Med & Health June 2026; 21(6)(Suppl): 47-55 https://doi.org/10.17576/MH.2026.s2106.08

CASE REPORT

Geriatric Case Report Presenting an Alzheimer's Disease Patient with Polypharmacy Resulting in Significant Drug-Drug Interaction

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Received: 22 April 2025 / Accepted: 13 September 2025

ABSTRAK

Polifarmasi dalam kalangan pesakit warga emas sering membawa kepada situasi klinikal yang rumit, terutamanya apabila melibatkan interaksi ubat-ubatan yang signifikan dalam pesakit yang didiagnosis dengan penyakit Alzheimer (AD). Laporan ini membincangkan kes seorang lelaki berusia 80 tahun yang menghidap pelbagai komorbiditi termasuk hipertensi, diabetes mellitus jenis 2, kegagalan jantung kronik, osteoartritis dan hiperplasia prostat benign, yang hadir dengan kemerosotan kognitif progresif yang menunjukkan ciri-ciri AD. Penilaian awal menunjukkan gangguan ingatan, apraksia, afasia ekspresif ringan dan disfungsi eksekutif, serta atrofi kortikal umum dan kehilangan isipadu hippocampus yang ketara berdasarkan pengimejan resonans magnetik otak. Pesakit telah dimulakan dengan terapi simptomatik menggunakan donepezil, iaitu perencat asetilkolinesterase, yang membawa kepada interaksi ubat yang signifikan dengan beta-blocker jangka panjang yang diambil oleh pesakit, metoprolol, menyebabkan bradikardia simptomatik yang ditunjukkan melalui pening, keletihan, kekeliruan yang semakin teruk dan hampir pengsan. Oleh itu, metoprolol telah dihentikan, namun pesakit kemudiannya mengalami hipertensi yang tidak terkawal (150/95 mmHg). Bagi mengoptimumkan kawalan tekanan darah sambil mengurangkan beban ubat-ubatan, doktor yang merawat telah menggantikan tamsulosin dengan doxazosin, yang berjaya mengawal kedua-dua simptom hipertensi dan hiperplasia prostat benign. Selepas pelarasan ini, tekanan darah dan kadar nadi pesakit kembali normal dan simptom kognitif menjadi stabil. Kes ini menekankan kerumitan klinikal dalam pengurusan pesakit warga emas dengan pelbagai penyakit kronik dan polifarmasi. Ia juga menegaskan kepentingan pemantauan rapi dan pemilihan ubat secara strategik untuk mengelakkan interaksi ubat-ubatan, khususnya apabila menetapkan ubat penambah kognitif seperti donepezil. Pertimbangan teliti terhadap profil individu pesakit dan penilaian semula berterusan terhadap rejimen ubat adalah penting dalam meningkatkan hasil klinikal dan keselamatan pesakit.

Kata kunci: *Bradikardia; donepezil; hipertensi; interaksi ubat-ubatan; penyakit Alzheimer; polifarmasi*

ABSTRACT

Polypharmacy in elderly patients often leads to complicated clinical scenarios involving significant drug-drug interactions, particularly among individuals diagnosed with Alzheimer's disease (AD). This report describes the case of an 80-year-old male with multiple comorbidities, including hypertension, type 2

diabetes mellitus, chronic heart failure, osteoarthritis and benign prostatic hyperplasia, who presented with progressive cognitive decline characteristic of AD. Initial evaluation revealed impaired memory, apraxia, mild expressive aphasia and executive dysfunction, alongside notable generalised cortical atrophy and hippocampal volume loss on brain magnetic resonance imaging. The patient was initiated on symptomatic therapy with donepezil, an acetylcholinesterase (AChE) inhibitor, leading to a significant drug-drug interaction with the patient's long-term beta-blocker, metoprolol, causing symptomatic bradycardia manifested as dizziness, fatigue, worsening confusion and near-syncope. Therefore, metoprolol was discontinued, but the patient subsequently developed poorly controlled hypertension (150/95 mmHg). To optimise blood pressure control while minimising medication burden, the treating physician replaced tamsulosin with doxazosin, effectively managing both hypertension and benign prostatic hyperplasia symptoms. Following these adjustments, the patient's blood pressure and heart rate normalised, and cognitive symptoms stabilised. This case highlights the clinical complexity inherent in managing elderly patients with multiple chronic conditions and polypharmacy. It underscores the importance of vigilant monitoring and strategic medication selection to avoid drug-drug interactions, particularly when prescribing cognitive enhancers such as donepezil. Careful consideration of individual patient profiles and continuous reassessment of medication regimens remain crucial for enhancing clinical outcomes and patient safety.

Keywords*:* Alzheimer's disease; bradycardia; donepezil, drug-drug interaction; hypertension; polypharmacy

INTRODUCTION

Polypharmacy in geriatric patients is associated with increased risks of drug-drug interactions, adverse drug reactions and complications that may obscure accurate diagnosis. Alzheimer's disease (AD) is a progressive neurodegenerative condition characterised by cognitive decline and memory loss (Scheltens et al. 2021). In elderly patients, the likelihood of drug-drug interactions is significantly heightened due to age-related changes in pharmacokinetics and pharmacodynamics, including altered renal and hepatic clearance, reduced plasma protein binding and increased drug sensitivity. These interactions can result in severe consequences such as hypotension, bradycardia, cognitive decline or exacerbation of comorbidities, many of which may be misattributed to underlying chronic illnesses or aging itself. Therefore, thorough medication reconciliation and vigilant clinical monitoring are essential in preventing morbidity and optimising therapeutic outcomes in the geriatric population (Khezrian et al. 2020). This report presents a geriatric patient with polypharmacy who recently exhibited clinical symptoms of AD complicated by a critical drug-drug interaction that warranted immediate medication adjustment.

Polypharmacy, commonly operationalised as the concurrent use of 5 long-term medicines and "hyper-polypharmacy" as 10, is not merely a medication count but a dynamic risk state driven by age-related pharmacokinetic/dynamic changes, multimorbidity and regimen complexity. In dementia, polypharmacy raises the likelihood of adverse drug events, interaction cascades such as rate-limiting agents with cholinergic therapies, falls and hospitalisation, underscoring the need for proactive medication review and deprescribing where appropriate (Wastesson et al. 2018; Khezrian et al. 2020). In this report, we use a polypharmacy lens to (i) quantify this patient's baseline risk; (ii) trace how the interaction between donepezil and metoprolol emerged; and (iii) demonstrate how targeted regimen simplification restored hemodynamic stability while preserving symptom control.

CASE REPORT

Polypharmacy Profile at Presentation

At presentation, the patient was taking seven chronic medications (metformin, enalapril, hydrochlorothiazide, metoprolol, atorvastatin, tamsulosin and as needed celecoxib), meeting the threshold for polypharmacy. Anticholinergic burden was minimal; however, rate-limiting potential (metoprolol) in combination with a cholinesterase inhibitor (donepezil) created a predictable bradycardic risk once cognitive therapy was initiated. This baseline profile guided our monitoring plan [electrocardiogram (ECG) and vitals surveillance] and informed the subsequent deprescribing/substitution steps that followed the adverse event.

Medical and Family History

The patient had a known medical history of type 2 diabetes mellitus, diagnosed 15 years ago (at the age of 65), which had been moderately controlled with metformin 1000 mg twice daily. Hypertension was diagnosed at age 68 and was managed with enalapril 10 mg and hydrochlorothiazide 25 mg once daily. However, blood pressure fluctuations were occasionally noted. He was also diagnosed with chronic heart failure at the age of 75. Metoprolol 50 mg twice daily had been prescribed for both hypertension and heart failure. Furthermore, the patient was diagnosed with benign prostatic hyperplasia (BPH) for more than 20 years and had been treated with tamsulosin 0.4 mg once daily for the last 15 years. His hyperlipidemia was managed with atorvastatin 20 mg once daily.

His family history was notable for AD in his mother, who developed symptoms in her late seventies, and for hypertension in two of his older siblings. This familial predisposition significantly increases his risk for neurodegenerative and vascular cognitive decline.

Lifestyle, Diet and Social History

The patient had been physically inactive for several years, primarily due to osteoarthritic knee pain and progressive fatigue. His diet was high in saturated fats and refined carbohydrates, with minimal intake of fruits, vegetables or omega-3-rich foods. He consumed processed foods frequently and described himself as a poor follower of the dietary recommendations for hypertension and diabetes. He had no history of tobacco or alcohol use, and there was no known exposure to neurotoxins or history of traumatic brain injury.

Socially, the patient lived with his daughter, who served as his primary caregiver. He had minimal social engagement, had retired from work nearly two decades ago, and spent most of his time at home watching television. He did not participate in cognitively stimulating or structured activities.

Physical Examination

On physical examination, the patient was hemodynamically stable (BP 135/85 mmHg, HR 74 beats/minute), afebrile and oriented only to self. General examination revealed frailty, mild pallor and bilateral peripheral pitting edema consistent with chronic heart failure.

Neurological Examination

Neurological evaluation revealed impaired recent memory, poor attention, apraxia, mild expressive aphasia, impaired judgment and executive dysfunction. Cranial nerves and motor function were intact. Reflexes were symmetrical, and sensory examination was normal.

Psychiatric Examination

Mental State Examination (MSE) revealed significant cognitive impairment (Mini-Mental State Examination (MMSE) score: 18/30). The patient was anxious and exhibited mild depressive symptoms. Insight and judgment were markedly impaired.

Investigations and Definitive Diagnosis

Routine laboratory tests (complete blood count, renal function, electrolytes, liver function, thyroid profile and vitamin B12) were within normal limits. A non-contrast brain magnetic resonance imaging (MRI) revealed generalised cortical atrophy and prominent hippocampal volume loss, consistent with AD, as evident in Figure 1. Cerebrospinal fluid (CSF) analysis showed reduced amyloid-beta 42 and elevated total and phosphorylated tau protein, confirming Alzheimer's pathology (Scheltens et al. 2021).

The biochemical CSF markers supported the imaging findings and clinical symptoms of episodic memory impairment, disorientation and executive dysfunction. In this patient, the degree of hippocampal volume loss correlated with an MMSE score of 18/30, suggesting moderate-stage AD.

Treatment and Drug-Drug Interaction Issue

The patient started symptomatic treatment with donepezil 5 mg daily. Within two weeks, he developed symptomatic bradycardia (HR 48 beats/minute), dizziness, fatigue and increased confusion. An ECG confirmed sinus bradycardia. Clinical pharmacological evaluation revealed a significant drug-drug interaction between donepezil and metoprolol. Donepezil, an AChE inhibitor, could enhance the vagal tone and reduce heart rate, potentiating the bradycardic effects of the beta-blocker, metoprolol, took by the patient (Colak & Oz 2022). Following the withdrawal of metoprolol, which the patient had been receiving at a dose of 50 mg twice daily, his symptomatic bradycardia resolved within one week. However, during follow-up in the subsequent week, a rise in blood pressure was observed, with repeated measurements showing consistently elevated BP at approximately 150/95 mmHg. This increase indicated suboptimal control of hypertension due to discontinuation of beta-blocker therapy.

In response to the elevated blood pressure, the attending physician substituted tamsulosin (0.4 mg daily) with doxazosin (2 mg once daily). This medication adjustment was chosen strategically, as doxazosin, unlike tamsulosin, provides dual therapeutic benefits by managing benign prostatic hyperplasia (BPH) symptoms and concurrently contributing to blood pressure reduction.

After this change, the patient's blood pressure gradually normalised to approximately 130/80 mmHg over the subsequent two weeks, and his heart rate remained stable between

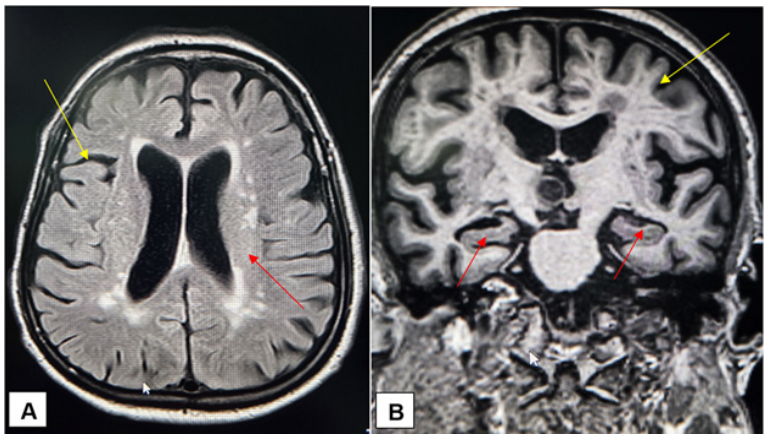

FIGURE 1: Non-contrast MRI of the patient's brain showing generalised cortical atrophy (yellow arrows) and loss of hippocampal volume (red arrows) in (A) FLAIR image and (B) Coronal T1 image of the patient's brain. These structural changes were consistent with neurodegenerative patterns observed in Alzheimer's disease.

65-72 beats/minute. The patient's symptoms improved significantly, with no recurrence of symptomatic bradycardia or hypertension-related complications. A visual illustration of the integrated diagnostic and therapeutic timelines was shown in Figure 2.

DISCUSSION

Polypharmacy significantly complicates geriatric patient management, especially when introducing new medications like AChE inhibitors. AD diagnosis depends on clinical presentation, cognitive assessment, imaging and supportive CSF biomarkers (Scheltens et al. 2021). Donepezil is a first-line symptomatic treatment of mild to moderate AD via its reversible inhibitory effect on AChE enzyme, thereby enhancing cholinergic neurotransmission by preventing the breakdown of acetylcholine. This leads to increased parasympathetic activity, which can exert vagotonic effects on the sinoatrial node, resulting in slowed heart rate and prolonged atrioventricular (AV) conduction (Morris et al. 2021). When combined with cardioselective beta-adrenergic blockers such as metoprolol, which independently decrease sinoatrial node automaticity and AV nodal conduction, the additive bradycardic effect can be clinically significant. The adverse event in this case is best understood as a polypharmacy-mediated interaction, not an idiosyncratic reaction. Specifically, introducing a cholinesterase inhibitor into a regimen already containing a beta-blocker increased vagotonic influence on the sinus node, precipitating symptomatic bradycardia. Framing management through polypharmacy principles enabled two key actions: (i) deprescribing a bradycardic contributor (metoprolol) once the clinical indication shifted; and (ii) substituting a single dual-purpose agent (doxazosin) for BPH and blood-pressure control to avoid re-introducing rate limitation and to reduce regimen complexity. This approach operationalises polypharmacy management beyond counting medicines, i.e. toward risk-directed simplification with measurable clinical benefit (blood pressure: 130/80 mmHg; heart rate: 65-72 beats/minute; no recurrence of symptoms).

Although several case reports and pharmacovigilance studies have documented bradycardia associated with donepezil,

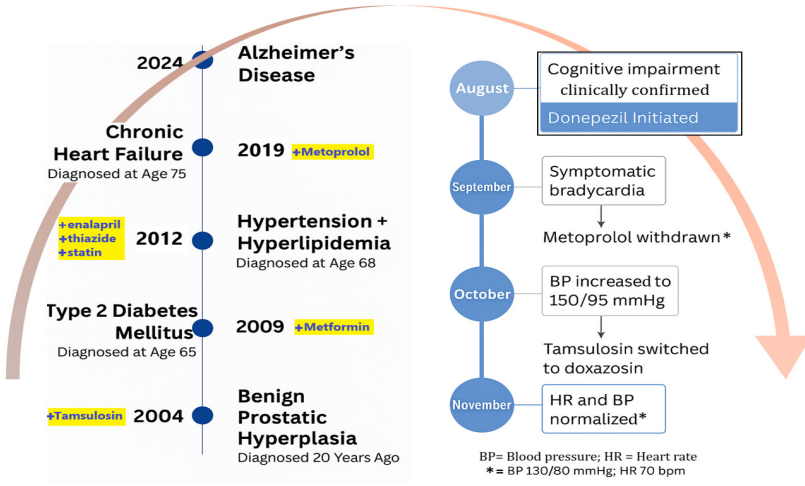

FIGURE 2: Integrated timeline of diagnostic milestones and pharmacological interventions in this elderly patient with Alzheimer's disease and multiple comorbidities. Left panel: yearly diagnoses and corresponding medications. Right panel: month-by-month therapeutic responses in 2024, highlighting the onset of bradycardia following donepezil initiation, withdrawal of metoprolol and stabilisation with doxazosin

especially when used alongside beta-blockers or other AV nodal inhibitors, most prior reports involved patients with either baseline conduction abnormalities or recent beta-blocker initiation (Odenigbo et al. 2024; Kho et al. 2021). In contrast, this case is notable for the delayed manifestation of bradycardia in a patient already tolerating long-term metoprolol therapy, prescribed initially for sinus tachycardia and heart failure, besides hypertension. Moreover, while most prior reports focused on dose adjustments or drug discontinuation, this case highlights a multifaceted deprescribing strategy, including the replacement of tamsulosin with doxazosin, to manage the emergent hypertension without reintroducing bradycardic risk. This layered approach exemplifies the importance of individualised polypharmacy management in geriatric dementia care and underlines the need for close ECG and symptom monitoring during co-prescription (Colak & Oz 2022). Elderly patients are particularly susceptible to cardiac symptoms due to diminished cardiovascular and cognitive reserve, potentially exacerbating existing cognitive dysfunction (Kusumoto et al. 2019). In situations where donepezil is contraindicated or poorly tolerated, such as in patients with symptomatic bradycardia or conduction abnormalities, alternative agents should be considered. Rivastigmine, available in both oral and transdermal formulations, offers comparable efficacy and may have a more favourable cardiac profile in some patients due to its central selectivity. Additionally, galantamine, which also enhances nicotinic receptor activity, may be better tolerated in selected patients and offers titration flexibility. For patients with moderate-to-severe AD, memantine, an N-methyl-D aspartate receptor antagonist, may be considered as monotherapy or in combination with cholinesterase inhibitors, particularly when behavioural symptoms or glutamatergic excitotoxicity are prominent (McShane et al. 2019). These alternatives provide clinicians with options to tailor cognitive therapy based on patient comorbidities, tolerability and disease stage.

In the current case report, even though the patient was on ACE inhibitor and thiazide diuretic therapy, metoprolol withdrawal led to diminished control of the patient's hypertension, which manifested clinically with increased blood pressure (150/95 mmHg). This necessitated further medication adjustments to ensure comprehensive clinical management without increasing the medication burden.

The replacement of tamsulosin with doxazosin was specifically selected because, unlike tamsulosin, which is a selective 1A-receptor antagonist effective only for lower urinary tract symptoms in BPH, doxazosin exhibits non-selective alpha-blocking properties that benefit both BPH and hypertension (Yoshida et al. 2021). Nevertheless, while the latter offers the advantage of treating both hypertension and BPH, it carries a known risk of first-dose orthostatic hypotension, particularly in frail or volume-depleted elderly patients. To mitigate this, doxazosin was initiated at the lowest effective dose (2 mg OD), with administration timed at bedtime. Postural blood pressure was closely monitored during the first week of therapy, and the caregiver was instructed to observe for signs of dizziness, falls or syncope. No such adverse effects were observed during follow-up, and the patient's blood pressure remained stable at 130/80 mmHg without recurrence of bradycardia. By replacing tamsulosin with doxazosin, clinicians aimed to achieve better control of hypertension without further polypharmacy, thus simplifying the patient's medication regimen while providing both cardiovascular and urological favourable outcomes (Whelton et al. 2018; Yoshida et al. 2021).

This case highlights the complexity of medication management in elderly patients with AD and multiple comorbidities, emphasising the critical role of individualised medication reviews and strategic drug selection to minimise complications and optimise therapeutic outcomes. Healthcare professionals must remain vigilant in geriatric patients prescribed multiple medications, closely monitoring for adverse drug-drug interactions to ensure patient safety

(Wastesson et al. 2018). Hence, this case also underscores the importance of system-level interventions to proactively prevent adverse drug interactions. Tools such as electronic prescribing systems with built-in drug–drug interaction alerts, Beers Criteria integration, and computerised decision support systems (CDSS) can provide point-of-care guidance to clinicians, especially when initiating agents like cholinesterase inhibitors in patients already receiving rate-limiting drugs. Moreover, regular medication reconciliation by clinical pharmacists and multidisciplinary geriatric pharmacotherapy reviews, especially during care transitions, can identify high-risk combinations early. Embedding these practices into institutional workflows enhances medication safety and supports more effective, personalised care for elderly patients with complex therapeutic regimens (Cooper et al. 2015; Shehab et al. 2016).

What distinguishes this case is not only the recognition of a well-documented drug-drug interaction between donepezil and beta-blockers, but also the systematic clinical reasoning and rational therapeutic substitutions that followed. The detection of symptomatic bradycardia, prompted by a classic but often underappreciated interaction, led to a thoughtful withdrawal of metoprolol. However, what truly sets this case apart is the substitution of tamsulosin with doxazosin, a decision that addressed both BPH and emergent hypertension in a single agent, aligning with principles of geriatric deprescribing and polypharmacy reduction. This dual-purpose intervention demonstrates how personalised, mechanism-based pharmacological reasoning can optimise outcomes in complex elderly patients, thereby supporting the educational and clinical value of this case report. Apart from the drug interaction point, it is worth mentioning that although the patient's clinical presentation and MRI findings, particularly hippocampal atrophy, were consistent with AD, CSF biomarker testing was pursued to strengthen diagnostic certainty and exclude mixed or atypical dementias, such as frontotemporal lobar degeneration or vascular cognitive impairment. Given the complex backdrop of polypharmacy, multiple comorbidities, and age-related brain changes, biochemical confirmation of reduced amyloid-β42 and elevated total and phosphorylated tau provided a clear pathophysiological signature of AD. According to recent consensus criteria, CSF biomarker analysis is especially valuable when clinical and imaging findings may be confounded by comorbid conditions or when early, accurate diagnosis informs disease management (Dubois et al. 2021; Jack et al. 2018). This not only helped validate the diagnosis but also supported the initiation of AChE inhibitor therapy with greater confidence, particularly when caregiver counseling and long-term planning were being addressed. A summary of clinical learning points from this case report is shown in Figure 3.

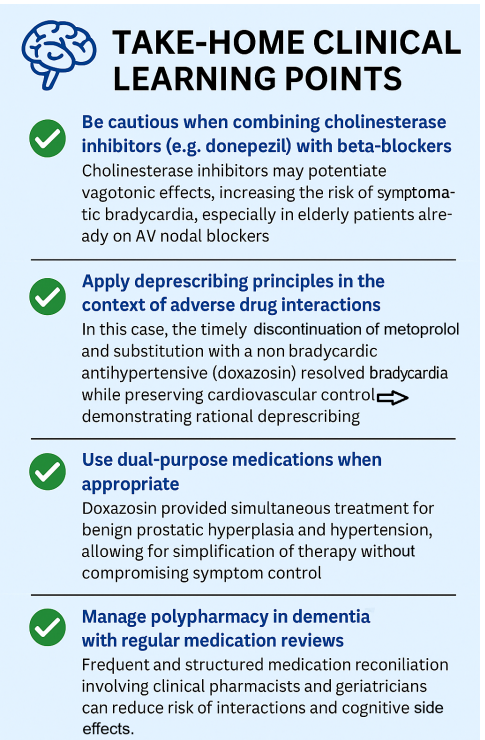

FIGURE 3: Take-home clinical learning points derived from the case report, summarising key principles in the management of polypharmacy, deprescribing and safe initiation of cognitive enhancers in geriatric patients

CONCLUSION

This case underscores the necessity for meticulous medication review and close clinical monitoring in geriatric patients receiving multiple medications. Early identification of drug-drug interactions, such as between donepezil and metoprolol and prompt medication adjustment are crucial in optimising patient outcomes, particularly in vulnerable populations diagnosed with AD. Overall, the patient's course illustrates how polypharmacy-aware prescribing, vigilant interaction surveillance and targeted deprescribing/substitution transform a complex regimen into a safer, simpler plan, reinforcing the central message of effective polypharmacy management in geriatric dementia.

Funding: This study received no external funding.

Acknowledgement: Not applicable.

Conflict of interest: The authors declare no conflict of interest in reporting this case.

Ethical statement:. Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical information. No personal information is disclosed in this report. As this is a single-patient case report and did not involve experimental intervention, formal ethical approval was not required.

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