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ORIGINAL ARTICLE

Preventable adverse drug events: Descriptive epidemiology

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Aim: Our objective was to identify preventable adverse drug events and factors contributing to their development.

Methods: We performed a retrospective chart review combining data from three prospective multicentre observational studies that assessed emergency department patients for adverse drug events. A clinical pharmacist and physician independently reviewed the charts, extracted data and rated the preventability of each adverse drug event. A third reviewer adjudicated all discordant or uncertain cases. We calculated the proportion of adverse drug events that were deemed preventable, performed multivariable logistic regression to explore the characteristics of patients with preventable events, and identified contributing factors.

Results: We reviewed the records of 1 356 adverse drug events in 1 234 patients. Raters considered 869 (64.1%) of adverse drug events probably or definitely preventable. Patients with mental health diagnoses (OR 1.8; 95% CI 1.3–2.5) and diabetes (OR 1.7; 95% CI 1.2–2.4) were more likely to present with preventable events. The medications most commonly implicated in preventable events were warfarin (9.4%), hydrochlorothiazide (4.5%), furosemide (4.0%), insulin (3.9%) and acetylsalicylic acid (2.7%). Common contributing factors included inadequate patient instructions, monitoring and follow-up, and reassessments after medication changes had been made.

Conclusions: Our study suggests that patients with mental health conditions and diabetes require close monitoring. Efforts to address the identified contributing factors are needed.

KEYWORDS

adverse drug events, contributing factors, medication safety, preventability

1 | INTRODUCTION

Adverse drug events, the unintended and harmful events associated with medications, represent a major burden on the healthcare system.[1-3] They are a leading cause of unplanned hospital admissions and emergency department visits.[2,4,5] Developing effective strategies to prevent adverse drug events has become an international research priority.[6,7] Current prevention efforts focus on vulnerable populations such as the elderly, and those taking medications that are commonly associated with clinically significant and measurable harms.[7] However, a focus on preventability is key to strategic planning, as policies that do not target factors contributing to *preventable* events cannot be expected to reduce adverse drug events.

Principal Investigator: The authors confirm that the Principal Investigator for this paper is Dr. Corinne Hohl and that she had direct clinical responsibility for patients.

Prospective studies indicate that between 28 and 80% of adverse drug events are preventable.[8-15] Most studies describe the type and severity of preventable events,[8,10,15-19] without identifying high-impact patient populations, system-level targets for intervention, or the contexts in which preventable events occur.[2,7,15,17,20-23] Some preventability assessment methods have made broad assumptions in assessing preventability.[24] For example, one algorithm automatically assumes that all adverse drug events due to medications amenable to monitoring using laboratory testing can be averted by increasing the frequency of laboratory monitoring.[24] However, it is possible that increasing the frequency of routine laboratory monitoring without understanding contextual or contributing factors risks being ineffective while unnecessarily increasing resource utilization.

Our main objective was to describe the characteristics of preventable adverse drug events experienced by patients presenting to emergency departments with an adverse drug event. Our secondary objective was to highlight factors that contributed to their development.

What is already known about the subject

- Adverse drug events represent a major burden on the healthcare system.
- Efforts to reduce adverse drug events should focus on preventable events and consider factors that contribute to their development.

What this study adds

- More than two-thirds of adverse drug events were rated as probably or definitely preventable.
- Patients with mental health conditions, diabetes, and those receiving high-risk medications (i.e., warfarin, hydrochlorothiazide, furosemide, insulin and acetylsalicylic acid) were at increased risk of experiencing a preventable adverse drug event.
- Contributing factors commonly included inadequate patient instructions, monitoring and follow-up, and reassessments after medication changes had been made.

2 | METHODS

This was a multi-centre retrospective research and/or medical record review conducted in four Canadian acute care hospitals. The institutional review board of the University of British Columbia and of each participating hospital approved the protocol for this study. The need for patient consent was waived during ethics review. The Drug Safety and Effectiveness Network, in collaboration with Health Canada and the Canadian Institutes of Health Research, supported this study. None of the funding organizations participated in the conceptualization of the study, the development of the research protocol, or in the collection, analysis or interpretation of data. The study authors wrote the manuscript.

2.1 | Population

We reviewed the medical and/or research records of all patients who had been diagnosed with one or more medication-related problems or adverse drug events in one of three prospective multi-centre parent studies conducted by our research group (Appendix A).[4,5,25,26] The first parent study, conducted in 2008–2009, derived a clinical decision rule to identify patients at high-risk of adverse drug events from 1 591 patients presenting to the emergency departments of two tertiary care hospitals, Vancouver General (VGH) and St. Paul's Hospitals (SPH), in Vancouver, British Columbia, Canada.[5] In this study, 226 of the enrolled patients were diagnosed with an adverse drug event. This parent study was approved by the UBC Clinical Ethics Board. The second parent study, conducted in 2011–2013, evaluated the impact of pharmacist-led medication review on health outcomes from 10 807 patients presenting to the emergency departments of VGH, Lions Gate Hospital (LGH), an urban community hospital in North Vancouver, British Columbia, and Richmond General Hospital (RGH), an urban community hospital in Richmond, British Columbia.[4] In this study, patients at high risk of adverse drug events based on the clinical decision rule derived and validated in the other two parent studies were systematically selected for medication review (Appendix A). Of these patients, 2862 were diagnosed with medication-related problems. The need for ethics review for this study was waived as this was a quality improvement project. The third parent study, conducted in 2014–2015, validated the previously derived clinical decision rules using 1 529 patients presenting to the emergency departments of VGH, LGH and the Ottawa Civic Hospital (OCH), an urban tertiary care hospital in Ottawa, Ontario, Canada.[25] In this study, 240 of the enrolled patients were diagnosed with an adverse drug event. This parent study was approved by the UBC Clinical Ethics Board. All three studies systematically enrolled patients presenting to an emergency department (Appendix B). In the three parent studies, clinical pharmacists and physicians evaluated all enrolled patients at the point-of-care, and documented medication-related problems or adverse drug events in research and medical records. All cases in which the clinical pharmacist and physician diagnoses were concordant were considered final. An independent committee adjudicated all cases in which their assessments were discordant or uncertain.

The current study was conceived after the completion of these three prior studies, as the parent studies had allowed us to compile a large database of prospectively identified adverse drug events. We reviewed the research records and/or medical records of the hospital that all participants diagnosed with a medication-related problem or adverse drug event presented to in the primary studies, and used charts to exclude patients no longer meeting our case definition of adverse drug event for the current study (Appendix C), or who had been diagnosed with an alternative diagnosis since the conclusion of the parent study. We excluded patients whose research and medical records could not be retrieved, and those with illegible records.[4,5,25,26]

FIGURE 1 Flow diagram of patients through the study

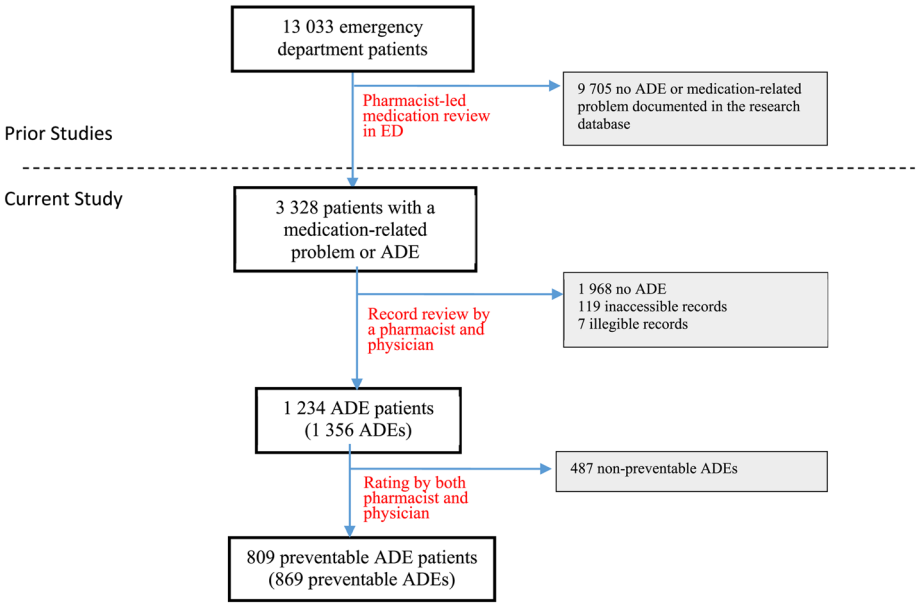

TABLE 1 Characteristics of 1 234 ADE patients by preventability

Patient characteristics	Patients with ≥1 preventable ADEs (*N* = 809)	Patients with only non-preventable ADEs (*N* = 425)
Median age, y (IQR)	71.0 (33.7)	66.5 (34.1)
Number ≥ 80 years, *n* (%)	284 (35.1)	124 (29.2)
Female, *n* (%)	452 (55.9)	244 (57.4)
Enrolling hospital, *n* (%)		
VGH	612 (75.6)	324 (76.2)
LGH	139 (17.2)	65 (15.3)
SPH	25 (3.1)	13 (3.1)
OCH	33 (4.1)	23 (5.4)
Comorbidites, *n* (%)		
Diabetes	195 (24.1)	63 (14.8)
Chronic heart failure	95 (11.7)	45 (10.6)
Atrial fibrillation	166 (20.5)	90 (21.2)
Renal failure	91 (11.2)	31 (7.3)
Dementia	62 (7.7)	21 (4.9)
Hypertension	387 (47.8)	169 (39.8)
Mental health diagnosis	180 (22.2)	63 (14.8)
Other condition	717 (88.6)	354 (83.3)

2.2 | Definitions

We defined adverse drug events as harm caused by a drug or the inappropriate use of a drug, consistent with its effective definition in clinical practice.[27] Adverse drug events included adverse drug reactions, undesirable effects to drugs occurring within the normal therapeutic range,[28,29] drug interactions, supra- and sub-therapeutic doses, events due to non-adherence or inappropriate drug withdrawal, and cases in which the patient was on an ineffective or on no drug despite previous documentation of an indication for and lack of contraindication to the drug (e.g., a patient presenting with an ischaemic stroke with a previously documented history of atrial fibrillation and a high stroke risk but no anticoagulation).[19] For events presenting with abnormal vital signs, we defined cut-offs *a priori*, excluding all other cases (Appendix B). For events involving laboratory abnormalities, we used the reference values of each participating hospital. We categorized severity as mild when the adverse drug event required no change in medical management, moderate when it required a change in medical management, and severe when it was either the primary reason for hospitalization, caused permanent disability, or proved fatal.

Based on our findings from previous work, we considered adverse drug events as preventable when there was "lack of adherence to best medical practice, including inappropriate drug, dosage, route or frequency of administration of a drug for the patient's clinical condition, age, weight or renal function; administration of a drug despite a known allergy, a previous adverse reaction to, or a drug interaction; non-adherence; laboratory monitoring not or inappropriately performed; prescribing or dispensing errors, or errors in drug administration."[30]

We defined contributing factors as any patient-, provider- or system-level factors that our reviewers deemed instrumental to the development of the event.

2.3 | Chart review methods

After excluding cases that did not meet our case definition, a clinical pharmacist (S.W.) and physician (one of C.H., D.V. or F.S.) reviewed the medical and/or research records of all patients diagnosed with one or more adverse drug events, and independently assessed each event's preventability. Events were categorized as definitely, probably or not preventable.[30] If preventability ratings were discordant, reviewers discussed the case until reaching consensus, and a third

TABLE 2 Multivariable associations between patient factors and preventable adverse drug events (≥1) versus patients with only non-preventable adverse drug events (*N* = 1 234)

Independent variables	Patients with preventable ADEs	Patients with ADE	Patients with preventable events (%)	OR[a] (95% CI)	*P*-value
Age ≤ 80 y	525	826	63.6	1.00	
Age > 80 y	284	408	69.6	1.2 (0.9–1.6)	0.26
Gender					
Male	357	538	66.4	1.00	
Female	452	696	64.9	0.9 (0.7–1.1)	0.39
Hospital					
VGH	612	936	65.4	1.00	
LGH	139	204	68.1	1.2 (0.9–1.7)	0.24
OCH	33	56	58.9	0.7 (0.4–1.3)	0.24
SPH	25	38	65.8	1.1 (0.5–2.1)	0.81
Comorbidities					
Diabetes[a]	195	258	75.6	1.7 (1.2–2.4)	**<0.01**
Chronic heart failure[a]	95	140	67.9	1.0 (0.6–1.5)	0.86
Atrial fibrillation[a]	166	256	64.8	0.9 (0.6–1.2)	0.37
Renal failure[a]	91	122	74.6	1.3 (0.8–2.1)	0.24
Dementia[a]	62	83	74.7	1.5 (0.8–2.5)	0.19
Hypertension[a]	387	556	69.6	1.3 (1.0–1.7)	0.11
Mental health diagnosis[a]	180	243	74.1	1.8 (1.3–2.5)	**<0.01**

[a]Dummy coded so that patients without the health condition are the reference category.

TABLE 3 Comparison of preventable with non-preventable adverse drug events

	Preventable ADEs (*N* = 869)	Non-preventable ADEs (*N* = 487)	*P*-value
ADE type, *n* (%)			
Non-adherence	245 (28.2)	15 (3.1)	**<0.01**
Adverse drug reaction	207 (23.8)	267 (54.8)	**<0.01**
High dose	118 (13.6)	41 (8.4)	**<0.01**
Needs additional drug/untreated indication	117 (13.5)	36 (7.4)	**<0.01**
Low dose	92 (10.6)	58 (11.9)	0.46
Other[a]	56 (6.4)	13 (2.7)	**<0.01**
Ineffective drug	34 (3.9)	57 (11.7)	**<0.01**
ADE severity, *n* (%)			
Mild	22 (2.6)	26 (5.3)	**<0.01**
Moderate	573 (65.9)	312 (64.1)	0.49
Severe/fatal	274 (31.5)	149 (30.6)	0.72
Outcomes, *n* (%)			
No harm	153 (17.6)	62 (12.8)	**0.02**
Temporary harm	692 (79.6)	414 (85.0)	**0.01**
Permanent harm/death	24 (2.8)	11 (2.3)	0.58

[a]Includes drug interactions, drug withdrawals, and drug transcription/dispensing/administration errors.

reviewer adjudicated all cases in which consensus was not easily achieved. One clinical pharmacist (S.W.) entered up to five culprit drugs for each adverse drug event and identified any number of potential contributing factors based on clinical judgement by reviewing the patient's research and/or medical record in detail.

2.4 | Statistical analysis

We conducted descriptive analyses on baseline demographics for all included patients. We calculated the proportion of preventable adverse drug events as the number of definitely and probably

TABLE 4 Comparison of medications implicated in preventable and non-preventable adverse drug events

	Preventable ADE drugs (*N* = 1 166)[a]	Non-preventable ADE drugs (*N* = 635)[a]	*P*-value
Top culprit medications, *n* (%)[a]			
Warfarin	110 (9.4)	57 (9.0)	0.75
Hydrochlorothiazide	52 (4.5)	14 (2.2)	**0.02**
Furosemide	47 (4.0)	24 (3.8)	0.80
Insulin (human)	45 (3.9)	11 (1.7)	**0.02**
Acetylsalicylic acid	32 (2.7)	23 (3.6)	0.30
Top culprit medication classes, *n* (%)[a]			
Coumarin derivatives	110 (9.4)	57 (9.0)	0.75
Opiate agonists	99 (8.5)	67 (10.6)	0.15
Atypical antipsychotics	61 (5.2)	9 (1.4)	**<0.01**
Thiazide diuretics	52 (4.5)	14 (2.2)	**0.02**
Loop diuretics	48 (4.1)	24 (3.8)	0.73

[a]There were often multiple drugs implicated per ADE. We used the total number of drugs for each class of ADE as the denominator for each column.

preventable events, divided by the overall number of adverse drug events. We determined the frequency and proportion of preventable *vs* non-preventable adverse drug events at different levels of severity and patient harm. We reported all odds ratios with 95% confidence intervals (95% CI). We tabulated the number and frequency of the different adverse drug event types and the most common culprit drugs among preventable and non-preventable events. We dichotomized all multi-level variables using dummy coding (i.e., present *vs* absent) and reported *P*-values from chi-square tests comparing the proportions of each adverse drug event-level characteristic between preventable and non-preventable events to indicate instances where a particular adverse drug event characteristic was significantly more common among one group compared to the other. We calculated the number and proportion of preventable and non-preventable adverse drug events in which one or more contributing factors were identified. We determined the frequency at which contributing factors were identified among preventable adverse drug events and grouped them thematically. We used multivariable logistic regression to identify factors associated with patients diagnosed with a preventable adverse drug event *vs* patients without any preventable events. We included all measured patient-level variables, including age, gender, hospital and major comorbidities in the model. We adjusted all inferential statistics (odds ratios and *P*-values) to account for the effects of clustering by adverse drug event, by patient and/or by hospital.

3 | RESULTS

We reviewed the charts of 3 202 patients, of whom 1 234 were diagnosed with at least one adverse drug event (Figure 1). Among these patients, 809 (65.6%) were diagnosed with one or more preventable events (Table 1). Patients with preventable adverse drug events were mostly female (56%), with a median age of 71 years (Interquartile Range (IQR) 33.7) and took a median of eight medications (IQR 8). The most common comorbidities among patients with preventable adverse drug events were hypertension (47.8%), diabetes (24.1%) and mental health diagnosis (22.2%). Patients with one or more preventable adverse drug events were more likely to have a mental health diagnosis (OR 1.8; 95% CI 1.3–2.5) or diabetes (OR 1.7; 95% CI 1.2–2.4) compared with patients without any preventable adverse drug events (Table 2).

The 1 234 patients included in the study experienced 1 356 adverse drug events. Of the 1 356 events reviewed, reviewers considered 869 (64.1%) to have been preventable. Among preventable events, non-adherence (28.2%), adverse drug reactions (23.8%) and supratherapeutic dosing (13.6%) were most common, while among non-preventable events adverse drug reactions (54.8%), low dose (11.9%) and ineffective drugs (11.7%) were more common (Table 3). Adverse drug events due to non-adherence were more likely to be considered preventable (28.2%) *vs* non-preventable (3.1%; $P < 0.01$; Table 3). In contrast, a lower proportion of the preventable ADEs were adverse drug reactions (23.8%) compared with the non-preventable ADEs (54.8%; $P < 0.01$; Table 3). Severe adverse drug events and those resulting in permanent harm or death were equally common between preventable and non-preventable events, but preventable events had a higher proportion of patients who suffered no harm compared to non-preventable events (Table 3).

The most common medications associated with preventable adverse drug events were warfarin (9.4%), hydrochlorothiazide (4.5%), furosemide (4.0%), insulin (3.9%) and acetylsalicylic acid (2.7%; Table 4). The top medication classes associated with preventable events included coumarin derivatives (9.4%), opiate agonists (8.5%), atypical antipsychotics (5.2%), thiazide diuretics (4.5%) and loop diuretics (4.1%). Of these medication classes, only atypical antipsychotics and thiazide diuretics were more common among preventable (5.2% and 4.5%, respectively) compared with non-preventable events (1.4% and 2.2%, respectively; $P < 0.01$ and $P = 0.02$; Table 4).

Multiple factors contributed to 262 (30.1%) preventable adverse drug events. Frequently identified contributing factors were related to medication prescribing (45.8%) and monitoring (35.5%), barriers to

TABLE 5 Most frequently identified factors that contributed to the development of preventable events (*N* = 782)

Contributing factors identified among 782 preventable ADEs[a]		*n* (%)
Communication problem	Lack of communication between a healthcare provider and a patient	58 (7.4)
	Lack of communication between physicians	18 (2.3)
	Lack of communication between nurses	6 (0.8)
	Lack of communication between physician and pharmacist	3 (0.4)
	Lack of communication between physician and a nurse	3 (0.4)
	Lack of communication between pharmacists	2 (0.3)
Drug delivery/labelling/ packaging/storage problem	Drug name, label or packaging problem	1 (0.1)
	Drug storage or delivery problem	1 (0.1)
EMS problem	Ambulance did not transport hypoglycaemic patient to hospital	3 (0.4)
Error	Provider error in drug administration	1 (0.1)
Inadequate monitoring	Delay in or inadequate clinical reassessment after medication change	122 (15.6)
	Insufficient laboratory monitoring	120 (15.3)
	Too aggressive medical therapy for patient's condition/age	36 (4.6)
Mental health illness/social problem-related	Non-adherence associated with mental health illness	53 (6.8)
	Patient confusion/dementia	16 (2.0)
	Substance misuse	15 (1.9)
Missing information	Critical information missing that could have prevented or mitigated the ADE	31 (4.0)
Non-adherence	Patient preference to not take medications	49 (6.3)
	Prior ADE leading to patient non-adherence	38 (4.9)
	Patient self-titrating medications inappropriately	30 (3.8)
	No compliance aid when required	20 (2.6)
	Patient non-adherence due to financial/lack of coverage	18 (2.3)
	Regimen too complex (e.g., high number of daily doses)	11 (1.4)
	Patient missed doses (forgetfulness/intoxication)	10 (1.2)
	Patient error in administration	7 (0.9)
	Patient hearing problem	1 (0.1)
Prior ADE	Missed/misdiagnosed previous ADE	3 (0.4)
Provider-level problem	Provided inadequate patient education or instructions	186 (23.8)
	Provider non-adherence with current treatment guidelines	101 (12.9)
	Lack of staff education	43 (5.5)
	Medication prescribed inappropriately because patient insisted	18 (2.3)
	Prescribed despite lack of clear indication for the culprit drug	10 (1.2)
Systems level problem	Environmental problem	4 (0.5)

(Continues)

TABLE 5 (Continued)

Contributing factors identified among 782 preventable ADEs[a]		*n* (%)
	Lack of quality control or independent check systems	4 (0.5)
Unable to access care	Patient unable to access a prescription refill	44 (5.6)
	Patient unable to access GP for appointment	15 (1.9)
	Patient unable to access specialist for appointment	8 (1.0)
	Patient unable to access appropriate level of care	4 (0.5)

[a]There were 87 preventable adverse drug events with no identified contributing factors

adherence (23.5%), problems with communication (11.5%), social factors (10.7%) and inadequate access to appropriate care (9.1%) (Table 5). The most frequently identified contributing factor among preventable adverse drug events was deemed to be inadequate patient education or instructions (23.8%). Common prescribing issues included delays to or inadequate clinical reassessments after medication changes (15.6%) and inadequate laboratory monitoring (15.3%; Table 5). Common barriers to adherence included mental health illness (6.8%) and patient preference (6.3%; Table 5).

4 | DISCUSSION

We sought to describe preventable adverse drug events from outpatient medications among adults presenting to emergency departments. Almost two-thirds of adverse drug events diagnosed in the emergency department were preventable. Patients with mental health conditions and diabetes were more likely to experience preventable events, while older patients were not. Atypical antipsychotics and thiazide diuretics were more commonly associated with preventable events, while other medication classes commonly targeted in preventative efforts, such as coumarin derivatives and anti-infectives, were not associated with preventable events.[31,32] Insufficient education and monitoring commonly contributed to preventable events.

Current efforts in adverse drug event prevention often target specific patient populations, such as the elderly, or those taking medication classes such as anticoagulants that are commonly associated with adverse drug events, regardless of their preventability.[32-34] Many adverse drug events experienced by older adults may not be preventable, given the complexities of their medication regimens.[35] This is in keeping with systematic reviews that have indicated that medication reviews in older patients may increase adherence and drug knowledge, without resulting in improvements in patient-oriented or system-level outcomes such as reduced hospitalizations and emergency department visits.[26,36] Developing strategies that specifically target patients and medications associated with preventable events may be an effective alternative.

Understanding contributing factors to preventable events can provide insight into why the adverse drug events occurred. Previous studies have recommended steps to improve patient adherence, encourage provider adherence to guidelines, increase diligence in monitoring patients, and optimize communication between providers and patients.[19,23,31,37] Others have highlighted inappropriate prescribing practices and insufficient monitoring of medications as contributing factors.[38,39] In a systematic review, identifying over-treated patients with diabetes and de-intensifying therapy was associated with reduced hypoglycaemic events without compromising glycaemic control.[40] Our findings support these conclusions, and highlighted the importance of enhanced monitoring for patients on thiazide diuretics and insulin, as these medications were commonly implicated in preventable events. Specifying medications at highest risk of preventable adverse drug events may assist in developing more specific recommendations to enhance the feasibility of and reduce the resource utilization associated with enhanced monitoring. Similarly, focusing resources to promote better education and monitoring for high-risk non-adherent patients may be advantageous.[41,42] For example, additional resources for mental health patients may include access to intense case management, a team-based model of care providing educational and environmental support to help patients remain adherent to medications.[42,43]

Our study is not without limitations. While our study was multicentre and conducted in two provinces, most cases were enrolled in British Columbian urban hospitals. Our results may therefore not be representative of the types of adverse drug events seen in other jurisdictions or contexts.

Our retrospective assessments of preventability and contributing factors were limited by the availability of the information documented in research records and/or paper-based and electronic medical records. It was often difficult to assess the preventability of an event without knowing the exact circumstances of the care that had been provided, or the patient's perspective. Individual and professional biases may have affected how reviewers perceived the preventability of an event.[30,44] Not all contributing factors were explicitly documented in the research or medical records, and therefore, undoubtedly, our clinical judgement, the patient's prior history, and documentation of the event's resolution informed our assessments. We assumed that if a clinician had addressed the contributing factor prior to the event, the event would have been prevented. To increase

the thoroughness and reduce the subjectivity of our preventability assessments, a second reviewer independently assessed the preventability of an event to produce a more robust assessment. However, this was not possible for the assessment of contributing factors, due to budgetary and time constraints.

Many contributing factors could be attributed to multiple non-exclusive domains. Often, the charts provided insufficient information to attribute a contributing factor to any one single domain, and might be attributable to more than one domain (e.g., communication could be a provider-level, patient-level or system-level issue). Given that prospective assessment and study of contributing factors is not feasible (it is not ethical to identify and observe contributing factors without intervening), this is a limitation inherent to this body of work.

In conclusion, efforts to reduce adverse drug events should focus on preventable adverse drug events and address common contributing factors. Our work suggests that close monitoring of patients with mental health conditions and diabetes is warranted. In addition, enhanced laboratory monitoring is indicated specifically for patients on insulin and thiazide diuretics.

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COMPETING INTERESTS

The authors have no competing of interest to declare.

CONTRIBUTORS

C.H., S.W., A.C. and M.W. conceived of and designed the study. S.W., C.H., F.S. and D.V. collected data. A.C., J.H. and M.W. cleaned and analysed the quantitative data. All authors contributed to, read, and approved of the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

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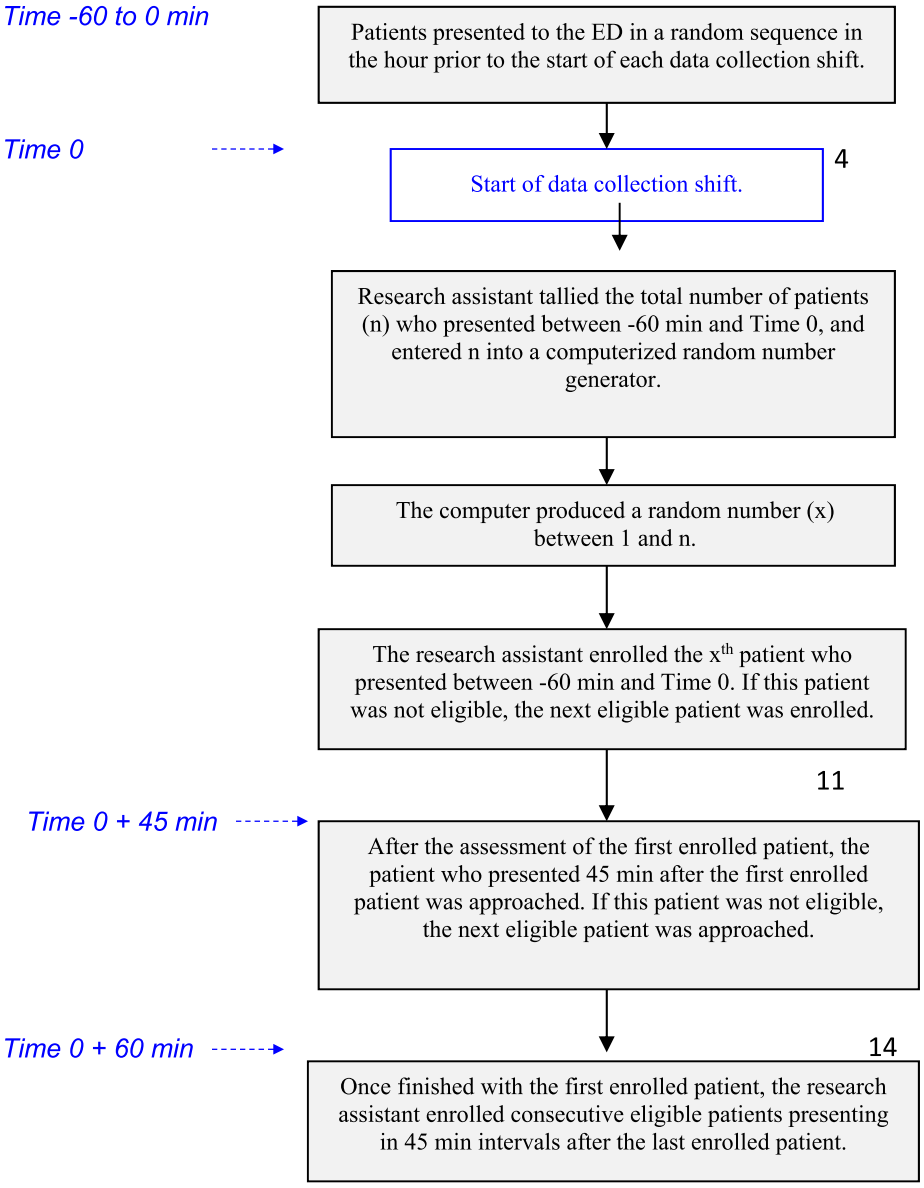
APPENDIX A: | Characteristics of the original studies from which patients with suspected adverse drug events were enrolled into the current study[44]

Study title	Cohort 1[5]	Cohort 2[4, 27]	Cohort 3[26]
Design	Prospective observational	Controlled clinical trial	Prospective observational
Primary study objective	To derive a clinical decision instrument to identify patients at high-risk of presenting with an adverse drug event	To evaluate the impact of emergency department-based pharmacist-led medication review on health outcomes.	To validate clinical decision instruments to identify patients at high-risk of presenting with an adverse drug event
Study period	2008–2009	2011–2013	2014–2015
Hospitals	VGH, SPH	VGH, LGH, RGH	VGH, LGH, OCH
Participants	**Included** • >19 years • used ≥1 prescription or OTC medication in the past 2 weeks • spoke English or translator available **Excluded** • violent behaviour • intentional self-poisoning • scheduled revisit • previously enrolled • transferred directly to an admitting service • left AMA	**Included** • >19 years • used ≥1 prescription or OTC medication in the past 2 weeks • spoke English or translator available • high-risk based on ADE decision rule[5,26] **Excluded** • required immediate resuscitation (CTAS = 1).[45] • multisystem trauma • scheduled re-visit • sexual assault • surgical complication • pregnancy complication • social problem	**Included** • >19 years • used ≥1 prescription or OTC medication in the past 2 weeks • spoke English or translator available **Excluded** • violent behaviour • intentional self-poisoning • scheduled revisit • previously enrolled • needle stick injury • sexual assault • triaged to fast track zone where time to disposition too rapid for enrolment • transferred directly to admitting service • left AMA
Enrolment (Appendix B)	Random selection of first patient with subsequent systematic selection	Random selection of first patient with subsequent systematic selection	Random selection of first patient with subsequent systematic selection
ADE definition	"Untoward and unintended event arising from the use of prescription or OTC medications."[28,30]	Same as in cohort 1. Medication-related problems were captured and documented in addition to ADEs.	"Untoward and unintended event arising from the appropriate or inappropriate use of a prescription or OTC medication."
Data collection process (Appendix C)	Trained clinical pharmacist and treating physician independently evaluated enrolled patients for ADEs. An independent committee adjudicated all discordant and uncertain cases by record review.	Clinical pharmacists working in the ED and treating physician independently evaluated enrolled patients for ADEs. Clinical pharmacists and physicians discussed uncertain or discordant cases in ED.	Trained clinical pharmacist and treating physician independently evaluated enrolled patients for ADEs. An independent committee adjudicated all discordant and uncertain cases by record review.
Follow-up duration	Until ED/hospital discharge, and by telephone follow-up if required	Until ED/hospital discharge, linkage with administrative database for health outcomes	Until ED/hospital discharge, and by telephone follow-up if required
No. participants	1591	10 807	1529
No. participants considered for enrolment in current study	226	2862	240

VGH, Vancouver General Hospital, a tertiary care hospital in Vancouver, BC, Canada; SPH, Saint Paul's Hospital, a tertiary care hospital in Vancouver, BC, Canada; LGH, Lions Gate Hospital, an urban community hospital in North Vancouver, BC, Canada; RGH, Richmond General Hospital, an urban community hospital in Richmond, BC, Canada; OCH, Ottawa Civic Hospital, a tertiary care hospital in Ottawa, ON, Canada; ADE, adverse drug event; AMA, against medical advice; OTC, over-the-counter; CTAS, Canadian Triage Acuity Score; ED, emergency department

APPENDIX B: | Patient enrolment algorithm

Appendix B. Patient Enrolment Algorithm



APPENDIX C: | Current study definitions

Adverse drug event (ADE):

"Unintended and harmful symptoms, signs or abnormal laboratory values arising from the appropriate or inappropriate use of medications (prescription, over-the-counter or complimentary and alternative medications)."

"Harm caused by the use of a drug."

- The sign(s) or symptom(s) are generally *not* deemed to have an alternate explanation by the pharmacist *and* the treating physician. In cases where alternative causes are possible (e.g., fall), the event should only be considered a suspect adverse drug event, if it is likely that the symptom would not have been as severe or not have occurred without the patient being on the drug (e.g., intracranial haemorrhage).
- Abnormal vital signs may constitute an adverse drug event, if the abnormal vital signs meet the cut-offs below, and treating the adverse drug event is medically appropriate according to the treating physician:
  - HR ≤ 50 and associated with symptoms (e.g., pre-syncope/syncope, prolonged sinus pauses on ECG)
  - HR ≥ 120 and associated with symptoms (e.g., pre-syncope/syncope, chest pain or palpitations)
  - BP ≥ 180 SBP or ≥ 100 DBP
- Abnormal laboratory tests can be considered an adverse drug event if they are outside of the hospital's reference range, and treating the adverse drug event is medically appropriate according to the treating physician.
- Harm caused by the use of alcohol or illicit drugs does *not* constitute an adverse drug event.

ADE classification:

Adverse drug reaction (ADR): "A response to a drug that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease".

Drug interaction.

Dosage Too High.

Dosage Too Low.

Non-adherence.

Inappropriate Drug Withdrawal.

Ineffective Drug.

Needs Additional Drug/Untreated Indication: This categorization should be reserved for cases in which there is clear previous documentation (i.e., before the index ED visit) in the patient's records about a hard indication for the drug, and lack of contra-indication for treatment.

Transcription/Dispensing/Administration Error.

ADE severity:

Fatal: The adverse event resulted in death.

Severe: The adverse drug event was the primary reason for the patient's hospitalization, caused permanent disability or was life-threatening.

Moderate: The adverse event required a change in medical management (medical therapy, a diagnostic procedure or consultation).

Mild: No change in medical therapy, including no adjustment of medications required.

ADE preventability:

Preventable if: there is a lack of adherence to best medical practice, including inappropriate drug, dosage, route or frequency of administration of a drug for the patient's clinical condition, age, weight or renal function; administration of a drug despite a known allergy, a previous adverse reaction to, or a drug interaction; non-adherence; laboratory monitoring not or inappropriately performed; prescribing or dispensing errors, or errors in drug administration.