Adverse drug reactions in older people and their prevention: the need for a new approach

Mirko Petrovic
Department of Geriatrics
Ghent University

CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to disclose

Drug related problems (DRPs) and adverse drug reactions (ADR) represent a major burden on health care

- **Somers A. et al.**, *Nutr Health Aging* 2003: Hospital admission related to ADRs in *older* inpatients
  → **20% of admissions due to ADRs (12% dominantly; 8% partly)**;

- **Pirmohammed M.** et al., *BMJ* 2004: 18820 adult admissions (all ages)
  → **6.5% of admissions due to ADRs**;
  → projected annual cost £466M (€706M) in UK
  → median LOS 8 days i.e. **4% of all NHS bed days**

- **Leendertse A. et al.** *Arch Intern Med* 2008: Hospital Admissions Related to Medication (HARM) study
  → **5.6% of unplanned admissions** (n=13000; all ages) due to adverse medication; 46.5% were *preventable*
  → **Average cost of €6000** for one preventable medication-related hospitalization (adults all ages)

- **Hamilton H.** et al. *Arch Intern Med* 2011: ADE prevalence in 600 consecutive acute admissions of *older* patients
  → **26.3% of patients had non-trivial ADEs at admission**
  → 2/3 ADEs causal/contributory to admission (69% avoidable)

Hospitalization and ADR *prevalence*

- **Alhawassi T.** et al., *Clin Interv Aging* 2014 : systematic review of prevalence and risk factors for ADRs in older people in the acute care setting

  → median **11.5% *prevalence* in hospital**;

  →ADR factors:

  female gender,
  multi-morbidity,
  polypharmacy

Hospitalization and ADR *incidence*

- **O'Connor et al.**, *Age & Ageing* 2011: prospective study of ADRs in 511 consecutive patients aged > 65 hospitalized with acute illness in one large teaching hospital in Ireland
  → **26% incidence** of non-trivial ADRs

- **Lattanzio et al.**, *J Am Med Dir Assoc* 2012: prospective observational study in 11 Italian medical centres
  →**11.5% incidence** of ADRs

- **SENATOR study** (unpublished, 2016): prospective analysis of ADRs during acute illness hospitalization in 650 consecutive patients aged over 65 yrs in 6 European centres
  → **21.6% incidence** of non-trivial ADRs

Rationale

- **Who** is most at risk of suffering an ADR?
- **What** makes them have a higher risk of an ADR?
- Can we **predict** who these people are?
- Can risk prediction models **identify** patients at risk of suffering an ADR?

Background

- Accurate risk prediction models are the result of **four key stages**: **development, validation, impact, and implementation**.
- Often only the first two stages are completed, the methods and outcomes of which are often poorly reported.
- To be of practical use, these models should
  - use **clearly defined easily obtainable data**,
  - have **good predictive power**,
  - be **tested in a large sample** representative of the target population, and
  - have **high reliability and face validity**.

Inclusion criteria

- Majority of patients ≥65 years old
- Included patients who experienced an adverse drug event (ADE) or ADR but excluded prescription errors
- A multivariable approach in design and analysis was followed
- The model had been validated

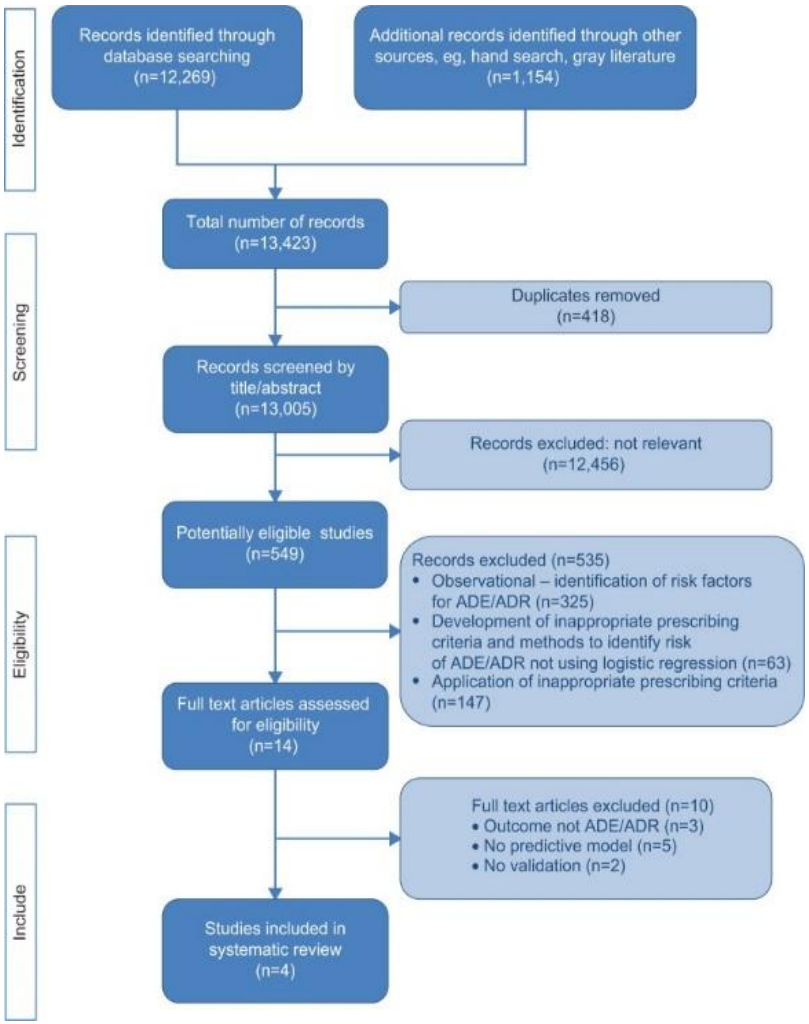
Stevenson J et al. *Clin Interv Aging* 2014; 9: 1581-1593

Quality assessment

- All studies were reviewed using a standard approach for developing and testing clinical prediction models to satisfy a range of criteria representing four stages:
  - development (identification of candidate predictor variables and model design);
  - validation (testing the performance of the model);
  - impact (measurement of usefulness in the clinical setting); and
  - implementation (widespread acceptance and adoption in clinical practice).

Quality assessment

- **Candidate predictor variables** were grouped into **three categories** to allow for comparison between studies: **demographic** factors; **medical** factors and **medication** factors.
- **Event rate** was calculated as **percentage ADR/ADE rate** where it was not reported by the authors in this form.
- **Quality of design** and reporting of the studies was compared based on ability to comply with the standard criteria derived from the published literature.
- The **overall performance** of the models was determined by review of their **accuracy, discrimination, and calibration through internal or external validation**.


Identification
Screening
Eligibility
Include
Records identified through database searching (n=12,269)
Additional records identified through other sources, eg, hand search, gray literature (n=1,154)
Total number of records (n=13,423)
Duplicates removed (n=418)
Records screened by title/abstract (n=13,005)
Records excluded: not relevant (n=12,456)
Potentially eligible studies (n=549)
Records excluded (n=535)
• Observational – identification of risk factors for ADE/ADR (n=325)
• Development of inappropriate prescribing criteria and methods to identify risk of ADE/ADR not using logistic regression (n=63)
• Application of inappropriate prescribing criteria (n=147)
Full text articles assessed for eligibility (n=14)
Full text articles excluded (n=10)
• Outcome not ADE/ADR (n=3)
• No predictive model (n=5)
• No validation (n=2)
Studies included in systematic review (n=4)

Included studies: McElnay J et al., 1997

Study design	Variable	Score	OR (95% CI)	Validation
Country: UK Setting: Hospital inpatient Outcome: inpatient ADE Inclusion: ≥65 years, non-elective admission, consent Method: Phase 1 variable identification and model design (n= 929), Phase 2 Internal validation (n=204). Chart review, computerised hospital records, structured patient interview within 72 hours of admission Assessment of ADE/ADR: Modified Naranjo	Antidepressants Digoxin GI problems Abnormal K^+ level Thinks drug responsible Angina COPD	No score	5.79 (2.12-5.85) 1.99 (1.05-2.33) 2.57 (1.35-4.91) 4.21 (2.18-8.14) 0.17 (0.07-0.42) 2.40 (1.06-5.44) Sig. p=0.15	Sensitivity=40.5% Specificity=69.0% Discrimination= not measured

Included studies: Tangiisuran B et al., 2014

Study design	Variable	Score	OR (95% CI)	Validation
Country: UK Setting: Hospital inpatient Outcome: inpatient ADR Inclusion: (Phase 1)≥65 years, not admitted with self^poisoning; medical notes available (validation) ≥65 years, consent, no anticancer medication, no ADR on/causing admission Method: Phase 1 variable identification and model design (n= 690), Phase 2 External validation (n=483). Review of drug chart, lab parametrs, reports/referrals from other healthcare providers, observational data on admission and daily thereafter Assessment of ADE/ADR: Hallas algorithm and likert scale derived by Bates et al. (Phase 1), naranjo (Phase 2)	Hyperlipidaemia No. of medications ≥8 Length of stay ≥12 days Hypoglycaemic agents High WBC (admission)	1 1 1 1 1	3.32 (1.81-6.07) 3.30 (1.93-5.65) 2.27 (1.35-3.83) 1.91 (1.04—3.49) 1.55 (0.94-2.55) Sig. p≤0.1	Sensitivity=80.0% Specificity=55.0% Discrimination (AUCROC)= 0.73 (95% CI, 0.66-0.80)

Included studies: Onder G et al., 2010

Study design	Variable	Score	OR (95% CI)	Validation
Country: Italy Setting: Hospital inpatient Outcome: inpatient ADR Inclusion: ≥65 years, taking medication, complete data for variables available, consent, not on anticancer medication, no ADR on/causing admission Method: Phase 1 variable identification and model design (n= 5936), Phase 2 External validation (n=483). Review of chart, x-ray films, lab parameters, medical histories to complete questionnaire an admission and daily thereafter Assessment of ADE/ADR: Naranjo	≥4 co-morbidities Heart failure Liver disease No. of drugs ≤5 No. of drugs 5-7 No. of drugs ≥8 Previous ADR Renal failure	1 1 1 0 1 4 2 1	1.31 (1.04-1.64) 1.79 (1.39-2.30) 1.36 (1.06-1.74) 1.00 reference 1.90 (1.35—2.68) 4.07 (2.93-5.65) 2.41 (1.79-3.23) 1.21 (0.96-1.51) Sig. p<0.1	Sensitivity=68.5% Specificity=65.0% Discrimination (AUCROC) = 0.70 (95% CI, 0.63-0.78)

Included studies: Trivalle C et al., 2011

Study design	Variable	Score	OR (95% CI)	Validation
Country: France Setting: Rehabilitation centres Outcome: inpatient ADE Inclusion: ≥65 years, present for study duration Method: n=576; Weakly chart review, patient and nurse reporting. Bootstrap validation. Assessment of ADE/ADR: 'Standardised 32 item checklist' with monthly analyses by MDT to check if met 4 key criteria	No. of medications 0-6 7-9 10-12 ≥13 Antipsychotic Recent anticoagulant	 0 6 12 18 9 7	1.9 (1.6-2.3) 2.5 (1.5-4.1) 2.0 (1.1-1.37) Sig. p<0.05	Sensitivity=not reported Specificity=not reported Discrimination (AUCROC) = 0.70 (95% CI, 0.635-0.74)

Included studies

- **Population characteristics**
- All included studies were conducted in **Europe**, and only in the **hospital setting**. Two studies represented patients over 80 years. Patient functionality was reported by three studies and was measured using patient-perceived health status, Katz Index, and Barthel Index.
- The primary outcome in all of the studies was ADR. The proportion of patients who experienced an ADR/ADE ranged from 6.5% to 39%, with **gastrointestinal, cardiovascular, and nervous systems** being those most frequently affected. Medications most frequently associated with ADRs/ADEs included **psychotropics, anticoagulants, and analgesics**.

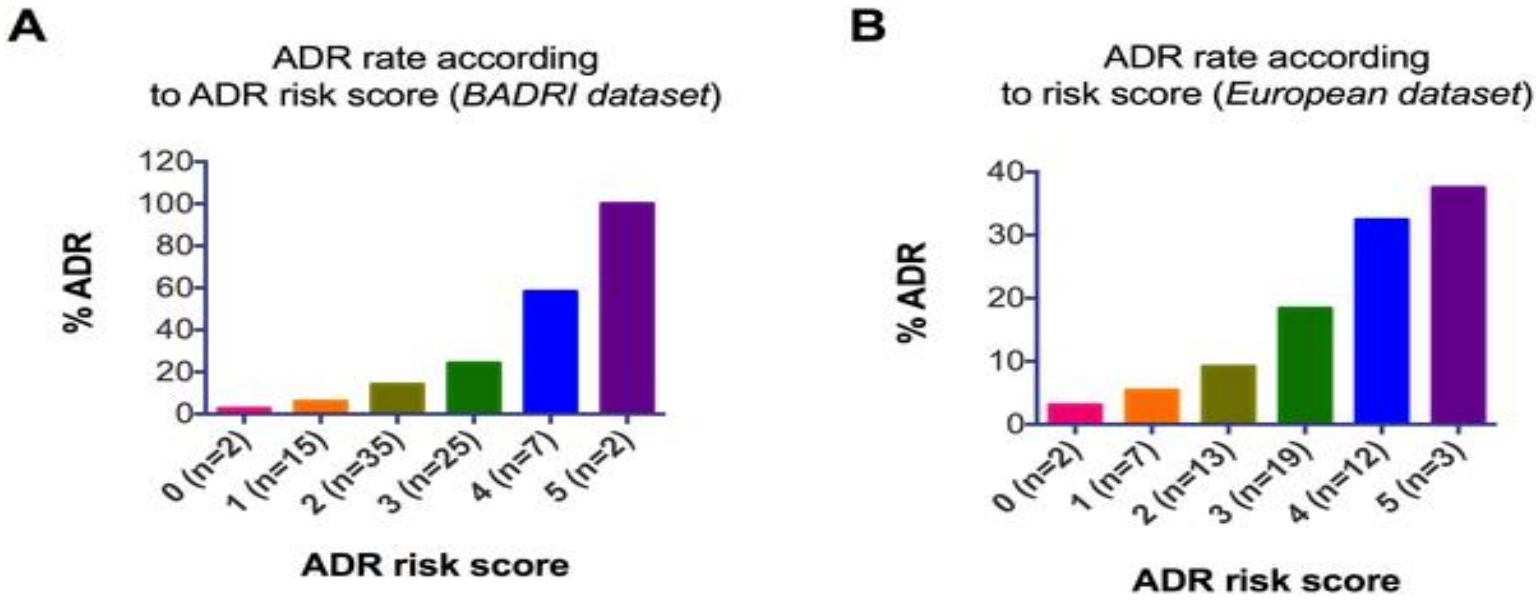
- **Quality assessment – overview**
- Whilst all models included the development and validation phases, **none addressed the impact and implementation phase**.

McElnay J et al. *Clin Drug Invest* 1997;13:47–55.
Tangiisuran B et al. *PLOS ONE* 2014; 9(10): e111254
Onder G, Petrovic M et al. *Arch Intern Med* 2010;170:1142–1148.
Trivalle C et al. *Eur Geriatr Med* 2011;2:284–289.

GerontoNet- additional external validations

- **O'Connor M. et al.** Age& Ageing 2012
  - 513 hospital inpatients
  - Median age 77 years (72—82)
  - AUCROC 0.62
- **Petrovic M. et al.** Drugs&Aging 2016
  - 1075 hospital inpatients
  - Mean age (SD) was 81.4 (7.4) years
  - **Fair diagnostic accuracy; AUCROC = [0.70; 0.79]:** Age ≥ 80 years; Heart failure; Diabetes, History of any previous ADR
  - **Good diagnostic accuracy; AUCROC = [0.80; 0.89]:** Low BMI (<18.5 kg/m2); MMSE score of >24/30 points; Osteoarthritis

BADRI- ADR rate according to ADR risk score



Tangiisuran B, Scutt G, Stevenson J, Wright J, Onder G, et al. (2014) 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 9(10): e111254.

Application of risk tools to inpatient population and assessment of usability of risk prediction tools

- **Stevenson J et al.**, unpublished data
  - 170 hospital inpatients
  - Median age = 82 years (66-104)
  - Mean number of co-morbidities: 9.7
  - Mean number of drugs per patient: On admission = 6.0 (0-17); On discharge = 8.9 (2-24)

ADR risk according to score

Tool	Risk variable and score		Total score	Percentage ADR risk
BADRI	Hyperlipidaemia	1	0	3%
	No. of medications ≥8	1	1	5%
	Length of stay ≥12 days	1	2	9%
	Hypoglycaemic agents	1	3	18%
	High WBC (admission)	1	4	32%
			5	38%
GerontoNet	>4 co-morbidities	1	0-1	5%
	Heart failure	1		
	Liver disease	1	2-3	4%
	No. of drugs ≤5	1		
	No. of drugs 5-7	1	4-5	7%
	No. Of drugs ≥8	4		
	Previous ADR	2	6-7	12%
	Renal failure	1		
			≥8	28%
Trivalle	No. of medications			
	0-6	0	0-6	12%
	7-9	6		
	10-12	12	7-12	28%
	≥13	18		
	Antipsychotic	9	13-18	35%
	Recent anticoagulant	7		
			>18	52%

Low Risk Medium Risk High Risk

Discussion

- While only **two** (Onder and Tangiisuran) were **externally validated**, their ability to discriminate between those who had experienced an ADR and those who had not was only **modest**.

- This could result in a failure to identify patients at high risk of experiencing an ADR.

- Furthermore, **none reported the findings of impact and implementation stages**, thus widening the gap between research potential and clinical application.

- Pressures within health care systems are driving a need for robust clinical risk-prediction models to inform care provision, but, to be useful, these models must be of high statistical quality and be clinically relevant.

Discussion

- All four studies had limitations commonly reported in the prognostic research literature.
- Three failed to provide sufficient information relating to events-per-variable ratio and one was insufficiently powered, so the **risk of a type II error** (false negative finding) was more likely.
- All studies **dichotomized their predictor variables and outcomes**, despite this practice being suboptimal.
- The **management of missing data** were also problematic, regardless of whether a retrospective or prospective design was used. In addition, there was often a lack of reporting of candidate predictor variables, which could hinder replication by others.

Conclusions

- This illustrates the complexity of medication risk in older adults and highlights the **multidimensional nature** of this field, which includes: **clinical** aspects; **social** risk factors, especially during the transfer of care between different settings; and **high-risk medicines**, where the risks are considered but not always balanced against the potential benefits.

- The difficulty in determining whether a patient has experienced an ADR is challenging given the progressive nature of aging, where functional decline and loss of independence are common.

- As older adults are often excluded from clinical trials, this can result in **inappropriate extrapolation** of clinical guidelines, often based on research in younger patients.

Conclusions (cont.)

- Currently four ADR risk-prediction models exist with **poor to modest performance** and overall quality.
- If these models are to be embraced as part of routine clinical care, further work needs to be conducted so that external validity can be assured and a **practical approach** upheld.
- Only then can implementation and impact be assessed with the view to adoption as part of a systems approach within routine clinical care.

How to proceed?

- In SENATOR trial, **prospective data** will be obtained in approximately 1800 older hospital inpatients in 6 European academic medical centres.
- ADR ascertainment is based on a **trigger list** of the 12 most common clinical manifestations of ADRs.
- SENATOR involves the creation of a large prospective database that includes ADRs defined by the trigger list method with **concurrent large amounts of clinical data** relating to older inpatients with multi-morbidity.
- ADRs are defined according to **independently adjudicated evidence forms** whenever one of the trigger listed clinical events occurs. The evidence forms are reviewed by blinded experts who adjudicate ADRs as being definite, probable, possible or unlikely.
- The SENATOR trial dataset with its specific focus on **rigorous ADR ascertainment** will determine if a highly predictive ADR risk assessment tool can be derived for routine clinical use.

How to proceed?

- While risk prediction models are **not intended to replace clinicians' decisions**, they should not stratify patients less accurately than clinicians.

- It would be helpful if future work could **compare a clinician's risk stratification against that of an ADR risk-prediction model**.

- This work would help inform the **clinical relevance** of the model and contribute to the impact and implementation research that is thus far lacking.