

A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting

Tariq M Alhawassi^{1,2}

Ines Krass¹

Beata V Bajorek^{3,4}

Lisa G Pont⁵

¹Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia;

²College of Pharmacy, King Saud University, Riyadh, Saudi Arabia;

³Graduate School of Health – Pharmacy, University of Technology Sydney, ⁴Pharmacy Department, Royal North Shore Hospital, ⁵Sydney Nursing School, University of Sydney, Sydney, NSW, Australia

Abstract: Adverse drug reactions (ADRs) are an important health issue. While prevalence and risk factors associated with ADRs in the general adult population have been well documented, much less is known about ADRs in the elderly population. The aim of this study was to review the published literature to estimate the prevalence of ADRs in the elderly in the acute care setting and identify factors associated with an increased risk of an ADR in the elderly. A systematic review of studies published between 2003 and 2013 was conducted in the Cochrane Database of Systematic Reviews, EMBASE, Google Scholar and MEDLINE. Key search terms included: “adverse drug reactions”, “adverse effects”, “elderly patients and hospital admission”, “drug therapy”, “drug adverse effects”, “drug related”, “aged”, “older patients”, “geriatric”, “hospitalization”, and “emergency admissions”. For inclusion in the review, studies had to focus on ADRs in the elderly and had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, and a clear description of the method used for ADR identification, and had to describe factors associated with an increased risk of an ADR. Fourteen hospital-based observational studies exploring ADRs in the elderly in the acute care setting were eligible for inclusion in this review. The mean prevalence of ADRs in the elderly in the studies included in this review was 11.0% (95% confidence interval [CI]: 5.1%–16.8%). The median prevalence of ADRs leading to hospitalization was 10.0% (95% CI: 7.2%–12.8%), while the prevalence of ADRs occurring during hospitalization was 11.5% (95% CI: 0%–27.7%). There was wide variation in the overall ADR prevalence, from 5.8% to 46.3%. Female sex, increased comorbid complexity, and increased number of medications were all significantly associated with an increased risk of an ADR. Retrospective studies and those relying on identification by the usual treating team reported lower prevalence rates. From this review, we can conclude that ADRs constitute a significant health issue for the elderly in the acute care setting. While there was wide variation in the prevalence of ADRs in the elderly, based on the findings of this study, at least one in ten elderly patients will experience an ADR leading to or during their hospital stay. Older female patients and those with multiple comorbidities and medications appear to be at the highest risk of an ADR in the acute care setting.

Keywords: drug utilization, hospital

Introduction

Pharmacotherapy plays an important role in the maintenance of health. Many conditions rely on medication to manage symptoms, slow disease progression, or to prevent the development of future illnesses. While medications may provide considerable benefit in the maintenance of health, all medications also have a risk of adverse or unwanted effects, and evaluating the risk/benefit associated with use of a particular medication is a critical step in the decision to use pharmacotherapy. Adverse drug

Correspondence: Lisa G Pont
M02 – Sydney Nursing School,
The University of Sydney,
NSW 2006, Australia
Tel +61 2 9351 0563
Fax +61 2 9351 0779
Email lisa.pont@sydney.edu.au

reactions (ADRs) are adverse or unintended effects associated with medication and have been defined by the World Health Organization (WHO) as “noxious and unintended responses to drugs occurring at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”.¹ ADRs are an important component of adverse drug events, which encompass medication-related harm associated with ADRs as well as that secondary to errors.²

ADRs have a significant impact on health, with between 5% and 7% of all hospitalizations being due to an ADR and with a further 10% to 20% of all hospitalized patients experiencing an ADR during their hospital admission.²⁻⁴ Between 3% and 6% of ADRs are fatal or have serious consequences, with an estimated 140,000 fatalities secondary to ADRs occurring annually in the USA.⁵⁻⁸ The estimated impact on hospital costs exceeds \$30 billion, or 5% of total hospital running costs per annum.⁸⁻¹⁰

While the prevalence and impact of ADRs has been well studied in the general adult population,¹¹ much less is known about ADRs in the elderly. Older persons experience an increased disease burden and a corresponding increase in medication utilization, which has been well documented.¹² With this increased medication use and health complexity, there is a corresponding increased risk of ADRs. As well as increases in medication number and comorbid conditions, there are a variety of age-related physiological changes affecting the pharmacokinetics and pharmacodynamics of medications, which may further increase the risk of ADRs in older persons.

Despite the potential increased risk of ADRs in older persons, little is known about the prevalence of ADRs and the associated risk factors in the elderly population. The aim of this review was to determine the prevalence of ADRs, leading to and during admission, in the elderly, to identify characteristics associated with an increased ADR risk in elderly persons and to examine how the prevalence varies with different study designs and identification strategies in the acute care setting.

Methods

Data sources and study selection

An electronic search of the Cochrane Database of Systematic Reviews, EMBASE, Google Scholar, and MEDLINE for studies published between 2003 and 2013 was conducted. Medical Subject Headings terminology was used where possible (in MEDLINE and Cochrane) and keywords used in those databases not using Medical Subject Headings

terminology (EMBASE and Google scholar). The terms used were: “adverse drug reactions”, “adverse effects”, and “elderly patients” and “hospital admission”. Additional search terms used included: “drug therapy”, “drug adverse effects”, “drug related”, “aged”, “older patients”, “geriatric”, “hospitalization”, and “emergency admissions”.

All titles and abstracts of identified studies were examined for potential relevance. Reference lists of identified studies were reviewed to locate other relevant original studies. Eligible study titles and abstracts were screened for relevance, and a manual cross-reference search of the relevant papers was performed to identify additional articles. Two independent reviewers assessed each study, and final consensus was reached regarding inclusion of each study before data extraction.

Inclusion criteria

Studies were included in the review if they were published in English with a primary aim to assess ADR prevalence, either leading to hospitalization or during admission, in the elderly (≥ 65 years) in an acute care setting, using observational methods. For inclusion in the review, studies had to include an explicit definition of what was considered an ADR and/or an explicit assessment of causality, as well as a clear description of the method used for ADR identification, and had to explore factors associated with an increased risk of an ADR.

Exclusion criteria

Studies lacking a precise ADR definition or those without explicit causality assessment criteria, those that focused on ADRs secondary to a specific medication or specific ADR, and studies that looked at ADR-related hospital readmissions were excluded from the review. Studies that did not report ADR prevalence data or allow calculation of prevalence were also excluded.

Data extraction, synthesis, and analysis

Data were extracted, including ADR definition, identification method, risk factors, and prevalence, using a custom-designed data extraction form. Where the prevalence was not directly reported in the original publication, it was calculated as the number of patients identified with an ADR out of all included patients. Extracted data were entered into Microsoft Excel™ for descriptive data analysis. Overall median ADR prevalence as well as median prevalence of ADRs, leading to hospitalization and those occurring during inpatient stay, were calculated along with the corresponding 95% confidence intervals (CIs). The quality of included studies was determined using the Strengthening

the Reporting of Observational Studies in Epidemiology (STROBE) criteria for observational studies.¹³ The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) international prospective register of systematic reviews (CRD42013006827).¹⁴

Results

Fourteen hospital-based observational studies exploring ADRs in the elderly in acute care settings were identified and eligible for inclusion in this review (Figure 1). The size and design of the studies varied from large retrospective observational administrative data cohorts to smaller prospective

studies in the clinical setting. The included studies ranged in size from a small prospective study of 80 patients presenting to Emergency in Belgium¹⁵ to a large population-based cohort of 64,446 Canadian hospital admissions.¹⁶ The majority of studies were conducted in Europe (n=10), with two studies from Asia and two from North America. Characteristics and a summary of the included studies are presented in Table 1.

Prevalence of ADRs in the elderly

The mean prevalence of ADRs in the elderly in the studies included in this review was 11.0% (95% CI: 5.1–16.8). The median prevalence of ADRs leading to hospitalization

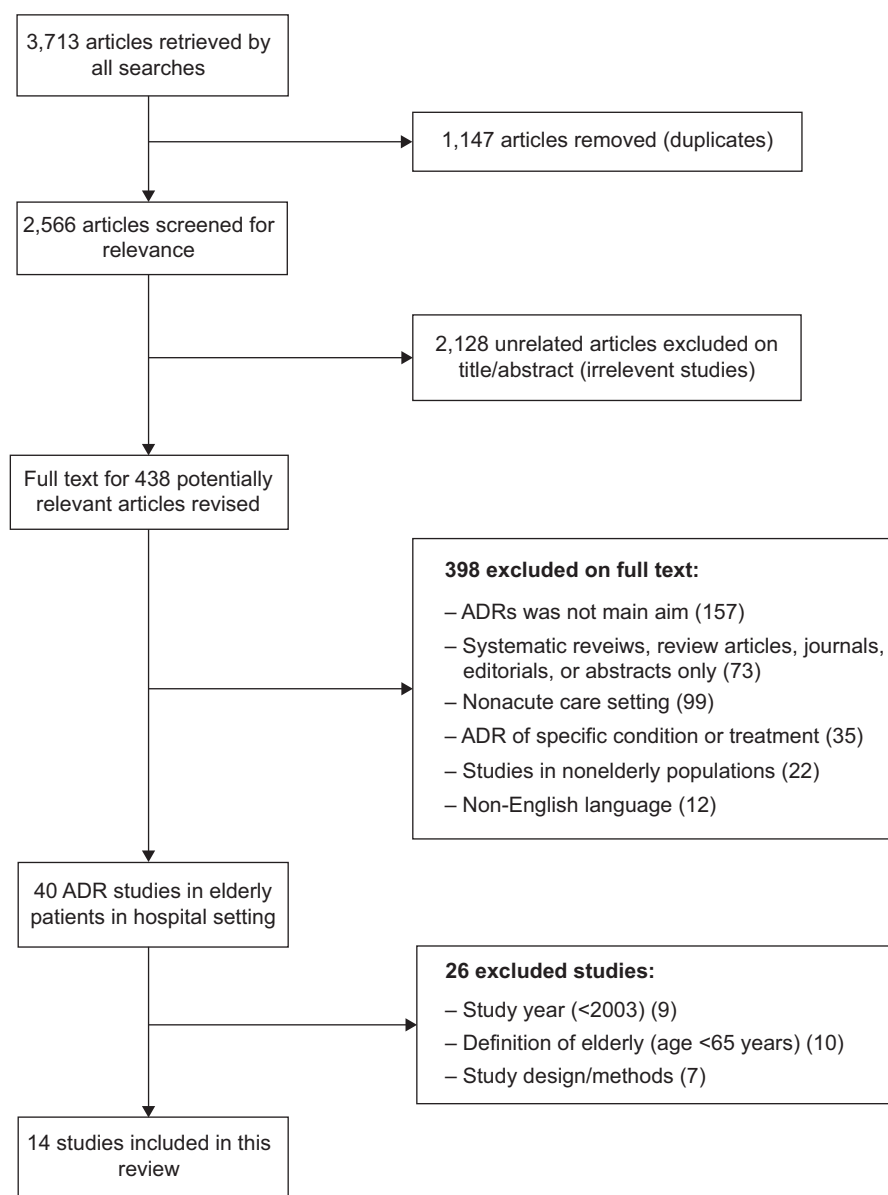


Figure 1 Search strategy and identification of included studies.
Abbreviation: ADR, adverse drug reaction.

Table 1 Characteristics of studies examining ADRs in the elderly included in the review

Reference	Country Year conducted	Size (N)	Mean age (years)	Design	Setting (specialty)	Prevalence ^a (rate)	ADR definition/ causality assessment*	Identification method	Quality assessment % STROBE criteria met
Conforti et al ²⁸	Italy 2009	1,023	81.9	Prospective cross-sectional	Geriatric	36.2% (370/1,023)	Edwards and Aronson/ no causality assessment	Systematic medical review	41
De Paepe et al ¹⁵	Belgium 2007	80	76	Prospective cross-sectional	Emergency	46.3% (37/80)	Edwards and Aronson/ Naranjo et al criteria	Systematic medical review	59
Franceschi et al ¹⁷	Italy 2004–2005	1,756	Not reported	Prospective cross-sectional	Geriatric	5.8% (102/1,756)	Edwards and Aronson/ Naranjo et al criteria	Physician reported	63
Helldén et al ³¹	Sweden 2002	154	82.1	Retrospective cross-sectional	Emergency	14.3% (22/154)	WHO/systematic medical review	Systematic medical review	66
Kojima et al ²⁰	Japan 1995–2010	2,412	78.7	Retrospective cross-sectional	Geriatric	10.4% (252/2,412)	Author defined/ no causality assessment	Physician reported	44
Laroche et al ¹⁸	France 1994–1996 1997–1999	2,018	85.2	Prospective cross-sectional	Geriatric	19.1% (385/2,018)	WHO/no causality assessment	Systematic medical review	69
Lattanzio et al ³⁰	Italy 2009	506	80.1	Prospective cross-sectional	Medical	11.5% (58/506)	WHO/French criteria	Systematic medical review	69
Ma et al ²⁷	China 2008–2011	4,760	87.5	Prospective cross-sectional	Emergency	6.9% (328/4,760)	WHO/no causality assessment	Physician reported	38
Marcum et al ³³	USA 2004–2006	678	76.4	Retrospective cohort	All admissions (veterans)	10.0% (68/678)	WHO/Naranjo et al criteria	Systematic medical review	71
O'Connor et al ³²	Ireland 2010	513	77	Prospective cross-sectional	General medical and surgical	26.3% (135/513)	WHO/WHO-UMC criteria	Systematic medical review	88
Olivier et al ²⁶	France 2002–2003	789	80.2	Prospective cross-sectional	Emergency	8.4% 66/789	Edwards and Aronson/ French criteria	Physician reported	81
Sikdar et al ¹⁶	Canada 1995–2007	64,446	Not reported	Retrospective cohort	All hospital admissions	6.3% (4,056/64,446)	Edwards and Aronson/ no causality assessment	Physician reported	74
Tangisuran et al ²⁹	UK 2007–2008	560	87.1	Prospective cross-sectional	Geriatric	13.2% 74/560	Edwards and Aronson/ Hallas et al criteria	Systematic medical review	78
Wawruch et al ²⁵	Slovakia 2003–2005	600	76.6	Retrospective cross-sectional	Internal medicine	7.8% (47/600)	Author defined	Physician reported	66

Notes: ^aWhere the prevalence was not directly reported in the original publication, it was calculated as the number of patients identified with an ADR out of all included patients. *Criteria are from Edwards and Aronson¹⁹, Naranjo et al²¹, Laroche et al¹⁸ and Hallas et al²³

Abbreviations: ADR, adverse drug reaction; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WHO, World Health Organization; UMC, Uppsala Monitoring Centre.

was 10.0% (95% CI: 7.2%–12.8%), while the prevalence of ADRs occurring during hospitalization was 11.5% (95% CI: 0%–27.7%). There was wide variation in the overall ADR prevalence reported in the studies in this review, from a prevalence of 5.8% in 1,756 older Italian patients¹⁷ to 46.3% in a smaller Belgian study.¹⁵ Prospective studies were associated with higher prevalence rates than were retrospective studies (Table 1). Larger studies generally tended to report higher prevalence rates, with the exception of the French study by Laroche et al.¹⁸

Defining and identifying ADRs

The use of a predefined definition of ADRs or explicit assessment of causality was an inclusion criterion for this analysis. In general, there was consensus regarding the definitions of ADRs. The majority of the studies (n=8) used either the WHO definition¹ or that proposed by Edwards and Aronson:

An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product.¹⁹

Only two studies used custom predefined definitions.^{20,21} Half (n=7) of the studies included in this review described an explicit causality assessment. The most commonly used criteria were the Naranjo et al criteria,²¹ used by three studies. Two studies used the French method of causality assessment,²² one used the Hallas et al criteria²³ and one the WHO-Uppsala Monitoring Committee criteria²⁵ (Table 1). There did not appear to be a relationship between the use of explicit casualty criteria and the ADR prevalence reported.

A number of methods were used to identify ADRs in the included studies. Most studies (n=8) used a systematic medical review where a dedicated study team identified potential ADRs. A number of studies (n=6) relied upon physician reporting, where ADRs were identified as part of usual care.^{16,17,20–27} Four prospective studies relied on identification of potential ADRs by physician reporting,^{17,21,26,28} while the remaining two studies were retrospective cohort studies using administrative datasets and identified potential ADRs retrospectively from the medical record.^{16,20} The majority of studies (n=10) outlined separate processes in addition to usual care for the identification of potential ADRs.^{15,17,18,27–33} These usually involved identification of a potential ADR by a member or members of the research team and then systematic medical review of the potential ADR via expert panel review.

Only one study provided explicit detail regarding the criteria used to screen patients for potential ADRs.³³

Medications associated with ADRs

There was considerable variation in the medications involved in the ADRs reported in the studies. Many studies found cardiovascular medications to be commonly associated with ADRs in the elderly, in particular antihypertensive and antithrombotic medications.^{16–18,26–28} Other implicated medications included antibiotics,^{26,27} nonsteroidal anti-inflammatories,^{17,27} and antidiabetic agents.²⁹

ADR-associated risk factors in the elderly

A number of risk factors associated with ADR in the elderly in acute care were identified in this review. These have been categorized as patient factors, disease factors, medication factors, or other factors (Table 2).

While all studies were conducted on populations aged 65 years or older, two studies found increasing age to be an independent ADR risk factor.^{16,32} Female sex was also consistently identified as a risk factor in the majority of studies.^{15,16,28,30}

Increasing medical complexity, both in terms of increasing comorbid burden^{16,25,29} and increased number of

Table 2 Identified risk factors associated with ADR in the elderly

Patient-related risk factors	Age ^{16,28}
	Female sex ^{15,24,26}
	Rural residential location ¹⁶
	Socioeconomic status ¹⁶
Disease-related risk factors	Comorbid burden ^{21,25}
	Cardiovascular disease ²¹
	Diabetes mellitus ²³
	Cancer ¹⁶
	Depression ²¹
	Impaired renal function ^{16,28}
	Dementia ²³
	Hyperlipidemia ²⁵
	Elevated white blood cell count ²⁵
	Liver disease ²⁸
Medication-related factors	Number of medications ^{15,20–23,25,26}
	Antihypertensive medications ^{23,24}
	Antithrombotic/anticoagulant medications ^{17,22,24}
	Antibacterials ^{22,23}
	Nonsteroidal anti-inflammatory drugs (NSAIDs) ^{17,23}
	Antidiabetic medications ²⁵
	Psycholeptics ²³
Other factors	Drug–drug interactions ¹⁷
	History of falls ²⁶
	Limitations in activities of daily living ²⁶

Abbreviation: ADR, adverse drug reaction.

medications,^{15,18,20,25–27,30,32} were both reported to be associated with an increased ADR risk, in a number of studies.

Discussion

The findings of this systematic review indicate that ADRs constitute a significant health care issue for the elderly in the acute care setting, suggesting that more than one in every ten older patients in the hospital setting experience an ADR, either leading to or during their hospital admission.

Previous work has estimated that up to 17% of all adult patients admitted to hospital experience an ADR either leading to or during their hospital admission.³⁴ A large meta-analysis suggested that the elderly had a four times higher risk of an ADR than did the general adult population; however, this meta-analysis was not focused specifically on the elderly and analyzed the over-65 age group as a subgroup analysis.³⁴ There was wide variability in the ADR prevalence rates reported in this review, ranging from just over 5% to almost 50% of elderly patients. Heterogeneity in how ADRs are defined and identified are likely to account for much of this variability. In our review, higher prevalence rates tended to be found in larger studies and those using a prospective design.

The majority of studies in the analyses used either the WHO definition¹ of an ADR or that proposed by Edwards and Aronson.¹⁹ While these definitions have fundamental similarities in terms of harm associated with use of pharmacological products, distinct differences exist in terms of what is considered an ADR under each definition, especially with respect to minor ADRs. The WHO definition does not specify a level of harm in the initial identification of a potential ADR and may capture more minor ADRs, which while having a significant impact on quality of life, do not lead to serious outcomes such as death, disability, or hospitalization. Another difference between the two definitions is the focus in the WHO description on a “drug” as the causative agent, rather than a “medicinal product”, as specified in the Edwards and Aronson definition. The broader Edwards and Aaronson definition may be interpreted to encourage the inclusion of reactions associated with complementary and herbal preparations and may thus affect the ADR prevalence rates reported. In general, in the studies included in this review, those using the WHO definition reported a narrower prevalence range than did those using the Edwards and Aaronson definition. However, ADR definition is only one factor that will contribute to differences reported between the studies with respect to prevalence.

Differences in the methods used to detect ADRs may be another factor contributing to the wide range of prevalence rates reported. A number of studies relied on the identification of ADRs during routine care; however, underidentification^{35,36} and underreporting^{37–39} of ADRs during routine care in the acute care setting has been well documented in the literature, and such methods are likely to underestimate the true prevalence of ADRs. This may have been the case in the Sikdar et al study, which relied on identification of ADRs during routine clinical care and then further relied on these episodes being accurately coded in the administrative dataset from which they were identified.¹⁶ While this study had the largest sample size in the review (n=64,446), the reliance on ADR identification during routine clinical care would have excluded undiagnosed ADRs and may have contributed toward one of the lowest reported prevalence rates among the included studies. It is important to note that retrospective studies rely on routine detection of ADRs as captured in medical records and case notes and may underrepresent the true ADR prevalence. Two other studies that also relied on routine detection of ADRs also reported relatively low prevalence rates,^{25,26} further supporting concerns regarding the possible underdetection of ADRs during routine care.

While there was variation in the medications associated with ADRs in the elderly across the 14 studies included in this review, there were medications common to a number of studies, which may raise concerns regarding their safe use in the elderly. Cardiovascular medications were associated with ADRs in the elderly in a number of the studies in this review.^{16–18,26–28} Specific cardiovascular medications identified included antihypertensives, diuretics, and angiotensin-converting enzyme inhibitors, all of which have been associated with a number of issues, such as falls and electrolyte disturbances, in the elderly;^{40,41} further investigation may be required to fully understand their role in ADR risk.

Despite the heterogeneity among the studies, there was considerable consistency in the risk factors associated with ADRs in elderly inpatients. Female sex was consistently identified as a risk factor; however, it was unclear whether this related to an increased ADR risk or an increased use of medications.^{15,16,28,30} Advanced age was found a risk factor by two of the studies in this review studies.¹⁶ Increased age was not only associated with increased frailty and physiological changes resulting in changed pharmacokinetics and dynamics, but also, with increased medical complexity, disease burden and medication use. Both increased disease burden and medication number were identified as independent risk

factors for ADRs in the elderly; however, teasing out the complex relationship between aging, disease burden, medication use, and the risk of an ADR remains problematic. While disease burden was identified as a risk factor in a number of studies,^{16,25,29} there was great diversity regarding the role of specific conditions, making it difficult to fully understand the contribution of specific conditions to the risk of ADRs in the elderly.

A main strength of this study was the strict inclusion criteria applied regarding ADR definitions and identification. The review was limited to studies that included explicit criteria for both what was considered an ADR and how the ADRs were assessed in terms of causality. In addition, all studies required clear description of the method applied in the identification of the ADRs. The review was limited to observational studies in the acute care setting that focused specifically on ADRs in patients aged 65 years and older, in an attempt to minimize the heterogeneity among included studies. However, despite the strict inclusion criteria, considerable heterogeneity was found among the 14 studies included in this review. The quality of included studies varied extensively. While most of the included studies fulfilled more than 50% of the STROBE criteria and could be considered to have moderate quality,⁴² no study met these criteria completely. Of particular note, only three studies reported a priori sample size calculations. Sample size calculations for cross-sectional studies are based upon the expected prevalence of the parameter under investigation, and small sample sizes may not provide adequate precision. In this review, studies with smaller sample sizes tended to have higher prevalence estimates. This heterogeneity limited the ability to pool data and provide summary estimates for ADR prevalence across the total review population.

Conclusion

ADRs constitute a significant health issue for the elderly in the acute care setting. This review identified that at a conservative estimate, one in ten elderly patients will experience an ADR leading to or during their hospital stay and that older patients with an increased disease burden and using a higher number of medications are at increased risk of an ADR leading to or during their hospital stay. Differences in what is considered an ADR and in the identification of potential ADRs lead to considerable heterogeneity between studies examining ADRs in the elderly. Future research focused on identifying and minimizing the risks of ADRs in the elderly is needed, to aid clinicians in the optimal use of pharmacotherapy in older patients.

Disclosure

The authors report no conflicts of interest in this work.

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