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# Medication-related harm in New Zealand general practice: a retrospective records review

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# ABSTRACT

**Background:** The extent of medication-related harm in general practice is unknown.

**Aim:** To identify and describe all medication-related harm in electronic general practice records.

**Design and Setting:** Retrospective cohort records review study in 44 randomly selected New Zealand general practices for the three years 2011-2013.

**Methods:** Eight general practitioners reviewed 9076 randomly selected patient records. Medication-related harms were identified when the causal agent was prescribed in general practice. Harms were coded by type, preventability, and severity. The number and proportion of patients who experienced medication-related harm was calculated. Weighted logistic regression was used to identify factors associated with harm.

**Results** 976/9076 study patients (10.8%) experienced 1,762 medication-related harms over three years. After weighting, the incidence rate of all medication-related harms was 73.9 harms per 1000 patient-years, and the incidence of preventable or potentially preventable medication-related harms was 15.6 per 1000 patient-years. Most harms were minor (1390/1762, 78.9%), but one in five harms were moderate or severe (373/1762, 21.1%); three patients died. Eighteen study patients were hospitalised; after weighting this correlates to a hospitalisation rate of 1.1 per 1000 patient-years. Increasing age, number of consultations, and number of medications were associated with increased risk of medication-related harm. Cardiovascular medications, antineoplastic and immunomodulatory agents, and anticoagulants caused most harm by frequency and severity.

**Conclusion** Medication-related harm in general practice is common. This study adds to the evidence about the risk posed by medication in the real world. Findings can be used to inform decision-making in general practice.

**How this fits in**

The extent of medication-related harm in general practice is unknown. This retrospective records review found that medication-related harm in general practice is common, and is typically minor and arising from standard care. This knowledge can inform shared-decision making about treatment options.

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## BACKGROUND

Reducing medication-related harm is a top priority for improving patient safety.<sup>1,2</sup> Primary healthcare settings remain relatively unexamined for patient harm.<sup>3</sup> It is possible patient harm in general practice has been underestimated.<sup>4</sup> Medication-related harm accounts for around 3% of all hospital admissions on average, with higher rates observed in older people.<sup>5-8</sup>

Clinical trials, event reporting, and compensation claims provide a limited perspective on medication-related harm in the real world, producing data not typically generalisable to general practice populations. Population-based records review research can identify harms experienced in the course of routine clinical care, and identify patients at increased risk of harm to improve patient safety.<sup>9</sup>

In this study we examine medication-related harm in general practice using a subset of data from a nation-wide retrospective cohort review of general practice electronic health records which was looking at all harms.<sup>10,11</sup> The primary aim of this paper was to estimate the incidence, preventability and severity of all harms attributable to medication prescribed in general practice in New Zealand. The secondary aim was to investigate factors potentially associated with medication-related harm, including age, gender, ethnicity, social deprivation, number of consultations, number of medications, general practice size and location.

## METHOD

### Setting

All New Zealand general practices were stratified by size and location.<sup>10,11</sup> Practice size was defined by the number of enrolled patients, divided into tertiles to form three groups consisting of large, medium and small practices. Location was defined as rural or urban based by practice address.<sup>10,11</sup>

Practice size and location defined six strata. Twelve practices were randomly selected by from each strata and invited to participate; 44 study practices consented to participate (72.6% of the 62 eligible randomly selected practices with compatible practice software).<sup>11</sup>

## Participants

Patients enrolled in recruited practices were randomly selected for participation at the mid-point of the study period; in total 9076 patients were randomly selected (based on prior power calculations).<sup>11</sup> The general practice records of the randomly selected patients for the 3 year study period (1 January 2011 to 31 December 2013, inclusive) were anonymised at time of electronic data extraction. The extracted records contained everything that is normally available in patient records, including demographic data, consultation notes, screening data, laboratory and radiology results, referral letters, alerts, and prescriptions. Secondary care referrals, discharge summaries and clinic letters were available where these had been stored electronically in the record.

Consent and data access were granted by each practice rather than from individual patients.<sup>12</sup> This research was approved by the University of Otago ethics committee (HD14/32), and reviewed by the Ngāi Tahu Research Consultation Committee.

## Reviewers

Each patient's file was examined by at least 1 of 8 clinically active GPs with a minimum of 10 years' experience. Reviewers participated in training sessions at the commencement of the study. Feedback from double-reviewed files (948/9076, 10.4%) was used to further improve reviewer consistency. The range of agreement between pairs of reviewers was 66.7-100.0%; overall kappa = 0.344,  $p < 0.001$ .

## Covariates

Patient demographic data including age at 1 July 2012, gender, self-identified ethnicity,<sup>13</sup> and socio-economic deprivation were obtained. Participants were sorted into one of five socio-economic categories ranging from 1 (least deprived) to 5 (most deprived) based on their home address and census-derived data for each area meshblock.<sup>14</sup> Information on the number of unique medications prescribed, and number of consultations were also obtained within the specified period. Practice size and location are defined above.

## Outcomes

Harm was defined as: *physical, emotional or financial negative consequences to patients directly arising from health care, beyond the usual consequences of care, and not attributable to patients' health conditions.*<sup>15</sup> Reviewers identified episodes where patients experienced harm, as documented in their records. Other patient safety measures, such as “near-misses”, “safety incidents”, “inappropriate prescribing” and “errors,” were not recorded unless they resulted in patient harm. Each patient record was recorded in binary terms: harm or no harm.

Harm was rated minor, moderate, severe or death.<sup>10</sup> Short-lived and relatively trivial harms were coded as minor (e.g. rashes, vomiting, and inconvenience to patients, such as being given the wrong prescription). Moderate harm was defined as having increased or persistent morbidity (e.g. fractures, untreated anaemia, and poor diabetic control). Severe harms included renal failure, pulmonary embolism, myocardial infarction, and morphine overdose. Reviewers used their clinical expertise to assess preventability from five categories.<sup>10,16</sup> Following discussion and consensus these options were aggregated in analysis to “preventable or potentially preventable” (original codes: “preventable and originated in primary care” and “potentially preventable and originated in primary care”) and “not preventable” (“not preventable, standard treatment,” “not preventable and

originated in primary care,” “not preventable and originated in secondary care,” and “preventable and originated in secondary care OR not preventable and originated in primary care,”).

Harms were documented in descriptive form, then coded using the Medical Dictionary for Regulatory Activities 18.0 codes.<sup>17</sup> Data extraction is depicted in Figure 1. Medications were coded by drug type using the Anatomical Therapeutic Chemical (ATC) classification system.<sup>18</sup>

## Statistical Analysis

The number and proportion of medication-related harms was calculated by patient demography (age, gender, ethnicity, deprivation), clinical information (number of consults and number of unique medications prescribed during the study period), and practice characteristics (practice size and practice location). Incidence rates were calculated as the number of events divided by the total number of person-years of follow-up (e.g. 3\*9076 years, 3 years per person). In order to obtain an estimate of the incidence of medication-related harm in New Zealand, sampling weights were applied to the incidence rates allowing for the probability of each practice being selected per strata, and each patient being selected per practice. Harms were examined by ATC classification. Individual medications were examined by rate of prescribing and percentage of patients harmed.

Logistic regression with robust standard error was used to explore associations between medication-related harm and patient demographics, clinical information and practice characteristics. The final model included all covariates listed above. Estimates were then adjusted using appropriate sampling weights.

Stata software version 15.1 was used for all statistical analyses. The Stata svy package was used for applying sample weights. Data were missing for ethnicity (144/9076 patients, 1.6%) and deprivation (894/9076, 9.9%). Complete data analyses were carried out on 8053 patients.

## RESULTS

From 2011-2013 inclusive, 7308 (80.5%) patients received 175,657 prescriptions for 846 different medications from their general practices; 1770 (19.5%) patients were not prescribed any medications. Patients were prescribed 0-53 different medications each, (median 4 (IQR 1-9)). Reviewers identified 1762 medication-related harms in 976/9076 (10.8%) patient records over the three year study period: 255 different medications were associated with harm. Medication-related harm accounted for 59% of all 2972 harms observed in the record review study. After applying weighting, the incidence rate of medication-related harm in New Zealand general practice was 73.9 harms per 1000 patient-years, and the incidence rate of preventable or potentially preventable medication-related harm was 15.6 harms per 1000 patient-years. Table 1 outlines the relationship between medication-related harms, patient demographics, clinical variables (numbers of consultations and medications) and practice characteristics as unweighted data and weighted estimates. Table 2 presents the logistic regression models of study variables in relation to medication-related harm.

### Patients

Older patients were more likely to experience medication-related harm. In the final model (adjusted and weighted) patients aged 60-74 years had double the odds of experiencing medication-related harm (OR 1.98, 95%CI 1.50-2.61), and patients 75 years and older had triple the odds (OR 3.08, 95%CI 2.15-4.41), compared to patients aged 15-59 years.

Females appeared to be at increased risk of medication-related harms in the unadjusted model, however after adjustment for the other variables there was no difference in risk by gender. The smallest ethnic group was Pasifika ethnicity (316/9076, 3.5%), which had a lower risk of experiencing

harm than Europeans (OR 0.43, 95%CI 0.19-0.98). There was no evidence that social deprivation was associated with medication-related harm.

## **Clinical exposure**

Increasing number of consultations and medications were correlated with increased risk of medication-related harm. Compared to patients who had 0-3 consultations over the study period, the odds of experiencing medication-related harm for patients that had 4-12 consultations over the three year study period is 5.38 (95%CI 1.55-18.67) times greater; for patients with (13+ consultations over 3 years) the odds were 11.83 (95%CI 4.27-32.80) times greater. Similarly, when compared with patients prescribed 0-4 unique medications in the study period, being prescribed 5-9 medications was associated with an increased odds ratio of medication-related harm of 3.05 (95%CI 2.10-4.44). Being prescribed 10+ medications was associated with an increased odds ratio of 5.71 (95%CI 3.83-8.50).

## **Practices**

Practice size was associated with risk of medication-related harm, but practice location was not. Patients attending small practices had a lower odds ratio of experiencing medication-related harm compared to patients attending large practices (OR for patients attending small practices 0.65, 95%CI 0.44-0.95; medium-sized practices 0.72, 95%CI 0.46-1.11).

## **Harms**

Most medication-related harm was directly related to the medication (1673/1762, 94.9%), but 5.1% was attributable to indirect causes such as access, communication (e.g. asthma deteriorated as patient did not understand fluticasone needed to be taken regularly), or procedures (e.g. local pain and swelling following administration of vaccine). Gastroenterological effects were the most

common harm type by body system (387/1762, 22.0%) (Table 3). Medication-related harms were mainly of minor severity (1432, 78.9%, e.g. ACE-inhibitor cough). Most medication-related harms were not preventable (1320, 81.2%, e.g. weight gain with oral contraceptive); the remainder were considered preventable or potentially preventable (330, 18.7%, e.g. cardiac arrest following co-prescription of medications which increased Q-T interval). One in five medication-related harms were moderately severe (329, 18.7%, e.g. developed type 2 diabetes following long-term course of prednisone) or severe (44, 2.5%, e.g. ventricular tachycardia and cardiac arrest attributed to amiodarone causing prolongation of the QT interval), and four harms were associated with the death of 3 patients (3, 0.2%). Eighteen patients were hospitalised as a result of medication-related harm, representing 0.2% (18/9076) of all study patients and corresponding to a weighted hospitalisation rate of 1.1 per 1000 patient-years.

## Medications

Table 4 shows harm by ATC classification group. Harms from cardiovascular medications (ATC Group C), predominantly antihypertensives and statins, affected the most patients; 517 patients were harmed of 5965 patients prescribed those medications (8.7%); 2.1% (11/517) of those harms were severe. Antineoplastic and immunomodulatory agents (ATC Group L) had the highest rate of harm (21/131, 16.0%) but none of the harms were severe, and these agents were taken by only 1.4% (131/9076) of patients. Medication relating to blood and blood forming organs (ATC Group B) were the third most harmful agents affecting 6.0% (102/1688) of study patients taking those medications, the most harmful being dabigatran (B01AE07), warfarin (B01AA03) and dipyridamole (B01AC07). This group had the highest proportion of severe harms (6.9%, 7/102). Analgesia, antibiotics and asthma medications were among the most commonly prescribed medication types. Of these commonly prescribed medications, diclofenac and amoxicillin with clavulanic acid were associated with the most harm (27/1016, 2.7% and 21/926, 2.3% respectively).

## DISCUSSION

The incidence rate of medication-related harm in New Zealand general practice after weighting was 73.9 harms per 1000 patient-years; the incidence rate of potentially preventable medication-related harm was 15.6 harms per 1000 patient-years. Most medication-related harms were of minor severity, but three patients died. The hospitalisation rate was 1.1 per 1000 patient-years. Factors strongly associated with medication-related harm were increasing age and clinical exposure. Pasifika ethnicity and attending a small practice were protective. Cardiovascular medications caused the most harm.

### Strengths and Limitations

General practice records are a rich data source permitting comprehensive review of medication-related harms.<sup>9</sup> We believe this large, detailed, retrospective review of a nationally representative sample of general practice records is likely to provide the closest possible estimate of medication-related harm in the real-world. Harm rates are generalisable to the entire country. There have been few appreciable changes in New Zealand general practice prescribing since the study period, although medication use and polypharmacy have increased slightly.<sup>19,20</sup>

Harm rates presented should be considered a conservative estimate. Only recorded harms are included; it is unknown how many additional harms occurred but were not recorded. We assume all patient participants selected at the mid-point of the study period remained enrolled for the three year study period. Medication-related harms were only included if there was a prescription for the corresponding agent in the electronic medical record. Therefore, harms arising from medications administered or dispensed in general practice without a prescription (e.g. some contraceptives, practitioner supply medications<sup>21</sup> etc.) were not included. Additionally, controlled drugs such as morphine and methylphenidate required a hand-written prescription during the study period, but a

concurrent electronic prescription may not have been generated. Harms were recorded verbatim – e.g. it is not possible to know whether someone would have experienced haematemesis regardless of whether they had been taking diclofenac.

Harm estimates are not easily comparable between studies due to variations in terminology and methodology.<sup>22-24</sup> Critics of the record review method point to this and object to low rates of reproducibility.<sup>25,26</sup> However, the records review method is comprehensive and provides unique insight into the patient experience of medication-related harm.<sup>9</sup> Reviewer training and feedback was used to improve reviewer concordance.

## **Comparison with existing literature**

Our research found medication-related harm was common, for several reasons. We examined records for all medication-related harm and not just preventable adverse events or patient-safety incidents; our patient-focussed definition of harm is comprehensive; and we examined all patient records (not just those considered high risk or identified by a trigger tool). Our figures are therefore higher than published figures, although comparisons between these types of studies is difficult. The most comparable systematic review estimated the incidence of preventable adverse drug events as 15 per 1000 person-years,<sup>23</sup> which is equivalent to our incidence rate for preventable or potentially preventable medication-related harm. Other studies indicate medication-related harm is a substantial problem, but are less comparable with our findings. One meta-analysis found up to 24 patient safety incidents per 100 primary care consultations, with up to 11% of medication-related incidents resulting in patient harm,<sup>27</sup> a literature review found up to 2.3% of deaths followed adverse events attributable to primary care treatment, with up to 42% of serious medication-related harms in primary care considered preventable,<sup>28</sup> while a record review study found 25.7% of preventable harms attributable to medication.<sup>29</sup>

## **Implications for research and practice**

General practice has been considered a relatively safe health care setting. We found medication-related harm is common in general practice, mostly minor and not preventable, often arising from standard care. However, sometimes harms resulted in severe outcomes including hospitalisation and death; one in four harms were considered at least potentially preventable. These findings reinforce the need for vigilance and care in even routine medication use.

This research adds to our knowledge of which patients are at highest risk of medication-related harm; namely, patients who are older and who take more medications. Identifying these patients may help inform shared decision-making at the time of prescribing and target risk monitoring. Further research is required to determine how best to address and reduce the risk of medication-related harm in the context of routine general-practice prescribing.

## **CONCLUSION**

Medication-related harm in general practice is common. This study builds on the evidence base about the risk posed by medication in the real world. Findings can be used to inform decision-making in general practice and to target patient safety initiatives towards patients at higher risk of harm.

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## **Contributor and guarantor information**

Leitch was a clinical coordinator for the study, recruited the study practices, reviewed general practice records, coded harms, conducted statistical analyses, and wrote this manuscript. Leitch is the guarantor for this research and as corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Dovey is the Principal Investigator, conceived and undertook the study design, obtained research funding, coded harms, and critically reviewed this manuscript. Cunningham reviewed general practice records, coded harms, and critically reviewed this manuscript. Smith and Zeng provided advice regarding the statistical analyses and critically reviewed this manuscript. Reith, Wallis, Eggleton, McMenamin, Williamson, Lillis, and Tilyard reviewed general practice records and critically reviewed this manuscript.

## **Transparency statement**

Leitch (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained. All reasonable requests for data sharing will be considered in light of the existing ethical approval.

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## Competing interests declaration

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: all authors apart from Smith and Zeng had financial support from the Health Research Council New Zealand for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

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**Figure title:**

Figure 1. Selection of medication-related harms data from records review study data.

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**Table 1. Demographic data of study patients, clinical exposure and practices in relation to medication-related harm related to GP prescribing**

		No Harm	Medicine-related harm	No Harm	Medicine-related harm
		Unweighted study data		Weighted data*	
<b>Totals N (%)</b>		8100 (89.3%)	976 (10.8%)	3,737,889 (88.2%)	502,404 (11.9%)
<b>PATIENTS</b>					
<b>Age</b> (missing=0)	0-4 years	296 (94.6)	17 (5.4)	146,698 (93.0)	11,114 (7.0)
	5-14 years	1283 (97.6)	32 (2.4)	599,128 (96.5)	21,511 (3.5)
	15-59 years	4765 (93.3)	345 (6.8)	2,274,914 (92.1)	195,620 (7.9)
	60-74 years	1217 (80.0)	305 (20.0)	504,945 (76.7)	153,736 (23.3)
	75+ years	539 (66.1)	277 (34.0)	212,204 (63.8)	120,424 (36.2)
<b>Gender</b> (missing=0)	Female	4189 (87.8)	583 (12.2)	1,972,810 (86.9)	298,012(13.1)
	Male	3911 (90.9)	394 (9.1)	1,765,079 (89.6)	204,392 (10.4)
<b>Ethnicity</b> (missing=139)	European	6092 (88.4)	797 (11.6)	2,901,377 (87.1)	428,700 (12.9)
	Māori	1207 (91.0)	119 (9.0)	385,728 (90.2)	42,081 (9.8)
	Pasifika	298 (94.3)	18 (5.7)	102,189 (95.1)	5,322 (5.0)
	Other	384 (94.6)	22 (5.4)	306,709 (93.6)	20,675(6.3)
<b>Deprivation*</b> (missing=894)	1	1762 (89.6)	204 (10.4)	1,165,530 (88.5)	150,861(11.5)
	2	1655 (89.7)	207 (11.1)	829,358 (87.4)	119,827 (12.6)
	3	1525 (89.7)	176 (10.4)	663,132 (89.2)	79,880 (10.8)
	4	1202 (88.8)	152 (11.2)	469,926 (87.0)	70,324 (13.0)
	5	1149 (88.5)	150 (11.6)	385,526 (87.1)	57,219 (12.9)
<b>No. of consults</b> (missing=0)	0-3	2466 (99.7)	8 (0.3)	1,081,613 (99.5)	5,567 (0.5)
	4-12	3096 (95.9)	132 (4.1)	1,476,184 (94.5)	86,466 (5.5)
	13+	2538 (75.2)	836 (24.8)	1,180,091 (74.2)	410,371 (25.8)
<b>No. of meds</b> (missing=0)	0-4	4601 (98.6)	64 (1.4)	2,115,238 (98.0)	43,101 (2.0)
	5-9	2099 (89.1)	257 (10.9)	956,015 (87.3)	139,267 (12.7)
	10+	1400 (68.1)	655 (31.9)	666,636 (67.6)	320,036 (32.4)
<b>PRACTICES</b>					
<b>Practice size</b> (missing=0)	Large	2650 (88.3)	353 (11.8)	2,409,416 (87.0)	358,999 (13.0)
	Medium	2729 (88.6)	351 (11.4)	927,812 (89.6)	107,132 (10.4)
	Small	2721 (90.9)	272 (9.1)	400,661 (91.7)	36,273 (8.3)
<b>Location</b> (missing=0)	Urban	4082 (89.8)	462 (10.2)	3,050,365 (88.0)	416,372 (12.0)
	Rural	4018 (88.7)	514 (11.3)	687,524 (88.9)	86,032 (11.1)

\*Weighting was applied based on the relative probability of each practice being selected per strata, and each person being selected to participate per practice, due to the complex sampling design of the study. Weighting means these results are nationally generalisable to the New Zealand population.

\*\*Deprivation is based on NZDep index of socioeconomic deprivation, where 1=least deprived, 5=most deprived.

**Table 2. Logistic regression of study variables in relation to harms arising from medication prescribed in general practice (binary outcome variables medication-related harm: harm or no harm)**

	Unadjusted*		Adjusted**		Adjusted & Weighted†	
Variable	OR (95% CI)	P Value	OR (95% CI)	P value	OR (95% CI)	P value
<b>PATIENTS</b>						
<b>Age</b>						
0-4 years	0.79 (0.48-1.31)	0.365	0.56 (0.31-1.00)	0.049	0.75 (0.42-1.33)	0.308
5-14 years	0.34 (0.24-0.50)	<0.001	0.60 (0.41-0.88)	0.010	0.58 (0.31-1.10)	0.095
15-59 years	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
60-74 years	3.46 (2.93-4.09)	<0.001	1.81 (1.49-2.19)	<0.001	1.98 (1.50-2.61)	<0.001
75+ years	7.10 (5.92-8.51)	<0.001	2.86 (2.30-3.56)	<0.001	3.08 (2.15-4.41)	<0.001
<b>Gender</b>						
Male	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Female	1.39 (1.21-1.59)	<0.001	1.07 (0.91-1.26)	0.397	0.98 (0.68-1.43)	0.931
<b>Ethnicity</b>						
European	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Māori	0.75 (0.62-0.92)	0.006	1.03 (0.81-1.32)	0.790	1.01 (0.81-1.27)	0.924
Pasifika	0.46 (0.29-0.75)	0.002	0.57 (0.33-0.96)	0.036	0.43 (0.19-0.98)	0.045
Other	0.44 (0.29-0.69)	<0.001	0.86 (0.52-1.42)	0.554	0.68 (0.41-1.15)	0.145
<b>Deprivation*</b>						
1	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
2	1.08 (0.88-1.33)	0.459	1.00 (0.80-1.27)	0.969	1.04 (0.79-1.37)	0.783
3	1.00 (0.81-1.23)	0.977	0.92 (0.72-1.18)	0.528	0.86 (0.58-1.29)	0.457
4	1.09 (0.87-1.36)	0.437	1.05 (0.82-1.36)	0.685	1.15 (0.80-1.65)	0.443
5	1.13 (0.90-1.41)	0.292	1.14 (0.87-1.49)	0.360	1.05 (0.58-1.90)	0.871
<b>Consultations</b>						
0-3	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
4-12	13.14 (6.43-26.88)	<0.001	6.18 (2.77-13.77)	<0.001	5.38 (1.55-18.67)	0.009
13+	101.54 (50.50-204.16)	<0.001	15.21 (6.74-34.34)	<0.001	11.83 (4.27-32.80)	<0.001
<b>Medications</b>						
0-4	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
5-9	8.80 (6.66-11.63)	<0.001	3.41 (2.45-4.74)	<0.001	3.05 (2.10-4.44)	<0.001
10+	33.63 (25.84-43.78)	<0.001	7.25 (5.19-10.11)	<0.001	5.71 (3.83-8.50)	<0.001
<b>PRACTICES</b>						
<b>Practice size</b>						
Large	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Medium	0.97 (0.83-1.13)	0.662	0.91 (0.75-1.10)	0.336	0.72 (0.46-1.11)	0.134
Small	0.75 (0.64-0.89)	<0.001	0.75 (0.61-0.93)	0.008	0.65 (0.44-0.95)	0.027
<b>Location</b>						
Urban	1 [Reference]	-	1 [Reference]	-	1 [Reference]	-
Rural	1.13 (0.99-1.29)	0.071	0.92 (0.78-1.08)	0.203	0.78 (0.55-1.09)	0.145

\*Unadjusted: Unweighted univariate logistic regression

\*\*Adjusted: Unweighted multiple logistic regression to adjust for potential confounders – all other variables were considered potential confounders

†Adjusted and Weighted: Multiple logistic regression weighted for the relative probability of each person being selected as a study participant

**Table 3. Harm types by system with examples**

System N (%)	Harm N (% of System)	Examples	
<b>General</b> 186 (10.6)	Generally unwell	63 (35.0)	75 year old female felt dizzy and sleepy after taking donepezil. Mild severity, not preventable.
	Fatigue	47 (26.1)	
	Weight change	24 (13.3)	10 year old male experienced anorexia and poor weight gain on methylphenidate. Mild severity, potentially preventable.
	Exacerbation of existing condition	20 (11.1)	
	Other	32 (17.2)	
<b>Gastro- enterology</b> 387 (22.0)	Nausea, vomiting, diarrhoea	213 (55.0)	2 year old female developed diarrhoea after taking amoxicillin. Mild severity, not preventable.
	Constipation	53 (13.7)	81 year old male developed severe constipation from codeine requiring hospitalisation. Severe harm, potentially preventable.
	Dyspepsia	48 (12.4)	
	Bleeding	28 (7.2)	
	Pain	12 (3.1)	
	Other	33 (8.5)	
<b>Cardiology</b> 217 (12.3)	Hypotension	136 (62.7)	93 year old male experienced recurrent falls secondary to hypotension while taking cilazapril, metoprolol, frusemide and isosorbide mononitrate. Moderate severity. Potentially preventable.
	Heart failure	39 (18.0)	
	Arrhythmias	27 (12.4)	
	Other	15 (6.9)	
<b>Neurology</b> 192 (10.9)	Cognition	61 (31.8)	83 year old woman experienced a haemorrhagic cerebrovascular accident after commencing aspirin and clopidogrel, resulting in death. Not preventable.
	Sensory	41 (21.4)	
	Headache	35 (18.2)	
	Balance	32 (16.7)	79 year old man developed postural hypotension while taking metoprolol and cilazapril. Fell and developed a subdural haematoma, died during hospitalisation for this. Potentially preventable.
	Movement	12 (6.3)	
	Intracerebral event	11 (5.7)	
<b>Renal</b> 161 (9.1)	Renal	139 (86.3)	69 year old male with severe chronic renal failure died within two weeks of an increased dose of metformin and allopurinol. Death. Potentially preventable.
	Urology	22 (13.7)	
<b>Musculo- skeletal</b> 107 (6.0)	Pain	75 (70.1)	81 year old male experienced repeated episodes of gout while taking bendrofluzide. Mild severity. Potentially preventable.
	Gout	18 (16.8)	
	Bones and joints	14 (13.1)	
<b>Skin</b> 104 (5.9)	Rash	50 (22.1)	8 year old female developed scalp irritation and discomfort after using malathion shampoo. Mild severity, not preventable.
	Itch	23 (48.1)	
	Other	31 (29.8)	
<b>Mental health</b> 101 (5.7)	Mood/affect	66 (65.3)	53 year old male experienced vivid dreams and sleep disturbance while taking varenicline. Mild severity. Not preventable.
	Sleep disturbance	26 (25.7)	43 year old female described as abusing prescribed codeine. Moderate severity. Potentially preventable.
	Addiction	9 (8.9)	
<b>Haematology</b> 81 (4.6)	Haematology	77 (95.1)	49 year old male developed thrombocytopenia while taking carbamazepine. Mild severity. Not preventable.
	Immunology	4 (4.9)	
<b>Endocrine</b> 71 (4.0)	Diabetes related	48 (67.6)	71 year old female taking glipizide and insulin experienced recurrent hypoglycaemic episodes. Moderate severity. Potentially preventable.
	Sweating and flushing	10 (14.1)	
	Other	13 (18.3)	
<b>Reproductive health</b> 60 (3.4)	Bleeding	34 (56.7)	51 year old female on dabigatran experienced menorrhagia requiring a blood transfusion. Moderate severity. Not preventable.
	Infection/discharge	18 (30.0)	
	Pregnancy	8 (13.3)	
<b>Respiratory</b> 57 (3.2)	Cough & wheeze	57 (100.0)	71 year old male developed acute pneumonitis while taking amiodarone. Severe harm. Not preventable.
<b>Economic</b> 38 (2.1)	Extra treatment required	38 (100.0)	32 year old male required hospitalisation and time off work for a GI bleed while taking diclofenac and no proton-pump inhibitor. Moderate severity. Potentially preventable.

**Table 4: Medication-related harm by Anatomical Therapeutic Chemical (ATC) classification group**

		Patients harmed/ Patients prescribed unique medicine* (%) 1,433/55,340 (2.6)	Percentage of patients harmed as a proportion of medication-related harm by ATC class 1,433/1,433 (100)
A	Alimentary tract and metabolism	124/6,174 (2.0)	8.7
B	Blood and blood forming organs	102/1,688 (6.0)	7.1
C	Cardiovascular system	517/5,956 (8.7)	36.1
D	Dermatologicals	25/6,385 (0.4)	1.7
G	Genitourinary system and sex hormones	52/1,482 (3.5)	3.6
H	Systemic hormonal preparations	30/1,653 (1.8)	2.1
J	Anti-infectives for systemic use	152/10,676 (1.4)	10.6
L	Antineoplastic and immunomodulating agents	21/131 (16.0)	1.5
M	Musculoskeletal system	91/4,600 (2.0)	6.4
N	Nervous system	291/9,178 (3.2)	20.3
P	Antiparasitics, insecticides and repellents	4/377 (1.1)	0.3
R	Respiratory system	16/5,612 (0.3)	1.1
S	Sensory organs	7/1,330 (0.5)	0.5
V	Various	1/98 (1.0)	0.1

\* Each unique medicine was counted once per patient. Patients may have been prescribed more than one medicine in each ATC code, therefore the total may be more than 100% of study patients in some categories.

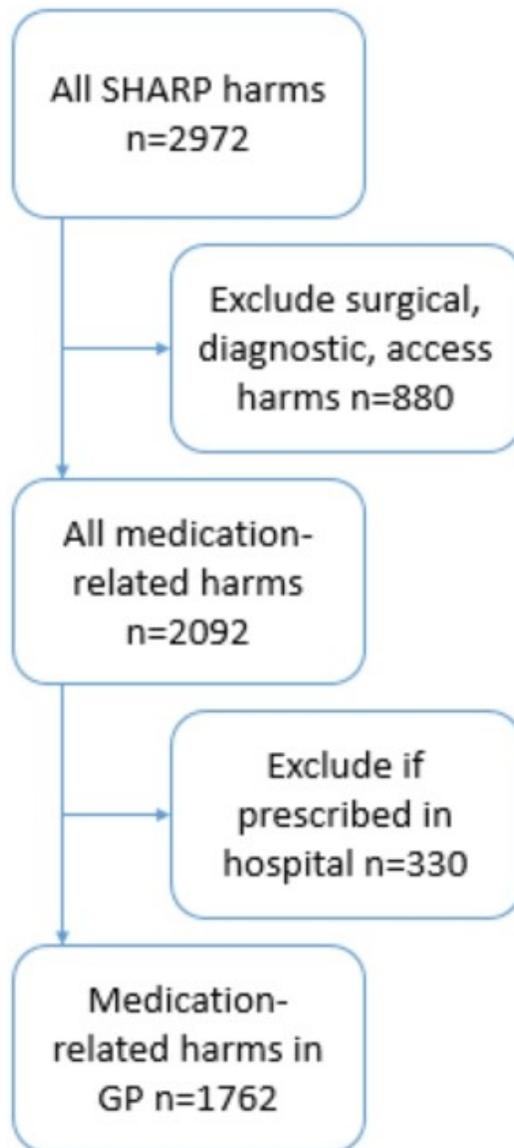


Figure 1. Selection of medication-related harms data from records review study data

84x173mm (96 x 96 DPI)