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Drug-related problems among older people with dementia: A systematic review

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ABSTRACT

Introduction: Dementia is a disorder that causes a decline of cognitive function, and it affects millions of people worldwide. Increased availability of medications used to treat dementia will inevitably increase the likelihood of drug-related problems (DRPs).

Objective: This systematic review sought to identify DRPs due to medication misadventures, including adverse drug reactions (ADRs), and use of inappropriate medications, among patients with dementia or cognitive impairments.

Methods: The included studies were retrieved from the electronic databases PubMed and SCOPUS, and a preprint platform (MedRxiv) which were searched from their inception through August 2022. The English-language publications that reported DRPs among dementia patients were included. The JBI Critical Appraisal Tool for quality assessment was used to evaluate the quality of studies included in the review.

Results: Overall, 746 distinct articles were identified. Fifteen studies met the inclusion criteria and reported the most common DRPs, which comprised medication misadventures (n = 9), such as ADRs, inappropriate prescription use, and potentially inappropriate medication use (n = 6).

Conclusion: This systematic review provides evidence that DRPs are prevalent among dementia patients, particularly the older people. It indicates that medication misadventures such as ADRs and inappropriate drug use, as well as potentially inappropriate medications, are the most prevalent DRPs among older people with dementia. Due to the small number of included studies, however, additional studies are required to improve comprehension about the issue.

1. Introduction

Dementia is a syndrome characterized by deteriorating cognitive function that can significantly interfere with a person's daily life and activities.¹ Dementia describes various neurological conditions that are irreversible, including Alzheimer's, Parkinson's, vascular dementia, frontotemporal dementia, and many other rarer forms.² Worldwide, dementia affects approximately a little over 50 million people, but it is

predicted that the figure could increase to an estimated 131.5 million people by 2050.³ On top of that, dementia has been known to have a more significant impact on the economy compared to cancer, heart disease, and stroke combined.⁴ The cost of healthcare for people with dementia would be approximately US\$20,000 higher per year than those without dementia.⁵

Furthermore, due to the increased availability of medications globally, drug-related problems (DRPs) are inevitable, especially among

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dementia patients.⁶ A DRP is defined as any unwanted event that patients encounter during drug therapy that can potentially affect desired health outcomes.⁷ Unwanted events include medication misadventures such as adverse drug reactions (ADRs), adverse drug events (ADEs), and medication errors (MEs).⁶ DRPs can be placed into seven subgroups: additional medication therapy needed, unnecessary medication therapy, ineffective therapy, under-doses, ADRs, over-doses, and noncompliance.⁷ The evaluation of drug-related problems among older people with dementia is highly concerning. Studies have stated that individuals of an older age suffering from dementia tend to be a more vulnerable population for DRPs. This could be due to several factors, including the presence of comorbidities, polypharmacy, physiological changes, and alterations in pharmacokinetics and pharmacodynamics.⁸

According to a French longitudinal study, more than 60% of patients suffering from dementia tend to suffer from at least three other chronic illnesses.⁹ Additionally, these patients tend to be prescribed an average of 5–10 medicines at a time.² Hence, dementia patients may be more vulnerable due to a higher incidence of polypharmacy. Furthermore, between 14 and 74% of dementia patients use potentially inappropriate medication (PIM).¹⁰ Both polypharmacy and PIM use are known to be associated with DRPs, such as an increased risk of adverse events,

greater healthcare utilization, and even death. In addition, approximately 30% of hospitalizations among older adults are due to DRPs.⁷ Moreover, people with dementia tend to have a higher risk of hospital admission compared to those without dementia. A study found that these hospitalizations were caused by problems such as changes in patient behavior, falls, neck femoral surgery, and cardiovascular complications such as heart failure.⁹

During hospital admission, the drug treatment for patients can often be changed, which can entail additional medications, adjustments of doses, or discontinuation of existing medicines.¹¹ Hence, pharmacist counseling is relatively important, as patients can find it challenging or confusing as to how or when they should take their medications.¹¹ With such counseling, certain DRPs and mortality rates can be reduced, and patient safety can be improved.¹¹

There is currently a lot of evidence that dementia can be a risk factor for drug-related problems. However, until now, studies investigating the association between drug-related problems and adverse health outcomes among people with dementia or cognitive impairment has been limited. In order to address the limitation in the literature, the present systematic review was conducted to identify the prevalence of, type of and factors associated with drug-related problems due to medication

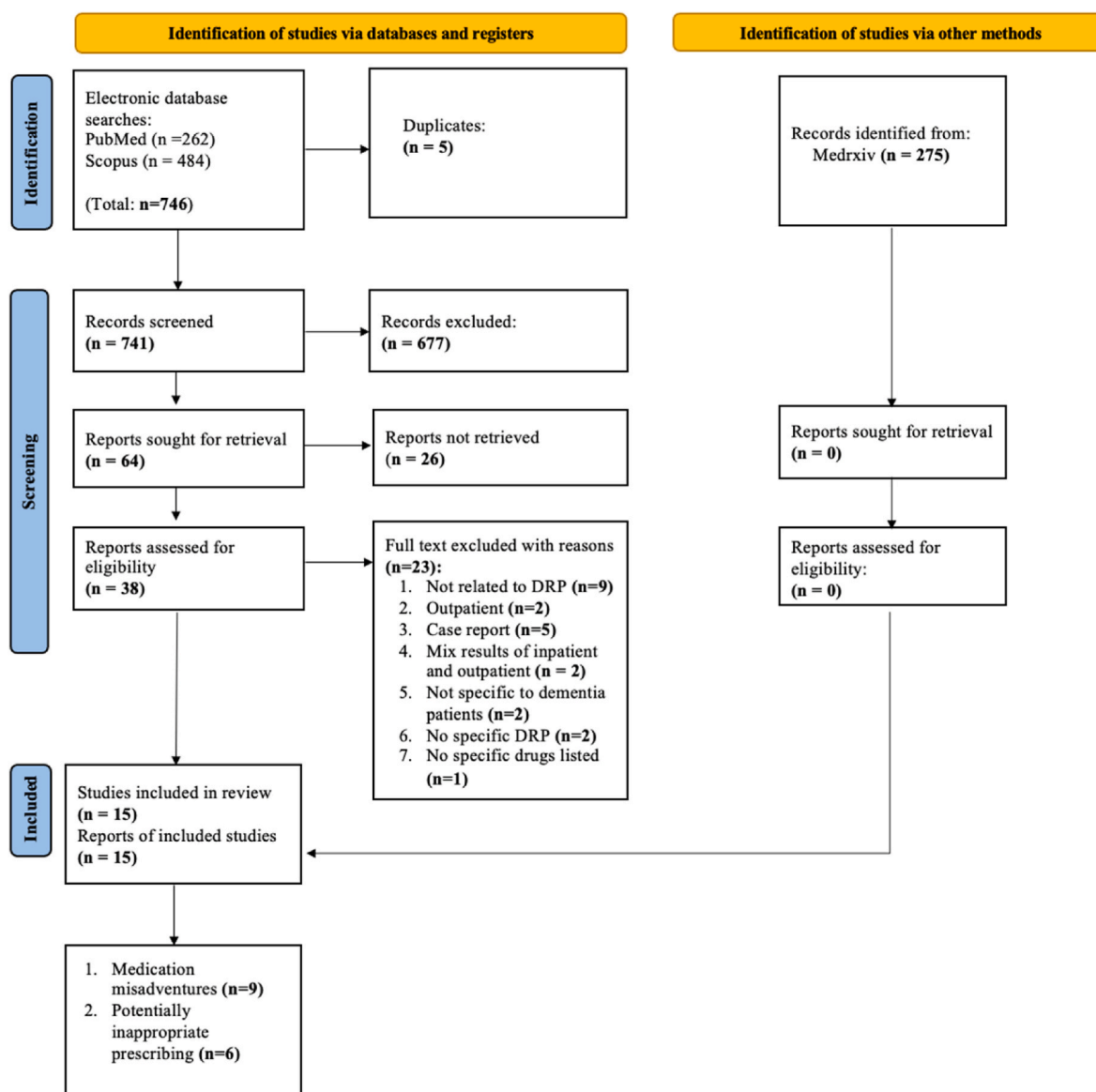


Fig. 1. PRISMA flowchart for the studies selected to be included into systematic review. Abbreviations: ADR, Adverse Drug Reactions; DRP, Drug-Related Problem.

Table 1
Characteristics of included studies.

Author, Year, Country	Study Design	Aim of study	Patient Details	Findings
Zaidi et al., 2022, Australia ³	Retrospective cohort study	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.	Total: 7552	ADR-related hospitalizations among people with dementia.
Delgado et al., 2021, England ²	Retrospective cohort study	To estimate rate of potentially inappropriate prescribing (PIP) and its effect on adverse health outcomes (AHO).	Total: 11,175	Dementia patients had an increased PIP risk .
Ferreira et al., 2020, Brazil ¹	Cross-sectional study	To determine the prevalence and severity of self-reported ADRs among patients with Alzheimer's disease in the Brazilian public health system.	Total: 250	ADR .
Murphy et al., 2020, Europe ¹⁰	Randomized Control Trial	To assess the patterns and associations of PIM use in older adults with mild-to-moderate Alzheimer's Disease.	Total: 448	Increased PIMs were associated with a greater risk of adverse events, serious adverse events, unscheduled hospitalizations and GP visits.
Mullan et al., 2019, Australia ⁶	Retrospective analysis	To compare rates and trends in hospital admissions due to medication misadventures for older adults (≥ 65 years) with and without dementia.	Total: 228,165	Medication misadventures contributed to hospital admissions.
François et al., 2018, France ⁹	Longitudinal study	To determine if the main adverse effects of cholinesterase inhibitors and memantine may be associated with increased hospitalization and to quantify the subsequent impact on healthcare expenditures.	Total: 111,133 observations over an 8-year period involving 7668 patients	The prescription of antedementia drugs, i.e., rivastigmine, increased the risk of hospitalizations due to their cardiac and gastrointestinal adverse effects and led to additional health care expenditures.
Renom-Guiteras et al., 2018, England, Estonia, Finland, France, Germany, the Netherlands, Spain and Sweden ²⁰	Prospective survey	To evaluate the frequency of PIM prescription among older people with dementia in eight countries, as well as the factors and adverse outcomes associated with PIM prescription.	Total: 2004	PIM use among people with dementia appeared to be associated with adverse outcomes.
Zerah et al., 2017, France ¹⁶	Longitudinal national database study	To examine the association between hospitalizations and iatrogenic alerts (IAs) in elderly patients treated for Alzheimer disease who are particularly sensitive to ADE.	Total: 10,754	An estimated 22% of all hospitalizations were associated with iatrogenic alerts (IAs), 80% of which were due to psychotropic IAs.
Sönnerstam et al., 2017, Sweden ¹³	Cross-sectional study	To investigate the prevalence of PIM among older patients with cognitive impairment.	Total: 428	There was a need to evaluate the use of PIMs in order to prevent ADRs, especially among people who have a higher number of medications prescribed.
Sönnerstam et al., 2016, Sweden ¹⁴	Cross-sectional study	To estimate the prevalence of impaired renal function and inappropriate prescription of renally cleared medications among older people, aged ≥ 65 years, with dementia or cognitive impairment.	Total: 428	Impaired renal function was common and inappropriate prescription was prevalent among older people with cognitive impairment.
Gustafsson et al., 2016, Sweden ⁷	Randomized Controlled Trial	To assess the occurrence and characteristics of DRPs that lead to acute hospital admissions among older people (≥ 65 years) with dementia or cognitive impairment.	Total: 458	DRPs were responsible for a major proportion of hospitalizations among older people with dementia or cognitive impairment. Type of DRPs identified: ADRs, dosage too high or low, interactions, need additional drug therapy, noncompliance, unnecessary drug therapy.
Sköldunger, 2015, Sweden ¹⁵	Longitudinal cohort study	To investigate inappropriate drug use (IDU) and the risk of hospitalizations and mortality in older persons and in persons with dementia, and to estimate the costs of IDU-related hospitalizations.	Total: 4108	IDU is associated with an increased risk of hospitalizations and mortality in older persons and in persons with dementia.
Kanagaratnam, 2014, France ¹⁷	Longitudinal study	To identify risk factors for the occurrence of ADRs and drug interactions.	Total: 293	Psychotropics were associated risks of ADRs and drug interactions .
Chen et al., 2012, Malaysia ¹⁸	Multicenter and cross-sectional study	To assess and characterize the prevalence of PIMs in nursing homes in Malaysia using the Screening Tool of Older People's Prescriptions (STOPP) and Beers criteria.	Total: 211	PIM were highly prevalent among older residents living in nursing homes and were associated with a higher number of medications used and longer nursing home stay.
Perri 3rd et al., 2005, Georgia ¹⁹	Cohort design	To identify the prevalence of inappropriate medication use among elderly patients in Georgia nursing homes using the Beers criteria and to identify the relationship between inappropriate drug use and the likelihood of an AHO.	Total: 519	Inappropriate medication use in elderly was associated with a higher risk of AHO.

misadventures among people with dementia or cognitive impairment.

2. Methods

2.1. Data sources and search strategy

Searches for this review were conducted using three electronic databases: PubMed, SCOPUS, and a preprint platform (MedRxiv), from the inception of the databases until August 2022. The entire flow of the selection process is illustrated in the PRISMA flow chart in Fig. 1. Two researchers conducted the screening independently, and any different decisions were resolved by using the opinion of the third researcher.

In summary, the search terms that were used covered all the terms, including *medication misadventure*, *adverse drug reactions*, *cognitive impairment*, *dementia*, *drug-related hospitalization*, *inpatient*, and *drug-related problems*. The specific search terms for this systematic review can be seen in Supplementary Information 1.

2.2. Inclusion and exclusion criteria

The systematic review included studies reported DRPs among inpatients with dementia published as an article, book chapter, or conference paper. We excluded papers in the form of reviews, case report, editorials, protocol, and letters, as well as texts not written in English.

2.3. Quality assessment

The quality of each included study was assessed using the JBI Critical Appraisal Tool.¹² This assessment was conducted to ensure that the included studies met the specific requirements for this systematic review. The studies were deemed good quality if they met the checklist criteria, including the appropriate target population, minimal bias in participant sampling, adequate sample size, detailed descriptions of participants and settings, reliable standardized conditions, valid data collection methods, appropriate statistical analysis, and adequate response rate. The tool has four response options: 'Yes', 'No', 'Unclear', and 'Not applicable'. Two researchers conducted the quality assessment independently and inter-rater disagreement was tackled using consensus.

3. Results

3.1. Overview of included studies

The search strategy yielded 746 studies that were potentially relevant to this systematic review topic. Using EndNote X9 (Clarivate, United States), 5 duplicate studies were excluded, and the remaining 741 studies were screened based on their titles and abstracts. From the screening, 38 were eligible and 23 were excluded as they did not meet the intended criteria.

Table 1 summarizes the characteristics of the included studies that investigated DRPs associated older people with dementia. Ultimately, 15 studies met the criteria for inclusion in this systematic review: 9 studies reported medication misadventures and 6 studies reported PIM use. Details of the search results can be seen in the PRISMA flowchart diagram in Fig. 1. PRISMA checklist is included as a Supplementary Material.

Four of the included studies were conducted in Sweden,^{7,13–15} three in France,^{9,16,17} two in Australia,^{3,6} and one each in England,² Brazil,¹ Europe,¹⁰ Malaysia,¹⁸ and Georgia.¹⁹ Additionally, one study²⁰ was conducted in a total of eight countries: England, Estonia, Finland, France, Germany, the Netherlands, Spain, and Sweden. The majority of the included studies were conducted in hospitals (n = 9), while the remaining studies were conducted in nursing homes (n = 3), community-dwelling settings (n = 2) and a healthcare center (n = 1).

The studies comprised four retrospective cohort studies,^{2,3,6,19} four

cross-sectional studies,^{1,13,14,18} two randomized controlled trials,^{7,10} four longitudinal studies,^{9,15–17} and one prospective survey study.²⁰ In the studies, the number of participants with dementia or cognitive impairment ranged from 211 to 228,165. Most of the studies (n = 13) included dementia patients, and the rest of the studies included patients with cognitive impairments (n = 2). Out of the 15 studies, 9 studies reported medication misadventures that included medication errors and adverse drug reactions.^{1,3,6,7,9,15–17,19} The other 6 studies focused on PIMs.^{2,10,13,14,18,20}

3.2. Quality assessment

According to the JBI Critical Appraisal Checklist provided in Table 2, all of the 15 included studies were generally of good quality. The quality was high for 11 studies^{1,2,6,9,10,13–15,17,19,20} and moderate for 4 studies.^{3,7,16,18}

3.3. Methods used in identifying drug-related problems (DRPs)

Four studies used the STOPP criteria to identify DRPs.^{2,10,13,18} The Beers' criteria were used in three studies have used.^{13,18,19} Two studies employed indicators established by the EU (7)-PIM list,^{13,20} while two others used the World Health Organization (WHO) guidelines to detect DRPs.^{7,17} Additionally, DRPs identified in two other studies used indicators developed by the Australian Institute of Health and Welfare³ and Swedish National Board of Health and Welfare.¹⁵ Table 3 lists the remaining methods used.

3.4. Prevalence of DRPs

The DRP prevalence ranged from 9.1 to 83.6% in the 15 studies. Table 3 shows the reported overall prevalence of the DRPs. One retrospective study reported that 23.5% out of 7552 patients had experienced at least one ADR-related hospitalization.³ One study¹⁷ found that 70 (24%) out of 356 patients experienced at least one ADR. Moreover, a similar study¹ found that 209 patients (83.6%) out of 250 also encountered at least one ADR. Gustafsson et al.⁷ reported that 189 patients (41.3%) experienced drug-related hospitalization and 86 (45.5%) of them had ADRs as a DRP. Another study by François et al.⁹ showed that there was a higher hospitalization rate among treated individuals compared to non-treated individuals, primarily with ChEIs (especially rivastigmine) for cardiac events (OR = 1.44, p = 0.002). Furthermore, another study investigating drug-related hospital admissions reported an increase in hospitalizations by 0.36 per year.¹⁶

Inappropriate medications given to patients were reported in one study.¹⁹ The study reported that 519 (46.5%) patients received at least one inappropriate medication, and 143 (12.8%) of the 519 patients experienced at least one adverse health outcome. Sköldunger et al.¹⁵ state that inappropriate drug use (IDU) causes a great risk of hospital admissions and mortality, especially in older people and in people suffering from dementia. The results of the study¹⁵ show that the prevalence of IDU among dementia patients was 27%, while the prevalence among patients without dementia was 12%.

The prevalence of PIMs ranged from 23.7 to 73.5%. A study by Sönnnerstam et al.¹⁴ stated that 50 (9.1%) out of 547 prescriptions were inappropriate; 17 (3.1%) of these prescriptions had doses that were too high, and 33 (6.9%) were contraindicated drugs. A similar study by Chen et al.¹⁸ reported that PIMs determined using the Beers and STOPP criteria were identified in 86 individuals (40.8%), and there was a significant difference in PIMs detected by STOPP (23.7%) and by Beers criteria (32.7%). Another study reported that 60% of the included individuals experienced at least one PIM prescription, while 26.4% experienced at least two.²⁰ Similarly, a study by Sönnnerstam et al.¹³ found that 175 (40.9%) of the individuals reported to have been prescribed PIMs; 130 (30.4%) had one PIM, 39 (9.1%) had two PIMs, and 6 (1.4%) had three PIMs. On top of that, Delgado et al.² showed that 8211

Table 2
Quality assessment scores of the included studies.

	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall Appraisal
Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	
Zaidi et al., 2022 [3]	Y	Y	Y	Y	Y	Y	Y	N	Y	I
Delgado et al., 2021 [2]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Ferreira et al., 2020 [1]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Murphy et al., 2020 [10]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Mullan et al., 2019 [6]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
François et al., 2018 [9]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Renom-Guiteras et al., 2018 [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Zerah et al., 2017 [16]	Y	Y	Y	Y	Y	Y	Y	N	Y	I
Sönnerstam et al., 2017 [13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Sönnerstam et al., 2016 [14]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Gustafsson et al., 2016 [7]	Y	Y	N	Y	Y	N	Y	Y	Y	I
Sköldunger et al., 2015 [15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Kanagaratnam et al., 2014 [17]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I
Chen et al., 2012 [18]	Y	Y	N	Y	Y	Y	Y	Y	Y	I
Perri 3 rd et al., 2005 [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	I

Abbreviations:
Y: yes; N: no; U: unclear; NA: not applicable; I: include

Table 3

Drug-related problem characteristics of the included studies.

Studies	Methods and resources used in detecting DRPs	Most common drugs	Overall prevalence
Zaidi et al., 2022 ³	Australian Institute of Health and Welfare	<ul style="list-style-type: none"> • Antithrombotics (19.3%) • Antihypertensives (11.5%) 	7552 people 1775 (23.5%) experienced at least one ADR-related hospitalization.
Delgado et al., 2021 ²	STOPP version 2 criteria	<ul style="list-style-type: none"> • Anticholinergic/antimuscarinic (46.1%) • Any duplicate drug class prescription (31.5%) • Non-steroidal anti-inflammatory drugs (22.5%) 	11,175 individuals 8211 had at least one PIP Prevalence of PIP was higher in dementia patients (73.5%) compared to people without dementia of similar age and gender (57%).
Ferreira et al., 2020 ¹	MEDEX system	<ul style="list-style-type: none"> • Donepezil • Galantamine • Rivastigmine • Memantine 	209 (83.6%) reported at least one ADR. Rivastigmine was associated with the highest number of ADRs per patient (7.9 ADRs/patient) followed by galantamine (5.9 ADRs/patient).
Murphy et al., 2020 ¹⁰	STOPP version 2 criteria	<ul style="list-style-type: none"> • Benzodiazepines >4 weeks without indication (11.6%) • Selective serotonin reuptake inhibitors without appropriate indication (11%) • Proton-pump inhibitors (PPIs) without appropriate indication (10.7%) • Anti-psychotic medication without appropriate indication (8%) • NSAID without PPIs cover (4.2%) 	Over half (55.8%) were prescribed a PIM. 30.1% prescribed 2+ PIMs
Mullan et al., 2019 ⁶	Illawarra Health Information Platform (IHIP) database	<ul style="list-style-type: none"> • Anticoagulants • Opioids/related analgesics 	228,165 admissions. 10,555 (4.6%) medication misadventures.
François et al., 2018 ⁹	<ul style="list-style-type: none"> • Echantillon généraliste des bénéficiaires (EGB) • Programme de m'édicalisation des syst'emes d'information (PMSI). 	<ul style="list-style-type: none"> • Cholinesterase inhibitors (ChEIs) • Donepezil • Galantamine • Rivastigmine • Memantine 	Treated patients were hospitalized significantly more than non-treated patients, mainly with cholinesterase inhibitors for cardiac adverse effects (especially with rivastigmine).
Renom-Guiteras et al., 2018 ²⁰	EU (7)-PIM list	<ul style="list-style-type: none"> • Psycholeptics • Drugs for acid related disorders • Cardiac therapy • Psychoanaleptics • Antithrombotic agents • Calcium channel blockers • Drugs for diabetes • Urologicals • Anti-inflammatory and antirheumatic products • Laxatives 	60% used at least one PIM prescription. 26.4% used at least 2 PIM prescriptions.
Zerah et al., 2017 ¹⁶	Two French National Health Insurance Information System: <ul style="list-style-type: none"> • Régime Social des Indépendants (RSI) • Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) 	<ul style="list-style-type: none"> • Benzodiazepines • Antipsychotic drugs • Co-prescription of 3 or more psychotropic drugs • Co-prescription of 2 or more diuretics • Co-prescription of 4 or more antihypertensive drugs 	Hospitalization rates increased by 0.36/year. 22% of all hospitalizations were associated with IAs; 80% were due to psychotropic IAs.
Sönnerstam et al., 2017 ¹³	<ul style="list-style-type: none"> • EU (7)-PIM list • Beers List • STOPP criteria • Laroche list 	<ul style="list-style-type: none"> • Zopiclone • Digoxin • Sodium picosulfate 	175 (40.9%) used one or more PIMs. 130 (30.4%) used one PIM. 39 (9.1%) used two PIMs. 6 (1.4%) used three PIMs.
Sönnerstam et al., 2016 ¹⁴	Geriatric Dosage Handbook (GDH) guidelines	Renally-cleared medications: <ul style="list-style-type: none"> • Allopurinol • Metformin 	547 prescriptions. 50 (9.1%) inappropriate prescriptions. 17 (3.1%) dose too high. 33 (6.9%) contraindicated drugs. 8 (47.1%) prescription with excessive doses - allopurinol 12 (36.4%) contraindicated prescriptions - metformin.
Gustafsson et al., 2016 ⁷	World Health Organization (WHO) criteria	<ul style="list-style-type: none"> • Cardiovascular drugs (29.5%) • Psychotropic drugs (27.3%) 	189 (41.3%) drug-related hospitalization. 86/189 (45.5%) DRPs was an ADR.
Sköldunger et al., 2015 ¹⁵	Swedish National Board of Health and Welfare	<ul style="list-style-type: none"> • Concurrent use of 3 or more psychotropic drugs (from any of antipsychotic, anxiolytic, hypnotic-sedative, and anti-depressant drug group) • Drugs with anticholinergic properties (urinary and gastrointestinal antispasmodics, anticholinergic antiemetics, class Ia antiarrhythmics, anticholinergic antiparkinsonian drugs, low-potency antipsychotics, tricyclic antidepressants, and 1st generation antihistamines) • Long-acting benzodiazepines (diazepam, nitrazepam, or flunitrazepam) 	Overall prevalence of IDU (13%). 27% of IDU involved among dementia patients 12% of IDU involved people without dementia
Kanagaratnam et al., 2014 ¹⁷	World Health Organization (WHO) criteria	<ul style="list-style-type: none"> • Anxiolytics and hypnotics (57.7%) • Antidementia drugs (54.6%) • Antidepressants (54.3%) • Antithrombotics (54.0%) 	Prevalence of ADRs was 24%.

(continued on next page)

Table 3 (continued)

Studies	Methods and resources used in detecting DRPs	Most common drugs	Overall prevalence
Chen et al., 2012 ¹⁸	STOPP and Beers criteria	<ul style="list-style-type: none"> • Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (37.5%) STOPP <ul style="list-style-type: none"> • First generation antihistamines • Duplication of drug classes • Glibenclamide • Anticholinergic agents Beers criteria <ul style="list-style-type: none"> • Nifedipine short acting • Chlorpheniramine • Diphenhydramine 	Prevalence of PIMs STOPP 50 residents (23.7%) Beers criteria 69 residents (32.7%)
Perri 3rd et al., 2005 ¹⁹	Beers criteria	<ul style="list-style-type: none"> • Propoxyphene (14.4%) • Promethazine (10%) • Hydroxyzine (7.1%) • High-dose iron supplements (6.8%) • Digoxin (4%) 	519 (46.5%) patients received at least one inappropriate medication. 143 (12.8%) patients experienced at least one adverse health outcome.

out of 11,175 people had at least one PIP; the prevalence of PIP was more significant in patients with dementia (73.5%), while patients without dementia of similar age and gender had a lower prevalence (57.0%) of receiving PIP. A study by Murphy et al. using STOPP version 2 criteria¹⁰ found that over half of respondents (55.8%) prescribed PIMs, while 30.1% were prescribed two or more PIMs.

3.5. Drugs linked to DRPs

In the 15 studies that were included, a large number of medicines linked to DRPs were mentioned. Some studies reported on specific drugs,^{1,9,13,14,19} other studies reported on specific drug classes,^{2,3,6,7,10,15–17,20} and one study reported on both specific drugs and drug classes based on the Beers criteria and STOPP.¹⁸ Overall, the most common drug classes linked to DRPs were psychotropic medications,^{7,10,15–17,20} antihypertensives,^{3,7,13,16–18,20} antihistamines,^{15,18,19} and antithrombotic drugs.^{3,6,17,20} The most common specific drugs linked to DRPs were antedementia drugs, including donepezil, galantamine, rivastigmine, and memantine.^{1,9} These results can be seen in Table 3.

3.6. Risk factors

The two most common risk factors for DRPs, which were both seen in the eight included studies, were old age^{1,2,6,9,10,15,16,20} and polypharmacy.^{3,7,10,13,16–19} Following this was comorbidity,^{1,2,6,13,15,16,20} gender,^{1–3,15} dementia,^{2,3,6,15} and living situations.^{14,15,18,20} The other risk factors included cognitive deficit, low adherence to drug therapy, long-term disease, drug interactions, and low education level (Table 4).

4. Discussion

Medication misadventures and PIMs are becoming increasingly common, particularly among older people with dementia or cognitive impairments. This review provides insights into the occurrences of medication misadventures and prevalence of PIMs among dementia patients based on fifteen included studies that were published between 2012 and 2022. While numerous drug classes have been linked to DRPs, the most common ones included antipsychotic agents, antihistamines, antihypertensives, and antithrombotic drugs.

According to a study by Mullan et al.⁶ hospitalization rates due to medication misadventures were more than three times higher among older people with dementia. Based on a survey by Gustafsson et al.,⁷ the most prevalent types of DRPs were ADRs, overdose, underdosing, drug interactions, the need for additional therapy, noncompliance, and inappropriate or unnecessary drug therapy. It is recognized that these

DRPs account for the majority of hospital admissions among older people with dementia or cognitive deficits.⁷ Antedementia drugs, including donepezil, galantamine, rivastigmine and memantine were the most common drugs linked to DRPs. Ferreira et al.¹ reported that 209 patients (83.6%) experienced at least one ADR; rivastigmine was associated with the highest number of ADRs per patient, followed by galantamine. Common ADRs for rivastigmine included confusion, hallucinations, ataxia, and impaired coordination, whereas for galantamine, somnolence, depression, and malaise were noted.

In this systematic review, medication misadventures were common. Previous studies indicated that dementia patients are more susceptible to medication misadventures. Consequently, medication misadventures contribute significantly to hospitalizations. According to a study by Mullan et al.,⁶ 10,555 out of 228,165 hospital admissions were due to medication misadventures. This DRP may arise for a variety of reasons, including miscommunications in medication orders, illegible and unclear handwriting, human error resulting in incorrect drug selections, and confusion from identical package or labeling.²¹ Additionally, the use of multiple medications, often known as polypharmacy, contributes significantly to the increased risk of ADRs.²² Hence, persons with a higher number of prescribed medicines should their need for medications that are regarded as PIMs reassessed in order to reduce the risks of ADRs.¹³

PIMs are frequently prescribed, particularly to older people with dementia or a cognitive impairment. This should be a cause for concern given PIMs are usually associated with adverse health outcomes and increased medical care expenditure.²³ The majority of studies included in this review identified PIMs using the Beers' or STOPP criteria. In this review, the prevalence of PIMs was high, ranging from 23.7% to 73.5%. PIMs were prescribed due to a variety of circumstances, including the condition of dementia itself, old age, living arrangements, poor adherence to drug therapy, polypharmacy, comorbidities, and drug interactions. According to Murphy et al.,¹⁰ higher PIM use can increase the risk of adverse drug events, serious adverse drug events, hospitalizations, and physician visits. Furthermore, PIMs are more common among older people residing in nursing homes, and this is related to the number of medications they use and the duration they stay in these facilities.¹⁸ Additionally, PIM risk increases in dementia patients compared to individuals without dementia.

According to the included studies in this systematic review, the most common drug classes linked to DRPs were psychotropic, antihypertensive, antihistamine, and antithrombotic drugs. It has been reported that dementia patients who prescribed psychotropic medicines have a higher rate of hospitalization. According to Zerah et al.,¹⁶ the rate of hospitalization increased by 0.36 per year. Moreover, Iatrogenic Alerts (IAs) were responsible for 22% of all hospitalizations, with psychotropic IAs accounting 80% of these.¹⁶ Based on a study, the risk of ADRs increases

Table 4

Risk Factors of DRPs identified in the included studies.

Risk factors	Zaidi et al., 2022 ³	Delgado et al., 2021 ²	Ferreira et al., 2020 ¹	Murphy et al., 2020 ¹⁰	Mullan et al., 2019 ⁶	François et al., 2018 ⁹	Renom-Guiteras et al., 2018 ²⁰	Zerah et al., 2017 ¹⁶
Old age		✓	✓	✓	✓	✓	✓	✓
Gender	✓	✓	✓					
Dementia	✓	✓						
Comorbidity		✓	✓		✓			✓
Polypharmacy	✓			✓				✓
Cognitive deficit	✓							
Low adherence to drug therapy	✓							
Long-term disease						✓		
Living situation							✓	
Risk factors	Sonnerstam et al., 2017 ¹³	Sonnerstam et al., 2016 ¹⁴	Gustafsson et al., 2016 ⁷	Skoldunger et al., 2015 ¹⁵	Kanagaratnam et al., 2014 ¹⁷	Chen et al., 2012 ¹⁸	Perri III et al., 2015 ¹⁹	
Old Age				✓				
Gender				✓				
Dementia				✓				
Comorbidity	✓			✓			✓	
Polypharmacy	✓		✓		✓	✓	✓	
Cognitive deficit	✓			✓				
Low adherence to drug therapy	✓							
Long-term disease								
Living situation		✓		✓		✓		
Drug interactions	✓				✓			
Low education level				✓				

considerably when patients take psychotropic drugs, ACEIs/ARBs, neuroleptics, antidepressants, or diuretics.¹⁷ Additionally, Chen et al.¹⁸ underlined that the most common PIMs identified in their study as defined by the STOPP criteria included medications such as benzodiazepines, antihistamines, and neuroleptics. According to Kanagaratnam et al.,¹⁷ antidepressants (23.3%), anxiolytics and hypnotics (21.7%), and neuroleptics (13.3%) were the medications most frequently implicated in drug-drug interactions.

Antidementia drugs such as donepezil, galantamine, rivastigmine and memantine were the most commonly associated with DRPs. According to Ferreira et al.,¹ 209 patients (83.6%) had at least one ADR, and rivastigmine was associated with the most ADRs per patient, followed by galantamine. Hospitalizations have also been documented as a result of galantamine and donepezil use, leading to further complications such as nausea and vomiting, abdominal discomfort, diarrhea and dehydration.¹

The findings of this study point to the necessity of expanding the role that pharmacists play in the evaluation of medication use among older people who suffer from dementia or other cognitive impairments. It is possible to achieve this goal by conducting medication reviews on patient group, focusing particularly on the elderly patients who are at advancing age and are taking multiple medications at the same time.

4.1. Limitations of the study

First, this study only included publications from eight countries. There was only one paper of Asian origin. There are no data from nations with low economic development. It is likely that these countries have a higher prevalence of DRPs due to medication errors. This suggests that our understanding of DRPs caused by medication misadventures, such as adverse drug reactions (ADRs) and use of inappropriate medications, among elderly patients with dementia or cognitive impairments is limited. Therefore, this systematic review's conclusion should be interpreted with caution and cannot be generalizable. In addition, studies included in this study reported, defined, interpreted, and classified data differently. Due to the exclusion of non-English articles, it is possible that critical information concerning the issues has been omitted.

5. Conclusion

This study shows that medication misadventures and the use of PIMs were common among older people with dementia. ADRs were the most prevalent medication misadventure, with antipsychotic medications such as antidepressants or anxiolytics being the most implicated substance. In addition, studies have demonstrated that the risk of hospitalizations and mortality is much higher in dementia patients than among those without dementia. PIMs were also associated with a higher risk of adverse drug events and hospitalizations. In the included studies, old age, polypharmacy, and comorbidities were the most common risk factors for DRPs. The results of this systematic review should be interpreted with caution and consideration due to the small number of studies included. Hence, this topic requires further comprehensive studies and analytical research for improved healthcare and better patients' quality of life.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sapharm.2023.02.015>.



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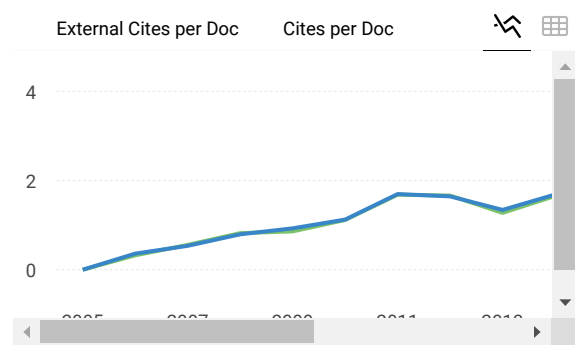
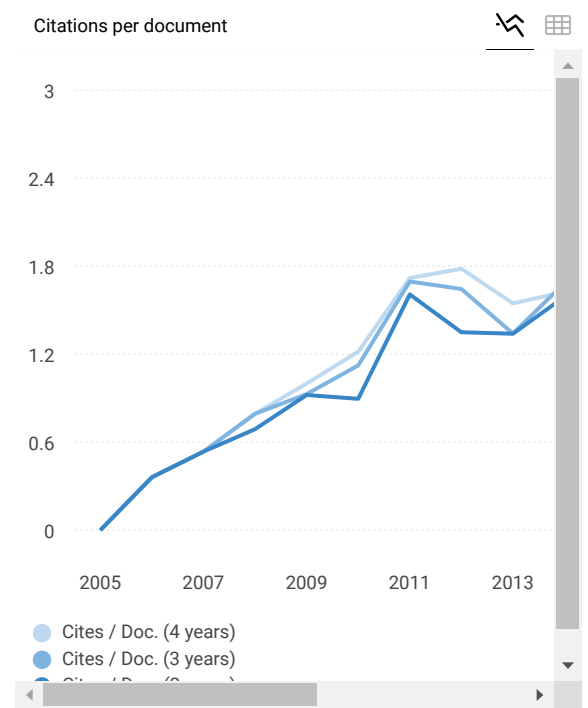
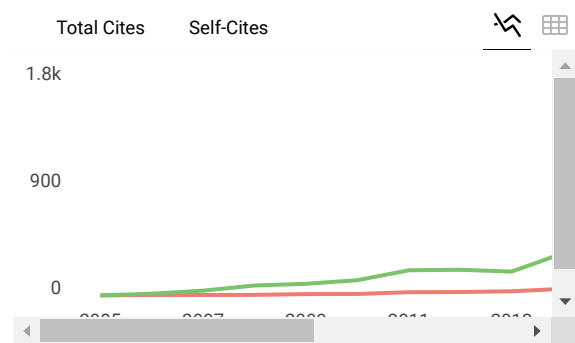
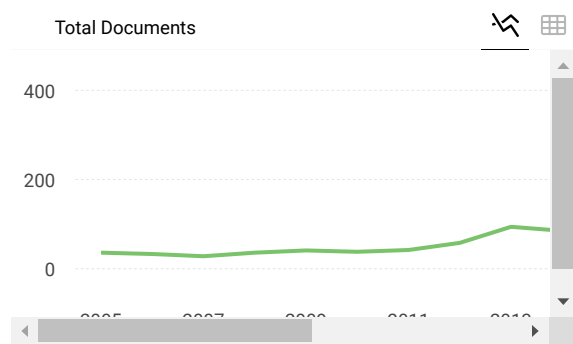
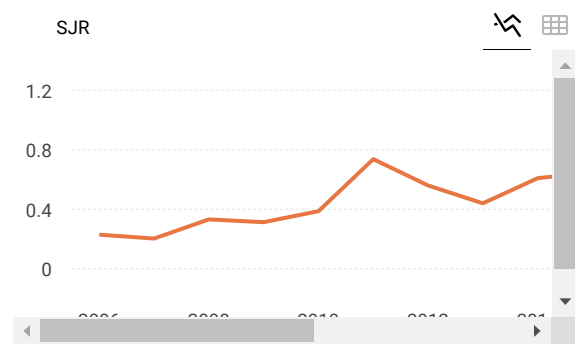
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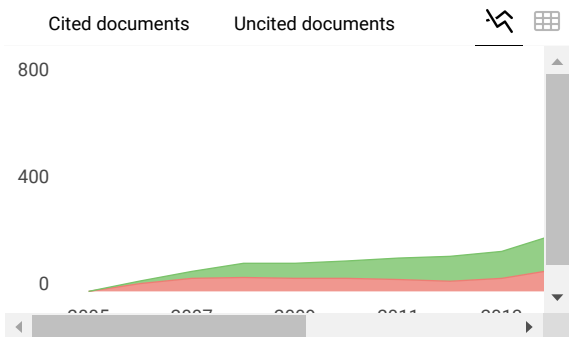
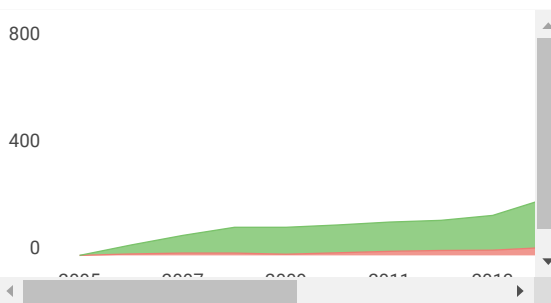
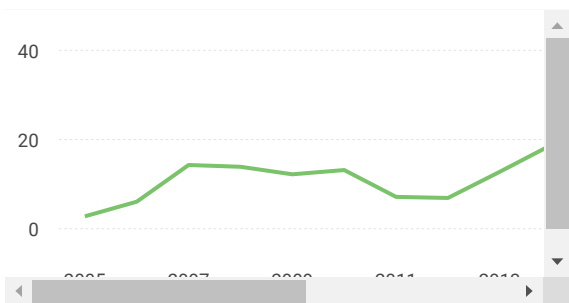
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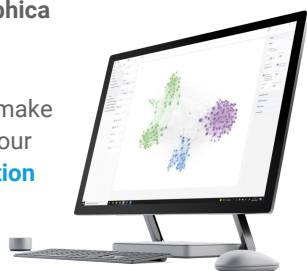
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