Identifying medication harm in hospitalised patients: a bimodal, targeted approach

Nazanin Falconer (iD), **Anne Spinewine, Matthew P. Doogue and Michael Barras**

Medication harm is in the spotlight with the World Health Organization's (WHO) Global Patient Safety challenge.[1] Defined as "any negative patient outcome or injury related to a medication",[2] it is a costly problem for healthcare systems. Mortality, secondary to medication harm, is reported at 0.3% of all hospital patients.[3,4] Recent local studies in two Australian hospitals linked medication harm to anticoagulants, insulin and antihypertensives,[5,6] which is similar to findings from other health systems.[7,8]

The WHO has set a target of reducing medication harm by 50%, in particular by expediting digital solutions. In response there has been a flurry of publications on predictive modelling to help with early detection and prediction of those at high risk.[5,9–11]

Identifying medication harm is challenging however, as it occurs in combination with other causal factors and spans all hospital events. The difficulty of defining causality is reflected in the wide ranges of reported rates of inpatient medication harm, ranging from 1.6% to 35% of admissions.[8,12,13] Incident reporting by clinicians is the traditional method of ascertaining medication harm. However, under-reporting is the norm and incident reports reflect only the tip of the medication-harm iceberg. Further, incident reporting systems focus on errors and do not include patient harm arising from appropriate medicines use. The gold standard method is a prospective appraisal of patient medical records, laboratory tests and interviews with patients and care providers.[14,15] This approach is considered the most reliable as it is likely to detect more incidents than retrospective methods, but it is resource intensive and not feasible in large patient cohorts.

Targeted review of medical records using coded data or trigger tools (TTs) to identify which records should be reviewed is one method to address this.[16,17] This is increasingly viable with the availability of digital healthcare data for triggers. Identification of medication harm using routinely collected patient data is important as it is a major opportunity for improving clinical care. We propose a bimodal, targeted approach combining triggers and diagnostic codes to identify inpatient medication harm. We also discuss how machine learning (ML) and clinicians working at the coal face can improve medication-harm detection.

Targeted retrospective medical record review in the hospital setting

Traditionally epidemiological evidence of medication harm is from studies using retrospective medical record review, for example the Harvard Medical Practice Study and other similar studies.[18,19] These studies retrospectively reviewed all patient records to detect the presence of harm. However, this non-targeted review (i.e. screening every patient record) is resource intensive and the determination of causality is difficult.[14] Methods to reduce the volume of records and improve validity are needed.

Two methods that use a targeted method to facilitate a structured approach to medical record review include the use of triggers[20,21] and clinical coding data.[22] The Adverse Drug Event Trigger Tool (ADE TT) described by Rozich[20] and later refined by the Institute for Health Care Improvement enables targeted medical record review.[23] The ADE TT contains a set of triggers which signal that medication harm may have occurred.[23] Triggers include administration of antidotes or out-of-range laboratory results, for

Correspondence to:
Nazanin Falconer
Department of Pharmacy, Ground floor, Princess Alexandra Hospital, Woolloongabba, QLD. Centre for Health Services Research, Faculty of Medicine and School of Pharmacy, The University of Queensland, Brisbane, QLD, 4102, Australia
n.ghahremanfalconer@ uq.edu.au

Anne Spinewine
Université catholique de Louvain, Louvain Drug Research Institute, Brussels, Belgium

Pharmacy Department, Université catholique de Louvain, CHU UCL Namur, Yvoir, Belgium

Matthew P. Doogue
Department of Medicine, University of Otago, Christchurch, New Zealand

Department of Clinical Pharmacology, Canterbury District Health Board, Christchurch, New Zealand

Michael Barras
School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia

Department of Pharmacy, Princess Alexandra Hospital, Woolloongabba, Brisbane, QLD, Australia

example, administration of protamine sulphate and/or a supratherapeutic activated partial thromboplastin time (aPTT), signalling a potential bleed due to heparin therapy.

There are now several TTs available. One study evaluated 8 different TT methods in 1115 adult inpatients and found low sensitivities, ranging from 2% to 16%, but high specificities of 99%.[24] A systematic review of automated ADE detection in electronic health records using TTs identified 11 studies (7 of which were in a paediatric population), with a median positive predictive (PPV) value of 40%.[25] Another TT for identifying medication harm in older adult inpatients (TRIGGER-CHRON) was evaluated across 12 Spanish hospitals and reported an overall PPV of 22%.[26] The differences in findings may in part be due to patient cohorts (i.e. age), and variations in trigger sets. It should be noted that TTs with high PPVs are possible through the selection of individual triggers with higher PPVs, however this comes at a cost of losing clinically important but rare adverse events.[27] Whilst a wide range of PPVs have been reported, findings indicate that there is the potential to use TTs to drive medication-harm detection and spearhead patient safety initiatives. The advent of electronic health records (EHRs) is well suited to the TT methodology, which can be systematically applied to hospital records (e.g. by specifying predetermined threshold changes for laboratory tests), using automated algorithms, to detect harm in real time and at an institutional level.[28] Work to update and standardise the triggers is needed.

A second method is the use of coding data. International Classification of Disease (ICD) codes are allocated for every hospital separation, primarily for reimbursement purposes. ICD-10-Y codes (medication-related codes) can be coupled with diagnosis codes (e.g. codes for bleeding or hypoglycaemia) as prompts for medical record review in large data sets.[29] Similar to TTs, studies evaluating ICD codes report variable accuracy, with sensitivities ranging from 6% to 56% and specificity ranging from 95% to 99%.[17,22,30] For example, a Canadian study reported sensitivities of 9–83% when evaluating ICD codes at four tertiary hospitals.[31] The wide range of sensitivities suggest that coding practices (i.e. extent of clinician documentation and the skill of coders) are likely to determine the effectiveness of coding.

One potential approach to improve validity is to use a bimodal approach using both ADE TT and coding in the same EHRs. This can be streamlined to flag patient records for potential medication harm for clinical review to establish causality. Furthermore, triggers can be adapted to local circumstances, and for special populations (e.g. older adults).[32] Validated causality assignment tools, such as the WHO Uppsala Monitoring Centre criteria, should be used to standardise assessments.[33] A review of the literature found no studies evaluating this bimodal approach.

ML and automated harm detection

ML methods are becoming increasingly popular in the healthcare setting to assist clinicians with diagnosis and prognosis.[34,35] Whilst in their infancy, studies have explored the use of ML to predict or detect medication harm. A recent study described the development of multiple risk prediction models.[36] The authors utilised a de-identified dataset from a Swedish hospital. A series of ICD-10 codes related to the diagnosis of medication harm were used as the outcomes for models (e.g. I95.2 = drug-related hypotension). Whilst some models achieved high area under the curve (AUC) for their predictive performance (ranging from 0.8 to 0.9), there was no clinical verification of the accuracy of the coded outcome data (i.e. causality assessment to ensure codes were correctly allocated).[36] An Australian study also reported using ML and ICD codes to detect medication harm in a tertiary hospital. The automated algorithm demonstrated promising performance with an AUC of 0.803.[37]

Whilst ML offers an exciting opportunity to detect harm on a large scale, its success is dependent on the availability of high-quality data. This is challenging with outcomes that are sparse and difficult to verify, such as medication harm. Furthermore compared with conventional statistical methods, the inner workings of ML models are not transparent and they can lack face validity.[38,39] This modelling approach can be abstract to clinicians, known as the so-called 'black box', it creates challenges in detection of bias, overfitting and for external evaluation and user acceptance testing.[40]

Conclusion

For harm-mitigation strategies to be successful a pragmatic standardised approach to detection is essential. Leveraging a targeted, bimodal method of medical record review enables healthcare professionals to capitalise on the availability of EHRs to assist with the detection of medication harm.

ORCID iD

Nazanin Falconer (iD) https://orcid.org/0000-0003-4682-7890

References

1. Dhingra N. WHO global patient safety challange – medication safety [WHO Global Consultation]. World Health Organisation (2016). Available from:https://www.who.int/patientsafety/policies/global-launch-medication-without-harm-Bonn/en/

2. Falconer N, Barras M, Martin J, *et al*. Defining and classifying terminology for medication harm: a call for consensus. *Eur J Clin Pharmacol* 2019; 75: 137–145.

3. Lazarou J, Pomeranz BH and Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; 279: 1200–1205.

4. Ohta Y, Sakuma M, Koike K, *et al*. Influence of adverse drug events on morbidity and mortality in intensive care units: the JADE study. *Int J Qual Health Care* 2014; 26: 573–578.

5. Falconer N, Barras M, Abdel-Hafez A, *et al*. Developement and validation of the Adverse Inpatient Medication Event model (AIME) *Br J Clin Pharmacol* 2020; 1-13 https:doi.org/10.1111/bcp.14560.

6. Paradissis C, Coombes ID, Donovan P, *et al*. The type and incidence of adverse drug events in ageing medical inpatients and their effect on length of hospital stay. *J Pharm Pract Res* 2017; 47: 347–354.

7. Davies EC, Green CF, Taylor S, *et al*. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS One* 2009; 4: e4439.

8. Tangiisuran B, Scutt G, Stevenson J, *et al*. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reactions Risk (BADRI) model. *PLoS One* 2014; 9: e111254.

9. Falconer N, Barras MA and Cottrell WN. Systematic review of predictive risk models for adverse drug events in hospitalised patients. *Br J Clin Pharmacol* 2018; 84: 846–864.

10. Geeson C, Wei L and Dean Franklin B. Development and performance evaluation of the Medicines Optimisation Assessment Tool (MOAT): a prognostic model to target hospital pharmacists' input to prevent medication-related problems. *BMJ Qual Saf* 2019; 28: 645–656.

11. Parekh N, Ali K, Davies JG, *et al*. Medication-related harm in older adults following hospital discharge: development and validation of a prediction tool. *BMJ Qual Saf* 2020; 29: 142–153.

12. Hakkarainen KM, Hedna K, Petzold M, *et al*. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug

reactions – a meta-analysis. *PLoS One* 2012; 7: e33236.

13. O'Connor MN, Gallagher P, Byrne S, *et al.* Adverse drug reactions in older patients during hospitalisation: are they predictable? *Age Ageing* 2012; 41: 771–776.

14. Murff HJ, Patel VL, Hripcsak G, *et al.* Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform* 2003; 36: 131–143.

15. Parameswaran Nair N, Chalmers L, Peterson GM, *et al.* Prospective identification versus administrative coding of adverse drug reaction-related hospitalizations in the elderly: a comparative analysis. *Pharmacoepidemiol Drug Saf* 2018; 27: 1281–1285.

16. Otero MJ, Toscano Guzmán MD, Galván-Banqueri M, *et al.* Utility of a trigger tool (TRIGGER-CHRON) to detect adverse events associated with high-alert medications in patients with multimorbidity. *Eur J Hosp Pharm*. Epub ahead of print 8 May 2020. DOI: 10.1136/ejhpharm-2019-002126.

17. Hohl C, Karpov A, Reddekopp L, *et al.* ICD-10 codes used to identify adverse drug events in administrative data: a systematic review. *J Am Med Inform Assoc* 2014; 21: 547–557.

18. Leape LL, Brennan TA, Laird N, *et al.* The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324: 377–384.

19. Wilson RM, Runciman WM, Gibberd RW, *et al.* The quality in Australian health care study. *Med J Aust* 1995; 163: 458–470.

20. Rozich JD, Haraden CR and Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003; 12: 194–200.

21. Carnevali L, Krug B, Amant F, *et al.* Performance of the adverse drug event trigger tool and the global trigger tool for identifying adverse drug events: experience in a Belgian hospital. *Ann Pharmacother* 2013; 47: 1414–1419.

22. Stausberg J and Hasford J. Identification of adverse drug events: the use of ICD-10 coded diagnoses in routine hospital data. *Dtsch Arztebl Int* 2010; 107: 23–29.

23. Institute for Healthcare Improvement. Trigger tool for measuring adverse drug events, http://www.ihi.org/resources/Pages/Tools/TriggerToolforMeasuringAdverseDrugEvents.aspx (2004, accessed April 3, 2020).

24. Karpov A, Parcero C, Mok CPY, *et al.* Performance of trigger tools in identifying adverse drug events in emergency department patients: a validation study. *Br J Pharmacol* 2016; 82: 1048–1057.

25. Musy SN, Ausserhofer D, Schwendimann R, *et al.* Trigger tool-based automated adverse event detection in electronic health records: systematic review. *J Med Internet Res* 2018; 20: e198.

26. Toscano Guzmán MD, Galván Banqueri M, Otero MJ, *et al.* Validating a trigger tool for detecting adverse drug events in elderly patients with multimorbidity (TRIGGER-CHRON). *J Patient Saf*. Epub ahead of print 9 November 2018. DOI: 10.1097/PTS.0000000000000552.

27. Murphy DR, Meyer AN, Sittig DF, *et al.* Application of electronic trigger tools to identify targets for improving diagnostic safety. *BMJ Qual Saf* 2019; 28: 151–159.

28. Szekendi MK, Sullivan C, Bobb A, *et al.* Active surveillance using electronic triggers to detect adverse events in hospitalized patients. *Qual Saf Health Care* 2006; 15: 184–190.

29. Walter SR, Day RO, Gallego B, *et al.* The impact of serious adverse drug reactions: a population-based study of a decade of hospital admissions in New South Wales, Australia. *Br J Clin* 2017; 83: 416–426.

30. Kuklik N, Stausberg J and Jöckel K-H. Adverse drug events in German hospital routine data: a validation of International Classification of Diseases, 10th revision (ICD-10) diagnostic codes. *PLoS One* 2017; 12: e0187510.

31. Quan H, Li B, Saunders LD, *et al.* Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res* 2008; 43: 1424–1441.

32. Thevelin S, Spinewine A, Beuscart J-B, *et al.* Development of a standardized chart review method to identify drug-related hospital admissions in older people. *Br J Clin Pharmacol* 2018; 84: 2600–2614.

33. World Health Organization. The use of the WHO-UMC system for standardised case causality assessment. Uppsala Monitoring Centre. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf.

34. Jeong E, Park N, Choi Y, *et al.* Machine learning model combining features from algorithms with different analytical methodologies to detect laboratory-event-related adverse drug reaction signals. *PLoS One* 2018; 13: e0207749.

35. Davenport T and Kalakota R. The potential for artificial intelligence in healthcare. *Future Healthc J* 2019; 6: 94–98.

36. Bagattini F, Karlsson I, Rebane J, *et al*. A classification framework for exploiting sparse multi-variate temporal features with application to adverse drug event detection in medical records. *BMC Med Inform Decis Mak* 2019; 19: 7.

37. McMaster C, Liew D, Keith C, *et al*. A machine-learning algorithm to optimise automated adverse drug reaction detection from clinical coding. *Drug Saf* 2019; 42: 721–725.

38. Scott IA, Cook D, Coiera EW, *et al*. Machine learning in clinical practice: prospects and pitfalls. *Med J Aust* 2019; 211: 203–205.e201.

39. Scott I. Hope, hype and harms of big data: big data critique. *Int Med J* 2019; 49: 126–129.

40. Faes L, Liu X, Wagner SK, *et al*. A clinician's guide to artificial intelligence: how to critically appraise machine learning studies. *Transl Vis Sci Technol* 2020; 9: 7.

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