

Ten-year trends in adverse drug reaction-related hospitalizations among people with dementia

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Abstract

Aim: Trends in the incidence of adverse drug reaction (ADR)-related hospitalizations have been studied in the general population, but not specifically in people with dementia. This study aimed to investigate trends in the incidence of ADR-related hospitalizations among people with dementia, and identify the most commonly implicated drugs and diagnoses in these admissions.

Methods: This study utilized the administrative data of all adults admitted to the four major public hospitals of Tasmania, Australia, with a primary or secondary diagnosis of dementia from July 2010 to December 2019. ADR-related hospitalizations were identified by using diagnosis-based and external cause codes. The Cochran–Armitage test was used to examine trends in the incidence of ADR-related hospitalizations.

Results: Of the 7552 people with dementia admitted to the hospital at least once within the study period, 1775 (23.5%) experienced at least one ADR-related hospitalization. The estimated annual incidence of ADR-related hospitalizations increased 18% (1484–1760 per 100,000 population with dementia, p for trend <0.05) from 2010 to 2019. For those ADR-related admissions with a drug code recorded, 19.3% were due to antithrombotics and 11.5% to antihypertensives. The most frequent ADR-related admission diagnoses were renal diseases (72.9%). Length of hospital stay and in-hospital mortality were both significantly greater for ADR-related, relative to non-ADR-related, admissions (median 7 *versus* 5 days and 11% *versus* 6.7%, respectively; $p < 0.001$).

Conclusion: The annual incidence of ADR-related hospitalizations in people with dementia increased between 2010 and 2019. Antithrombotics were the most commonly implicated drug class. The ADR-related hospitalizations were associated with increased length of stay and greater mortality.

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Plain Language Summary Adverse drug reaction-related hospitalizations among people with dementia

Introduction: This study aimed to investigate trends in hospitalizations associated with medication problems among people with dementia, and identify the most commonly implicated drugs and diagnoses in these admissions.

Methods: This study utilized the administrative data of all adults admitted to the four major public hospitals of Tasmania, Australia, with dementia from July 2010 to December 2019.

Results: The annual incidence of hospitalizations associated with medication problems among people with dementia increased nearly 20% over 10 years. The length of hospital stay and in-hospital mortality were significantly greater for hospitalizations related to medication problems.

Conclusion: The incidence of hospitalizations associated with medication problems in people with dementia increased between 2010 and 2019.

Keywords: ADR, adverse drug reactions, dementia, drug-related, elderly, hospital admission, hospitalization, re-admission, trends

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Introduction

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is defined as ‘a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function’.¹ ADRs entail a substantial burden not only on patients but also on the health care system.² Of particular concern are ADR-related hospitalizations, which have a median prevalence rate of 6% of all admissions.³ Antithrombotic, non-steroidal anti-inflammatory and cardiovascular drugs have been reported as the most common groups implicated in ADR-related hospitalizations.³

Dementia affects over 50 million people globally, and it is predicted that by 2050, the numbers will surge to 131.5 million.^{4,5} Dementia is the second leading cause of death in Australia.⁶ Older adults are at an increased risk of developing an ADR due to multiple factors such as polypharmacy, comorbidities, cognitive impairment and physiological changes affecting the pharmacokinetics and pharmacodynamics of many drugs.⁷ Evidence suggests that ADRs are common among people with dementia,⁸ but there is comparatively little research regarding the epidemiology of ADR-related hospitalizations among these individuals. With an ageing population and associated increasing prevalence of dementia, trends in the incidence of ADR-related hospitalizations, with a particular focus on people with dementia, should be investigated. The extent of the problem could be identified, and studies could be designed with targeted interventions. This research, therefore, aimed to investigate 10-year trends in the incidence of ADR-related hospitalizations in people with dementia, and identify the most commonly implicated drugs and diagnoses in these admissions.

Methods

Study design and setting

A retrospective study design involving the Tasmanian population was conducted. Tasmania

is an island state of Australia, home to 539,600 people,⁹ and the study data were compiled from the four major public hospitals.

Dataset

This study utilized the Admitted Patient Care National Minimum Dataset (APC-NMDS).¹⁰ The APC-NMDS consists of clinical, as well as administrative, data elements collected from Australian public hospitals and includes information related to each patient’s sociodemographic characteristics, principal diagnosis and any additional diagnoses associated with their admission, based on the *International Statistical Classification of Diseases and Related Health Problems, 10th edition, Australian Modification (ICD-10-AM)*.¹⁰

Study population and admissions

The study population consisted of people aged ≥ 18 years who had a public hospital admission in Tasmania, with a primary or secondary diagnosis of dementia, from July 2010 to December 2019. The diagnosis of dementia was based on the ICD-10-AM codes listed in Appendix 1 of the Supplementary Material. The study population was then stratified based on whether they had an ADR-related hospital admission or not at any time during the study period.

Admissions were classified as ADR-related when an ICD-10-AM external cause code between Y40 and Y59 was recorded in the APC-NMDS as a diagnosis associated with the hospitalization. Codes Y40–Y59 align with the WHO’s ADR definition and are commonly used for ADR identification.^{11,12} Du *et al.*’s¹³ codes were also employed to identify additional ADRs. These codes predominantly refer to drug-induced symptoms or conditions without explicitly specifying the ADR’s external cause. Code categories A1, A2, C and D were included. All external or Du *et al.*’s ADR codes associated with each admission were recorded. If the ADR developed during the hospital episode, then the admission was not classified as ADR-related.

Incidence of ADR-related hospitalizations

The annual incidence of ADR-related hospitalizations (per 100,000 population) was defined as the number of annual cases divided by the end of the calendar year Tasmanian population with dementia, estimated by the Australian Institute of Health and Welfare, between July 2010 and December 2019.^{14,15}

Age-specific incidence rates were calculated using the number of ADR-related hospital admissions in that specific age group, divided by the estimated total Tasmanian population within that specific age group.¹⁶

Measures

The socioeconomic status of each patient was determined using the Socioeconomic Indexes for Areas–Index of Relative Socioeconomic Advantage and Disadvantage (SEIFA-IRSAD), based on the Australian Bureau of Statistics (ABS) 2016 census data.¹⁷ The SEIFA-IRSAD provide summary measures of several census variables related to relative socioeconomic disadvantage and/or advantage of geographical areas in Australia.¹⁷ The SEIFA-IRSAD are ranked into deciles (1–10) based on the post-code of residence, where decile 1 represents the most socioeconomic disadvantaged area and decile 10 the most socioeconomic advantaged. We ranked deciles into three categories – 1–3 (low socioeconomic class), 4–6 (middle socioeconomic class) and 7–10 (high socioeconomic class) – based on an approximately equal distribution of the study population.

Geographic location was determined through the ABS Accessibility/Remoteness Index of Australia plus (ARIA+ 2016).¹⁸ The ARIA+ classified geographical areas into five groups: major cities, inner regional, outer regional, remote and very remote Australia. However, none of the geographical regions in Tasmania is classified as a major city based on the ARIA+ 2016.¹⁸ Therefore, the postcodes were re-coded into inner regional, outer regional and remote/very remote Australia. The ARIA+ classifications were generated using the University of Sydney ARIA Lookup tool,¹⁹ and areas with multiple classifications were identified using the ARIA+ 2016 demonstration map.²⁰

Statistical analysis

Statistical Package for the Social Sciences (IBM Corp., Released 2012, IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA) and Microsoft Office Excel 2019 and its XLSTAT version were used for data analysis. Normality of continuous variables was determined using the Kolmogorov–Smirnov test. Descriptive statistics were used to summarize patients' demographic and health-related characteristics. A chi-square test/Mann–Whitney *U* test/Kruskal–Wallis test was applied, as appropriate, to make comparisons between groups. A *p* value <0.05 was considered statistically significant. The Cochran–Armitage test for trend was used to determine significant trends in the incidence of ADR-related hospitalization.

Ethics

The Tasmanian Health and Medical Human Research Ethics Committee provided approval to undertake this study (reference number H0018582).

Results

Patients' characteristics

Of the 7552 people, including 3496 males (46.3%), admitted to a hospital at least once within the study period with a primary (12.4%) or secondary (87.6%) diagnosis of dementia, 1775 (23.5%) experienced at least one ADR-related hospitalization. People with an ADR-related hospitalization had a median age of 83 years (interquartile range, IQR: 77–87) at the time of their index ADR-related hospitalization, and 905 (51%) were male. There were a total of 14,692 admissions. Of these, 2468 (16.8%) were ADR-related admissions. The length of hospital stay (median: 7 *versus* 5 days) and in-hospital mortality (11% *versus* 6.7%) were significantly greater for ADR-related admissions (Table 1).

Trends in the incidence of ADR-related hospitalizations

Figure 1 shows the trends in the annual incidence of ADR-related hospitalizations and non-ADR-related hospitalizations among people with dementia between 2010 and 2019. Overall, there was an increasing trend in the annual incidence of ADR-related hospitalizations from 2010 to 2017,

Table 1. Characteristics of the study population ($n = 7552$).

Sociodemographic characteristics	ADR-related hospitalization		<i>p</i> value
	Yes ($n = 1775$)	No ($n = 5777$)	
Age at index admission (years), median [IQR]	83 [77–87]	83 [76–88]	0.476
Sex, n (%)			
Male	905 (51.0)	2591 (44.9)	<0.001
Socioeconomic status, SEIFA-IRSAD (deciles), n (%) ^a			
1–3 (low socioeconomic class)	801 (46.1)	2701 (47.7)	0.321
4–6 (middle socioeconomic class)	134 (7.7)	389 (6.9)	
7–10 (high socioeconomic class)	804 (46.2)	2571 (45.5)	
Geographic location (ARIA+), n (%) ^b			
Inner regional	1118 (63.0)	3506 (60.7)	0.395
Outer regional	604 (34.0)	2089 (36.2)	
Remote	43 (2.4)	146 (2.5)	
Very remote	10 (0.6)	34 (0.6)	
Ethnicity, n (%)			
Australian-born	1399 (78.8)	4531 (78.4)	0.730
Indigenous status, n (%)			
Not stated/inadequately described/neither Aboriginal nor Torres Strait Islander origin	1749 (98.5)	5707 (98.8)	0.405
Aboriginal and/or Torres Strait Islander	26 (1.5)	70 (1.2)	
Admission characteristics	All ADR-related hospitalizations ($n = 2468$)	All non-ADR-related hospitalizations ($n = 12,224$)	<i>p</i> value
Length of hospital stay (days), Median [IQR] ^c	7 [3–16]	5 [1–12]	<0.001
In-hospital mortality, n (%)	272 (11.0)	815 (6.7)	<0.001

ADR, adverse drug reaction; ARIA, Accessibility/Remoteness Index of Australia; IQR, interquartile range; SEIFA-IRSAD, Socioeconomic Indexes for Areas–Index of Relative Socioeconomic Advantage and Disadvantage.
Cochran–Armitage test for trend significant at $p < 0.05$ for both ADR-related hospitalizations and non-ADR-related hospitalizations.
^a152 missing cases.
^b2 missing cases.
^cLength of hospital stay was calculated after excluding in-hospital deaths.
The bold-faced values are statistically significant ($p < 0.05$) for better readability.

followed by a slight decline in the remaining years. The annual incidence of ADR-related hospitalizations increased by 18% (1484–1760 per 100,000 estimated population with dementia, p for trend <0.05), whereas it decreased by 7%

(8516–7969 per 100,000 population, p for trend <0.05) for non-ADR-related hospitalizations from 2010 to 2019, respectively. Approximately 2% of Tasmanians with dementia experienced an ADR-related hospital admission per annum.

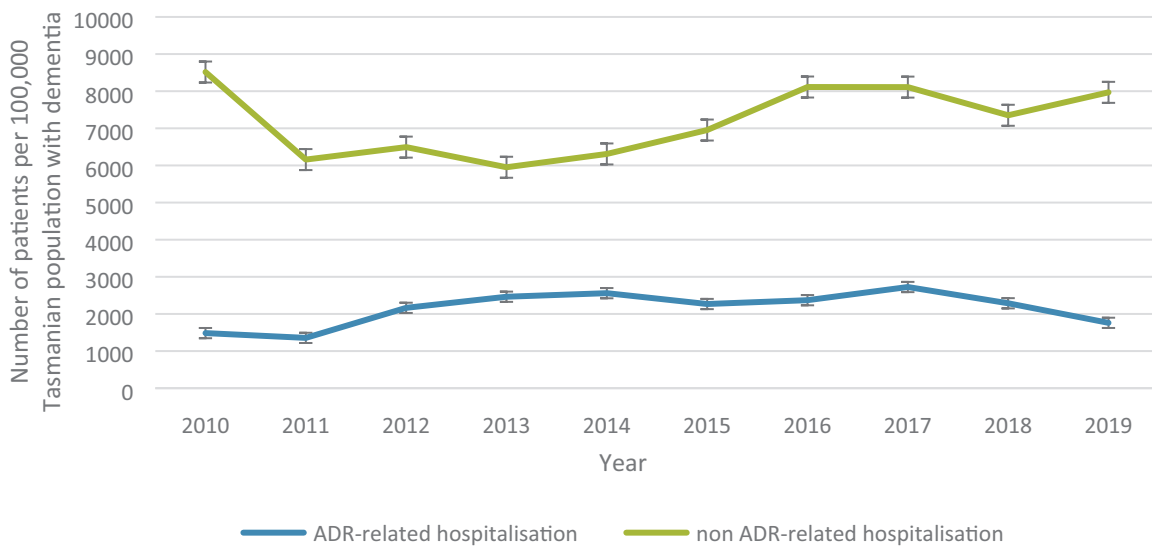


Figure 1. Trends in the annual incidence of ADR-related hospitalization and non-ADR-related hospitalization among people with dementia per 100,000 Tasmanian population with dementia.

The year-wise trends in the incidence of ADR-related hospitalizations with respect to sociodemographic characteristics are available in Supplementary Table 1. No significant changes over time in sociodemographic characteristics were observed for ADR-related hospitalizations. The trends in the annual incidence of ADR-related hospitalization by age group are shown in Supplementary Figure 1. The annual incidence of ADR-related hospitalization increased by 95.3% (279–545 per 100,000 population, p for trend <0.05) from 2010 to 2019 among people with dementia aged ≥ 85 years.

Most commonly implicated drugs and diagnoses in ADR-related hospitalizations

Drug codes were present in only 21.1% of the ADR-related hospitalizations. Of these, 19.3% were due to antithrombotics and 11.5% to anti-hypertensives. Opioids, psychotropics (excluding antidepressants) and antidepressants were present among 11.1%, 7.7% and 6.7%, respectively, of ADR-related hospitalizations with a drug code (Supplementary Table 2).

The most frequent ADR-related admission diagnoses were renal diseases (72.9%). Haematologic disorders, ophthalmic diseases, gastrointestinal disorders and hypotension were present as ADR-related admission diagnoses in 5.2%, 3.2%, 3%

and 2% of total ADR-related hospitalizations, respectively (Supplementary Table 3).

Discussion

This study provides important insights into the burden of ADR-related hospitalization in people with dementia. Approximately 2% of Tasmanians with dementia experienced an ADR-related hospital admission per annum. Parameswaran Nair *et al.*²¹ reported that dementia itself serves as a risk factor of ADR-related hospitalization. A combination of external cause codes and diagnosis-based codes was used for the identification of ADR-related hospitalizations among people with dementia, where the drug class (antithrombotics) most commonly implicated with ADR-related hospitalizations was more prevalent in males. Multiple studies have shown that the use of antithrombotics for cardiovascular conditions is more prominent in males.^{22,23}

Our study showed that the length of hospital stay and in-hospital mortality were significantly greater for ADR-related hospitalizations among people with dementia. A study conducted among the general population of Singapore had also shown a greater length of hospital stay among people with ADR-related hospitalizations.²⁴ Occupying a bed in a hospital due to ADR entails a substantial burden on the health care system,

where an estimated cost per bed day is approximately Aus\$1901.²⁵ Patel and Patel have reported ADR-related hospitalizations as an important cause of mortality in a meta-analysis.²⁶

We ascertained that the annual incidence of ADR-related hospitalization in people with dementia increased nearly 20% between 2010 and 2019. It is possible that increased use of medications over this time period may have led to an increase in ADR presentations. Moreover, cognitive deficit, low adherence to drug therapy and increased sensitivity to anticholinergic drugs are risk factors for adverse reactions in patients with dementia.²⁷ Our estimate of ADR-related hospitalizations (16.8%) was almost double as compared with the average (8.7%) reported by Oscanoa *et al.*² in patients over 60 years of age. A meta-analysis found that up to 88% of the ADR-related hospitalizations among the elderly were considered preventable.²⁸ Strategies for preventing ADRs such as home medicines reviews by establishing a liaison between patients and health care professionals, patient education, and developing and implementing a tool for predicting ADR-related hospitalization among people with dementia may help to improve medication safety.²⁹ Our study showed that while the annual incidence of ADR-related hospitalizations increased from 2010 to 2017, from 2017 to 2019, the incidence showed some decline. The exact reason for this drop is unclear, and further research is warranted. It is noteworthy that dementia was recognized as a public health priority by the WHO in May 2017, followed by the endorsement of the global action plan on the public health response to dementia 2017–2025.³⁰ Consequently, steps were taken to improve the care of patients with dementia.^{31,32}

Our study showed that drug codes were present in less than one-quarter of the ADR-related hospitalizations. Antithrombotics and antihypertensives were most commonly implicated in ADR-related hospitalizations. Previous research has reported antithrombotic agents to be most commonly implicated.^{33,34} Antithrombotics are frequently prescribed to older people and patients with cardiovascular problems, who are more prone to ADRs.³⁵ The risk of major cardiovascular events like cerebrovascular accidents and myocardial infarctions is related to many factors that are also risk factors for dementia, including

age and cardiovascular disease.³⁶ Antithrombotics such as aspirin are prescribed to people with dementia for reducing the risks of major cardiovascular events.³⁶ Our study reported that more than half of ADR-related hospitalizations were due to renally related ADRs. Contrary to this, most studies have reported bleeding as the most common ADR-related diagnosis of hospitalizations.^{37,38} Pedrós *et al.*,³⁹ however, reported acute renal failure related to renin–angiotensin system inhibitors as the most frequent ADR leading to hospital admission. A similar result may have occurred in this study, with renin–angiotensin system inhibitors being the most commonly implicated antihypertensives in ADRs.

To the best of our knowledge, this is the first study investigating the trends in the annual incidence of ADR-related hospitalizations among people with dementia over an extensive period. A combination of external cause codes and diagnosis codes were used for ensuring maximum coverage of ADR-related hospitalizations. One of the main study limitations was the lack of adjustment for comorbidities (as pre-existing conditions were not routinely recorded in the dataset), which might limit the understanding of risk factors of ADR-related hospitalizations. Another limitation was the reliance on data collated from a national administrative dataset, which may be prone to coding errors and variation. Furthermore, medicines-related information was missing in the dataset, limiting our ability to investigate the ADR details for specific drugs. It must be taken into consideration that there might be some underestimation of ADRs because it was a retrospective study utilizing administrative data that detect ADR-related admissions at a relatively low rate. Approximately 18–35% of ADR-related admissions captured prospectively can be identified through administrative data sources; however, these rates may be affected by the ICD codes used.^{40,41} Parameswaran Nair *et al.*⁴¹ have shown that 15% of medical admissions in older patients were classified as ADR-related, based on a prospective review, compared with 2.7% of the same patient cohort using administrative coding.

Conclusion

Approximately 2% of Tasmanians with dementia experienced an ADR-related hospital admission per annum. The annual incidence of ADR-related

hospitalization increased nearly 20% over 10 years among people with dementia. Antithrombotics were the most commonly implicated medications. Strategies focusing on identifying the risk of ADR-related hospitalization and cautious prescribing of implicated medicines could help mitigate the morbidity and mortality burden of ADR-related hospital admissions among people with dementia.

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Author contributions

Anum Saqib Zaidi: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft.

Gregory M. Peterson: Conceptualization; Investigation; Methodology; Supervision; Visualization; Writing – review & editing.

Luke R.E. Bereznicki: Conceptualization; Methodology; Supervision; Writing – review & editing.

Colin M. Curtain: Conceptualization; Methodology; Supervision; Writing – review & editing.

Mohammed S. Salahudeen: Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – review & editing.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.


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