Brazilian Journal of Psychiatry
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Revista Brasileira de Psiquiatria
Brazilian Psychiatric Association
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Original Article

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http://doi.org/10.47626/1516-4446-2026-4811

Submitted: 14-Jan-2026

Accepted: 23-Oct-2026

This is a preliminary, unedited version of a manuscript that has been accepted for publication in the Brazilian Journal of Psychiatry. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form. The final version may present slight differences in relation to the present version.

Drugs associated with dementia-related adverse event reports: a real-world pharmacovigilance study

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Abstract

Objective: Numerous pharmacological agents have been implicated in elevating the risk of dementia onset. The present study employs a systematic methodology to examine drugs associated with dementia-related adverse event reports.
Methods: The present study extracted case of drugs associated with dementia-related adverse event reports from the FDA Adverse Event Reporting System (FAERS) covering the period from the first quarter of 2004 to the first quarter of 2025. The Reporting Odds Ratio (ROR) was employed as the principal metric for disproportionality analysis. Methodological robustness was validated through the application of the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi-item Gamma Poisson Shrinker (MGPS). Variable selection was facilitated using least absolute shrinkage and selection operator (LASSO) regression. Temporal relationships were examined via Time-to-Onset analysis. Clinical outcomes among patients with dementia-related adverse event reports were evaluated, including rates of mortality

and disability. Furthermore, the clinical indications for the implicated pharmaceuticals were systematically investigated.

Results: A total of 13 pharmaceutical agents were ultimately identified as exhibiting a potential association with dementia onset: Apixaban, Insulin glargine, Tafamidis, Insulin lispro, Sacubitril valsartan, Quetiapine, Zoledronic acid, Alendronic acid, Enzalutamide, Pregabalin, Rofecoxib, Dapagliflozin, and Valproic acid. The median time to dementia development following drug initiation was 73 days (interquartile range: 529 days), indicating that 75% of reported cases occurred within approximately 1.45 years post-exposure. Furthermore, the top five agents associated with the highest mortality rates in dementia-related adverse event reports associated with drug exposure were identified as Rofecoxib, Zoledronic acid, Tafamidis, Alendronic acid and Enzalutamide, while the top five agents linked to the highest disability rates included Valproic acid, Alendronic acid, Insulin glargine, Rofecoxib and Zoledronic acid. Finally, the primary clinical indications for these 13 drugs were analyzed. Clinicians should exercise heightened vigilance regarding the potential onset of dementia when utilizing these medications in patient care.

Conclusion: These findings contribute to early signal detection for pharmacologically associated dementia and may guide clinical medication management, yet they remain pharmacovigilance signals that require prospective confirmation.

Keywords: dementia; FAERS; pharmacovigilance; real-world study; LASSO

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Introduction

Dementia constitutes a clinically significant decline in cognitive function that substantially impairs an individual's capacity for independent daily living. It is more accurately characterized as a heterogeneous neurocognitive syndrome rather than a singular disease entity, arising from diverse etiologies including primary neurodegenerative disorders, cerebrovascular pathologies, neuropsychiatric conditions, and systemic medical illnesses. The syndrome frequently reflects multifactorial pathophysiology, with multiple co-existing diseases often contributing

to the clinical presentation in a single patient(1). Its manifestations comprise a constellation of progressive deficits, typically resulting from structural or functional damage to the brain, which emerge as deteriorating memory, executive function, and behavioral control, commonly accompanied by affective disturbances, linguistic impairments, and reduced motivation(2). Epidemiological studies indicate that dementia affects up to 7% of adults aged 65 years and older globally, with prevalence rates rising to 8–10% in developed nations—a variation largely attributable to extended life expectancies and aging demographics(3). Established risk factors include advanced age, genetic predisposition, and systemic vascular conditions(4). As a progressive and currently incurable disorder, advanced dementia follows a terminal trajectory marked by severe and irreversible disability; in the final year of life, affected individuals typically exhibit profound mnestic disturbances including inability to recognize family members, marked expressive and receptive aphasia, loss of independent ambulation, complete functional dependence, and both urinary and fecal incontinence(5).

Pharmacological agents are increasingly recognized as a significant etiological factor in the development of dementia. Medications can impair cognitive function through diverse mechanisms, including indirect metabolic disturbances such as drug-induced hypoglycemia, modulation of immunological factors within the central nervous system, and disruption of synaptic transmission. Among the most commonly implicated drug classes are benzodiazepines, antihypertensive agents, and compounds with anticholinergic properties, each of which is associated with distinct profiles of neuropsychological deficits(6). Furthermore, the use of antidepressant medications has been epidemiologically linked to an elevated risk of dementia onset(7). A broad spectrum of both licit and illicit substances has the potential to alter mental status and compromise cognitive faculties, thereby contributing to an increased vulnerability to dementia(8). As dementia profoundly diminishes patients' quality of life and complicates clinical management, it also exacts a substantial societal burden in terms of healthcare costs, caregiver strain, and associated morbidity and mortality. Consequently, the identification of modifiable risk factors—including iatrogenic contributors—has emerged as a

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critical research priority. Investigating the role of medication-induced cognitive decline is thus of paramount importance for the development of effective dementia prevention strategies.

The FDA Adverse Event Reporting System (FAERS) is a large-scale spontaneous surveillance database that aggregates adverse event reports for pharmaceutical and biological products, submitted by healthcare professionals, manufacturers, and patients or consumers. Recognized as one of the most comprehensive pharmacovigilance databases globally, FAERS supports the identification of potential, new, or previously overlooked drug safety signals through systematic examination of its extensive report collection. Over recent years, this resource has been extensively applied in pharmacoepidemiological research to detect drug-induced risks for a range of diseases and adverse effects(9, 10). In this study, we employ robust analytical approaches to extract, assess, and rank medications most strongly associated with dementia-related adverse events reports from the FAERS database. The findings are expected to provide critical evidence for developing rational pharmacotherapeutic strategies, potentially decreasing the incidence of dementia-related adverse event reports. Accordingly, this research has considerable public health relevance and advances primary prevention initiatives designed to mitigate the growing burden of dementia. The overall methodological approach and sequential analytical steps are illustrated in **Figure 1**.

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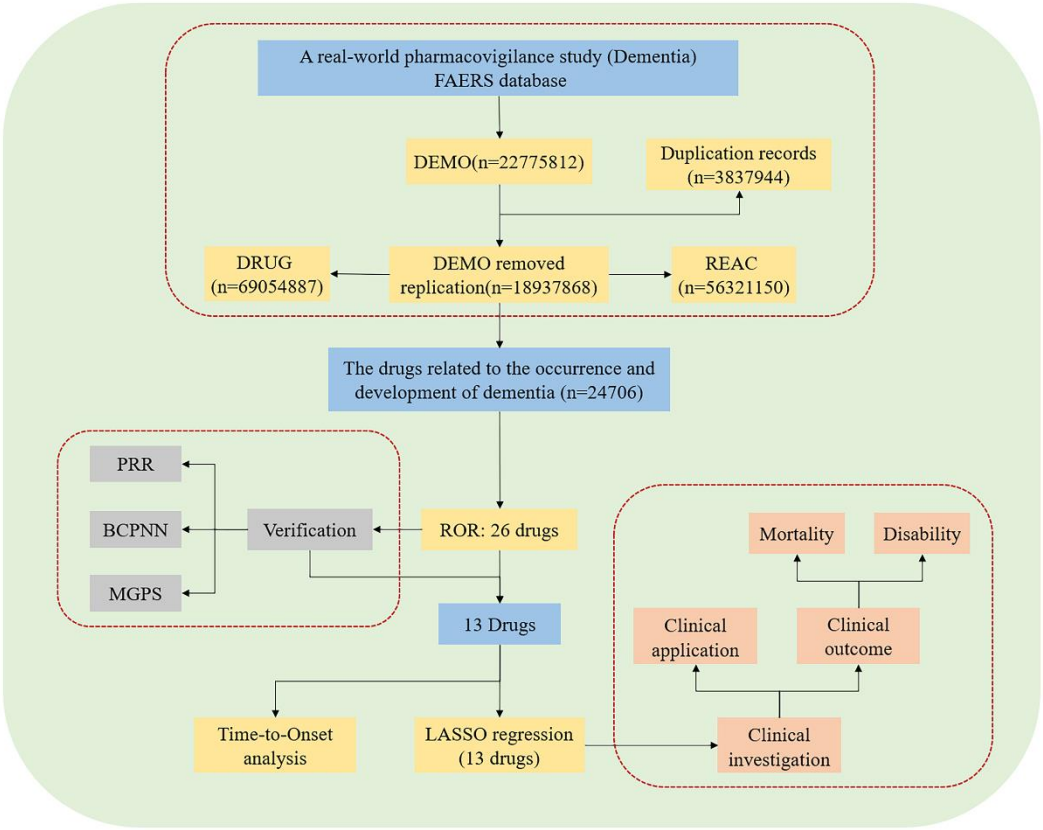


Figure 1: The flowchart of this study.

Materials and Methods

Data acquisition and deduplication

Data for this study were extracted from the FAERS database, covering the period from the first quarter of 2004 to the first quarter of 2025. Each case submission encompassed seven standardized data segments: DEMO (demographic and administrative information, including unique report identifiers), REAC (adverse events encoded using MedDRA terminology), DRUG (pharmacologic agents linked to reported events), OUTC (clinical outcomes of the events), RPSR (sources of the reports), THER (temporal data regarding drug therapy), and INDI (medical indications encoded in MedDRA). In accordance with FDA guidelines, a systematic deduplication procedure was applied: for entries sharing identical case identifiers, the most recent submission (based on the fda_dt field) was retained; among entries with identical case identifier and fda_dt values, the record possessing the highest primary ID was selected. Adverse events were

categorized according to MedDRA preferred terms (PT), with dementia specified as the outcome of interest. Drug-event relationships were classified based on therapeutic role (including primary suspect, secondary suspect, concomitant, or interacting); only drugs designated as primary suspects were included in subsequent exposure analyses.

Pharmacovigilance analysis

This pharmacovigilance investigation utilized disproportionality analysis to evaluate associations between drugs and adverse events, employing four quantitative signal detection techniques. The Reporting Odds Ratio (ROR) served as the primary measure, supported by the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi-item Gamma Poisson Shrinker (MGPS) as confirmatory methodologies(11, 12). Initial screening of potential medications was conducted using the ROR method, applying the following criteria: a lower limit of the 95% confidence interval (CI) for ROR > 1, a count of reported cases (a) > 100, and P-adjust < 0.01. Subsequently, compounds identified through this screening process were subjected to validation via three additional methods: PRR (the lower limit of the 95% CI > 1), BCPNN (IC025 > 0), and MGPS (EBGM05 > 2). Only those pharmacological agents satisfying all validation criteria were advanced to further analytical stages.

LASSO regression analysis

In order to identify predictive variables and develop a parsimonious predictive model, this investigation initially applied least absolute shrinkage and selection operator (LASSO) regression for variable selection. All pharmacological agents identified in prior analytical stages were incorporated into the LASSO regression model, wherein dementia was specified as the dependent variable. The optimal regularization parameter λ was ascertained via 10-fold cross-validation. The model corresponding to the λ value associated with minimal cross-validation error (lambda.min) was selected, retaining only variables demonstrating non-zero coefficients for further analysis. This approach facilitated both variable selection

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and model complexity reduction, thereby mitigating the risk of overfitting while improving the overall interpretability of the final model.

Time-to-Onset analysis

A systematic Time-to-Onset analysis was performed to assess the temporal relationship between pharmacotherapeutic interventions and the emergence of dementia. The Time-to-Onset interval was defined as the period from treatment initiation (START_DT) to the onset of the adverse event (EVENT_DT), thereby clarifying the chronological progression from drug exposure to dementia development.

Outcomes of patients

To evaluate the clinical outcomes of dementia-related adverse event reports associated with drug exposure identified within the LASSO regression model, mortality and disability rates among affected patients were quantified. This analytical approach serves to deepen the understanding of the potential relationship between pharmacological exposure and dementia-related morbidity and mortality.

Clinical application

In order to investigate the clinical disease associations pertinent to dementia-related adverse event reports associated with drug exposure, the therapeutic indications of medications associated with an elevated risk of dementia were systematically compiled. This analysis seeks to further elucidate which clinical conditions, when treated with these pharmacological agents, may confer an increased risk of dementia. The findings thereby contribute to the refinement of clinical disease management strategies, optimization of drug utilization, and enhanced prevention and treatment of associated complications.

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Statistical analysis

To delineate the clinical characteristics of patients implicated in reports of dementia-related adverse event reports associated with drug exposure, a comprehensive descriptive statistical analysis was undertaken. All data processing and statistical computations in the present study were performed utilizing R statistical software (version 4.5.0), with a pre-established significance threshold of P-adjust < 0.01 applied to all inferential statistical evaluations.

Results

Data acquisition results

A systematic analysis of the FAERS database, spanning from the first quarter of 2004 to the first quarter of 2025, identified 24,706 documented cases pertaining to dementia-related adverse event reports associated with drug exposure onset and progression. This comprehensive pharmacovigilance repository establishes a substantiative evidentiary basis for investigating potential associations between specific pharmacological interventions and dementia pathogenesis.

Baseline characteristics of dementia

The international pharmacovigilance analysis incorporated drugs associated with dementia-related adverse event reports from 78 countries. The United States contributed the largest proportion of cases, followed, in descending order of frequency, by Japan, Canada, the United Kingdom, and Germany **(Figure 2A)**. Temporal assessment revealed a gradual increase in reporting rates from 2004 through 2024. As only data from the first quarter of 2025 were available, the annual reporting rate for 2025 was projected based on existing trends and is anticipated to exceed that of 2024 **(Figure 2B)**. Analysis of reporter distribution by gender indicated that females accounted for 51.34% of reports, males for 40.86%, with the remaining 7.80% missing gender information. Age-stratified analysis demonstrated the highest incidence of dementia-related adverse event reports associated with drug exposure among elderly individuals (aged 65-85 years), constituting 36.38% of cases, followed by the oldest group (aged 85 and above, accounting for 9.74%).

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The adult population (aged 18-65) accounts for 8.69%, while the number of cases in children (under 18 years old) is relatively small (0.92%). Weight distribution analysis, excluding records with missing data, indicated a predominance of individuals within the 50-100 kg range (15.01%), with lower proportions observed among underweight (<50 kg; 2.21%) and obese (>100 kg; 1.46%) populations. Assessment of clinical outcomes categorized cases as follows: death (13.01%), hospitalization (22.23%), life-threatening events (1.63%), disability (1.99%), congenital anomaly (0.01%), with the majority classified as "other" outcomes (61.05%) **(Figure 3)**.

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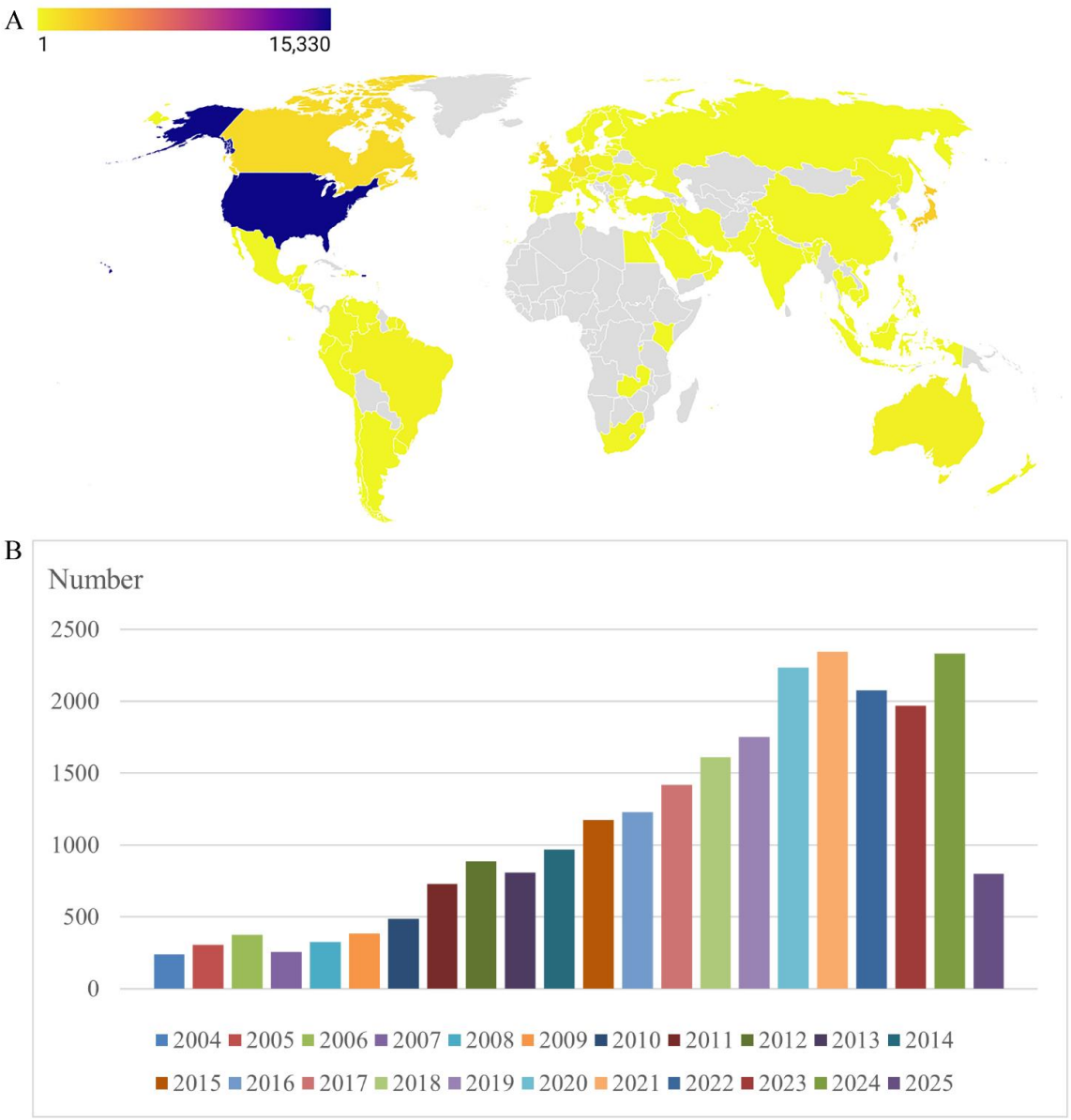


Figure 2: The global and chronological distribution of drugs associated with dementia-related adverse event reports. A. Illustrates the spatial variation in reporting frequencies across nations. B. Depicts the temporal trends in the incidence and documentation of dementia-related adverse event reports associated with drug exposure between 2004 and 2025.

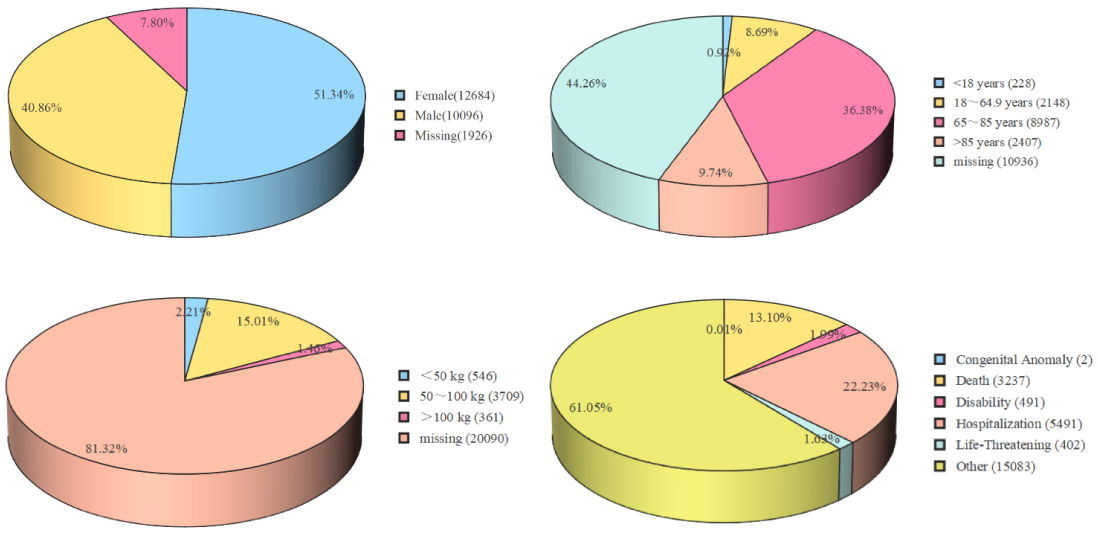


Figure 3: Comprehensive demographic and clinical characteristics of drugs associated with dementia-related adverse event reports, encompassing gender distribution, age stratification, weight profiles, and patient outcomes.

Pharmacovigilance analysis

Employing disproportionality analysis based on the ROR method, 26 pharmaceutical agents were initially identified as potentially linked to dementia-related adverse event reports **(Figure 4)**. These candidate agents subsequently underwent rigorous pharmacovigilance validation through three complementary disproportionality techniques: PRR, BCPNN, and MGPS. This multi-methodological validation process confirmed statistically significant associations for 13 drugs with dementia-related adverse event reports associated with drug exposure, namely: Apixaban, Insulin glargine, Sacubitril valsartan, Insulin lispro, Quetiapine, Pregabalin, Zoledronic acid, Enzalutamide, Alendronic acid, Rofecoxib, Valproic acid, Dapagliflozin and Tafamidis **(Table 1)**.

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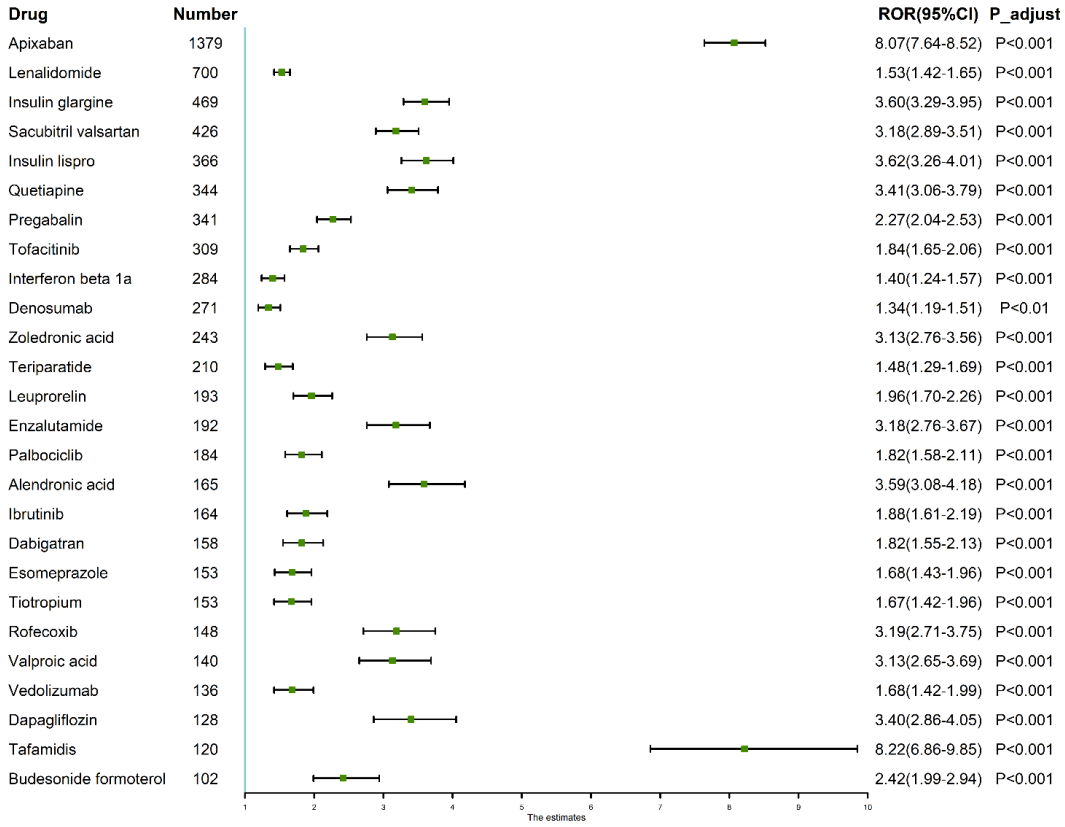


Figure 4: Utilizing the ROR methodology, 26 drugs were identified as exhibiting a potential association with dementia-related adverse event reports.

Table 1 The 13 drugs associated with dementia-related adverse event reports

		PRR	BCPNN	MGPS
Drugs	**Number**	**PRR(χ^2)**	**IC(IC025)**	**EBGM(EBGM05)**
Apixaban	1379	8.00 (7980.73)	2.93 (2.84)	7.61 (7.20)
Insulin glargine	469	3.59 (860.62)	1.82 (1.68)	3.54 (3.23)
Sacubitril valsartan	426	3.18 (624.84)	1.65 (1.50)	3.14 (2.85)
Insulin lispro	366	3.61 (680.69)	1.84 (1.67)	3.57 (3.22)
Quetiapine	344	3.40 (573.99)	1.75 (1.58)	3.36 (3.02)
Pregabalin	341	2.27 (239.41)	1.17 (1.01)	2.25 (2.02)
Zoledronic acid	243	3.13 (348.27)	1.63 (1.44)	3.10 (2.74)
Enzalutamide	192	3.17 (283.95)	1.66 (1.43)	3.16 (2.74)
Alendronic acid	165	3.58 (304.51)	1.83 (1.58)	3.56 (3.05)
Rofecoxib	148	3.18 (220.07)	1.66 (1.40)	3.17 (2.69)
Valproic acid	140	3.12 (200.59)	1.64 (1.37)	3.11 (2.63)
Dapagliflozin	128	3.39 (214.80)	1.76 (1.47)	3.38 (2.84)
Tafamidis	120	8.14 (749.42)	3.02 (2.67)	8.11 (6.77)

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LASSO regression analysis

Based on the foregoing validation outcomes, LASSO regression models were constructed for the 13 candidate pharmaceuticals. The resulting coefficients for all agents were non-zero: Apixaban (-0.003), Insulin glargine (-0.003), Tafamidis (-0.004), Insulin lispro (-0.003), Sacubitril valsartan (-0.004), Quetiapine (-0.002), Zoledronic acid (0.001), Alendronic acid (0.035), Enzalutamide (-0.003), Pregabalin (-0.002), Rofecoxib (0.004), Dapagliflozin (-0.004), and Valproic acid (-0.004). The model corresponding to the minimum cross-validation error (λ.min) retained all 13 drugs **(Figure 5A)**. Consequently, these findings further support the association between these drugs and dementia-related adverse event reports.

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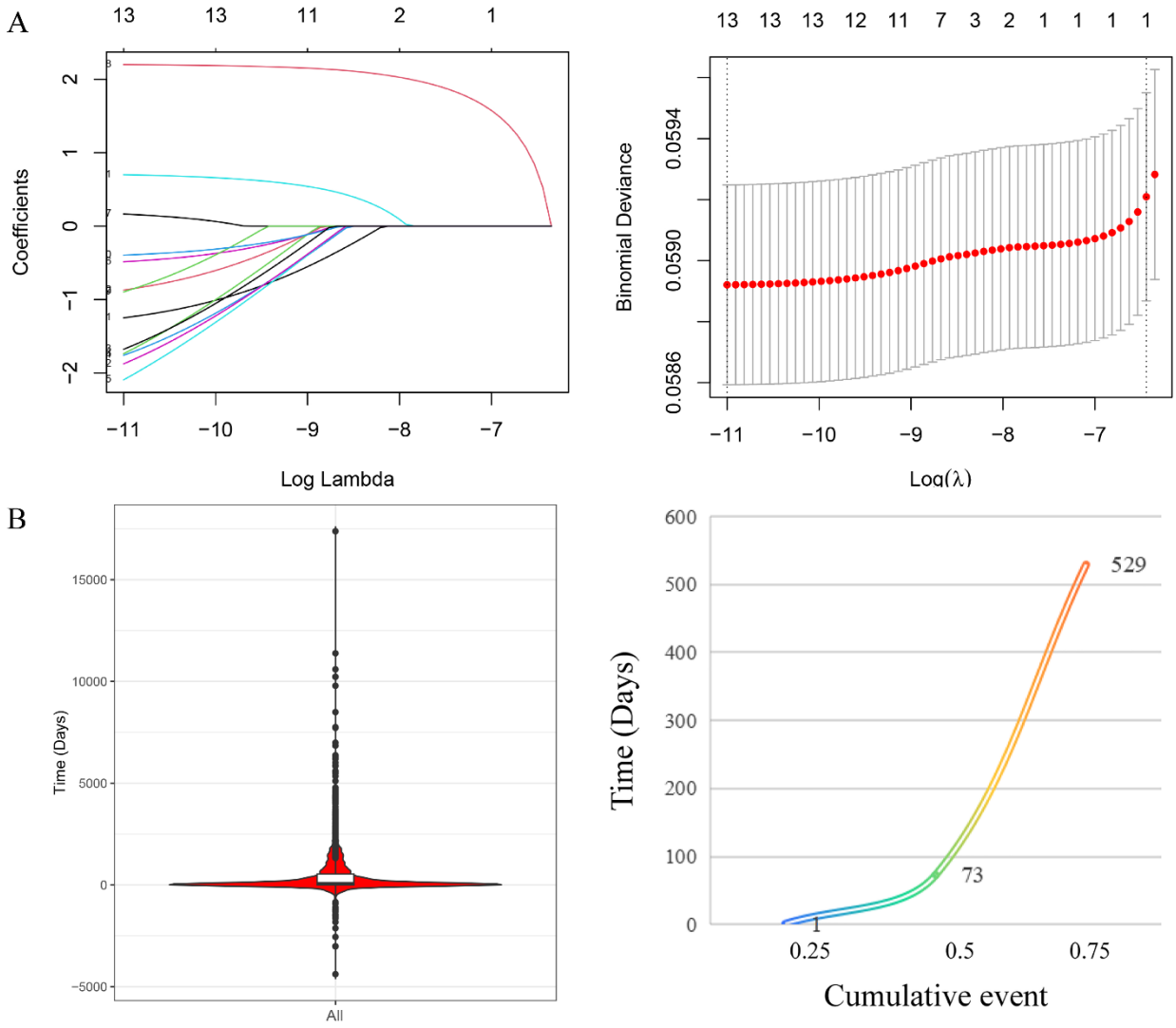


Figure 5: The drugs associated with dementia-related adverse event reports. A. LASSO regression analysis identified 13 potentially drugs associated with dementia-related adverse event reports. B. Temporal interval between drug administration and the onset of dementia-related adverse event reports.

Time-to-Onset analysis

To characterize the temporal association between pharmacological exposure and the emergence of dementia, a comprehensive latency analysis was performed. The median time interval from drug initiation to the development of dementia was 73 days (interquartile range: 529 days), indicating that 75% of reported cases occurred within approximately 1.45 years following initial medication exposure **(Figure 5B)**.

Outcomes of patients

An analysis of mortality and disability rates among patients diagnosed with dementia-related adverse event reports associated with drug exposure was conducted. Among the 13 pharmaceuticals associated with this condition, the five agents exhibiting the highest mortality rates were identified as Rofecoxib (32.43%), Zoledronic acid (27.57%), Tafamidis (25.00%), Alendronic acid (20.00%) and Enzalutamide (17.71%). Concurrently, the five medications associated with the highest disability rates were Valproic acid (10.00%), Alendronic acid (5.45%), Insulin glargine (3.41%), Rofecoxib (2.70%) and Zoledronic acid (1.23%) **(Figure 6)**.

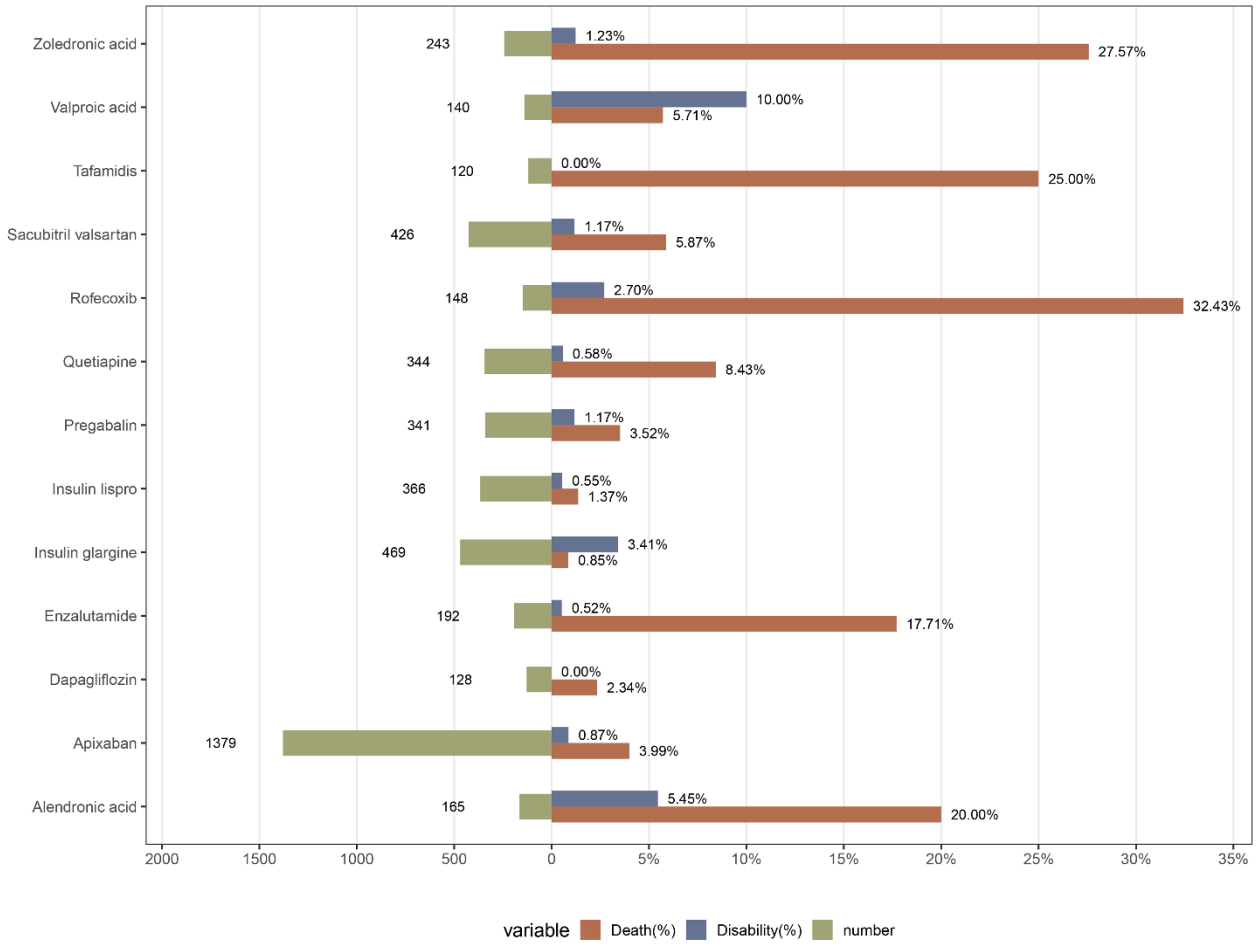


Figure 6: An evaluation of mortality and disability outcomes among patients diagnosed with dementia-related adverse event reports associated with drug exposure.

Clinical application

A statistical analysis was conducted to characterize the clinical applications of the 13 drugs associated with dementia-related adverse event reports associated with drug exposure. Pregabalin is chiefly employed for a range of conditions including restless legs syndrome, gait disturbance, herpes zoster, epilepsy, paraesthesia, dystonia, scoliosis, spinal osteoarthritis, anxiety disorder, rheumatoid arthritis, decubitus ulcer, nerve injury, pain, carpal tunnel syndrome, abnormal blood glucose, lumbosacral radiculopathy, lumbar disc herniation, and intervertebral disc degeneration. Insulin glargine and Insulin lispro are primarily indicated for the treatment of diabetes mellitus. Enzalutamide is chiefly employed in cases of prostate cancer, bone cancer, and prostatic disorders. Dapagliflozin is mainly administered for renal disorders. Apixaban finds its main application in arterial occlusive diseases, cardiac disorders, thrombosis, confusional states, and peripheral swelling. Alendronic acid is largely indicated for conditions including decreased bone density, arthritis, hormone replacement therapy, post-menopausal states, and hip fractures **(Figure 7)**.

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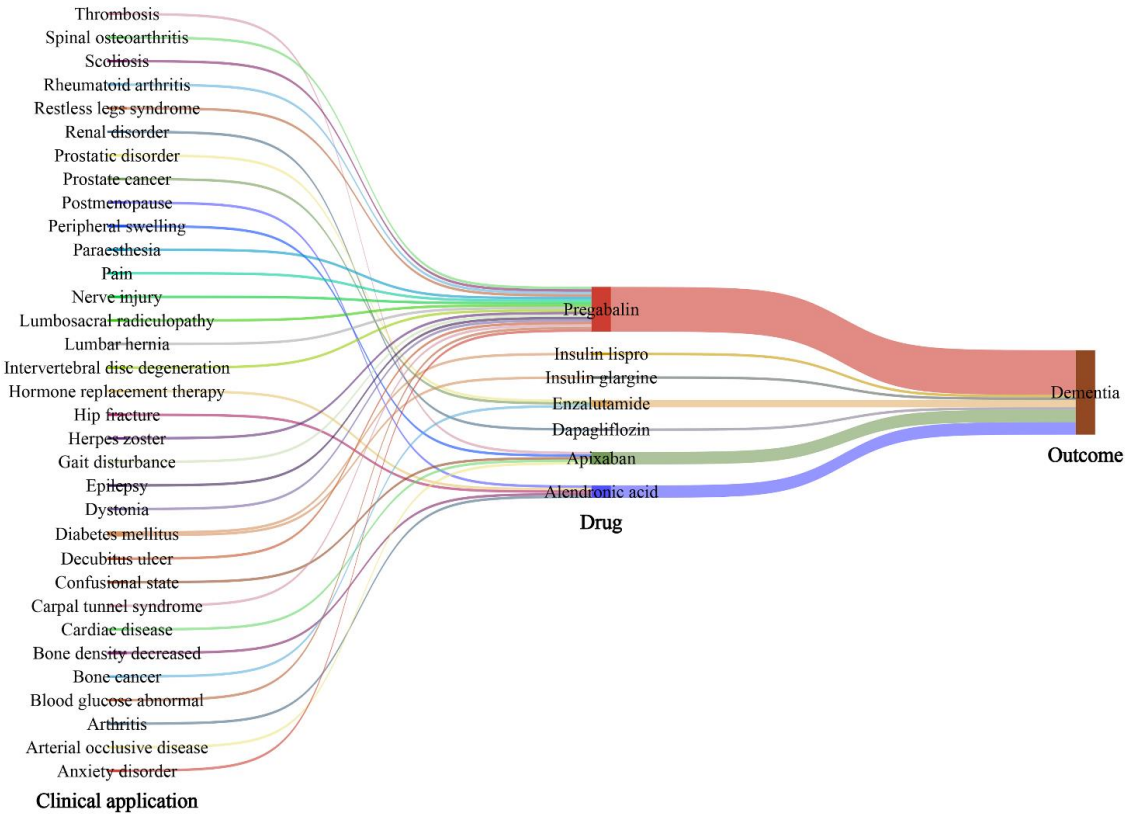


Figure 7: Clinical application of the drugs associated with dementia-related adverse event reports, including Pregabalin, Insulin lispro, Insulin glargine, Enzalutamide, Dapagliflozin, Apixaban and Alendronic acid.

Zoledronic acid is primarily indicated for the clinical management of malignancy-related hypercalcemia, fractures, osteoporosis, plasma cell myeloma, prostate cancer, and breast cancer. Valproic acid is predominantly utilized in the treatment of persistent depressive disorder, epilepsy, hyperammonemic encephalopathy, edema, and manic episodes. Tafamidis is chiefly employed for conditions including congestive heart failure, amyloidosis, pulmonary disorders, dyspnea, cerebral injury, tachycardia, and bradycardia. Sacubitril valsartan is mainly applied in cases of hypertension, chronic cardiac failure, and cerebral hypoxia. Rofecoxib is frequently prescribed for multiple sclerosis, osteoarthritis, ankylosing spondylitis, pain management, gout, inflammatory conditions, and analgesic therapy. Quetiapine is predominantly utilized in the treatment of schizophrenia, craniocerebral injury, affective disorders, insomnia, sleep disturbances, depression, and sedation. **(Figure 8)**.

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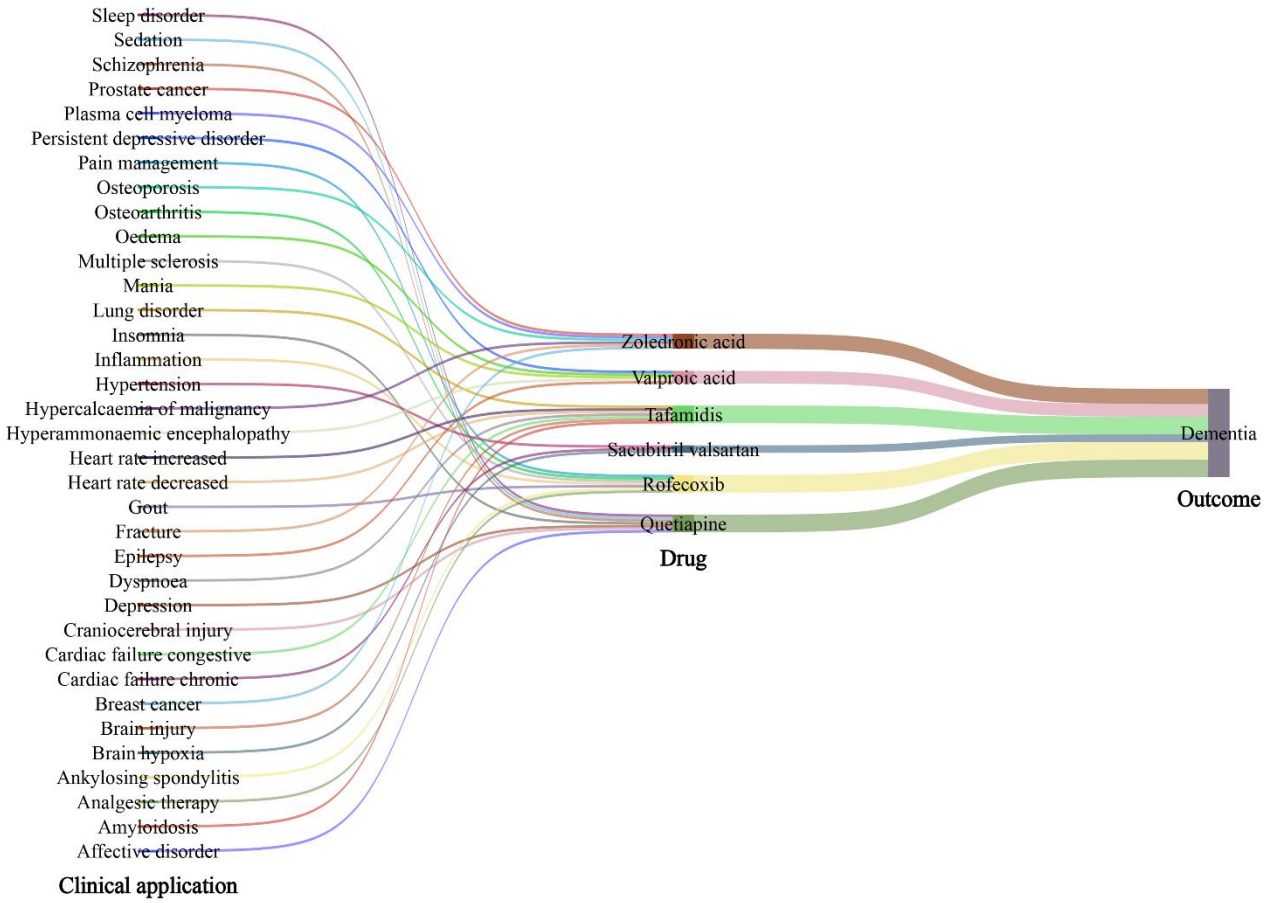


Figure 8: Clinical application of the drugs associated with dementia-related adverse event reports, including Zoledronic acid, Valproic acid, Tafamidis, Sacubitril valsartan, Rofecoxib and Quetiapine.

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Discussion

This comprehensive pharmacovigilance study was designed to systematically identify and evaluate drugs associated with dementia-related adverse event reports. Through rigorous disproportionality analysis and subsequent validation, 13 drugs were identified as possessing a potential association with dementia onset: Apixaban, Insulin glargine, Tafamidis, Insulin lispro, Sacubitril valsartan, Quetiapine, Zoledronic acid, Alendronic acid, Enzalutamide, Pregabalin, Rofecoxib, Dapagliflozin, and Valproic acid. The median latency period from drug initiation to dementia development was 73 days (interquartile range: 529 days), indicating that 75% of reported cases occurred within approximately 1.45 years following

treatment initiation. Furthermore, the agents associated with the highest mortality rates in drugs associated with dementia-related adverse event reports were Rofecoxib, Zoledronic acid, Tafamidis, Alendronic acid and Enzalutamide, while those linked to the highest disability rates included Valproic acid, Alendronic acid, Insulin glargine, Rofecoxib and Zoledronic acid. The primary clinical indications for these medications were also analyzed; for instance, Alendronic acid is largely indicated for conditions including decreased bone density, arthritis, hormone replacement therapy, post-menopausal states, and hip fractures. These findings underscore the importance of heightened clinical vigilance regarding potential cognitive adverse effects when utilizing these therapeutic agents in patient care.

Previous clinical observations have documented the deterioration of behavioral and psychological symptoms of dementia in two patients following the initiation of direct oral anticoagulants from the factor Xa inhibitor class, specifically Apixaban and rivaroxaban. Notably, a marked symptomatic improvement occurred within two weeks after transitioning to alternative anticoagulant regimens(13). Of particular mechanistic relevance, rivaroxaban shares structural homology with the antibiotic linezolid, which has previously been associated with mitochondrial toxicity(14). Supporting this potential mechanism, an in vitro investigation utilizing rat kidney mitochondria demonstrated evidence of mitochondrial swelling and collapse of membrane potential following exposure to low concentrations of Rivaroxaban(15). These findings are consistent with a broader scientific consensus that implicates impaired cerebral mitochondrial function not only as correlative but potentially contributory to the etiology of neuropsychiatric symptoms and disorders(16). Sacubitril valsartan, as the first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), has received regulatory approval in both the United States and European Union for the management of heart failure (HF), with particular emphasis on hypertensive heart failure (HHF). While sacubitril-mediated inhibition of neprilysin confers beneficial cardiovascular effects, it also elevates concerns regarding potential amyloid-beta accumulation and a consequent increased risk of Alzheimer’s disease(17). Thus, despite its cardioprotective efficacy, Sacubitril valsartan may concurrently contribute to memory impairment,

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cognitive dysfunction, or exacerbation of Alzheimer's disease(18). Alendronic acid is widely employed in clinical practice for the treatment of osteoporosis(19). Previous epidemiological studies have further identified a significant association between higher medication compliance with Alendronic acid and an increased incidence of dementia(20).

A clinically nuanced interpretation of the signals for Quetiapine, Pregabalin, and Valproic acid must first recognize that these medications are frequently prescribed to patient populations with pre-existing neuropsychiatric symptoms, behavioral disturbances, mood disorders, sleep disturbances, or chronic pain. These clinical features are not merely incidental; they are themselves robustly associated with cognitive dysfunction and an elevated long-term risk of dementia, independent of any drug exposure. Quetiapine, which possesses relatively low anticholinergic activity and thus is less prone to exacerbating cognitive deficits, is frequently prescribed for behavioral and psychological symptoms of dementia (BPSD). Nevertheless, a case study reported absence seizures in an elderly patient receiving quetiapine for BPSD(21). Pregabalin has been proposed as a well-tolerated option for managing anxiety in dementia with Lewy bodies(22), and a randomized, double-blind, placebo-controlled trial confirmed that 300 mg/day of pregabalin significantly reduced the frequency and severity of behavioral symptoms in Alzheimer's disease(23). However, a population-based study from the National Health Insurance Research Database found that gabapentin or pregabalin use was associated with increased dementia risk, advocating judicious prescribing in at-risk groups(24). Valproic acid exhibits modest efficacy as monotherapy in dementia, with its main utility possibly as an adjunctive agent for agitation(25); insufficient evidence supports its role in improving cognitive or psychiatric symptoms(26). Of note, valproic acid use in bipolar disorder has been linked to a 73–95% greater dementia risk(27). In clinical practice, these agents are often prescribed off-label or used in elderly patients with multimorbidity, where distinguishing the contribution of the drug from that of the underlying condition is particularly challenging. The overlap between indications—such as using quetiapine for sleep or agitation, pregabalin for pain or anxiety, and valproic acid

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for mood stabilization or seizure control—further complicates causal attribution, as the same drug may be given for diverse symptoms that themselves carry varying degrees of cognitive risk.

Preclinical investigations have demonstrated synergistic neuroprotective effects between Rofecoxib and statins in rodent models of malonic acid-induced Huntington's disease-like symptoms and associated cognitive deficits(28). However, these experimental observations have not translated into clinical benefit; a randomized, double-blind trial found no evidence that Rofecoxib delays Alzheimer's disease diagnosis, and the cumulative lack of efficacy across earlier studies indicates that COX-2 inhibition is unlikely to represent a viable therapeutic approach for Alzheimer's(29). Furthermore, robust evidence is lacking to support low-dose aspirin or NSAIDs—including celecoxib, Rofecoxib, or naproxen—for dementia prevention, with some data even pointing to possible harm(30). With respect to Dapagliflozin, although neuromodulatory properties have been suggested in the Alzheimer's context(31), meta-analyses of randomized controlled trials have not demonstrated a significant reduction in dementia or Parkinson's disease risk, reinforcing conclusions from prior meta-analyses(32). Increasing evidence implicates impaired cerebral insulin signaling as a key pathophysiological contributor to Alzheimer's disease, with hypoinsulinemia predominating in type 1 diabetes and insulin resistance coupled with reduced secretion in type 2 diabetes(33). Insulin glargine exhibits more robust central nervous system effects than albumin-sensitive analogs such as insulin detemir or insulin degludec(34). Both basal Insulin glargine 100 U/mL and prandial Insulin lispro have long been used in clinical practice, supported by a substantial evidence base confirming their safety and efficacy in basal-bolus and basal-plus regimens for type 1 and type 2 diabetes(35). Preclinical and phase I/II data indicate that Insulin lispro provides non-inferior glycemic control relative to Insulin glargine, may confer weight reduction, and displays low mitogenic potential with preferential hepatic glucose regulation; nevertheless, it has been associated with transaminase elevations and lipid profile changes(36). In V30M hereditary TTR amyloidosis patients receiving oral Tafamidis (20 mg Tafamidis meglumine daily), the drug was detected in both

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CSF and vitreous humor, with a CSF TTR tetramer-to-Tafamidis stoichiometry of approximately 2:1, confirming moderate kinetic stabilization and demonstrating that Tafamidis penetrates both the blood–CSF and blood–ocular barriers(37). Falls affect 47–90% of individuals with dementia annually and represent a leading cause of hospitalization in this population(38, 39). A narrative systematic review suggested that annual Zoledronic acid administration might reduce recurrent falls, yet considerable between-study heterogeneity limits the strength and generalizability of this conclusion(40). Finally, a retrospective cohort study identified a history of seizures—especially with prior anticonvulsant use—as a significant predictor of subsequent seizures in metastatic castration-resistant prostate cancer patients, providing clinically relevant insights for those receiving androgen receptor antagonists such as Enzalutamide(41).

Among the 13 pharmacological agents identified in this study, several—including Apixaban, Sacubitril valsartan, and Alendronic acid—have been previously associated with an elevated risk of dementia, a finding that corroborates the reliability and validity of the present results. For other agents, such as Quetiapine, Pregabalin, Rofecoxib, Dapagliflozin, and Valproic acid, the evidence regarding their influence on dementia onset and progression remains inconclusive, reflecting ongoing ambiguity in the current literature. Furthermore, the effects of several additional drugs—namely Insulin glargine, Insulin lispro, Tafamidis, Zoledronic acid, and Enzalutamide—on dementia have not yet been clearly established, highlighting a salient gap in existing pharmacovigilance knowledge. It is also imperative to explicitly address the issue of confounding by indication, as many of these therapies are prescribed for underlying conditions that themselves are well-established risk factors for dementia. Moreover, the extensive polypharmacy typical of these comorbid conditions further complicates causal inference, as the combined effects of multiple concurrent medications cannot be fully disentangled in a spontaneous reporting database. The associations identified herein may bear substantial implications for dementia prevention strategies. Consequently, while our findings provide valuable pharmacovigilance signals, they must be interpreted with careful consideration of these indication-related

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confounders; clinical application of these agents, particularly for the indications discussed, warrants heightened vigilance and more stringent regulatory oversight, ideally guided by future prospective studies designed to differentiate drug-specific effects from the cognitive burden imposed by the underlying disease states.

Polypharmacy represents a major interpretive challenge that merits careful consideration in this study. Older adults—the primary population at risk for dementia—frequently receive multiple pharmacotherapies to manage coexisting conditions, including cardiovascular disorders, diabetes, psychiatric illness, pain syndromes, and osteoporosis. Under such circumstances, the cognitive events documented in spontaneous reports may not signify a direct effect of any one agent, but rather the combined neurocognitive impact of several medications used concurrently, each possessing its own central nervous system profile. The potential for drug–drug interactions compounds this complexity; for instance, the simultaneous prescription of anticholinergic drugs, sedative-hypnotics, and psychotropic medications—a common pattern in geriatric care—may exert additive or synergistic adverse effects on cognition that resist clear attribution to a single substance. In addition, the extensive medical complexity of these patients, typified by multimorbidity, frailty, frequent hospitalizations, and age-associated alterations in drug metabolism and clearance, further hinders the isolation of drug-specific effects from dementia-related reporting. Given that the FAERS database lacks detailed medication records and comprehensive clinical information, our analysis cannot adequately adjust for these polypharmacy-related confounders. Hence, the signals detected in this study should be interpreted as aggregate pharmacovigilance indicators that may arise from a convergence of multiple factors—drug actions, interactive pharmacological effects, and the inherent frailty of the patient cohort—rather than as definitive evidence of drug-specific causation. Future research that incorporates thorough medication reconciliation, validated comorbidity measures, and prospective cognitive follow-up will be essential to separate the contributions of individual agents from the broader polypharmacy environment in which they are prescribed.

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A further caveat pertains to the interpretation of the median time-to-onset observed in this study (73 days). Although this interval may appear relatively short, it should be interpreted with considerable circumspection, as the FAERS database does not provide sufficient clinical granularity to ascertain whether the reported events represent true incident dementia, acute delirium, transient dementia secondary to medication, or an exacerbation of pre-existing cognitive decline. This interval may represent delirium, acute confusional states, medication-related dementia, worsening of pre-existing impairment or coding ambiguity rather than true incident dementia. The onset date recorded in a spontaneous report often reflects the time when symptoms came to medical attention, rather than the biological initiation of a neurodegenerative process; consequently, the observed latency could be influenced by reporting practices, patient recall bias, or diagnostic coding ambiguity. Moreover, in elderly or multimorbid patients, the distinction between new-onset dementia and worsening of subclinical cognitive dysfunction is particularly challenging without baseline neurocognitive assessments, which are unavailable in this dataset. Therefore, the reported median onset should not be construed as a precise temporal window for drug-induced dementia, but rather as a rough pharmacovigilance signal that highlights the need for structured, prospective evaluations with standardized cognitive batteries and longitudinal follow-up to clarify the true temporal relationship and the nature of the cognitive events.

The present findings carry meaningful clinical implications that merit practical translation. Importantly, these results should not be interpreted as mandating blanket avoidance or withdrawal of any of the 13 drugs identified, as such an approach could deny patients substantial therapeutic benefits and potentially lead to adverse outcomes from undertreated underlying conditions. Instead, the signals detected should prompt heightened clinical vigilance and more systematic patient monitoring. For example, when initiating Apixaban, Sacubitril valsartan, or Insulin glargine in older adults—particularly those with cardiovascular or metabolic risk factors—clinicians should incorporate periodic cognitive screening and maintain a low threshold for detecting early memory changes or confusion. For psychiatric agents such as Quetiapine, Pregabalin, and Valproic acid, routine medication

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reconciliation and deprescribing reviews are advisable, especially with off-label use or in patients with multiple neuropsychiatric comorbidities; prescribing should aim for the lowest effective dose over the shortest necessary duration, with close monitoring for cognitive effects. In patients on Zoledronic acid or Alendronic acid for osteoporosis, fracture-prevention benefits must be weighed against potential cognitive risks, particularly in frail older adults with multiple fall-related risk factors. Similarly, for Enzalutamide in prostate cancer and for antidiabetic therapies, individualized risk-benefit discussions should account for baseline cognitive status, overall comorbidity burden, and treatment objectives. Multidisciplinary medication reviews—involving geriatricians, neurologists, and clinical pharmacists—are essential to systematically evaluate cognitive changes within the context of the patient's complete therapeutic regimen. Ultimately, decisions to continue, adjust, or discontinue therapy should be guided by comprehensive clinical assessment, availability of alternatives, and severity of the underlying condition. The overarching goal is not avoidance of these valuable agents, but their judicious use with proactive monitoring and ongoing risk-benefit reassessment, thereby optimizing patient safety while preserving essential clinical benefits. Future work should prioritize developing validated risk stratification tools that integrate both drug-specific and patient-specific factors to enable more precise, individualized prescribing in older and cognitively vulnerable populations.

Several limitations of the present work merit careful consideration. First, because the FAERS is a passive, spontaneously reported surveillance system, it is inherently affected by reporting biases and underreporting; adverse event may be preferentially or selectively reported, whereas many others go unrecorded, which introduces uncertainty in the completeness of the case series. Additionally, the database lacks reliable denominator data on the total number of patients exposed to each drug, thereby precluding any estimation of incidence rates or relative risks. Second, the individual case reports are not clinically adjudicated, meaning that the diagnostic accuracy and temporal plausibility of the reported events cannot be independently verified, and the quality of submitted information is heterogeneous. Third, the observational nature of the data presents notable challenges with

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respect to confounding by indication and reverse causality. Specifically, patients receiving a particular drug may already have underlying conditions or disease severities that predispose them to dementia-like symptoms, making it difficult to disentangle the drug effect from the effect of the illness itself. Conversely, reverse causality cannot be excluded, as early subclinical manifestations of dementia might have prompted drug prescription, rather than the drug causing the cognitive decline. Fourth, polymedication is common in this patient population, and the concurrent use of multiple agents—each with potential neurocognitive effects—complicates the attribution of the observed outcomes to any single compound; despite our efforts to adjust for available covariates, residual confounding arising from unmeasured or poorly recorded factors may persist. Taken together, these limitations underscore that our results should be regarded as generating pharmacovigilance signals worthy of further exploration, rather than as definitive evidence of causality. Well-designed prospective studies with rigorous exposure assessment, clinical validation, and adequate control for confounding are essential to corroborate the associations identified here.

Conclusion

This study employed a real-world pharmacovigilance approach to systematically investigate drugs associated with dementia-related adverse event reports. Through comprehensive disproportionality analysis and subsequent validation, a total of 13 pharmaceutical agents were identified as exhibiting potential statistical associations with dementia-related adverse event reports. These findings contribute to the early detection of potential medication-related cognitive signals and may serve as a useful reference for clinical awareness and drug safety monitoring; however, they should not be interpreted as establishing causal relationships. The observed associations warrant further investigation, and prospective studies with rigorous methodological designs are necessary to confirm these signals and to explore the underlying biological mechanisms. Clinicians are advised to consider these findings as part of a broader risk-benefit assessment

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when prescribing these agents to vulnerable populations, while recognizing the inherent limitations of spontaneous reporting data.

Ethics approval and consent to participate

The research utilized exclusively publicly available data from open-access databases. As such, this study did not involve direct human subject participation or collection of private health information, and therefore did not require institutional review board approval or informed consent procedures.

Consent for publication

All authors have thoroughly reviewed and approved the final version of the manuscript for publication. Each author has provided explicit consent for the manuscript's submission and agrees to its publication in its current form.

Availability of data and materials

The study utilized open-access data obtained from the public repositories: the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Competing interests

The authors of this article declare that they have no conflicts of interest to disclose.

Funding

This work was financially supported by the Shaanxi Province Natural Science Foundation Research Program (No. 2025JC-YBQN-1266).

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have

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agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Edited by: Tania Correa de Toledo Ferraz Alves

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