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ORIGINAL RESEARCH ARTICLE

Trazodone and Risk of Orthostatic Hypotension, Syncope and Falls in Geriatric Outpatients with Hypertension

Giulia Rivasi[1] · Marco Capacci[1] · Lorenzo Maria Del Re[1] · Ilaria Ambrosino[1] · Ludovica Ceolin[1] · Alessandra Liccardo[1] · Maria Francesca Bisignano[1] · Giuseppe D'Ambrosio[1] · Greta Ceccarelli[1] · Giulia Matteucci[1] · Enrico Mossello[1] · Andrea Ungar[1]

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Abstract

Introduction In older adults, trazodone is frequently prescribed for anxiety and insomnia owing to its perceived greater tolerability in comparison with benzodiazepines. However, it may have hypotensive effects.

Aim The aim of this study is to investigate the effects of trazodone on orthostatic blood pressure (BP) response and risk of syncope and falls in hypertensive older adults.

Patients and Methods A longitudinal observational study involving patients ≥ 75 years was conducted in two geriatric outpatient clinics in Florence, Italy. At baseline, participants underwent a 3-min active stand test, office BP measurement and home and ambulatory BP monitoring. At follow-up, syncope and falls were recorded.

Results Among 123 participants (mean age 81 years, 59% female), 12 (10%) reported regular trazodone use. Trazodone users showed lower office diastolic BP (71.8 versus 80.1 mmHg, $p = 0.042$), a greater systolic and diastolic BP reduction immediately after standing ($\Delta\text{systolic}_{T0}$ 23.8 versus 14.3 mmHg, $p = 0.037$; $\Delta\text{diastolic}_{T0}$ 8.9 versus 1.6 mmHg, $p = 0.004$) and a greater diastolic BP reduction after 1-min standing ($\Delta\text{diastolic}_{T1}$ 6.5 versus 0 mmHg, $p = 0.029$). No differences were reported for home or ambulatory BP. Incidence of syncope and falls was 25%, with a significantly higher rate in patients receiving trazodone (58.3% versus 21.2%, $p = 0.001$). Trazodone use predicted syncope and falls independently of age, disability and fall history. This association was not confirmed when adjusting for dementia diagnosis. BP values were not associated with the study outcome.

Conclusions In older hypertensive outpatients, trazodone is associated with a greater orthostatic BP drop and may predispose them to an increased risk of syncope and falls.

Key Points

Hypertensive older outpatients receiving trazodone have a greater orthostatic BP drop.

Trazodone may increase the risk of syncope and falls, independently of age, recent fall history and disability.

Orthostatic blood pressure and fall risk factors should be systematically assessed among trazodone users.

✉ Giulia Rivasi
giulia.rivasi@unifi.it

[1] Division of Geriatric and Intensive Care Medicine, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla 3, 50139 Florence, Italy

1 Introduction

Trazodone is one of the most commonly prescribed medications in older adults, being increasingly used even at low doses for management of sleep disorders, anxiety and behavioural and psychological symptoms associated with dementia [1, 2]. Trazodone is usually perceived as a safer alternative to other psychoactive agents owing to the lack of anti-cholinergic activity and cardiotoxicity. For this reason, it is frequently prescribed among functionally dependent and comorbid older adults, including those with dementia, gait or balance disorders and high fall risk [3]. However, it is known that trazodone may have hypotensive effects owing to the inhibition of α-adrenergic receptors, and orthostatic hypotension (OH) is one of the most common adverse effects reported among trazodone users [4–6].

OH is highly prevalent in older adults [7–9] and is associated with both short- and long-term unfavourable

consequences, including falls, cardiovascular events, cognitive impairment and mortality [9–11]. Moreover, hypotension may cause symptoms such as dizziness, lightheadedness and fatigue, which negatively impact patients' quality of life and autonomy in daily living [12, 13]. In older adults, medications with hypotensive effects represent the main cause of non-neurogenic OH, i.e. OH which is not related to disorders affecting central or peripheral autonomic structures. Drug-related OH is most commonly attributed to antihypertensive medications such as beta-blockers, alpha-blockers and diuretics. However, psychoactive medications such as benzodiazepines, antipsychotics and antidepressants may likewise be associated with OH, although their hypotensive effects are frequently overlooked in research studies and in clinical practice [14, 15]. Indeed, although trazodone is widely used in older patients at high risk of hypotension-related adverse events, the effects of trazodone on blood pressure (BP) and orthostatic BP response have scarcely been investigated.

The present study aimed to investigate the effects of trazodone on BP, including orthostatic BP response, and on the risk of syncope and falls in hypertensive older adults.

2 Patients and Methods

This study presents a secondary analysis of the observational prospective longitudinal HYPER-FRAIL pilot study, that was conducted at the Division of Geriatric Medicine of the Careggi University Hospital, Florence, Italy, as detailed elsewhere [16]. Briefly, study participants included hypertensive outpatients aged 75 or older undergoing a comprehensive geriatric assessment including full medical history and investigation of frailty (defined as presence of ≥ 3 items of the Fried Frailty Phenotype) [17], disability in basic and instrumental activities of daily living (defined as loss of autonomy in ≥ 2 basic and ≥ 1 instrumental activity, respectively) [18, 19], physical performance (assessed using the Short Physical Performance Battery) [20], cognitive status and depressive symptoms. Medical therapy was ascertained from participants and/or caregivers, focusing on drug classes with possible hypotensive effects (i.e. antihypertensive and psychoactive medications). Falls in the previous 12 months were also investigated.

BP was assessed with office BP measurement and 24-h ambulatory blood pressure monitoring (ABPM). Home BP was also recorded, if a home BP diary was available. Office BP was measured twice in the sitting position after 5-min resting. ABPM was performed using a validated oscillometric device (TM-2430, A&D, Tokyo, Japan) and mean daytime, night-time and 24-h systolic and diastolic BP were recorded. Hypotensive episodes consisting of ≥ 1 daytime systolic BP measures < 90 mmHg [22] were also investigated. Home BP was recorded as the average of available readings, provided that BP had been measured with an electronic upper-arm cuff validated device for at least 7 days, with two measurements recorded on each occasion.

Orthostatic BP response was assessed during a 3-min lying-to standing active stand test, with BP recorded in the supine position after 5-min resting (supine BP), immediately after standing (T0), at 1 (T1) and 3 min (T3) after the posture change. OH was defined as a systolic BP fall ≥ 20 mmHg or to < 90 mmHg and/or a diastolic BP fall ≥ 10 mmHg [21]. Moreover, the orthostatic systolic (Δsystolic) and diastolic (Δdiastolic) BP drops were analysed, expressed as both absolute values (i.e. the difference between supine BP and orthostatic BP at T0, T1 and T3) and percentages of supine BP, calculated as follows:

$$\%\Delta BP = \left[(\text{supine BP} - \text{orthostatic BP}) / \text{supine BP}\right] \times 100,$$

where orthostatic BP corresponds to systolic or diastolic BP at T0, T1 or T3.

The study outcome was defined as a composite of syncope episodes or falls, which were assessed on the basis of clinical records and phone interviews with participants and/or their caregivers.

2.1 Statistical Analysis

Data were summarised as means with standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables and frequencies with percentages for categorical variables. Bivariate analyses were performed to compare trazodone users with the rest of the sample. Differences in continuous variables were tested using the independent samples *t*-test or the Mann–Whitney *U* test, as appropriate. For categorical variables, differences between groups were tested using the chi-squared test. Kaplan–Meier curves were generated to compare incidence of syncope and falls between trazodone users and other participants, and the log-rank test was performed to test differences. Multivariate Cox regression models were used to identify independent predictors of syncope and falls, with adjustment for those covariates showing a significant relationship to the outcome in this cohort. Intercorrelations among predictors were checked using a correlation matrix of two-sided Spearman rho correlation coefficients to avoid multicollinearity in multivariate models. Correlations of 0.50 or more were considered large. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS software version 26 (SPSS, Inc., Chicago, Illinois, USA)

3 Results

The study sample included 123 participants (mean age 81.3 years, SD 4.4 and 59.3% female). Regular use of trazodone was reported by 12 (9.8%) patients. Trazodone users were older and showed a higher prevalence of dementia and disability (Table 1). Moreover, they were more frequently treated with antipsychotics, whereas antihypertensive prescriptions were similar between the two groups (Supplementary Table 1).

Table 2 described BP values in the overall sample and by trazodone use. Patients receiving trazodone had lower office diastolic BP (71.8 mmHg versus 80.1 mmHg, $p = 0.042$) and similar office systolic BP compared with patients not receiving trazodone. During the active stand test, trazodone users showed a greater systolic and diastolic BP reduction immediately after standing ($\Delta\text{systolic}_{T0}$ 16.2 mmHg versus 9.7 mmHg, $p = 0.038$; $\Delta\text{diastolic}_{T0}$ 11 mmHg versus 1.7 mmHg, $p = 0.003$) and a greater diastolic BP reduction at T1 (Fig. 1). The estimated difference of systolic blood pressure drop at T0 between trazodone users and non-users was 9.5 mmHg (95% confidence intervals, CI, 0.6–18.4) in absolute terms and 6.4% (95% CI 0.4–12.5) as percentage change. Similarly, the difference of diastolic blood pressure drop at T0 was 7.4 mmHg (95% CI 2.3–12.4) and 9.2% (95% CI 3.1–15.4). Prevalence of OH was 43.8% and was higher—although not significantly different—in the trazodone group. No differences were reported for home BP, ambulatory BP or the number of hypotensive episodes detected by ABPM (Table 2).

Follow-up data were available in 116 participants. During a median follow-up of 11.8 months (IQR 8.8–18), 25 (22%) participants experienced at least one fall and 4 (3%) experienced a syncope. The composite outcome occurred in 29 (25%) participants. Kaplan–Meier curves showed an increased risk of syncope and falls among trazodone users (outcome incidence 58.3% versus 21.2%, log-rank test $p = 0.001$) (Fig. 2).

Trazodone use was associated with an increased risk of syncope and falls independently of age, poor physical performance, disability, antihypertensive medication burden and recent fall history. This association was not confirmed when multivariate Cox analysis was adjusted for dementia diagnosis (Table 3). BP values, including orthostatic BP response, and treatment with antihypertensive drugs (both as drug number and specific drug classes) were not associated with the study outcome (Supplementary Table 2). Benzodiazepines and antipsychotics showed no relevant impact on BP values, except for a higher prevalence of orthostatic

Table 1 Characteristics of the study sample and comparison by trazodone use

	Overall sample ($n = 123$)	Trazodone users ($n = 12$)	Others ($n = 111$)	p
Age (years), mean (SD)	81.3 (4.4)	84.3 (3.9)	80.9 (4.3)	0.010
Female sex, *n* (%)	73 (59.3)	9 (75.0)	64 (57.7)	0.245
Charlson Comorbidity Index, median (IQR)*	1 (0–2)	1.5 (1–3.5)	1 (0–2)	0.097
No. daily medications, median (IQR)	7 (5–9)	8 (7–9)	6 (5–9)	0.072
No. daily antihypertensive medications, median (IQR)	2 (2–3)	2 (1–2)	2 (2–3)	0.087
Mild cognitive impairment, *n* (%)	11 (8.9)	0	11 (9.9)	0.253
Dementia, *n* (%)	37 (30.1)	10 (83.3)	27 (24.3)	< 0.001
Depression, *n* (%)	36 (29.3)	5 (41.7)	31 (27.9)	0.320
Depressive symptoms, *n* (%)	35 (28.4)	3 (25)	32 (28.8)	0.752
History of falls, *n* (%)	28 (22.8)	4 (33.3)	24 (21.6)	0.358
Parkinson's disease, *n* (%)	5 (4.1)	0	5 (4.5)	0.453
Coronary artery disease, *n* (%)	19 (15.4)	2 (16.7)	17 (15.3)	0.902
Heart failure, *n* (%)	6 (4.9)	1 (8.3)	5 (4.5)	0.559
Previous stroke/transient ischemic attack, *n* (%)	28 (22.8)	4 (33.3)	24 (21.6)	0.358
Diabetes, *n* (%)	28 (22.8)	3 (25)	25 (22.5)	0.846
Chronic kidney disease, *n* (%)	77 (62.6)	7 (58.3)	70 (63.1)	0.748
SPPB score ≤ 8, *n* (%)	49 (39.8)	7 (58.3)	42 (37.8)	0.168
Frailty, *n* (%)	52 (42.3)	7 (58.3)	45 (40.5)	0.236
ADL disability, *n* (%)	23 (18.7)	6 (50)	17 (15.3)	0.003
IADL disability, *n* (%)	64 (52)	12 (100)	52 (46.8)	< 0.001

SD, standard deviation; IQR, interquartile range; SPPB, Short Physical Performance Battery; ADL, activities of daily living; IADL, instrumental activities of daily living. *not age-adjusted

Table 2 Office, orthostatic, ambulatory and home blood pressure profile in the overall sample and by trazodone use

Blood pressure mean (SD)	Overall sample ($n = 123$)	Trazodone users ($n = 12$)	Others ($n = 111$)	p
Office systolic BP	152.4 (21.1)	145.4 (26.3)	153.2 (20.5)	0.227
Office diastolic BP	79.3 (13.6)	71.8 (10.6)	80.1 (13.6)	0.042
24-h systolic BP (ABPM)	147.1 (15.6)	143.1 (13.6)	147.6 (15.7)	0.345
24-h diastolic BP (ABPM)	76.7 (8.8)	77.7 (7)	76.5 (9)	0.685
Daytime systolic BP (ABPM)	149.6 (15.3)	146.5 (13)	150 (15.5)	0.472
Daytime diastolic BP (ABPM)	79 (8.9)	80.3 (7.3)	78.8 (9.11)	0.586
Night-time systolic BP (ABPM)	138 (20.9)	134.2 (16.1)	138.4 (21.3)	0.511
Night-time diastolic BP (ABPM)	68.7 (10.2)	69.6 (7.0)	68.6 (10.5)	0.757
Hypotensive episodes (ABPM), *n* (%)	20 (16.3)	3 (25.0)	17 (15.3)	0.388
Home systolic BP	137.2 (11.9)	141.4 (11.8)	136.8 (11.9)	0.326
Home diastolic BP	73.7 (8.4)	78.0 (8.4)	73.5 (8.4)	0.244
Orthostatic blood pressure response				
Orthostatic hypotension, *n* (%)	53 (43.8)	8 (66.7)	45 (41.3)	0.093
Supine systolic BP	149.4 (21.1)	149.3 (17.3)	149.3 (21.5)	0.944
Systolic BP_{T0} ($n = 114$)	134.2 (26.1)	125.5 (21.1)	135.1 (26.5)	0.230
$\Delta systolic_{T0}$ ($n = 114$)	15.3 (14.9)	23.8 (11.1)	14.3 (15.0)	0.037
$\%\Delta systolic_{T0}$ ($n = 114$)	10.4 (10.2)	16.2 (7.9)	9.7 (10.3)	0.038
Systolic BP_{T1} ($n = 112$)	139.1 (24.3)	136.8 (18.5)	139.3 (25)	0.744
$\Delta systolic_{T1}$ ($n = 112$)	10.7 (18.6)	11.3 (14.36)	10.6 (19.1)	0.908
$\%\Delta systolic_{T1}$ ($n = 112$)	7.0 (11.6)	7.4 (8.9)	6.9 (11.9)	0.892
Systolic BP_{T3} ($n = 110$)	142.2 (21.7)	138 (18.2)	142.6 (22.1)	0.546
$\Delta systolic_{T3}$ ($n = 110$)	7.68 (14.5)	10 (15.4)	7.4 (14.4)	0.623
$\%\Delta systolic_{T3}$ ($n = 110$)	4.8 (9.4)	6.2 (9.8)	4.7 (9.4)	0.625
Supine diastolic BP	77 (11.9)	81.1 (14.8)	76.5 (11.6)	0.209
Diastolic BP_{T0} ($n = 114$)	74.7 (13)	72.2 (16.5)	75.1 (12.6)	0.476
$\Delta diastolic_{T0}$ ($n = 114$)	2.3 (8.6)	8.9 (9.4)	1.6 (8.2)	0.004
$\%\Delta diastolic_{T0}$ ($n = 114$)	2.7 (10.5)	11 (11.8)	1.7 (10)	0.003
Diastolic BP_{T1} ($n = 112$)	76.4 (11.7)	74.6 (7.9)	76.6 (12.1)	0.594
$\Delta diastolic_{T1}$ ($n = 112$)	0.8 (9.2)	6.5 (11.6)	0 (8.7)	0.029
$\%\Delta diastolic_{T1}$ ($n = 112$)	0.5 (10.7)	6.4 (11.3)	0 (10.4)	0.051
Diastolic BP_{T3} ($n = 110$)	77.2 (11)	77.0 (9.2)	77.2 (11.2)	0.950
$\Delta diastolic_{T3}$ ($n = 110$)	0.2 (7.7)	11 (4.1)	0 (7.5)	0.075
$\%\Delta diastolic_{T3}$ ($n = 110$)	−0.3 (8.8)	3.8 (9)	0 (8.6)	0.101

BP, blood pressure; ABPM, ambulatory blood pressure monitoring

hypotension and lower systolic BP values at T3 in patients receiving antipsychotics (Supplementary Table 3 and Supplementary Table 4). The association of trazodone with the risk of syncope and falls was confirmed when adjusting for benzodiazepines (BDZs) or antipsychotic use, while the latter were not associated with the study outcome (Supplementary Table 5).

4 Discussion

The present study investigated the BP effects of trazodone in a sample of older hypertensive outpatients. The study results showed that trazodone use was associated with a greater systolic and diastolic BP reduction immediately after standing and a possible increase in risk of syncope and falls, independently of age, recent fall history and disability.

Trazodone is an antidepressant medication with a dual mechanism of action involving inhibition of the serotonin transporter (SERT) and serotonin type 2 receptor (5-HT_{2A} and 5-HT_{2C} receptors). Moreover, it exerts antagonistic

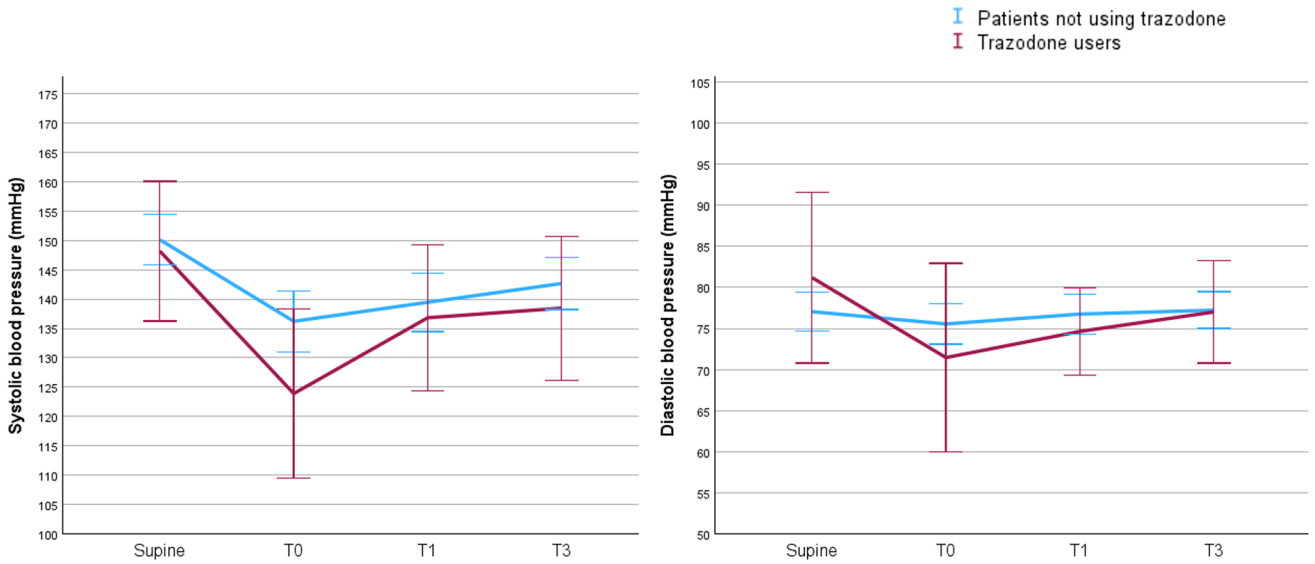

Fig. 1 Systolic (left panel) and diastolic (right panel) blood pressure values during active standing by trazodone use. Error bars represent 95% confidence intervals

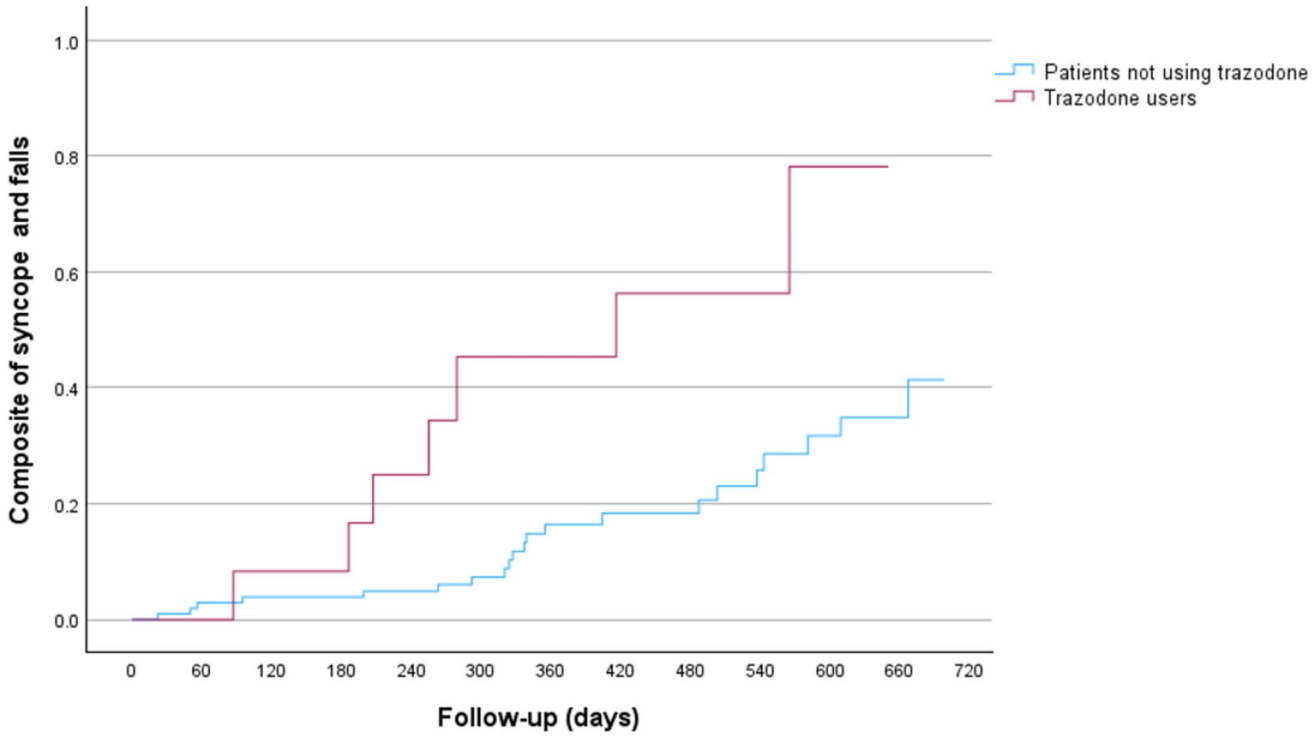

Fig. 2 Kaplan–Meier curves for the composite outcome of syncope and falls, stratified by trazodone use (log-rank test $p = 0.001$)

properties against histamine H1 receptor and α_1- and α_2-adrenergic receptors [4, 23]. Previous studies report OH as one of the adverse effects of trazodone therapy, especially common in older adults and in patients with pre-existing cardiac disease [5, 6]. However, to the best of our knowledge, this is the first study to explore the effects of trazodone on different BP measurements, including a detailed analysis of the orthostatic BP response.

The hypotensive effect of trazodone is primarily attributed to the inhibition of α1-adrenergic receptors [23]. It is usually

Table 3 Cox regression analysis to identify predictors of syncope and falls

	Unadjusted HR (95% CI)	HR (95% CI) – model A	HR (95% CI) – model B
Age, years	1.124 (1.039–1.215)	1.092 (1.000–1.192)	0.838 (0.374–1.877)
Female sex	1.174 (0.541–2.547)	0.791 (0.347–1.802)	0.838 (1.022–1.210)
Trazodone	3.803 (1.600–9.037)	2.463 (0.901–6.729)	2.955 (1.118–7.807)
Dementia	3.899 (1.790–8.492)	2.036 (0.758–5.467)	–
History of falls	2.379 (1.095–5.166)	2.353 (1.046–5.295)	2.441 (1.069–5.574)
Poor physical performance	1.721 (0.816–3.628)	–	–
IADL disability	2.661 (1.196–5.919)	–	1.368 (0.534–3.506)

Variables included in model A: age, sex, fall history, trazodone use and dementia. Variables included in model B: age, sex, fall history, trazodone use and disability in instrumental activities of daily living (IADL). Full univariate analysis is detailed in Supplementary Table 2

transient and dose-related, being less pronounced when low doses or prolonged-release formulations are used [4]. The inhibition of α-adrenergic receptors provides a likely explanation for the greater BP drop reported among trazodone users in our study sample. A similar effect has been described for benzodiazepines, although different underlying mechanisms have been hypothesised [24]. Trazodone users also showed lower office diastolic BP consistently, with a possible vasodilating effect deriving from α-adrenergic blockade. We cannot exclude that this BP profile may have been influenced also by other predisposing factors for OH which commonly coexist in older adults, such as advanced age, dementia, polypharmacy and physical deconditioning. In particular, the association of trazodone with orthostatic BP drop may be partly explained by the higher prevalence of dementia among trazodone users, resulting in orthostatic hypotension owing to autonomic dysfunction. Consistently, prevalence of OH was relevant in our study (43.8%), as it might be expected in a sample of frail older patients.

The present study also identified a significant association between trazodone use and the risk of syncope and falls, which was at least partly independent of other predisposing factors such as old age, fall history and disability. While no study has investigated the association between trazodone and syncope, our findings agree with previous data describing an increased risk of falls in community-dwelling older adults and long-term care residents receiving trazodone [25–28]. In particular, some evidence suggests that trazodone may carry a similar fall risk compared with benzodiazepines and zopiclone in frailer individuals such as nursing home residents [28, 29]. Of note, treatment with benzodiazepine and antipsychotics was not associated with fall risk in the present sample. Fall risk associated with trazodone is typically attributed to daytime drowsiness and dizziness deriving from its sedative effects. The impact of trazodone on orthostatic BP observed in the present study suggests that also BP fluctuations may play a role; however, we reported no association between BP drop and the study outcome. Moreover, the association between trazodone and fall risk appears weakened when dementia was considered as a confounder, suggesting that trazodone use is not a risk factor per se and that the association results from the cumulative effect of several risk factors. In fact, fall susceptibility in older individuals derives from the synergic effects of multiple predisposing factors, such as medications, cognitive and physical impairment, BP and sensory deficits [30, 31]. The association between trazodone use and fall risk should thus be interpreted in the context of this multifactorial phenomenon, taking into consideration that multiple different conditions may modulate each individual's risk of falling. On the basis of our findings, we may hypothesise that trazodone may interfere with the BP response to standing and potentially contribute to increase the risk of syncope and falls in older adults with greater cumulative fall risk, especially older subjects with dementia, in whom trazodone use is more common. Therefore, OH and fall risk should be carefully investigated before trazodone initiation, and modifiable risk factors should be addressed to minimise the risk of fall-related complications. Moreover, the use of prolonged-release formulations and/or fractionate doses may be preferred, given the lower BP effects [4].

Some limitations of the present study should be considered. First, detailed information on trazodone dosage, formulation (e.g. prolonged release formulations) and treatment duration (new/chronic use) was not available in our dataset. Second, details on the circumstances and characteristics of syncope and falls were not recorded, and we were unable to draw any conclusion on the aetiology of events or on their correlation with BP values and trazodone use. Third, our results may not apply to older adults from other clinical settings, e.g. community-dwelling subjects of younger ages or individuals with lower frailty and disability level, that may show a lower risk of hypotension and falls. Finally, the small sample size and the low number of trazodone users ($N = 12$, 9.8% of the whole sample) may have influenced the analysis of BP values and did not allow for a subgroup analysis investigating trazodone effects in subjects with a different predisposition to hypotension and falls. Moreover,

we cannot exclude that the low number of trazodone users might indicate a selection bias.

5 Conclusions

In older hypertensive adults, trazodone use is associated with a greater BP drop immediately after standing and may predispose them to an increased risk of syncope and falls. Caution is advised when prescribing trazodone in older patients at high risk of hypotension and falls, and orthostatic BP should be assessed—together with other risk factors for falls—among vulnerable senior trazodone users. Studies with larger samples are needed to better define the risk of fall and syncope associated with trazodone use.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-025-01196-3.

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Declarations

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Conflicts of Interest Giulia Rivasi, Marco Capacci, Lorenzo Maria Del Re, Ilaria Ambrosino, Ludovica Ceolin, Alessandra Liccardo, Maria Francesca Bisignano, Giuseppe D'Ambrosio, Greta Ceccarelli, Giulia Matteucci, Enrico Mossello, and Andrea Ungara declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Availability of Data and Material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local research ethics committee (protocol number: 16539_oss).

Consent to Participate Informed consent was obtained from all individual participants or his/her legal representative included in the study.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions Conceptualization: Giulia Rivasi, Andrea Ungar, Enrico Mossello, and Marco Capacci. Acquisition, analysis, or interpretation of data: all authors. Writing – original draft preparation: Giulia Rivasi, Andrea Ungar, Enrico Mossello, Marco Capacci, and Lorenzo Del Re. Writing – review and editing: all authors. All authors read and approved the final version.

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