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i. Short informative title:

**High-risk medicines associated with clinically relevant medication-related problems in United Kingdom hospitals: a prospective observational study**

ii. Short running title:

**Quantifying risk of medicine use in hospitals**

iii. Full names of all authors:

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iv. PI statement:

This study was an observational study that did not involve interventions with human subjects or require substances to be administered to human subjects/patients (other than required for standard care). As such the principal investigator for this paper (Cathy Geeson) did not require direct clinical responsibility for patients.

v. Authors' institutional affiliations:

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vi. Main text:

## **Abstract**

The aim of this prospective observational study was to establish associations between the use of high-risk medicine groups and the study outcome: occurrence of at least one moderate or severe preventable medication-related problem (MRP). Data on MRPs, high-risk medicines, and other potential risk factors were collected from adults on medical wards in two UK hospitals. Logistic regression modelling was used to determine relationships between high-risk medicines and the study outcome. Among 1,503 eligible admissions, six high-risk medicine groups were associated with the study outcome on univariable analysis; multivariable analysis found only systemic antimicrobials and epilepsy medicines to be independently associated with the outcome (adjusted odds ratio 1.44, 95% confidence interval 1.08-1.92 and adjusted odds ratio 1.61, 95% confidence interval 1.16-2.25 respectively). Identification of high-risk medicine groups has potential to permit targeting of patients at highest risk of avoidable medication-related harm, but multivariable analysis suggests risk is likely to be multifactorial.

## **What is Already Known about this Subject**

- Medicines are integral to healthcare, but there is growing evidence of a need to improve medication safety.
- Previous research has identified medicines that are potentially high-risk in hospital inpatient settings, but no statistical assessment of high-risk medicines and clinically relevant medication-related problems (MRPs) has yet been conducted.

## **What this Study Adds**

- Only two of eleven groups of high-risk medicines (systemic antimicrobials and epilepsy medicines) were significantly associated with moderate or severe preventable MRPs on multivariable analysis.
- Identification of high-risk medicines has potential to permit targeting of patients at risk of avoidable medication-related harm, however, additional risk factors will also need to be considered.

## Introduction

Medicines are integral to the prevention, treatment and management of health,[1] but there is growing evidence of a need to improve medication safety.[1-8] Regarding hospitalised patients in England, it has been estimated that the prescribing error rate is almost 9%,[9] and that one in seven patients experience harm from their medicines.[10]

Previous research has identified medicines that are potentially high-risk when used in a hospital inpatient setting,[11-21] but no statistical assessment of high-risk medicines and *clinically relevant* medication-related problems (MRPs) has yet been conducted. Statistical assessment has potential to quantify the impact of groups of high-risk medicines on the risk of developing clinically relevant MRPs, and to explore potential correlation between high-risk medicines and other risk factors such as age and renal function. Statistical assessment could therefore inform targeting of patients at highest risk of avoidable medication-related harm. The aim of the present study was therefore to establish the univariable and multivariable associations between high-risk medicines and the study outcome, which was occurrence of at least one moderate or severe preventable MRP.

## Methods

### Study design

This prospective observational study involved adults admitted to the medical wards of two hospitals in South East England, described in detail elsewhere.[22, 23] A summary is provided in appendix S1.

MRPs were defined as all circumstances involving a patient's drug treatment that actually, or potentially, interfere with the achievement of an optimal outcome.[24-26] Previous research suggests a significant proportion of hospitalised patients experience MRPs, but many are of limited clinical significance.[27] We therefore chose a clinically relevant outcome measure based on severity: *moderate or severe* MRPs. Similarly, we selected *preventable* MRPs to focus on patients with MRPs amenable to intervention. Severity was assessed by an expert panel comprising the principal investigator, a hospital pharmacist, a senior nurse and a consultant physician using a validated visual analogue scale.[28] At the point of identification, pharmacy staff recorded whether they considered the MRP was preventable, expressed as a dichotomous variable of yes or no. A second check was performed by the principal investigator. Examples of MRPs, classified by severity and preventability, have been published previously.[23] MRP data were identified and recorded by pharmacists at the study sites as part of their routine daily clinical assessment of patients. Data on 18 potential

risk factors, including use of high-risk medicines, were collected retrospectively by a researcher. Further details are provided in appendix S1.

High-risk medicines were grouped into 11 categories (Table 1), selected based on previously published research.[11-21]. Grouping was used rather than considering medicines individually since different organisations are likely to use different specific medicines. It also reduced the risk of model overfitting associated with using too many variables.[29] A category of 'other high-risk medicines' was used to permit inclusion of medicines considered to be high-risk, but where use was too infrequent to model individually (i.e. fewer than 5% of the study population).[30, 31] A summary of the medicines included in each category is given in appendix S1.

This study received NHS ethical approval (16/WA/0016).

## **Data analysis**

We performed univariable analyses to provide data on the unadjusted association between the preselected groups of high-risk medicines and the outcome event. Multivariable analysis was used to identify the high-risk medicines that were independently associated with the study outcome after adjusting for other potential risk factors: use of other high-risk medicines, age, socioeconomic status, previous allergy, body mass index, number of hospital admissions in previous six months, primary diagnosis, number of comorbidities, history of dementia, number of regular medicines prescribed on the first day of admission, parenteral medicines administration, renal function, liver disease, serum albumin, serum potassium, white cell count and platelet count. The extent of missing data has been reported previously.[23] In summary, of 1,503 included admissions, 387 (25.7%) had one or more missing data points, accounting for 1.6% of total risk factor data. Exploratory analysis found that data were likely to be 'missing at random', missing data were therefore handled using multiple imputation. Information on the potential impact of excluded patients is given in appendix S2.

Logistic regression modelling was performed using a generalised estimating equation approach, this was to account for possible correlation between patients admitted more than once during the study period.[32] Odds ratios (OR) were obtained, a *p* value below 0.05 was regarded as statistically significant and 95% confidence intervals (CI) are reported.

Results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for observational studies.[33] All analyses were conducted using Stata version 14.2.



## Results

An overview of the 1,503 included patient admissions has been described in detail elsewhere.[23] A summary is provided in appendix S2. In total, 610 admissions experienced the study outcome.

### Associations between the high-risk medicines and study outcome

The results of univariable and multivariable analyses between the preselected groups of high-risk medicines and the study outcome are shown in Table 1. The univariable analyses showed there was strong evidence for statistically significant associations between the study outcome and the use of the following high-risk medicines: systemic antimicrobials ( $p<0.001$ ), aminoglycosides/glycopeptides ( $p=0.006$ ), antidepressants ( $p=0.001$ ), anticoagulants ( $p=0.001$ ), anti-diabetic medication ( $p<0.001$ ), and epilepsy medicines ( $p<0.001$ ).

Multivariable analysis showed that only two medicine groups (systemic antimicrobials and epilepsy medicines) were still associated with increased risk of the study outcome (systemic antimicrobials adjusted OR 1.44, 95% CI 1.08 to 1.92,  $p=0.013$  and epilepsy medicines adjusted OR 1.61, 95% CI 1.16 to 2.25,  $p=0.005$ ).

## Discussion

### Key findings

In the univariable analyses six of eleven preselected high-risk medicine groups were significantly associated with the study outcome, experiencing at least one moderate or severe preventable MRP: systemic antimicrobials, aminoglycosides/glycopeptides, antidepressants, anticoagulants, anti-diabetic medication and epilepsy medicines. However, on multivariable analysis only two high-risk medicines groups were independently associated with the study outcome: systemic antimicrobials and epilepsy medicines.

### Comparison with previous work

Previous research has identified medicines that are potentially high-risk when used in a hospital inpatient setting,[11-21] but direct comparison between sources is difficult due to differences in study design, outcome measures, and the way medicines were grouped. To our knowledge, the present study is the first to identify high-risk medicines that are associated with moderate or severe preventable MRPs.

## Strengths and limitations

Strengths of this research include adherence to prognostic modelling recommendations;[34-36] this has the potential to enhance the quality of data collection and reduce bias. Other strengths include the relatively large sample size and use of two study sites to increase generalisability. The choice of study sites is also a strength; their size, range of services and demographics make them broadly representative of other acute district general hospitals in the England.

The observational nature of the study is a potential limitation, as data collection was not carried out under strict trial conditions. This led to a small amount of missing data, and the possibility that MRP prevalence was underestimated. To minimise under-reporting of MRPs we provided regular training for all staff involved. Another possible limitation is risk of bias due to exclusion of admissions whose prescribing records were not reviewed by a clinical pharmacist during admission. However, as discussed in appendix S2, this impact is likely to be minimal. Finally, while it was necessary to categorise high-risk medicines, we appreciate that medicines within the same category may not have equivalent risks, for example insulin and oral diabetes medication.

## Interpretation

We have quantified the impact of high-risk medicines on the risk of developing clinically relevant MRPs; this has potential to inform targeting of patients at highest risk of avoidable medication-related harm. The univariable analyses suggest strong evidence for associations between the study outcome and six of 11 high-risk medicines groups. Despite strong univariable associations, only two of these medicine groups remained statistically significant in multivariable analysis: systemic antimicrobials (excluding aminoglycosides and glycopeptides) and epilepsy medicines. This suggests the association between the study outcome and high-risk medicines can be explained, either partly or fully, by additional risk factors in the multivariable model. While risk of medication-related harm associated with medicines such as anticoagulants and antidiabetic medicines is well recognised,[37, 38] the present study suggests such risk is likely to be multifactorial and subject to residual confounding, with use of high-risk medicines alone being unlikely to accurately predict the occurrence of moderate or severe preventable MRPs. The present study therefore suggests that while identification of high-risk medicines associated with clinically relevant MRPs has potential to inform targeting of patients for medicines optimisation activities, additional risk factors also need to be considered.[23] Further studies in different settings are needed to confirm these findings.

## Conclusion

We found that six of eleven groups of high-risk medicines were associated with moderate or severe preventable MRPs on univariable analysis. While identification of these high-risk groups has potential to permit targeting of patients at highest risk of avoidable medication-related harm only two medicine groups (systemic antimicrobials and epilepsy medicines) were significantly associated with the study outcome on multivariable analysis. This suggests that additional risk factors may also need to be considered when predicting overall risk.

## Supplementary material

Appendix S1 – Supplementary information on methods

Appendix S2 – Supplementary information on results

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## **Authors' contributions**

CG is the principal investigator, and is responsible for the initial concept, study design and analysis plan. BDF and LW refined the design and analysis plan. CG applied for NIHR fellowship funding, with the support and guidance of BDF and LW. CG drafted the manuscript, which was then critically reviewed by BDF and LW. All authors approved the final version.

## **Conflict of interest declaration**

There are no competing interests to declare.

## **Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Accepted Article

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**Table 1 – Univariable and multivariable associations between high-risk medicines and outcome events**

High-risk medicine	Occurrence of outcome event		Univariable analysis		Multivariable analysis <sup>a</sup>	
	No (%)	Yes (%)	Odds ratio (95% CI)	p value <sup>b</sup>	Odds ratio (95% CI)	p value <sup>b</sup>
Systemic antimicrobials (excluding aminoglycosides and glycopeptides)	512 (57.3)	525 (69.7)	1.71 (1.37 to 2.12)	<0.001	1.44 (1.08 to 1.92)	0.013
Aminoglycosides and glycopeptides	49 (5.5)	56 (9.2)	1.73 (1.17 to 2.58)	0.006	1.39 (0.89 to 2.18)	0.144
Antidepressants	182 (20.4)	169 (27.7)	1.50 (1.18 to 1.91)	0.001	1.22 (0.93 to 1.61)	0.146
Anticoagulants	161 (18.0)	151 (24.8)	1.50 (1.17 to 1.92)	0.001	1.12 (0.83 to 1.50)	0.468
Anti-diabetic medication	146 (16.4)	153 (25.1)	1.71 (1.33 to 2.20)	<0.001	1.25 (0.92 to 1.69)	0.147
Epilepsy medicines <sup>c</sup>	104 (11.7)	123 (20.2)	1.92 (1.45 to 2.56)	<0.001	1.61 (1.16 to 2.25)	0.005
Therapeutic heparin	119 (13.3)	103 (16.9)	1.32 (0.99 to 1.76)	0.057	1.31 (0.92 to 1.86)	0.134
Antiarrhythmics	78 (8.7)	72 (11.8)	1.40 (1.00 to 1.96)	0.052	0.95 (0.64 to 1.40)	0.778
Opioids <sup>d</sup>	76 (8.5)	69 (11.3)	1.37 (0.97 to 1.93)	0.075	1.01 (0.67 to 1.52)	0.949
Antipsychotics	50 (5.6)	43 (7.1)	1.27 (0.83 to 1.93)	0.270	1.18 (0.72 to 1.94)	0.511
Other high-risk medicines <sup>e</sup> (anti-retrovirals, medicines for Parkinson's disease, theophylline and aminophylline, immunosuppressants, cytotoxics, lithium)	62 (6.9)	55 (9.0)	1.32 (0.92 to 1.90)	0.134	1.13 (0.76 to 1.68)	0.557

a Adjusted for age, socioeconomic status, previous allergy, body mass index, number of hospital admissions in previous six months, primary diagnosis, number of comorbidities, history of dementia, number of regular medicines prescribed on the first day of admission, parenteral medicines administration, renal function, liver disease, serum albumin, serum potassium, white cell count, platelet count.

b Test for difference between admissions with and without occurrence of outcome event. Obtained from regression modelling.

c Includes use for all potential indications.

d Codeine, tramadol, meptazinol & dihydrocodeine excluded to restrict analysis to stronger opioids.

e High-risk medicines/groups used in fewer than 5% of the study population.

CI = confidence interval

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