; xerostomia; oral bisphosphonate
Seamless care issue or intervention to improve seamless care	unclear prescription/unclear or non-available dosage regimen at discharge; multiple treating physicians; missing instruction of relatives; medication-taking gap; briefing of the patient
Synonym terms	- behaviour at home during an ADR; earlier experiences with medication → included as: experience with ADR - impaired mobility → included as: High risk of falls, motion insecurity - language → included as: language issues - oral corticosteroid; systemic corticosteroids → included as: corticosteroids - parallel therapy →incl. as: self-medication with non-prescribed medicines
Unpredictable event or circumstance	confusion of drug names; new medication / lots of changes/ alternating dosages; changes in therapy: stop due to hospitalisation/discharge/generic medication; unscheduled discharge

Table 2a: Final ranking list of the 27 risk factors contributing to the occurrence of DRPs rated by the expert panel as important or rather important. The sequence represents the ratings of the Delphi survey indicating median ratings and interquartile range [IQR]), and appearance in the literature. Factors with no reference in the literature section, were only mentioned by the experts.

Risk factor	Delphi		Literature
	Median	IQR	
Dementia, cognitive situation, Low IQ, confused patient	4	4.00 – 4.00	Leendertse [10], McCusker [17], Meldon [18], Runciman [19], Gallagher [20]
Polypharmacy (number of drugs >5)	4	4.00 – 4.00	Leendertse [10], McCusker [17], Meldon [18], Hanlon [21], Onder [22], Krähenbühl-Melcher [5]
Antiepileptics	4	4.00 – 4.00	Howard [23, 24], Gallagher [20], Hamilton [25]
Anticoagulants	4	4.00 – 4.00	Leendertse [10], Hanlon [21], Howard [23], Davies [26], Krähenbühl-Melcher [5]
Combinations of non-steroidal anti-inflammatory drugs (NSAID) and oral anticoagulants	4	4.00 – 4.00	Gallagher [20]
Insulin	4	4.00 – 4.00	Leendertse [10], Howard [23, 24]
Missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy	4	4.00 – 3.25	Howard [11]
Medication with a narrow therapeutic window	4	4.00 – 3.25	Krähenbühl-Melcher [5]
Non-adherence	4	4.00 – 3.00	Leendertse [10]
Polymorbidity	3.5	4.00 – 3.00	Leendertse [10], Onder [22]
Digoxin	3	4.00 – 3.00	Howard [24], Gallagher [20], Lipton [27]
Renal impairment (eGFR <30 ml/min)	3	4.00 – 3.00	Leendertse [10], Onder [22], Gallagher [20]
NSAIDs	3	4.00 – 3.00	Leendertse [10], Hanlon [21],Howard [23, 24],Hamilton [5,

Risk factor	Delphi		Literature
	Median	IQR	
			25]
Experience of ADR	3	3.75 – 3.00	Onder [22]
Medication which is difficult to handle	3	3.75 – 3.00	
Language issues (i.e. non-native speakers)	3	3.00 – 3.00	
Diuretics	3	3.00 – 3.00	Leendertse [10], Howard [23, 24], Davies [26], Runciman [19], Hamilton [25], Krähenbühl-Melcher [5]
Tricyclic antidepressants	3	3.00 – 3.00	Hanlon [21], Gallagher [20]
Hepatic impairment	3	3.00 – 3.00	Onder [22], Gallagher [20]
Self-medication with non-prescribed medicines	3	3.00 – 3.00	
Impaired manual skills (causing handling difficulties)	3	3.00 – 3.00	
Visual impairment	3	3.00 – 3.00	McCusker [17]
Anticholinergic drugs	3	3.00 – 3.00	Laroche [28]
Benzodiazepines	3	3.00 – 3.00	Hanlon [21], Gallagher [20], Laroche [28], Hamilton [25], Berdot [29]
Opiates/Opioids	3	3.00 – 3.00	Leendertse [10], Howard [23], Davies [26], Gallagher [20], Hamilton [25]
Corticosteroids	3	3.00 – 2.00	Leendertse [10], Howard [23, 24]
Oral antidiabetics	3	3.00 – 2.00	Leendertse [10], Howard [23, 24]

Table 2b: Risk factors contributing to the occurrence of DRPs rated from the expert panel as rather unimportant and therefore not included in the final list of risk factors

Risk factor	Delphi		Literature
	Median	IQR	
Age	2.5	3.75 – 2.00	Marcantonio [30], Krähenbühl-Melcher [5]
Extreme body weight (too high or too low)	2	3.00 – 2.00	
Antiplatelet drugs	2	3.00 – 2.00	Leendertse [10], Howard [23, 24]
Drugs affecting the renin-angiotensin-aldosterone-system (RAAS)	2	3.00 – 2.00	Leendertse [10], Howard [23]
Patient living alone	2	3.00 – 2.00	Meldon [18], Runciman [19], Rowland [31]
Calcium antagonists	2	3.00 – 2.00	Leendertse [10], Howard [23], Gallagher [20]
Nitrates	2	3.00 – 2.00	Howard [23, 24]
Patient's education about his therapy	2	2.75 – 2.00	Howard [11]
Beta-blockers	2	2.00 – 2.00	Leendertse [10], Howard [23, 24], Gallagher [20], Hamilton [25]
Antacids	2	2.00 – 2.00	
High risk of falls, motion insecurity	2	2.00 – 2.00	Meldon [18], Runciman [19], Rowland [31], Gallagher [20], Hamilton [25], Laroche [28], Berdot [29]
Previous hospitalisation in the last 30 days	2	2.00 – 2.00	McCusker [17], Meldon [18], Marcantonio [30]
Need for caregiver at home	2	2.00 – 2.00	Leendertse [10]
Calcium containing drugs	2	2.00 – 1.00	Lipton [27]
Respiratory drugs	2	3.00 – 1.00	Leendertse [10], Howard [23], Davies [26]

NGT discussion:

The qualitative analysis of the discussion confirmed the factors identified in the rating process but also revealed additional 13 risk factors. Main topics were high-risk drugs, communication issues between healthcare professionals, patient education and questions of responsibility.

The experts agreed that high-risk drugs frequently associated with drug-related problems. Noted high-risk drugs were drugs with a narrow therapeutic window, those which are difficult to handle, or those with a high risk for serious ADEs. *"Medication with a narrow therapeutic range is always a challenge in management"* (PHARMACOLOGIST). In a short discussion they stated their points of concern. *"The combination of non-steroidal anti-rheumatics and anticoagulants is what we see most within the emergency unit. If we are having problems with medications, it is this combination."* (EMERGENCY PHYSICIAN)

Insufficient information transfer between the primary and secondary care setting was mentioned as a big handicap in daily practice. Problems already start at hospital admission where patients often arrive without any information about their current long-term medication. In the emergency department, physicians need to treat the patients without having sufficient knowledge of current diagnosis and therapies. *"Sunday afternoon on the emergency ward, we received a geriatric patient, collapsed at home, disoriented and neglected and polymorbid for sure. And in this moment in time, we had no idea what medication this man has currently been taking"* (EMERGENCY PHYSICIAN). During the hospital stay, the medication of the patient undergoes significant changes. Lack of communication among the different healthcare providers leads to confusion. What information is the most accurate one? Which medication should be stopped at discharge? Did we record every medication the patient has to take after his/her hospital stay? Did we restart the therapies that had been discontinued at admission? *"On the emergency ward, I often have to stop parts of a patient's long-term medication, because it causes more harm than benefit in this situation. Unfortunately, this*

medication often remains stopped and is not restarted at the point of discharge." (EMERGENCY PHYSICIAN)

Physicians underscored that junior physicians struggle with long working hours and time pressure. They are challenged by ill patients, worried relatives, and demanding healthcare providers. *"For our residents, medication safety is one of ten problems they see during the day. It would be useful to support them concerning the pharmacotherapy*" (HOSPITAL PHYSICIAN).Their lack of time to carefully check all discharge prescriptions and discuss medication issues with the patients seems to be a source for DRPs. *"We often see discharge prescriptions with a mixture of brand names and generic drug names and lots of changes in the long-term medication of the patient. Without proper instruction, the patient goes home and overdoses himself, because he got confused."* (CLINICAL PHARMACIST) Panellists from every healthcare area emphasised the importance of patient information. They were aware that patients' knowledge about their medication is often incomplete. Self-medication is seldom mentioned in the discussion with the healthcare professionals, because the patient does not regard his/her vitamin pills and herbal supplements as a real medication. Community pharmacists complain about having insufficient access to patients' medical records which hinders them in advising the patient in a comprehensive way. *When I ask the patient about his/her long-term medication, he/she tells me, that he/she does not take any medication at all. When I ask more precisely, the patient tells me about over-the-counter (OTC) drugs, vitamin supplements, etc. Patients do not regard the tablets purchased by themselves in a supermarket as real medication."* (COMMUNITY PHARMACIST)

To improve the education of patients and to guarantee the transfer of information about patients' medication, panellists acknowledged the benefit of appointing an individual who would be responsible for the medication management and the education of the patient.

The experts stated that an ideal medication manager should be walking across all floors of the hospital, meeting with newly admitted patients, compiling a complete medication history,

and checking for DRPs. This medication manager should monitor the patient throughout the hospital stay and at the patient's discharge, be the one who does the final medication check to identify potential DRPs and to ensure that the patient understands the prescribed therapy and knows how to take the medication. After discharge, the medication manager should ensure that the correct information is shared with the community pharmacy and the general practitioner in order to guarantee seamless care. The medication manager should serve as a consultant and not as a replacement for the prescribing physician. The panellists considered clinical pharmacists or pharmacologists the most appropriate professionals for this task, due to their broad knowledge about medication.

DISCUSSION

We were able to determine 27 risk factors which seem to contribute substantially to the occurrence of DRPs. The triangulation, for which we used the nominal group technique with its rating process, the expert panel, and a literature search, enhanced the accuracy of our findings and ensured their practical relevance. In agreement with previous quantitative studies, we identified in our literature search expected and well-known risk factors. With the inclusion of the expert panel, we gained valuable risk factors often seen in their daily practice and rarely described in the literature. The composition of the expert panel was multidisciplinary by choice, because we aimed to bring together all stakeholders in the medication process of a patient. By performing an NGT instead of interviews, we gave the panellists the possibility not only to answer to our questions, but to discuss their different views with other healthcare professionals. The panellists were highly motivated and held an engaged and informative discussion. Despite their different professional backgrounds, they agreed on many discussion points. They appreciated the interdisciplinary exchange and found that it would be worthwhile to conduct such discussion rounds more frequently.

The ensuing Delphi process enabled the desired consensus-forming. By conducting the Delphi process with online questionnaires, where the participants were anonymous, we avoided any psychosocial biases. In the first round, the total amount of IQRs was 30.0, whereas it was 20.0 in the second round. This means that the degree of consensus increased amongst the participants.

Study limitations

There are some general concerns about the validity and generalisability of information created by qualitative research methods. Both the Delphi and NGT approaches are often criticised for showing a lack of research-based evidence concerning diverse feedback methods and their influence on the validity and reproducibility of the decisions reached by the panel members.[14] Other influences on the whole group dynamic are psychosocial biases,

which were described by Pagliari and colleagues.[32] We addressed this by assigning each panellist a place in the NGT in order to avoid grouping of friends or panellists with the same profession. We decided to use a small expert panel with 10 panellists. Although larger groups would provide a more extensive representation, they may be difficult to lead, which may only be resolved by introducing more structure and role definition into the process.[32]

A limitation of our Delphi technique after employing NGT is the restricted number of participants. We chose the same very motivated experts for the Delphi and the NGT, because they were already familiar with the topic.

In conclusion, the gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. In a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Contributions of authors statement (with relevance to the ICMJE Guidelines):

C.P. Kaufmann:
Contribution to the study design and the analysis and interpretation of data, manuscript writing, final approval of the version to be published.
Substantially involved in the literature search, the conduction of the Nominal Group Technique (NGT) and the Delphi questionnaire.

D. Stämpfli:
Contribution to the study design and the analysis and interpretation of data, the literature search, the conduction of the NGT and the Delphi questionnaire.

K.E. Hersberger:
Manuscript review and final approval of the version to be published

M.L. Lampert:
Contribution to the study design and the analysis and interpretation of data, the NGT and Delphi survey. Did the manuscript review and contributed to the final approval of the version to be published

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Competing interests:

The authors declare that they have no conflicts of interest.

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Data sharing statement:

No additional data available

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LEGEND OF FIGURES

Figure 1: Flow chart of eliciting risk factors possibly leading to DRPs.

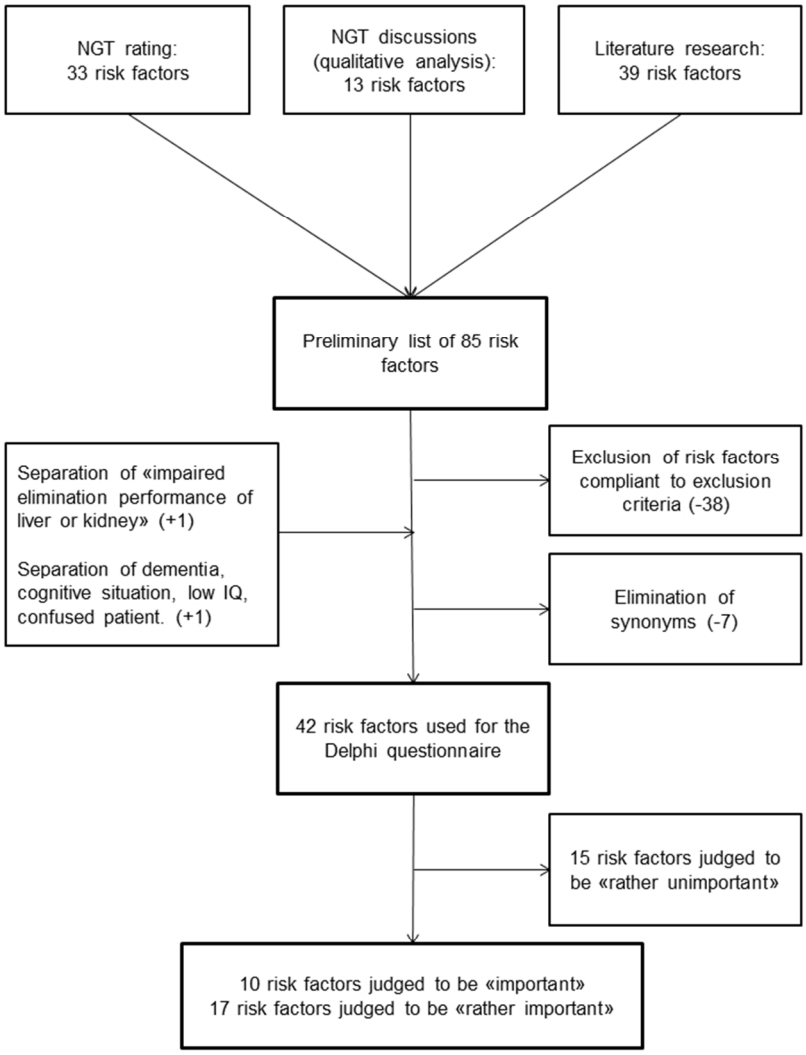

Figure 1: Flow chart of eliciting risk factors possibly leading to DRPs.
190x275mm (96 x 96 DPI)

Research Checklist

Determination of risk factors for drug-related problems: A multidisciplinary triangulation process

Completed COREQ Checklist

We would like to emphasize, that our research study followed a comprehensive approach with the combination of qualitative and **quantitative** research. The COREQ Checklist was applied only for the qualitative part of the study.

1. Interviewer/facilitator (see page 5)

CK conducted the Nominal Group Technique (NGT)

2. Researcher's credentials

CK: MSc Pharm, Clinical Pharmacist

DS: MSc Pharm

KH: Professor, PhD

ML: PhD, Clinical Pharmacist

3. Occupation

CK: PhD Student at the Pharmaceutical Care Research Group, Clinical Pharmacist at the Kantonsspital Baselland

DS: Pharmacist in a community pharmacy

KH: Head of the Pharmaceutical Care Research Group at the University of Basel, Community Pharmacist

ML: Senior researcher and lecturer at the Pharmaceutical Care Research Group, Deputy chief pharmacist and Clinical Pharmacist at the Kantonsspital Baselland

4. Gender

CK: female

DS, KH, ML: male

5. Experience and training

The principal researcher (CK) has no formal education or training in qualitative research. But she provided a professional background with large experience in detecting and managing drug-related problems as a result of the work as a clinical pharmacist. And as a PhD-Student, CK is used to work scientifically, what enabled her to conduct the NGT in a professional way.

6. Relationship established

	CK	DS	KH	ML
Hospital physician 1	A	X	C	A
Hospital physician 2	B	X	X	B
Emergency physician	B	X	C	B
General practitioner	X	X	C	X
Clinical pharmacologist	X	X	C	C
Clinical pharmacist	C	X	C	C
Nurse	X	X	X	C
Home care nurse	X	X	X	X
Community pharmacist 1	X	X	X	X
Community pharmacist 2	C	x	C	C

Legend: A: professional relationship in the same institution on a regular basis B: professional relationship in the same institution irregularly C: professional relationship sporadically x: no relationship

7. Participant knowledge of the researcher

The researcher (CK) introduced herself, the background and the aim of her research study to the participants at the first contact per mail as well as at the beginning of the NGT.

8. Interviewer characteristics

We reported the interest of the researcher in the research topic (PhD-Project, general Interest as a clinical pharmacist on the improvement of the patient safety).

9. Methodological orientation and Theory

Information to the background of our research project is explained in the introduction part of the manuscript (see page 3-4 in the manuscript)

10. Sampling (see page 5)

Purposive, the selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience.

11. Method of approach (see page 5)

The experts where contacted by email. The email contained basic information about the study and the request for participating in the NGT.

12. Sample size (see page 5)

Ten experts participated in the study

13. Non-participation

One expert refused to participate due to a lack of time.

14. Setting

The NGT was held in a conference room at the University of Basel

15. Presence of Non-Participants

No one else was present besides the participants and researchers

16. Description of sample (see page 5)

The experts were all medical professionals and every expert needed to have at least 5 years of professional experience.

17. Interview guide (see page 5)

The author CK guided the NGT and provided the questions for the participants.

18. Repeat interview

The expert meeting was carried out once. No repeat interviews were carried out.

19. Audio/visual recording (see page 5)

The whole expert meeting was audiotaped.

20. Field notes

No major field notes where made.

21. Duration

The expert meeting lasted for two hours.

22. Data saturation (see page 5)

The structure and duration of the NGT was predefined by the authors. The highly structured methodology of the NGT determined to a high degree the data saturation. The NGT discussion aimed at a satisfactory level of consensus.

23. Transcripts returned (see page 5)

The transcript of the expert meeting was not returned to the participants.

24. Number of data coders (see page 5)

DS and CK coded the data

25. Coding tree (see page 5)

The authors DS and CK labelled every fragment with a unique index number to assure transparency. No coding tree was necessary.

26. Derivation of themes

Themes were derived from the gathered data.

27. Software (see page 5)

An excel database was used to manage the data. We did not use any other software.

28. Participant checking (see page 5)

Participants had the possibility to provide feedback to the findings in the Delphi-Questionnaire following the NGT. No participant provided feedback.

29. Quotations presented (see page 13-15 of the manuscript)

Participant quotations were presented and each quotation was identified.

30. Data and findings consistent (see page 8-15 of the manuscript)

Presented data underlined our findings.

31. Clarity of major themes (see page 8-15 of the manuscript)

Major themes were clearly presented in the results-part of the manuscript.

32. Clarity of minor themes (see page 8-15 of the manuscript)

Minor themes were presented in the results- part of the manuscript.

BMJ Open

Determination of risk factors for drug-related problems: A multidisciplinary triangulation process

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Determination of risk factors for drug-related problems:

A multidisciplinary triangulation process

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ABSTRACT

Introduction and objectives: Drug-related problems (DRPs) constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. Because many DRPs are preventable, the specific risk factors that facilitate their occurrence are of considerable interest. The objective of our study was to assess risk factors for the occurrence of DRPs with the intention to identify patients at risk for DRPs to guide and target preventive measures in patients where they are needed most.

Design: Triangulation process using a mixed methods approach.

Methods: We conducted an expert panel, using the nominal group technique (NGT) and a qualitative analysis, to gather risk factors for DRPs. The expert panel consisted of two senior hospital physicians (internal medicine and geriatrics), one emergency physician, one general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse and two community pharmacists. The literature was searched for additional risk factors. Gathered factors from the literature search and the NGT were assembled and validated in a two-round Delphi questionnaire.

Results: The NGT resulted in the identification of 33 items with additional 13 risk factors from the qualitative analysis of the discussion. The literature search delivered another 39 risk factors. The 85 risk factors were refined to produce 42 statements for the Delphi online questionnaire. Of these, 27 risk factors were judged to be “important” or “rather important”.

Conclusion: The gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. As a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Strengths and limitations of this study:

- This research project followed a comprehensive triangulation method to gather risk factors for drug related problems integrating experts’ opinion and literature data, which represents – to our knowledge a new approach in this topic.
- Participating experts represented a wide variety of settings of patient care and steps in the medication process. This allowed a broad view on the topic of DRPs.
- Inviting actively practising healthcare professionals as experts ensures the practical relevance of gathered risk factors.
- The restricted number of participants in the NGT may have limited the diversity of risk factors.

INTRODUCTION

Drug-related problems (DRPs), defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”,[1] constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. The term DRP embraces medication errors (MEs), adverse drug events (ADEs), and adverse drug reactions (ADRs). A medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer“.[2] An adverse drug event can be defined as “an injury – whether or not causally related to the use of a drug”.[3] Adverse drug reactions include “any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological functions”.[4] In a systematic review of the years from 1991 to 2001, Krähenbühl et al. found that approximately 8% of hospitalised patients experience an ADE, and 5-10% of all drug prescriptions or drug applications are erroneous.[5] In general internal medicine, about 15% of hospitalised patients and 12% to 17% of patients after discharge experience ADEs.[6, 7] In a group of 435 patients with discharge prescriptions from six different European countries, Paulino et al. found a DRP in at least 63% of cases.[8] In a Swiss study, 89 of 264 (34%) discharge prescriptions contained qualitative deficiencies and 72 (27%) showed DRPs.[9] Thus, unplanned medication-related readmissions within a short time after discharge are frequent. In a multicentre, observational study with a prospective follow up, 5.6% of 12,793 unplanned admissions were medication-related and of these, 46.5% were potentially preventable.[10]

Because DRPs are an important problem and many of them are preventable, the specific risk factors that facilitate the occurrence of DRPs are of considerable interest. Previous studies have determined numerous risk factors for DRPs. In a literature review, female sex, polypharmacy, administration of drugs with a narrow therapeutic range or renal elimination, age over 65 years, and the use of oral anticoagulants and diuretics were identified as relevant risk factors for ADEs and ADRs.[5] Leendertse and colleagues considered risk factors, such as four or more comorbidities, polypharmacy, dependent living situation, impaired cognition, impaired renal function, and non-adherence to medication regimen as independent and significant risk factors potentially responsible for preventable hospital admission.[10]

These publications mostly rely on retrospective data and often focus on specific points in the whole care process of a patient, e.g. hospital admission or discharge. Thus, data from the literature might not fully reflect the current problems of practising healthcare providers, especially when the information comes from another country with a completely different health care system. Few studies used a qualitative approach and attempted to reflect real-life situations by interviewing patients and healthcare providers. Risk factors reported in such studies differed from those found in quantitative studies. Howard et al. conducted qualitative interviews with patients, general practitioners, and community pharmacists and concluded that communication failures and knowledge gaps at multiple stages in the medication process are important risk factors for preventable drug-related admissions.[11] A combination of both a qualitative and a quantitative approach in gathering risk factors for DRPs has not been very prevalent in the current literature.

The aim of our study was to determine the individual risk factors for DRPs by combining current evidence from the literature with the professional experience of healthcare providers throughout the entire medication process. A triangulation process with quantitative and qualitative research methods in combination with consensus techniques served as a comprehensive approach to bridge the gap between research results and professional experience. It is hoped that this will lead to a list of risk factors for DRPs that accurately reflects the reality of daily practice. Risk factors collected will help to characterise and identify patients at risk for DRPs and will enable clinical pharmacists to guide and target preventive measures in order to minimise the occurrence of DRPs.

METHODS

Nominal group technique (NGT)

As method for eliciting risk factors we used the NGT.[12-14] We set up an expert panel consisting of two consultant hospital physicians (internal medicine and geriatrics), one emergency physician, one independent general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse, and two independent community pharmacists. The selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience, held a senior/executive position and was involved in daily patient care.

We set the duration of the NGT to 2 hours. The moderator (CK) started the NGT meeting with a short introduction to the topic with the aim of communicating the goal of the meeting and bringing everybody's knowledge about DRPs up to the same level. The participants were then asked to write down as many risk factors for DRPs as they could spontaneously think of. To avoid double-nominations, synonyms, and very closely related terms (e.g. "dementia" and "cognitive impairment"), two clinical pharmacists (ML, DS) and a community pharmacist (KH) grouped the gathered risk factors while retaining each individual factor in the list. Subsequently, we presented the collected risk factors to the participants and invited them to rank each risk factor by its relevance. Each expert allocated 50 points (1.5 times the number of risk factors [=33]). We determined the amount of points by ourselves. Experts should be able to rank every risk factor, instead of choosing a defined number of most important factors. However, we limited the amount of points to force a consensus finding. Experts could assign as many points to as many of the risk factors as they wanted until all points were used. After the first ranking, we collected the ranking sheets and summarised the points to create a first ranking list. We discussed the ranking list with the expert panel, paying special attention to high and low scoring and discrepancies in the ranking among participants. In the second round of the ranking process, panellists had only as many points as the number of available risk factors, forcing them to fine-tune their previous ranking and to reach a consensus. We collected the rerated lists, created the new ranking, and then returned the resulting ranking list to all participants for final comments. Because we worked neither with patient data nor with patients themselves, we did not need an ethical approval.

We audiotaped the entire discussion session of the expert panel and transcribed it into a written text for qualitative analysis. One of the authors (DS) split the transcript in fragments and a second author (CK) checked the splitting. Afterwards the two authors (DS, CK) together rearranged the fragments in groups treating related subjects. The whole grouping

was then discussed by three authors (CK, DS, ML). The level of agreement was good. Disagreements were discussed until the three authors reached consensus. We labelled every fragment with a unique index number to assure transparency.

Literature search

We conducted a non-systematic literature search to supplement the findings of the expert panel. Our goal was to gain an impression of the current state of research in the field of risk factors leading to DRPs. We wanted to know which risk factors for DRPs were described in current literature and which ones were most mentioned. We conducted our search on PubMed and Embase. Language was restricted to German and English. The following search terms were used in Embase: ‘drug related problems' AND 'risk'/exp AND factors AND [systematic review]/lim AND ([english]/lim OR [german]/lim) AND [humans]/lim.; 'Triage'/exp OR 'triage'/syn AND ('risk'/exp OR 'risk'/syn) AND assessment AND ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([meta-analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim).; 'Adverse drug reaction'/exp AND 'screening'/exp AND 'high risk patient'/exp AND [humans]/lim AND [english]/lim

The following search terms were used in PubMed:

"Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Drug Toxicity"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; (("Drug Toxicity"[Mesh]) OR "Medication Errors"[Mesh]) AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Medication Errors"[Mesh] AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; ("Risk Factors"[MeSH Terms]) AND "Hospitalization/statistics and numerical data"[MAJR]

"Risk Assessment/methods"[MeSH Terms] AND "Medication Errors"[Mesh]

Titles and abstracts were screened for relevance. Abstracts needed to mention the terms “risk factors”, “predictors”, or “high risk” in combination with “drug related problems” or subterms of its definition. ~~The study design had to be a controlled trial, a cohort study, or a case-control study.~~

We checked the reference list of each paper selected for further possible hits. Besides this literature search, we reviewed different tools focusing on the assessment of inappropriate prescribing which we identified in a previous systematic review.[15] Inappropriate prescribing is a known source of DRPs, ADEs, and ADRs. Original publications of these tools were screened for risk factors associated with inappropriate prescribing that are connected with negative outcomes, e.g. DRPs, ADEs, ADRs, and rehospitalisation. PubMed and Embase

were searched for validation studies using the name of the tool and if necessary “outcome” or “assessment” as MeSH terms or by checking publications which cited the original paper.

Delphi process

We validated the risk factors collected from the literature search and the NGT by using the Delphi technique.[16] Before integrating the risk factors in the questionnaire, we condensed them by using the following exclusion criteria:

- The risk factor is mentioned in only one of the relevant publications.
- The risk factor, set in the lowermost quartile of our NGTs ranking list, is not mentioned anywhere else.
- The risk factor is categorised as an issue of seamless care (e.g. lack of communication between healthcare professionals, patient information, and discharge management).
- The risk factor represents a hardly predictable event or circumstance (e.g. unscheduled discharge, confusion of drug names by professionals).

We excluded seamless care issues, because they are not individual risk factors, but instead reflect system failures; they are, therefore, not assessable for an individual patient. In addition, we combined synonyms in one term.

In a two-round online Delphi survey (Flexi Form, In. 2.0 ed.), following two months after the NGT, the NGT participants rated each risk factor on a four-item Likert scale (1 = “unimportant”, 2= “rather unimportant”, 3= “rather important”, 4 = “important”) according to its potential to cause DRPs.

The questionnaire for the second rating started two weeks after the end of the first rating and included the same questions as the first one, but the sequence represented the ranking list of the first round. We presented the median score and the inter-quartile range (*IQR)* of each question to the participants to give them the possibility to consider the group’s rating for their own re-rating. Below the Likert scale of each question, the number of participants, who rated for the respective relevance, was shown. After the second rating, the median scores and IQRs were calculated and a final ranking list of risk factors collected was established.

RESULTS

NGT rating and literature search (see figure 1):

The ranking process of the NGT resulted in 33 items. The qualitative analysis of the discussion confirmed risk factors identified in the rating process but also revealed additional 13 risk factors. Main topics were high-risk drugs, communication issues between healthcare professionals, patient education and questions of responsibility. The literature search resulted in additional 39 factors, which were not mentioned in the NGT.

Delphi questionnaire:

In total, we gathered a preliminary list of 85 risk factors. Of these, we excluded 38 risk factors because they fulfilled our exclusion criteria (see table 1). Twice, we split a risk factor into two parts, and we eliminated seven synonyms. Ultimately, we used 42 risk factors in the Delphi questionnaire.

In table 2a&b, the results of the Delphi technique are shown. They are arranged by median score of the second round. In the second round, 10 risk factors were assessed as “important” (Likert scale: 4) concerning their contribution to the occurrence of DRPs, 17 risk factors as “rather important” (Likert scale: 3), 15 risk factors as “rather unimportant” (Likert scale: 2), and none as “unimportant” (Likert scale: 1). The sum of the IQRs changed from 30 in the first round to 20 in the second round representing a stronger consensus between the participants. Finally, we created a list of 27 risk factors, rated as important or rather important for the occurrence of DRPs.

Table 1: Risk factors excluded from the Delphi questionnaire, including information to their origin. L: Literature search, N: NGT ranking list, Q: Qualitative analysis of the NGT

Excluded risk factors	
Mentioned in only one of the selected publications	heart failure(L); liver disease (not hepatic impairment)(L); problems with "water works"(L); antidepressant(L); drugs with positive inotrope effects(L), potassium channel activators(L); antibacterial drugs(L); laxatives(L); corticosteroids for inhalation(L), loperamide(L); statins(L); cephalosporins(L); compound analgesics (with opioids)(L); low molecular weight heparins(L); macrolide antibiotics(L); penicillin(L); aspirin(L); salbutamol(L); antihypertensives(L); bladder antimuscarinic drugs(L); cerebral vasodilators(L); nitroglycerine(L); ranitidine(L); 1st generation antihistamines(L)
Lowermost quartile of the NGT ranking list and not mentioned elsewhere	Money(N); Morbus Parkinson(N); xerostomia(N); oral bisphosphonate(N)
Seamless care issue or intervention to improve seamless care OR Unpredictable event or circumstance	unclear prescription/unclear or non-available dosage regimen at discharge(N); multiple treating physicians(L,N); missing instruction of relatives(N); medication-taking gap(N); briefing of the patient(L;Q); confusion of drug names(N); new medication / lots of changes/ alternating dosages(N); changes in therapy: stop due to hospitalisation/discharge/generic medication(N,Q); unscheduled discharge(N)
Synonyms	
- behaviour at home during an ADR(N); earlier experiences with medication (N,Q) → included as: experience with ADR (Q) - impaired mobility (L,N) → included as: High risk of falls, motion insecurity (L,N,Q) - language(Q) → included as: language issues (N) - oral corticosteroid (L); systemic corticosteroids (L) → included as: corticosteroids (L) - parallel therapy (N) →incl. as: self-medication with non-prescribed medicines (N,Q)	

Table 2a: Final ranking list of the 27 risk factors contributing to the occurrence of DRPs rated by the expert panel as “important” (Likert scale: 4) or “rather important” (Likert scale: 3).
The sequence represents the ratings of the Delphi survey indicating median ratings and interquartile range [IQR]), and appearance in the NGT ranking list, the qualitative analysis of the NGT and in literature. Factors with no reference in the literature section were only mentioned by the experts.

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Dementia, cognitive situation, Low IQ, confused patient	4	4.00 – 4.00	YES		[10], [17], [18], [19], [20]
Polypharmacy (number of drugs >5)	4	4.00 – 4.00	YES	YES	[10], [17], [18], [21], [22], [5]
Antiepileptics	4	4.00 – 4.00		YES	[23, 24], [20], [25]
Anticoagulants	4	4.00 – 4.00		YES	[10], [21], [23], [26], [5]
Combinations of non-steroidal anti-inflammatory drugs (NSAID) and oral anticoagulants	4	4.00 – 4.00		YES	[20]
Insulin	4	4.00 – 4.00	YES		[10], [23, 24]
Missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy	4	4.00 – 3.25	YES		[11]
Medication with a narrow therapeutic window	4	4.00 – 3.25	YES	YES	[5]
Non-adherence	4	4.00 – 3.00	YES		[10]
Polymorbidity	3.5	4.00 – 3.00	YES	YES	[10], [22]
Digoxin	3	4.00 – 3.00			[24], [20], [27]
Renal impairment (eGFR <30 ml/min)	3	4.00 – 3.00	YES		[10], [22], [20]
NSAIDs	3	4.00 – 3.00		YES	[10], [21], [23, 24], [5, 25]
Experience of ADR	3	3.75 – 3.00	YES	YES	[22]

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Medication which is difficult to handle	3	3.75 – 3.00	YES		
Language issues (i.e. non-native speakers)	3	3.00 – 3.00	YES	YES	
Diuretics	3	3.00 – 3.00		YES	[10], [23, 24], [26], [19], [25], [5]
Tricyclic antidepressants	3	3.00 – 3.00			[21], [20]
Hepatic impairment	3	3.00 – 3.00	YES		[22], [20]
Self-medication with non-prescribed medicines	3	3.00 – 3.00	YES	YES	
Impaired manual skills (causing handling difficulties)	3	3.00 – 3.00	YES		
Visual impairment	3	3.00 – 3.00	YES	YES	[17]
Anticholinergic drugs	3	3.00 – 3.00			[28]
Benzodiazepines	3	3.00 – 3.00			[21], [20], [28], [25], [29]
Opiates/Opioids	3	3.00 – 3.00			[10], [23], [26], [20], [25]
Corticosteroids	3	3.00 – 2.00			[10], [23, 24]
Oral antidiabetics	3	3.00 – 2.00			[10], [23, 24]

Table 2b: Risk factors contributing to the occurrence of DRPs rated from the expert panel as “rather unimportant” (Likert scale: 2) or “unimportant” (Likert scale: 1) and therefore not included in the final list of risk factors.
The sequence represents the ratings of the Delphi survey indicating median ratings and interquartile range [IQR]), and appearance in the NGT ranking list, the qualitative analysis of the NGT and in literature. Factors with no reference in the literature section were only mentioned by the experts.

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Age	2.5	3.75 – 2.00		YES	[30], [5]
Extreme body weight (too high or too low)	2	3.00 – 2.00	YES		
Antiplatelet drugs	2	3.00 – 2.00			[10], [23, 24]
Drugs affecting the renin-angiotensin-aldosterone-system (RAAS)	2	3.00 – 2.00			[10], [23]
Patient living alone	2	3.00 – 2.00	YES		[18], [19], [31]
Calcium antagonists	2	3.00 – 2.00			[10], [23], [20]
Nitrates	2	3.00 – 2.00			[23, 24]
Patient’s education about his therapy	2	2.75 – 2.00		YES	[11]
Beta-blockers	2	2.00 – 2.00			[10], [23, 24], [20], [25]
Antacids	2	2.00 – 2.00			
High risk of falls, motion insecurity	2	2.00 – 2.00	YES	YES	[18], [19], [31], [20], [25], [28], [29]
Previous hospitalisation in the last 30 days	2	2.00 – 2.00			[17], [18], [30]
Need for caregiver at home	2	2.00 – 2.00	YES		[10]
Calcium containing drugs	2	2.00 – 1.00			[27]

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Respiratory drugs	2	3.00 – 1.00			[10], [23], [26]

DISCUSSION

We were able to determine 27 risk factors that seem to contribute substantially to the occurrence of DRPs. The triangulation, for which we used the NGT with its rating process, the expert panel and a literature search, enhanced the accuracy of our findings and ensured their practical relevance. In agreement with previous quantitative studies, we identified in our literature search expected and well-known risk factors. The inclusion of an expert panel gave us a valuable insight on problems healthcare professionals are confronted with and what risk factors they judge as important or not. As we expected, risk factors that were prevalent in the literature were mentioned by the experts as well, for example some high risk drugs (like anticoagulants and insulin), polypharmacy and renal impairment. Apart from that, the expert panel showed us valuable risk factors often seen in their daily practice and less described in literature. Insufficient information transfer between the primary and secondary care setting was considered an important handicap in daily practice. Problems already start at hospital admission where patients often arrive without any information about their current long-term medication. During the hospital stay, the medication of the patient undergoes significant changes. Lack of communication among the different healthcare providers leads to confusion.

Community pharmacists complained about having insufficient access to patients' medical records, which hinders them in advising the patient in a comprehensive way. Panellists from every healthcare area emphasised the importance of patient information. They were aware that patients' knowledge about their medication is often incomplete. Self-medication is rarely mentioned in the dialogue with the healthcare professionals, because the patient does not regard his/her vitamin pills and herbal supplements as real medication.

An increasing amount of patients speaks a foreign language, which complicates communication. To improve the education of patients and to guarantee the transfer of information about patients' medication, panellists acknowledged the benefit of appointing an individual who would be responsible for the medication management and the education of the patient.

The experts stated that an ideal medication manager should be walking across all floors of the hospital, meeting with newly admitted patients, compiling a complete medication history, and checking for DRPs. This medication manager should monitor the patient throughout the hospital stay, at the patient's discharge, he/she should do the final medication check to identify potential DRPs and ensure that the patient understands the prescribed therapy and knows how to take the medication. After discharge, the medication manager should ensure that the correct information is shared with the community pharmacy and the general practitioner in order to guarantee seamless care. The medication manager should serve as a consultant and not as a replacement for the prescribing physician. The panellists considered clinical pharmacists or pharmacologists the most appropriate professionals for this task, due to their broad knowledge about medication.

The risk factor "age" does not belong to the final list of the most important risk factors. The experts stated clearly that an 80-year-old patient could be in a much healthier condition than a 60-year-old. When talking about geriatric patients we are aware of risk factors like polypharmacy, renal impairment, dementia and many more. The expert panel rated these risk factors as more important than the factor "age" itself.

The composition of the expert panel was multidisciplinary by choice, because we aimed to bring together all stakeholders in the medication process of a patient. By performing an NGT instead of interviews, we gave the panellists the possibility not only to answer to our questions, but to discuss their different views with other healthcare professionals. The panellists were highly motivated and discussed in an engaged and informative way. Despite their different professional backgrounds, they agreed on many discussion points. They appreciated the interdisciplinary exchange and found that it would be worthwhile to conduct such discussion rounds more frequently.

The ensuing Delphi process enabled the desired consensus forming. By conducting the Delphi process with online questionnaires, where the participants were anonymous, we avoided any psychosocial biases. In the first round, the total amount of IQRs was 30.0, whereas it was 20.0 in the second round. This means that the degree of consensus increased amongst the participants.

Study limitations

There are some general concerns about the validity and generalizability of information created by qualitative research methods. Both the Delphi and NGT approaches are often criticised for showing a lack of research-based evidence concerning diverse feedback methods and their influence on the validity and reproducibility of the decisions reached by the panel members.[14] Other influences on the whole group dynamic are psychosocial biases, which were described by Pagliari and colleagues.[32] We addressed this by assigning each panellist a place in the NGT in order to avoid grouping of friends or panellists with the same profession. We decided to use a small expert panel with 10 panellists. Although larger groups would provide a more extensive representation, they may be difficult to lead, which may only be resolved by introducing more structure and role definition into the process.[32]

A limitation of our Delphi technique after employing NGT is the restricted number of participants. We chose the same very motivated experts for the Delphi and the NGT, because they were already familiar with the topic.

In conclusion, the gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. In a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Contributions of authors statement (with relevance to the ICMJE Guidelines):

C.P. Kaufmann:
Contribution to the study design and the analysis and interpretation of data, manuscript writing, final approval of the version to be published.
Substantially involved in the literature search, the conduction of the Nominal Group Technique (NGT) and the Delphi questionnaire.

D. Stämpfli:
Contribution to the study design and the analysis and interpretation of data, the literature search, the conduction of the NGT and the Delphi questionnaire.

K.E. Hersberger:
Manuscript review and final approval of the version to be published

M.L. Lampert:
Contribution to the study design and the analysis and interpretation of data, the NGT and Delphi survey. Did the manuscript review and contributed to the final approval of the version to be published

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Competing interests:

The authors declare that they have no conflicts of interest.

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Data sharing statement:

No additional data available

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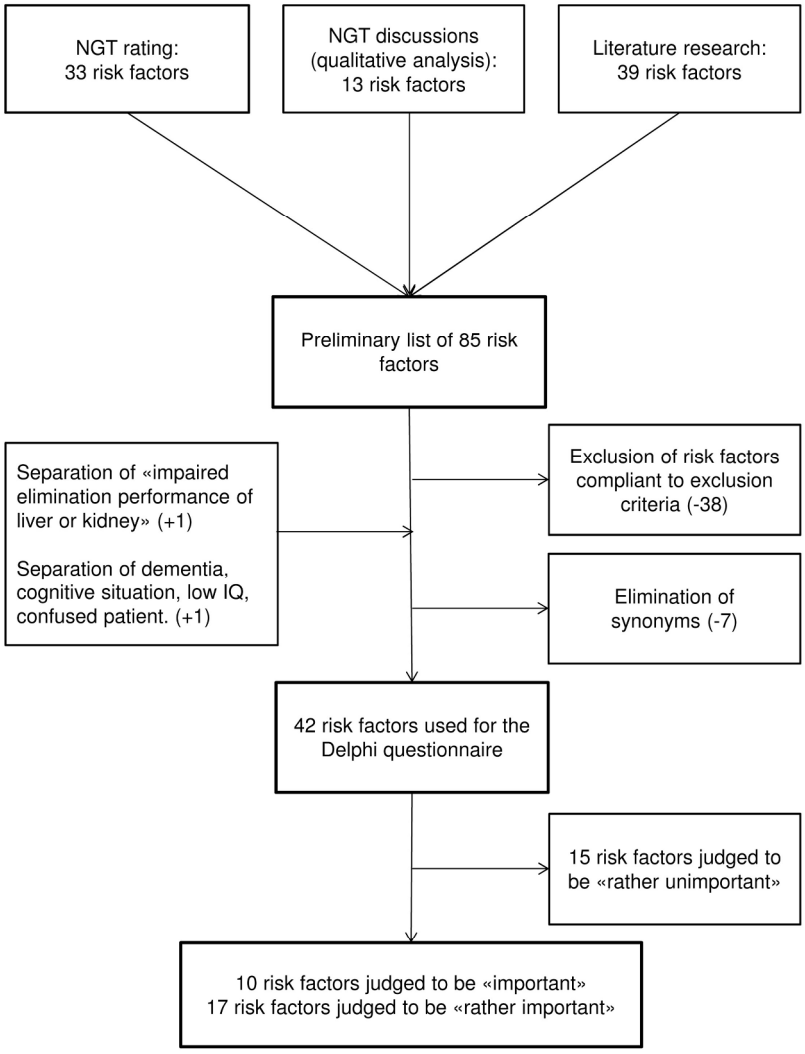
LEGEND OF FIGURES

Figure 1: Flow chart of eliciting risk factors possibly leading to DRPs.



193x279mm (300 x 300 DPI)

Research Checklist

Determination of risk factors for drug-related problems: A multidisciplinary triangulation process

Completed COREQ Checklist

We would like to emphasize, that our research study followed a comprehensive approach with the combination of qualitative and **quantitative** research. The COREQ Checklist was applied only for the qualitative part of the study.

1. Interviewer/facilitator (see page 5)

CK conducted the Nominal Group Technique (NGT)

2. Researcher's credentials

CK: MSc Pharm, Clinical Pharmacist

DS: MSc Pharm

KH: Professor, PhD

ML: PhD, Clinical Pharmacist

3. Occupation

CK: PhD Student at the Pharmaceutical Care Research Group, Clinical Pharmacist at the Kantonsspital Baselland

DS: Pharmacist in a community pharmacy

KH: Head of the Pharmaceutical Care Research Group at the University of Basel, Community Pharmacist

ML: Senior researcher and lecturer at the Pharmaceutical Care Research Group, Deputy chief pharmacist and Clinical Pharmacist at the Kantonsspital Baselland

4. Gender

CK: female

DS, KH, ML: male

5. Experience and training

The principal researcher (CK) has no formal education or training in qualitative research. But she provided a professional background with large experience in detecting and managing drug-related problems as a result of the work as a clinical pharmacist. And as a PhD-Student, CK is used to work scientifically, what enabled her to conduct the NGT in a professional way.

6. Relationship established

	CK	DS	KH	ML
Hospital physician 1	A	X	C	A
Hospital physician 2	B	X	X	B
Emergency physician	B	X	C	B
General practitioner	X	X	C	X
Clinical pharmacologist	X	X	C	C
Clinical pharmacist	C	X	C	C
Nurse	X	X	X	C
Home care nurse	X	X	X	X
Community pharmacist 1	X	X	X	X
Community pharmacist 2	C	x	C	C

Legend: A: professional relationship in the same institution on a regular basis B: professional relationship in the same institution irregularly C: professional relationship sporadically x: no relationship

7. Participant knowledge of the researcher

The researcher (CK) introduced herself, the background and the aim of her research study to the participants at the first contact per mail as well as at the beginning of the NGT.

8. Interviewer characteristics

We reported the interest of the researcher in the research topic (PhD-Project, general Interest as a clinical pharmacist on the improvement of the patient safety).

9. Methodological orientation and Theory

Information to the background of our research project is explained in the introduction part of the manuscript (see page 3-4 in the manuscript)

10. Sampling (see page 5)

Purposive, the selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience.

11. Method of approach (see page 5)

The experts where contacted by email. The email contained basic information about the study and the request for participating in the NGT.

12. Sample size (see page 5)

Ten experts participated in the study

13. Non-participation

One expert refused to participate due to a lack of time.

14. Setting

The NGT was held in a conference room at the University of Basel

15. Presence of Non-Participants

No one else was present besides the participants and researchers

16. Description of sample (see page 5)

The experts were all medical professionals and every expert needed to have at least 5 years of professional experience.

17. Interview guide (see page 5)

The author CK guided the NGT and provided the questions for the participants.

18. Repeat interview

The expert meeting was carried out once. No repeat interviews were carried out.

19. Audio/visual recording (see page 5)

The whole expert meeting was audiotaped.

20. Field notes

No major field notes where made.

21. Duration

The expert meeting lasted for two hours.

22. Data saturation (see page 5)

The structure and duration of the NGT was predefined by the authors. The highly structured methodology of the NGT determined to a high degree the data saturation. The NGT discussion aimed at a satisfactory level of consensus.

23. Transcripts returned (see page 5)

The transcript of the expert meeting was not returned to the participants.

24. Number of data coders (see page 5)

DS and CK coded the data

25. Coding tree (see page 5)

The authors DS and CK labelled every fragment with a unique index number to assure transparency. No coding tree was necessary.

26. Derivation of themes

Themes were derived from the gathered data.

27. Software (see page 5)

An excel database was used to manage the data. We did not use any other software.

28. Participant checking (see page 5)

Participants had the possibility to provide feedback to the findings in the Delphi-Questionnaire following the NGT. No participant provided feedback.

29. Quotations presented (see page 13-15 of the manuscript)

Participant quotations were presented and each quotation was identified.

30. Data and findings consistent (see page 8-15 of the manuscript)

Presented data underlined our findings.

31. Clarity of major themes (see page 8-15 of the manuscript)

Major themes were clearly presented in the results-part of the manuscript.

32. Clarity of minor themes (see page 8-15 of the manuscript)

Minor themes were presented in the results- part of the manuscript.

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Determination of risk factors for drug-related problems: A multidisciplinary triangulation process

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Determination of risk factors for drug-related problems:

A multidisciplinary triangulation process

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ABSTRACT

Introduction and objectives: Drug-related problems (DRPs) constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. Because many DRPs are preventable, the specific risk factors that facilitate their occurrence are of considerable interest. The objective of our study was to assess risk factors for the occurrence of DRPs with the intention to identify patients at risk for DRPs to guide and target preventive measures in patients where they are needed most.

Design: Triangulation process using a mixed methods approach.

Methods: We conducted an expert panel, using the nominal group technique (NGT) and a qualitative analysis, to gather risk factors for DRPs. The expert panel consisted of two senior hospital physicians (internal medicine and geriatrics), one emergency physician, one general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse and two community pharmacists. The literature was searched for additional risk factors. Gathered factors from the literature search and the NGT were assembled and validated in a two-round Delphi questionnaire.

Results: The NGT resulted in the identification of 33 items with additional 13 risk factors from the qualitative analysis of the discussion. The literature search delivered another 39 risk factors. The 85 risk factors were refined to produce 42 statements for the Delphi online questionnaire. Of these, 27 risk factors were judged to be “important” or “rather important”.

Conclusion: The gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. As a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Strengths and limitations of this study:

- This research project followed a comprehensive triangulation method to gather risk factors for drug related problems integrating experts’ opinion and literature data, which represents – to our knowledge a new approach in this topic.
- Participating experts represented a wide variety of settings of patient care and steps in the medication process. This allowed a broad view on the topic of DRPs.
- Inviting actively practising healthcare professionals as experts ensures the practical relevance of gathered risk factors.
- The restricted number of participants in the NGT may have limited the diversity of risk factors.

INTRODUCTION

Drug-related problems (DRPs), defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes”,[1] constitute a frequent safety issue among hospitalised patients leading to patient harm and increased healthcare costs. The term DRP embraces medication errors (MEs), adverse drug events (ADEs), and adverse drug reactions (ADRs). A medication error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer“.[2] An adverse drug event can be defined as “an injury – whether or not causally related to the use of a drug”.[3] Adverse drug reactions include “any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of diseases, or for the modification of physiological functions”.[4] In a systematic review of the years from 1991 to 2001, Krähenbühl et al. found that approximately 8% of hospitalised patients experience an ADE, and 5-10% of all drug prescriptions or drug applications are erroneous.[5] In general internal medicine, about 15% of hospitalised patients and 12% to 17% of patients after discharge experience ADEs.[6, 7] In a group of 435 patients with discharge prescriptions from six different European countries, Paulino et al. found a DRP in at least 63% of cases.[8] In a Swiss study, 89 of 264 (34%) discharge prescriptions contained qualitative deficiencies and 72 (27%) showed DRPs.[9] Thus, unplanned medication-related readmissions within a short time after discharge are frequent. In a multicentre, observational study with a prospective follow up, 5.6% of 12,793 unplanned admissions were medication-related and of these, 46.5% were potentially preventable.[10]

Because DRPs are an important problem and many of them are preventable, the specific risk factors that facilitate the occurrence of DRPs are of considerable interest. Previous studies have determined numerous risk factors for DRPs. In a literature review, female sex, polypharmacy, administration of drugs with a narrow therapeutic range or renal elimination, age over 65 years, and the use of oral anticoagulants and diuretics were identified as relevant risk factors for ADEs and ADRs.[5] Leendertse and colleagues considered risk factors, such as four or more comorbidities, polypharmacy, dependent living situation, impaired cognition, impaired renal function, and non-adherence to medication regimen as independent and significant risk factors potentially responsible for preventable hospital admission.[10]

These publications mostly rely on retrospective data and often focus on specific points in the whole care process of a patient, e.g. hospital admission or discharge. Thus, data from the literature might not fully reflect the current problems of practising healthcare providers, especially when the information comes from another country with a completely different

health care system. Few studies used a qualitative approach and attempted to reflect real-life situations by interviewing patients and healthcare providers. Risk factors reported in such studies differed from those found in quantitative studies. Howard et al. conducted qualitative interviews with patients, general practitioners, and community pharmacists and concluded that communication failures and knowledge gaps at multiple stages in the medication process are important risk factors for preventable drug-related admissions.[11] A combination of both a qualitative and a quantitative approach in gathering risk factors for DRPs has not been very prevalent in the current literature.

The aim of our study was to determine the individual risk factors for DRPs by combining current evidence from the literature with the professional experience of healthcare providers throughout the entire medication process. A triangulation process with quantitative and qualitative research methods in combination with consensus techniques served as a comprehensive approach to bridge the gap between research results and professional experience. It is hoped that this will lead to a list of risk factors for DRPs that accurately reflects the reality of daily practice. Risk factors collected will help to characterise and identify patients at risk for DRPs and will enable clinical pharmacists to guide and target preventive measures in order to minimise the occurrence of DRPs.

METHODS

Nominal group technique (NGT)

As method for eliciting risk factors we used the NGT.[12-14] We set up an expert panel consisting of two consultant hospital physicians (internal medicine and geriatrics), one emergency physician, one independent general practitioner, one clinical pharmacologist, one clinical pharmacist, one registered nurse, one home care nurse, and two independent community pharmacists. The selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience, held a senior/executive position and was involved in daily patient care.

We set the duration of the NGT to 2 hours. The moderator (CK) started the NGT meeting with a short introduction to the topic with the aim of communicating the goal of the meeting and bringing everybody's knowledge about DRPs up to the same level. The participants were then asked to write down as many risk factors for DRPs as they could spontaneously think of. To avoid double-nominations, synonyms, and very closely related terms (e.g. "dementia" and "cognitive impairment"), two clinical pharmacists (ML, DS) and a community pharmacist (KH) grouped the gathered risk factors while retaining each individual factor in the list. This work was done during the NGT. Subsequently, we presented the collected risk factors to the participants and invited them to rank each risk factor by its relevance. Each expert allocated 50 points (1.5 times the number of risk factors [=33]). We determined the amount of points by ourselves. Experts should be able to rank every risk factor, instead of choosing a defined number of most important factors. However, we limited the amount of points to force a consensus finding. Experts could assign as many points to as many of the risk factors as they wanted until all points were used. After the first ranking, we collected the ranking sheets and summarised the points to create a first ranking list. We discussed the ranking list with the expert panel, paying special attention to high and low scoring and discrepancies in the ranking among participants. In the second round of the ranking process, panellists had only as many points as the number of available risk factors, forcing them to fine-tune their previous ranking and to reach a consensus. We collected the rerated lists, created the new ranking, and then returned the resulting ranking list to all participants for final comments. Because we worked neither with patient data nor with patients themselves, we did not need an ethical approval.

We audiotaped the entire discussion session of the expert panel and transcribed it into a written text for qualitative analysis. One of the authors (DS) split the transcript in fragments and a second author (CK) checked the splitting. Afterwards the two authors (DS, CK)

together rearranged the fragments in groups treating related subjects. The whole grouping was then discussed by three authors (CK, DS, ML). Disagreements were discussed until the three authors reached consensus. We labelled every fragment with a unique index number to assure transparency.

Literature search

We conducted a non-systematic literature search to supplement the findings of the expert panel. Our goal was to gain an impression of the current state of research in the field of risk factors leading to DRPs. We wanted to know which risk factors for DRPs were described in current literature and which ones were most mentioned. We conducted our search on PubMed and Embase. Language was restricted to German and English. The following search terms were used in Embase: ‘drug related problems' AND 'risk'/exp AND factors AND [systematic review]/lim AND ([english]/lim OR [german]/lim) AND [humans]/lim.; 'Triage'/exp OR 'triage'/syn AND ('risk'/exp OR 'risk'/syn) AND assessment AND ([child]/lim OR [adolescent]/lim OR [adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND ([meta-analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [review]/lim).; 'Adverse drug reaction'/exp AND 'screening'/exp AND 'high risk patient'/exp AND [humans]/lim AND [english]/lim

The following search terms were used in PubMed:

"Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Drug Toxicity"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; (("Drug Toxicity"[Mesh]) OR "Medication Errors"[Mesh]) AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; "Medication Errors"[Mesh] AND "Triage/methods"[MAJR] AND "Risk Assessment/methods"[MeSH Terms]; ("Risk Factors"[MeSH Terms]) AND "Hospitalization/statistics and numerical data"[MAJR]

"Risk Assessment/methods"[MeSH Terms] AND "Medication Errors"[Mesh]

Titles and abstracts were screened for relevance. Abstracts needed to mention the terms “risk factors”, “predictors”, or “high risk” in combination with “drug related problems” or subterms of its definition. ~~The study design had to be a controlled trial, a cohort study, or a case-control study.~~

We checked the reference list of each paper selected for further possible hits. Besides this literature search, we reviewed different tools focusing on the assessment of inappropriate prescribing which we identified in a previous systematic review.[15] Inappropriate prescribing is a known source of DRPs, ADEs, and ADRs. Original publications of these tools were screened for risk factors associated with inappropriate prescribing that are connected with negative outcomes, e.g. DRPs, ADEs, ADRs, and rehospitalisation. PubMed and Embase

were searched for validation studies using the name of the tool and if necessary “outcome” or “assessment” as MeSH terms or by checking publications which cited the original paper.

Delphi process

We validated the risk factors collected from the literature search and the NGT by using the Delphi technique.[16] Before integrating the risk factors in the questionnaire, we condensed them by using the following exclusion criteria:

- The risk factor is mentioned in only one of the relevant publications.
- The risk factor, set in the lowermost quartile of our NGTs ranking list, is not mentioned anywhere else.
- The risk factor is categorised as an issue of seamless care (e.g. lack of communication between healthcare professionals, patient information, and discharge management).
- The risk factor represents a hardly predictable event or circumstance (e.g. unscheduled discharge, confusion of drug names by professionals).

We excluded seamless care issues, because they are not individual risk factors, but instead reflect system failures; they are, therefore, not assessable for an individual patient. In addition, we combined synonyms in one term. Any ambiguous risk factors were discussed by experts to decide about their inclusion or exclusion on a case-to-case basis.

In a two-round online Delphi survey (Flexi Form, In. 2.0 ed.), following two months after the NGT, the NGT participants rated each risk factor on a four-item Likert scale (1 = “unimportant”, 2= “rather unimportant”, 3= “rather important”, 4 = “important”) according to its potential to cause DRPs.

The questionnaire for the second rating started two weeks after the end of the first rating and included the same questions as the first one, but the sequence represented the ranking list of the first round. We presented the median score and the inter-quartile range (*IQR)* of each question to the participants to give them the possibility to consider the group’s rating for their own re-rating. Below the Likert scale of each question, the number of participants, who rated for the respective relevance, was shown. After the second rating, the median scores and IQRs were calculated and a final ranking list of risk factors collected was established.

RESULTS

NGT rating and literature search (see figure 1):

The ranking process of the NGT resulted in 33 items. The qualitative analysis of the discussion confirmed risk factors identified in the rating process but also revealed additional 13 risk factors. Main topics were high-risk drugs, communication issues between healthcare professionals, patient education and questions of responsibility. The literature search resulted in additional 39 factors, which were not mentioned in the NGT.

Delphi questionnaire:

In total, we gathered a preliminary list of 85 risk factors. Of these, we excluded 38 risk factors because they fulfilled our exclusion criteria (see table 1). Twice, we split a risk factor into two parts, and we eliminated seven synonyms. Ultimately, we used 42 risk factors in the Delphi questionnaire.

In table 2a&b, the results of the Delphi technique are shown. They are arranged by median score of the second round. In the second round, 10 risk factors were judged as “important” (Likert scale: 4) concerning their contribution to the occurrence of DRPs, 17 risk factors as “rather important” (Likert scale: 3), 15 risk factors as “rather unimportant” (Likert scale: 2), and none as “unimportant” (Likert scale: 1). The sum of the IQRs changed from 30 in the first round to 20 in the second round representing a stronger consensus between the participants. Finally, we created a list of 27 risk factors, rated as important or rather important for the occurrence of DRPs.

Table 1: Risk factors excluded from the Delphi questionnaire, including information to their origin. L: Literature search, N: NGT ranking list, Q: Qualitative analysis of the NGT

Excluded risk factors	
Mentioned in only one of the selected Publications	heart failure(L); liver disease (not hepatic impairment)(L); problems with "water works"(L); antidepressant(L); drugs with positive inotrope effects(L), potassium channel activators(L); antibacterial drugs(L); laxatives(L); corticosteroids for inhalation(L), loperamide(L); statins(L); cephalosporins(L); compound analgesics (with opioids)(L); low molecular weight heparins(L); macrolide antibiotics(L); penicillin(L); aspirin(L); salbutamol(L); antihypertensives(L); bladder antimuscarinic drugs(L); cerebral vasodilators(L); nitroglycerine(L); ranitidine(L); 1st generation antihistamines(L)
Lowermost quartile of the NGT ranking list and not mentioned elsewhere	Money(N); Morbus Parkinson(N); xerostomia(N); oral bisphosphonate(N)
Seamless care issue or intervention to improve seamless care OR Unpredictable event or circumstance	unclear prescription/unclear or non-available dosage regimen at discharge(N); multiple treating physicians(L,N); missing instruction of relatives(N); medication-taking gap(N); briefing of the patient(L;Q); confusion of drug names(N); new medication / lots of changes/ alternating dosages(N); changes in therapy: stop due to hospitalisation/discharge/generic medication(N,Q); unscheduled discharge(N)
Synonyms	
- behaviour at home during an ADR(N); earlier experiences with medication (N,Q) → included as: experience with ADR (Q) - impaired mobility (L,N) → included as: High risk of falls, motion insecurity (L,N,Q) - language(Q) → included as: language issues (N) - oral corticosteroid (L); systemic corticosteroids (L) → included as: corticosteroids (L) - parallel therapy (N) →incl. as: self-medication with non-prescribed medicines (N,Q)	

Table 2a: Final ranking list of the 27 risk factors contributing to the occurrence of DRPs rated by the expert panel as "important" (Likert scale: 4) or "rather important" (Likert scale: 3).
The sequence represents the ratings of the Delphi survey indicating median ratings and interquartile range [IQR]), and appearance in the NGT ranking list, the qualitative analysis of the NGT and in literature. Factors with no reference in the literature section were only mentioned by the experts.

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Dementia, cognitive situation, Low IQ, confused patient	4	4.00 – 4.00	YES		[10], [17], [18], [19], [20]
Polypharmacy (number of drugs >5)	4	4.00 – 4.00	YES	YES	[10], [17], [18], [21], [22], [5]
Antiepileptics	4	4.00 – 4.00		YES	[23, 24], [20], [25]
Anticoagulants	4	4.00 – 4.00		YES	[10], [21], [23], [26], [5]
Combinations of non-steroidal anti-inflammatory drugs (NSAID) and oral anticoagulants	4	4.00 – 4.00		YES	[20]
Insulin	4	4.00 – 4.00	YES		[10], [23, 24]
Missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy	4	4.00 – 3.25	YES		[11]
Medication with a narrow therapeutic window	4	4.00 – 3.25	YES	YES	[5]
Non-adherence	4	4.00 – 3.00	YES		[10]
Polymorbidity	3.5	4.00 – 3.00	YES	YES	[10], [22]
Digoxin	3	4.00 – 3.00			[24], [20], [27]
Renal impairment (eGFR <30 ml/min)	3	4.00 – 3.00	YES		[10], [22], [20]
NSAIDs	3	4.00 – 3.00		YES	[10], [21], [23, 24], [5, 25]
Experience of ADR	3	3.75 – 3.00	YES	YES	[22]

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Medication which is difficult to handle	3	3.75 – 3.00	YES		
Language issues (i.e. non-native speakers)	3	3.00 – 3.00	YES	YES	
Diuretics	3	3.00 – 3.00		YES	[10], [23, 24], [26], [19], [25], [5]
Tricyclic antidepressants	3	3.00 – 3.00			[21], [20]
Hepatic impairment	3	3.00 – 3.00	YES		[22], [20]
Self-medication with non-prescribed medicines	3	3.00 – 3.00	YES	YES	
Impaired manual skills (causing handling difficulties)	3	3.00 – 3.00	YES		
Visual impairment	3	3.00 – 3.00	YES	YES	[17]
Anticholinergic drugs	3	3.00 – 3.00			[28]
Benzodiazepines	3	3.00 – 3.00			[21], [20], [28], [25], [29]
Opiates/Opioids	3	3.00 – 3.00			[10], [23], [26], [20], [25]
Corticosteroids	3	3.00 – 2.00			[10], [23, 24]
Oral antidiabetics	3	3.00 – 2.00			[10], [23, 24]

Table 2b: Risk factors contributing to the occurrence of DRPs rated from the expert panel as “rather unimportant” (Likert scale: 2) or “unimportant” (Likert scale: 1) and therefore not included in the final list of risk factors.
The sequence represents the ratings of the Delphi survey indicating median ratings and interquartile range [IQR]), and appearance in the NGT ranking list, the qualitative analysis of the NGT and in literature. Factors with no reference in the literature section were only mentioned by the experts.

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Age	2.5	3.75 – 2.00		YES	[30], [5]
Extreme body weight (too high or too low)	2	3.00 – 2.00	YES		
Antiplatelet drugs	2	3.00 – 2.00			[10], [23, 24]
Drugs affecting the renin-angiotensin-aldosterone-system (RAAS)	2	3.00 – 2.00			[10], [23]
Patient living alone	2	3.00 – 2.00	YES		[18], [19], [31]
Calcium antagonists	2	3.00 – 2.00			[10], [23], [20]
Nitrates	2	3.00 – 2.00			[23, 24]
Patient’s education about his therapy	2	2.75 – 2.00		YES	[11]
Beta-blockers	2	2.00 – 2.00			[10], [23, 24], [20], [25]
Antacids	2	2.00 – 2.00			
High risk of falls, motion insecurity	2	2.00 – 2.00	YES	YES	[18], [19], [31], [20], [25], [28], [29]
Previous hospitalisation in the last 30 days	2	2.00 – 2.00			[17], [18], [30]
Need for caregiver at home	2	2.00 – 2.00	YES		[10]
Calcium containing drugs	2	2.00 – 1.00			[27]

Risk factor	Delphi		NGT		Literature
	Median	IQR	Ranking list	Qual. anal.	
Respiratory drugs	2	3.00 – 1.00			[10], [23], [26]

DISCUSSION

We were able to determine 27 risk factors that seem to contribute substantially to the occurrence of DRPs. The triangulation, for which we used the NGT with its rating process, the expert panel and a literature search, enhanced the accuracy of our findings and ensured their practical relevance. In agreement with previous quantitative studies, we identified in our literature search expected and well-known risk factors. The inclusion of an expert panel gave us a valuable insight on problems healthcare professionals are confronted with and what risk factors they judge as important or not. As we expected, risk factors that were prevalent in the literature were mentioned by the experts as well, for example some high risk drugs (like anticoagulants and insulin), polypharmacy and renal impairment. Apart from that, the expert panel showed us valuable risk factors often seen in their daily practice and less described in literature. Insufficient information transfer between the primary and secondary care setting was considered an important handicap in daily practice. Problems already start at hospital admission where patients often arrive without any information about their current long-term medication. During the hospital stay, the medication of the patient undergoes significant changes. Lack of communication among the different healthcare providers leads to confusion.

Community pharmacists complained about having insufficient access to patients' medical records, which hinders them in advising the patient in a comprehensive way. Panellists from every healthcare area emphasised the importance of patient information. They were aware that patients' knowledge about their medication is often incomplete. Self-medication is rarely mentioned in the dialogue with the healthcare professionals, because the patient does not regard his/her vitamin pills and herbal supplements as real medication.

An increasing amount of patients speaks a foreign language, which complicates communication. To improve the education of patients and to guarantee the transfer of information about patients' medication, panellists acknowledged the benefit of appointing an individual who would be responsible for the medication management and the education of the patient.

The experts stated that an ideal medication manager should be walking across all floors of the hospital, meeting with newly admitted patients, compiling a complete medication history, and checking for DRPs. This medication manager should monitor the patient throughout the hospital stay, at the patient's discharge, he/she should do the final medication check to identify potential DRPs and ensure that the patient understands the prescribed therapy and knows how to take the medication. After discharge, the medication manager should ensure that the correct information is shared with the community pharmacy and the general practitioner in order to guarantee seamless care. The medication manager should serve as a consultant and not as a replacement for the prescribing physician. The panellists considered clinical pharmacists or pharmacologists the most appropriate professionals for this task, due to their broad knowledge about medication.

The risk factor "age" does not belong to the final list of the most important risk factors. The experts stated clearly that an 80-year-old patient could be in a much healthier condition than a 60-year-old. When talking about geriatric patients we are aware of risk factors like polypharmacy, renal impairment, dementia and many more. The expert panel rated these risk factors as more important than the factor "age" itself.

The composition of the expert panel was multidisciplinary by choice, because we aimed to bring together all stakeholders in the medication process of a patient. By performing an NGT instead of interviews, we gave the panellists the possibility not only to answer to our questions, but to discuss their different views with other healthcare professionals. The panellists were highly motivated and discussed in an engaged and informative way. Despite their different professional backgrounds, they agreed on many discussion points. They appreciated the interdisciplinary exchange and found that it would be worthwhile to conduct such discussion rounds more frequently.

The ensuing Delphi process enabled the desired consensus forming. By conducting the Delphi process with online questionnaires, where the participants were anonymous, we avoided any psychosocial biases. In the first round, the total amount of IQRs was 30.0, whereas it was 20.0 in the second round. This means that the degree of consensus increased amongst the participants.

Study limitations

There are some general concerns about the validity and generalizability of information created by qualitative research methods. Both the Delphi and NGT approaches are often criticised for showing a lack of research-based evidence concerning diverse feedback methods and their influence on the validity and reproducibility of the decisions reached by the panel members.[14] Other influences on the whole group dynamic are psychosocial biases, which were described by Pagliari and colleagues.[32] We addressed this by assigning each panellist a place in the NGT in order to avoid grouping of friends or panellists with the same profession. We decided to use a small expert panel with 10 panellists. Although larger groups would provide a more extensive representation, they may be difficult to lead, which may only be resolved by introducing more structure and role definition into the process.[32]

A limitation of our Delphi technique after employing NGT is the restricted number of participants. We chose the same very motivated experts for the Delphi and the NGT, because they were already familiar with the topic.

In conclusion, the gathered risk factors may help to characterise and identify patients at risk for DRPs and may enable clinical pharmacists to guide and target preventive measures in order to limit the occurrence of DRPs. In a further step, these risk factors will serve as the basis for a screening tool to identify patients at risk for DRPs.

Contributions of authors statement (with relevance to the ICMJE Guidelines):

C.P. Kaufmann:
Contribution to the study design and the analysis and interpretation of data, manuscript writing, final approval of the version to be published.
Substantially involved in the literature search, the conduction of the Nominal Group Technique (NGT) and the Delphi questionnaire.

D. Stämpfli:
Contribution to the study design and the analysis and interpretation of data, the literature search, the conduction of the NGT and the Delphi questionnaire.

K.E. Hersberger:
Manuscript review and final approval of the version to be published

M.L. Lampert:
Contribution to the study design and the analysis and interpretation of data, the NGT and Delphi survey. Did the manuscript review and contributed to the final approval of the version to be published

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Competing interests:

The authors declare that they have no conflicts of interest.

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Data sharing statement:

No additional data available

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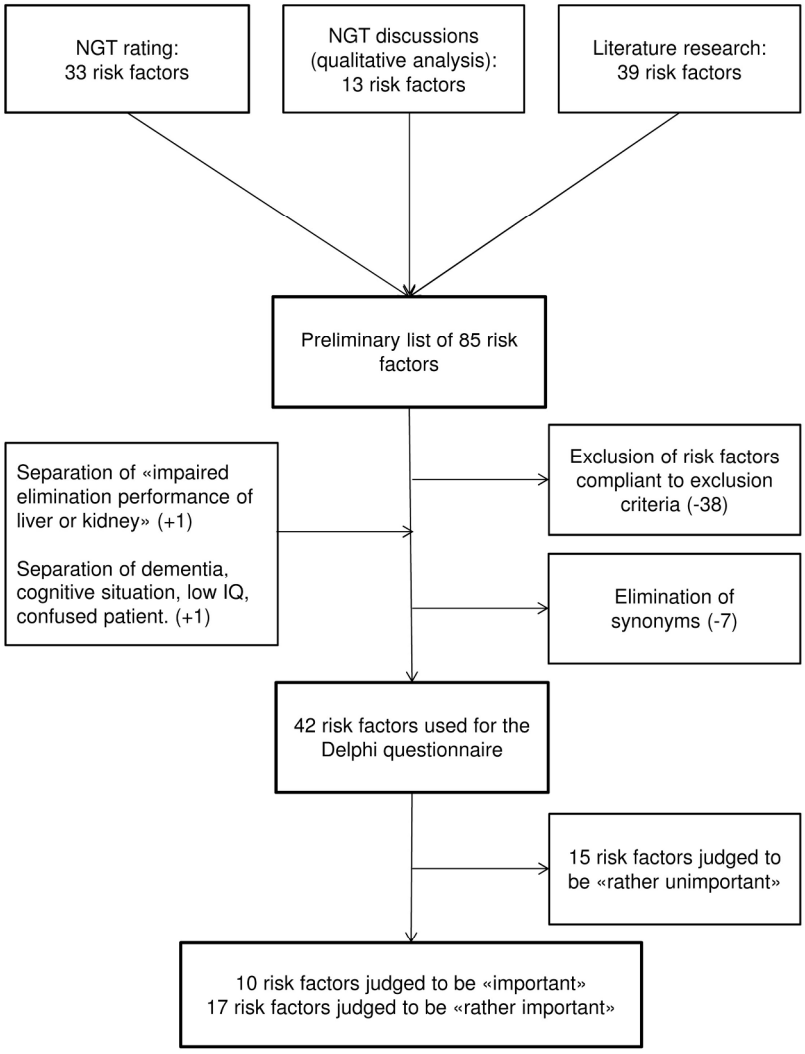
LEGEND OF FIGURES

Figure 1: Flow chart of eliciting risk factors possibly leading to DRPs.



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Research Checklist

Determination of risk factors for drug-related problems: A multidisciplinary triangulation process

Completed COREQ Checklist

We would like to emphasize, that our research study followed a comprehensive approach with the combination of qualitative and **quantitative** research. The COREQ Checklist was applied only for the qualitative part of the study.

1. Interviewer/facilitator (see page 5)

CK conducted the Nominal Group Technique (NGT)

2. Researcher's credentials

CK: MSc Pharm, Clinical Pharmacist

DS: MSc Pharm

KH: Professor, PhD

ML: PhD, Clinical Pharmacist

3. Occupation

CK: PhD Student at the Pharmaceutical Care Research Group, Clinical Pharmacist at the Kantonsspital Baselland

DS: Pharmacist in a community pharmacy

KH: Head of the Pharmaceutical Care Research Group at the University of Basel, Community Pharmacist

ML: Senior researcher and lecturer at the Pharmaceutical Care Research Group, Deputy chief pharmacist and Clinical Pharmacist at the Kantonsspital Baselland

4. Gender

CK: female

DS, KH, ML: male

5. Experience and training

The principal researcher (CK) has no formal education or training in qualitative research. But she provided a professional background with large experience in detecting and managing drug-related problems as a result of the work as a clinical pharmacist. And as a PhD-Student, CK is used to work scientifically, what enabled her to conduct the NGT in a professional way.

6. Relationship established

	CK	DS	KH	ML
Hospital physician 1	A	X	C	A
Hospital physician 2	B	X	X	B
Emergency physician	B	X	C	B
General practitioner	X	X	C	X
Clinical pharmacologist	X	X	C	C
Clinical pharmacist	C	X	C	C
Nurse	X	X	X	C
Home care nurse	X	X	X	X
Community pharmacist 1	X	X	X	X
Community pharmacist 2	C	x	C	C

Legend: A: professional relationship in the same institution on a regular basis B: professional relationship in the same institution irregularly C: professional relationship sporadically x: no relationship

7. Participant knowledge of the researcher

The researcher (CK) introduced herself, the background and the aim of her research study to the participants at the first contact per mail as well as at the beginning of the NGT.

8. Interviewer characteristics

We reported the interest of the researcher in the research topic (PhD-Project, general Interest as a clinical pharmacist on the improvement of the patient safety).

9. Methodological orientation and Theory

Information to the background of our research project is explained in the introduction part of the manuscript (see page 3-4 in the manuscript)

10. Sampling (see page 5)

Purposive, the selection was based on the desirability of including a wide variety of experts from different settings, who are all involved in the patients' medication management. Every expert had at least 5 years of professional experience.

11. Method of approach (see page 5)

The experts where contacted by email. The email contained basic information about the study and the request for participating in the NGT.

12. Sample size (see page 5)

Ten experts participated in the study

13. Non-participation

One expert refused to participate due to a lack of time.

14. Setting

The NGT was held in a conference room at the University of Basel

15. Presence of Non-Participants

No one else was present besides the participants and researchers

16. Description of sample (see page 5)

The experts were all medical professionals and every expert needed to have at least 5 years of professional experience.

17. Interview guide (see page 5)

The author CK guided the NGT and provided the questions for the participants.

18. Repeat interview

The expert meeting was carried out once. No repeat interviews were carried out.

19. Audio/visual recording (see page 5)

The whole expert meeting was audiotaped.

20. Field notes

No major field notes where made.

21. Duration

The expert meeting lasted for two hours.

22. Data saturation (see page 5)

The structure and duration of the NGT was predefined by the authors. The highly structured methodology of the NGT determined to a high degree the data saturation. The NGT discussion aimed at a satisfactory level of consensus.

23. Transcripts returned (see page 5)

The transcript of the expert meeting was not returned to the participants.

24. Number of data coders (see page 5)

DS and CK coded the data

25. Coding tree (see page 5)

The authors DS and CK labelled every fragment with a unique index number to assure transparency. No coding tree was necessary.

26. Derivation of themes

Themes were derived from the gathered data.

27. Software (see page 5)

An excel database was used to manage the data. We did not use any other software.

28. Participant checking (see page 5)

Participants had the possibility to provide feedback to the findings in the Delphi-Questionnaire following the NGT. No participant provided feedback.

29. Quotations presented (see page 13-15 of the manuscript)

Participant quotations were presented and each quotation was identified.

30. Data and findings consistent (see page 8-15 of the manuscript)

Presented data underlined our findings.

31. Clarity of major themes (see page 8-15 of the manuscript)

Major themes were clearly presented in the results-part of the manuscript.

32. Clarity of minor themes (see page 8-15 of the manuscript)

Minor themes were presented in the results- part of the manuscript.