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RESEARCH PAPER

Clinical profile of trazodone users in a multisetting older population: data from the Italian GeroCovid Observational study

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Key summary points

Aim To comparatively assess the clinical profiles of older patients treated with trazodone or other antidepressants in a large dataset from the GeroCovid Observational multiscope and multisetting study.

Findings 10.8% out of 3396 persons included used trazodone and the 8.5% other antidepressants; the use of trazodone was highly prevalent in functionally dependent and comorbid older adults admitted to long-term care facilities or living at home. Conditions associated with trazodone use included depression, dementia and behavioral and psychological symptoms of dementia.

Message The present data suggest an off-label use of trazodone as a possible therapeutic option in the challenging field of behavioral and psychological disturbances in older adults with dementia.

Abstract

Background and objectives Depression is highly prevalent in older adults, especially in those with dementia. Trazodone, an antidepressant, has shown to be effective in older patients with moderate anxiolytic and hypnotic activity; and a common off-label use is rising for managing behavioral and psychological symptoms of dementia (BPSD). The aim of the study is to comparatively assess the clinical profiles of older patients treated with trazodone or other antidepressants.

Methods This cross-sectional study involved adults aged ≥ 60 years at risk of or affected with COVID-19 enrolled in the GeroCovid Observational study from acute wards, geriatric and dementia-specific outpatient clinics, as well as long-term care facilities (LTCF). Participants were grouped according to the use of trazodone, other antidepressants, or no antidepressant use.

Results Of the 3396 study participants (mean age 80.6 ± 9.1 years; 57.1% females), 10.8% used trazodone and 8.5% others antidepressants. Individuals treated with trazodone were older, more functionally dependent, and had a higher prevalence of dementia and BPSD than those using other antidepressants or no antidepressant use. Logistic regression analyses found that the presence of BPSD was associated with trazodone use (odds ratio (OR) 28.4, 95% confidence interval (CI) 18-44.7 for the outcome trazodone vs no antidepressants use, among participants without depression; OR 2.17, 95% CI 1.05-4.49 for the outcome trazodone vs no antidepressants use, among participants with depression). A cluster analysis of trazodone use identified three clusters: cluster 1 included mainly women, living at home with assistance, multimorbidity, dementia, BPSD, and depression; cluster 2 included mainly institutionalized women, with disabilities, depression, and dementia; cluster 3 included mostly men, often living at home unassisted, with better mobility performance, fewer chronic diseases, dementia, BPSD, and depression.

Discussion The use of trazodone was highly prevalent in functionally dependent and comorbid older adults admitted to LTCF or living at home. Clinical conditions associated with its prescription included depression as well as BPSD.

Keywords Depression · Dementia · Trazodone · BPSD, Profile, Clinical characteristics

The members of The GeroCovid Observational Working Group are listed in Acknowledgements.

Extended author information available on the last page of the article

Introduction

Depression is a highly prevalent, yet commonly underdiagnosed condition in older patients across all settings of care [1–3]. A wide range of depressive traits, from mild to major depression symptoms, can be found in advanced age associated with numerous psychiatric and non-psychiatric conditions [4]. Clinical expression of depression in old age is highly variable. Approximately, one-third of older patients with dementia show depressive symptoms associated with other neuropsychiatric symptoms, while those with depression (without dementia) more frequently have atypical behavioral disorders [2, 5, 6], such as sleep troubles, anorexia, agitation, and confusion [7], compared to younger adults. Moreover, anxiety often coexists in comorbid older persons with depression and prevalence estimates ranging from 23 to 48% [8]. Due to this clinical heterogeneity, the choice of an antidepressant treatment is often guided by the expected activity of the drug on coexistent neuropsychiatric symptoms. For this reason, real-life prescription studies of different antidepressant drugs according to clinical profiles may shed light on the available literature [9].

Among various antidepressants, trazodone qualifies as an eclectic drug showing an effective antidepressant action as well as moderate anxiolytic and hypnotic activities in older patients [10, 11]. Due to this sedative action, trazodone is often used in older people with dementia or delirium to manage agitation, insomnia, and other behavioral and psychological symptoms of dementia (BPSD) [12, 13]. However, available literature on the prescribing patterns of trazodone in different care settings is lacking. Iaboni et al. [14] described an increased use of trazodone and quetiapine over years, paralleling decreased benzodiazepine prescription in older adults with dementia in Canada, in both long-term care facilities (LTCF) and in the community.

In this context, the GeroCovid Observational initiative offered a unique opportunity of exploring the use of trazodone in older individuals from an epidemiological point of view. This observational study was launched by the Italian Society of Gerontology and Geriatrics (SIGG) to assess the direct and indirect impact of the COVID-19 pandemic on the health of older people in different care settings, including acute wards, dementia and geriatric outpatient clinics, home services, and LTCF. In addition to COVID-19-related information, the initiative also included data collection related to chronic diseases and treatments, which allowed for secondary analyses exploring the current management of diverse common conditions.

In this work, we aimed to characterize the prescription patterns of trazodone in comparison with other antidepressants in older people across different settings of care. In particular, we aimed at investigating the versatile use of trazodone in older persons with dementia and BPSD across diverse clinical settings.

Methods

Study design

This is a cross-sectional study using data from GeroCovid Observational, an initiative involving adults aged ≥ 60 years evaluated during the COVID-19 pandemic. GeroCovid Observational is a multicenter, multiscope, and multisetting study designed by the Italian Society of Gerontology and Geriatrics and is structured into the following research settings (details can be found in previous publications [15, 16]: GeroCovid acute care wards (including patients hospitalized for SARS-CoV-2 infection), GeroCovid home and outpatient care (including individuals accessing geriatric outpatient or home care services), GeroCovid dementia–drug monitoring and GeroCovid dementia–psychological health (including outpatients with cognitive impairment), GeroCovid long-term care facilities (LTCF) (including residents with suspected or confirmed SARS-CoV-2 infection), and GeroCovid outcomes (including individuals followed up after a COVID-19-related hospitalization). The study was conducted following the STROBE guidelines. Data registration was performed using a dedicated electronic register designed by Bluecompanion (UK, France) to collect all clinical data from every investigational site across Italy.

The GeroCovid Observational study protocol was approved by the Campus Bio-Medico University Ethical Committee in April 2020. All participating investigational sites further submitted relevant sub-protocols to their competent local ethical committee and institutional review boards, as applicable according to Italian regulations. All investigators accepted to work according to the Good Clinical Practice (GCP) (ICH E6-R2). Written or dematerialized informed consent was obtained from each participant. Alternatively, a written declaration was kept on file by the local investigator, which responded to applicable derogations during the pandemic.

Data collection

Data collection for this study included: demographic characteristics (age, sex), lifestyle (smoking habits, alcohol consumption), mobility (independent walking, walking with a cane or walker, bed-rest condition), social determinants (care setting: nursing home, in-patient, outpatients, home-based; household: lives at home alone and is autonomous, lives at home regularly assisted, lives at home alone with informal caregiver, lives at home with family and is autonomous, lives in a nursing home; social distancing impact:

major impact, no or moderate impact), chronic diseases from medical records coded according to Medical Dictionary for Regulatory Activities (MedDRA) [17] (hypertension, cardiovascular diseases, diabetes mellitus, osteoarthritis, chronic obstructive pulmonary disease (COPD), obesity, depression, BPSD, mild cognitive impairment (MCI), dementia, and type of dementia), and functional status with activity of daily livings (ADL) by Katz index and instrumental activity daily livings (IADL) by Lawton and Brody index. Based on the list of drugs chronically used by the study participants, coded according to the ATC, we identified participants treated with trazodone (TRAZ), other antidepressants (AnDep), or no antidepressant treatment (No AnDep). All participants with a sars-cov-2 infection (diagnosed with a real-time PCR) were included in the inpatient care setting, while in the other care settings only 26 participants were tested and resulted negative.

Statistical analysis

The characteristics of the study participants are presented as means ± standard deviation (SD), or median and interquartile range [25th–75th percentile] for quantitative measures, or counts and percentages for categorical variables. Normality of the distributions was evaluated considering the Kolmogorov–Smirnov test. No imputation of missing values was performed.

The study participants were grouped according to the use of antidepressants (TRAZ, AnDep, No AnDep) and compared according to sociodemographic characteristics (age, gender), lifestyle (smoking habits, alcohol habits, physical activity), mobility, social determinants (care setting, household, and social distancing impact), chronic conditions, functional status, and SARS-CoV-2 infection, using the Chi-squared or Fisher exact tests for categorical variables and generalized linear model testing for homoscedasticity through the Levene's test for quantitative variables. Post hoc analyses with Bonferroni adjustment for multiple comparisons were applied.

A multinominal logistic regression model with outcome groups defined according to antidepressant drugs, TRAZ, AnDep, or No AnDep use, was defined with the following independent variables: age, gender, mobility, household, chronic conditions (hypertension, cardiovascular diseases, stroke, diabetes mellitus, osteoarthrosis, chronic obstructive pulmonary disease, chronic renal failure, obesity, depression, mild cognitive impairment, dementia, and behavioral disorders)a. A block entering of independent variables was applied and results are presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Multiplicative interactions between the variables were also tested in the logistic models.

A cluster analysis based on k-means method was used to classify participants using TRAZ into clusters of coexisting characteristics. K-means algorithm divides the *n* sample into k clusters so that internal similarity of the clusters is high and the external similarity of the clusters is low. The optimal number of clusters was determined by comparing pseudo-*F* statistic and cubic clustering criterion for models with different number of clusters. The characteristics of participants in different clusters were compared using Chi-squared, Fisher exact tests or generalized linear model, as appropriate. All statistical tests were two tailed and statistical significance was assumed for p value < 0.05. The analyses were performed using SAS, V.9.4 (SAS Institute, Cary, NC).

Results

Out of the 3396 cases included in the analysis, 367 (10.8%) were using TRAZ and 288 (8.5%) AnDep. As shown in Table 1, the mean age was significantly higher in the TRAZ (84.3 ± 6.6) and AnDep (82.5 ± 7.2) groups than the No AnDep group (80.0 ± 9.4) ($F = 44.5$, $df = 2$, $p < 0.0001$). Over 60% of women were using antidepressants. Mobility deficits were approximately 50% in the entire study group ($n = 3170$). Patients using TRAZ had significantly lower levels of independent mobility than those taking AnDep or No AnDep treatments (32%, 36%, and 55% can walk independently, respectively) ($\chi^2 = 101.5$, $df = 6$, $p < 0.0001$).

In the entire study population, we found that the prescription of TRAZ was higher in outpatient settings (mainly outpatients followed for cognitive deficits), while any AnDep use was higher in inpatients ($\chi^2 = 47.9$, $df = 6$, $p < 0.0001$). In the TRAZ group, there was a significantly greater need for patient assistance either at home from informal caregivers or in nursing homes ($\chi^2 = 170.4$, $df = 8$, $p < 0.0001$).

The prevalence of chronic diseases, the use of antipsychotics, and TRAZ dosages are reported in Table 2. A recorded diagnosis of depression was present in 54% of those using AnDep, in 28% of those using TRAZ, and in 12% of those not treated (No AnDep). ($\chi^2 = 344.7$, $df = 2$, $p < 0.0001$). More than half of the participants suffering from depression (55%) were not undergoing any pharmacological treatment for depression. In the TRAZ and AnDep groups, approximately 70% had three or more chronic diseases vs. 40% in the No AnDep group ($\chi^2 = 177.1$, $df = 2$, $p < 0.0001$). In particular, hypertension, cardiovascular diseases, and osteoarthritis were more prevalent in the TRAZ and AnDep groups compared to the No AnDep group (for hypertension, 72.2% and 72.9% vs 58%, respectively, $p < 0.0001$; for cardiovascular diseases, 48.8% and 47.6% vs 41.2%, $p = 0.0048$; for osteoarthrosis, 36.5% and 35.5% vs 22.3%, $p < 0.0001$). Dementia reached 28% prevalence with a higher prevalence in the TRAZ group (67%) than the AnDep (49%) and the

Table 1 Demographic, lifestyle, and social characteristics of the GeroCovid population according to TRAZ, AnDep, and No AnDep groups

	All ($n=3396$)	TRAZ ($n=367$)	AnDep ($n=288$)	No AnDep ($n=2741$)	p value
Demographic characteristics					
Age (years)	80.6 ± 9.1	84.3 ± 6.6	82.5 ± 7.2	80.0 ± 9.4	< 0.0001[abc]
Gender (Female)	1938 (57.1)	251 (68.4)	191 (66.3)	1496 (54.6)	< 0.0001[ab]
Lifestyle					
Smoking habits (available for $n=1830$)					0.0077[a]
Current smoker	86 (4.7)	10 (4.9)	8 (4.7)	68 (4.7)	
Former smoker	371 (20.3)	26 (12.8)	24 (14.2)	321 (22.0)	
Never smoker	1373 (75.0)	168 (82.4)	137 (81.1)	1068 (73.3)	
Alcohol consumption (available for $n=1707$), yes	158 (9.3)	9 (3.8)	6 (3.6)	143 (11.0)	< 0.0001[ab]
Mobility (available for n = 3170)					< 0.0001[ab]
Walks independently	1615 (51.0)	112 (32.4)	99 (36.4)	1404 (55.0)	
Walks with help (cane or walker)	613 (19.3)	95 (27.4)	79 (29.0)	439 (17.2)	
Wheelchair (autonomous or pushed)	334 (10.5)	57 (16.5)	43 (15.8)	234 (9.2)	
Bed-rest condition	608 (19.2)	82 (23.7)	51 (18.8)	475 (18.6)	
Social determinants					
Care setting (available for $n=2974$)					< 0.0001[ab]
Outpatients	918 (30.9)	114 (33.8)	60 (22.6)	744 (31.4)	
Nursing home	559 (18.8)	72 (21.4)	63 (23.7)	424 (17.9)	
Inpatient	1113 (37.4)	89 (26.4)	91 (34.2)	933(39.3)	
Home based	384 (12.9)	62 (18.4)	52 (19.6)	270 (11.4)	
Household (available for $n=2763$)					< 0.0001[abc]
Lives at home alone, autonomous	160 (5.8)	11 (3.2)	11 (4.3)	138 (6.3)	
Lives at home alone, regularly assisted	195 (7.1)	25 (7.4)	29 (11.3)	141 (6.5)	
Lives at home alone, informal caregiver	528 (19.1)	125 (37.0)	67 (26.3)	336 (15.5)	
Lives at home with family, autonomous	1057 (38.2)	52 (15.4)	66 (25.9)	939 (43.3)	
Lives in a nursing home	823 (29.8)	125 (37.0)	82 (32.2)	616 (28.4)	
Social distancing impact (available for $n=1477$)					0.0030[a]
Major impact	543 (36.8)	64 (27.7)	51 (33.3)	428 (39.2)	
No or moderate impact	934 (63.2)	167 (72.3)	102 (66.7)	665 (60.8)	

Numbers are mean ± SD, or count (%), as appropriate

TRAZ (participants on trazodone); AnDep (participants taking other antidepressants; No AnDep (participants not taking antidepressants); SD (standard deviation)

Overall p value is calculated among the three groups of antidepressant users/not users

[a]Significant post hoc difference for TRAZ vs NoAnDep

[b]Significant post hoc difference for AnDep vs NoAnDep

[c]Significant post hoc difference for TRAZ vs AnDep

No AnDep group (21.6%) ($\chi^2=384.3$, $df=2$, $p<0.0001$). Similarly, BPSD and antipsychotic treatments were more prevalent in the TRAZ group: BPSD were present in 34.6% of the individuals in the TRAZ group, 13.9% in the AnDep group, and 3.8% in the No AnDep group ($p<0.0001$); antipsychotic treatments were used in 44.7% of individuals in the TRAZ group, 30.9% in the AnDep group, and 10.7% in the No AnDep group ($p<0.0001$). The daily dosage of TRAZ was lower than 100 mg in most of the participants (Table 2).

Clinical variables associated with the use of TRAZ or AnDep in multinomial models are reported in Table 3. Motor disability, depression, and dementia (with or without the presence of BPSD) were associated with an increased likelihood of using TRAZ or AnDep compared to not being treated. The interaction between depression and dementia (with or without BPSD) was statistically significant, meaning that the relationship between dementia and the outcome (use of TRAZ or AnDep or NoAnDep) depends on the presence of depression ($\chi^2=23.7$, $df=4$, $p<0.0001$). In fact, the association of dementia (and especially of dementia with BPSD) with the outcome was stronger in participants without depression compared to those with depression. In particular, in participants without depression, the association between TRAZ and dementia with BPSD (OR 28.4, 95% CI

Table 2 Health-related, functional, and frailty characteristics of the GeroCovid population according to the TRAZ, AnDep, and No AnDep groups

	All ($n=3396$)	TRAZ ($n=367$)	AnDep ($n=288$)	No AnDep ($n=2741$)	p value
Chronic conditions					
Hypertension (available for $n=3236$)	1972 (60.9)	262 (72.2)	210 (72.9)	1500 (58.0)	<0.0001[ab]
Cardiovascular diseases* (available for $n=3219$)	1371 (42.6)	177 (48.8)	136 (47.6)	1058 (41.2)	0.0048[a]
Stroke (available for $n=3212$)	305 (9.5)	44 (12.3)	35 (12.2)	226 (8.8)	0.0285
Diabetes mellitus (available for $n=3217$)	684 (21.3)	76 (21.1)	61 (21.3)	547 (21.3)	0.9970
Osteoarthrosis (available for $n=3213$)	806 (25.1)	131 (36.5)	102 (35.5)	573 (22.3)	<0.0001[ab]
Chronic obstructive pulmonary disease (available for $n=3211$)	426 (13.3)	52 (14.5)	36 (12.5)	338 (13.2)	0.7367
Chronic renal failure (available for $n=3213$)	384 (12.0)	49 (13.7)	40 (13.9)	295 (11.5)	0.2691
Obesity (available for $n=3224$)	254 (7.9)	25 (7.0)	24 (8.4)	205 (8.0)	0.7689
Depression (available for $n=3213$)	564 (17.6)	101 (27.9)	155 (54.0)	308 (12.0)	<0.0001[abc]
Mild cognitive impairment	140 (4.1)	15 (4.1)	10 (3.5)	115 (4.2)	0.8410
Dementia	978 (28.8)	245 (66.8)	141 (49.0)	592 (21.6)	<0.0001[abc]
If dementia, specify					
Alzheimer's disease	402 (11.8)	119 (32.4)	62 (21.5)	221 (8.1)	<0.0001[abc]
Vascular dementia	151 (4.5)	33 (9.0)	14 (4.9)	104 (3.8)	<0.0001[a]
Dementia with Lewy bodies	18 (0.5)	6 (1.6)	3 (1.0)	9 (0.3)	0.0039[a]
Frontotemporal dementia	10 (0.3)	3 (0.8)	2 (0.7)	5 (0.2)	0.0311
Mixed dementia	105 (3.1)	24 (6.5)	19 (6.6)	62 (2.3)	<0.0001[ab]
Other	253 (7.5)	46 (12.5)	40 (13.9)	167 (6.1)	<0.0001[ab]
Dementia due to Parkinson's disease	11 (0.3)	2 (0.5)	0 (0.0)	9 (0.3)	0.5098
Dementia due to other medical condition	10 (0.3)	4 (1.1)	0 (0.0)	6 (0.2)	0.0389
Dementia with BPSD	270 (8.0)	127 (34.6)	40 (13.9)	103 (3.8)	<0.0001[abc]
*Comorbidities**, 3+*	1546 (45.5)	245 (66.8)	205 (71.2)	1096 (40.0)	<0.0001[ab]
Functional status					
Activities of daily living, median (Q1, Q3) (available for $n=1668$)	4 (1, 6)	2 (1, 4)	3 (1, 5)	4 (1, 6)	<0.0001[abc]
Instrumental activities of daily living, median (Q1, Q3) (available for $n=1444$)	1 (0, 5)	0 (0, 1)	1 (0, 4)	2 (0, 6)	<0.0001[abc]
Antipsychotic drugs use, n (%)	545 (16.1)	164 (44.7)	89 (30.9)	292 (10.7)	<0.0001[abc]
Trazodone dose, n (%)			–	–	
> 100 mg/day		19 (7.8)			
≤ 100 mg/day		226 (92.2)			

Numbers are mean ± SD, median (Q1, Q3) or count (%), as appropriate

TRAZ, participants on trazodone; AnDep, participants assuming other antidepressants; No AnDep, participants not taking antidepressant; SD, standard deviation; BPSD, behavioral and psychological symptoms of dementia

Overall p value is calculated among the three groups of antidepressant users/not users

*Includes atrial fibrillation, peripheral arteriopathy, heart failure, and cardiomyopathy

**Total number of comorbidities, considering hypertension, cardiovascular diseases, stroke, diabetes mellitus, osteoarthrosis, chronic obstructive pulmonary disease, chronic renal failure, obesity, depression, behavior disorders, mild cognitive impairment, and dementia

[a]Significant post hoc difference for NoAnDep vs TRAZ

[b]Significant post hoc difference for NoAnDep vs AnDep

[c]Significant post hoc difference for TRAZ vs AnDep

18.8, 44.7; Wald $\chi^2=209.1$, $df=1$, $p<0.0001$) was significant, as well as the association between AnDep and dementia with BPSD (OR 5.68, 95% CI 2.94, 10.9; Wald $\chi^2=26.7$, $df=1$, $p<0.0001$). Among individuals with depression, an independent association between TRAZ and dementia with or without BPSD was still present, while no association was observed between AnDep and dementia. Stratifying analyses by care setting (Supplementary Table S1), results were substantially confirmed in home-based, nursing home, and outpatient participants, while a significant association between

TRAZ and dementia without BPSD and between AnDep and dementia with BPSD among participants without depression was found for inpatients.

The cluster analysis according to TRAZ use characterized three clusters (Supplementary Table 1; Figs. 1, 2). Cluster 1 included mainly older women living at home requiring assistance due to functional limitations (more than 60% moved with help or in a wheelchair), multimorbidity (73%), dementia (82%), and BPSD (62% among those with dementia); one out of four had a diagnosis of depression. Cluster 2 was mainly composed of institutionalized women with disabilities and chronic diseases (in particular, hypertension, diabetes mellitus, COPD, and obesity). Approximately 30% had depression, while 55% had dementia, but only 5% among those with dementia had BPSD. Cluster 3 included younger participants, mostly men, often living at home unassisted, with better mobility performance and fewer chronic diseases; however, 58% had dementia and 36% BPSD, while only 21% had depression.

In all clusters, the dose of TRAZ was mainly < 100 mg/day and over 40% were using antipsychotics with a slightly higher frequency in cluster 1.

Discussion

In this sample of older participants with, or at risk of, COVID-19, approximately one out of five persons (18.5%) over 60 years of age received an antidepressant, with trazodone being the most prescribed drug (10.8% vs. 8.5% other

Table 3 Multinomial logistic regression model with outcome "Trazodone", "Other antidepressants" or "No antidepressants" use in the Gero-Covid population

	TRAZ vs no AnDep			AnDep vs no AnDep			TRAZ vs AnDep		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Age, years	1.01	0.99–1.03	0.4027	1.00	0.98–1.02	0.8798	1.01	0.98–1.04	0.4446
Gender, female vs male	1.15	0.85–1.55	0.3694	1.05	0.76–1.45	0.7689	1.09	0.73–1.63	0.6602
Mobility vs walks independently									
Walks with help	1.28	0.87–1.89	0.2047	1.45	0.96–2.17	0.0749	0.89	0.54–1.46	0.6391
Wheelchair	2.00	1.23–3.25	0.0055	1.95	1.16–3.27	0.0120	1.03	0.55–1.91	0.9356
Bed-rest condition	1.34	0.85–2.13	0.2096	1.31	0.79–2.16	0.2969	1.03	0.56–1.89	0.9286
Household vs lives at home alone, autonomous									
Lives at home alone, regularly assisted	1.12	0.48–2.61	0.7924	1.36	0.60–3.08	0.4678	0.83	0.28–2.44	0.7304
Lives at home alone, informal caregiver	1.67	0.78–3.55	0.1874	1.14	0.53–2.45	0.7447	1.47	0.54–3.97	0.4520
Lives at home with family, autonomous	0.90	0.43–1.91	0.7901	0.96	0.46–2.00	0.9043	0.95	0.35–2.53	0.9101
Lives in a nursing home	1.67	0.77–3.63	0.1954	1.00	0.46–2.18	0.9901	1.68	0.61–4.66	0.3198
Hypertension	1.20	0.89–1.62	0.2248	1.39	1.00–1.93	0.0474	0.87	0.58–1.29	0.4773
Cardiovascular diseases	1.16	0.88–1.53	0.3009	1.16	0.86–1.57	0.3221	1.00	0.69–1.43	0.9814
Stroke	1.19	0.78–1.80	0.4213	1.16	0.74–1.82	0.5138	1.02	0.60–1.75	0.9343
Diabetes mellitus	0.85	0.61–1.18	0.3332	0.90	0.64–1.28	0.5707	0.94	0.61–1.45	0.7733
Osteoarthrosis	1.14	0.85–1.53	0.3832	1.07	0.78–1.47	0.6837	1.07	0.73–1.56	0.7423
Chronic obstructive pulmonary disease	1.12	0.76–1.65	0.5792	0.89	0.58–1.36	0.5877	1.26	0.75–2.11	0.3880
Chronic renal failure	0.78	0.52–1.16	0.2183	0.99	0.65–1.50	0.9625	0.79	0.47–1.31	0.3594
Obesity	0.86	0.51–1.47	0.5862	1.12	0.67–1.86	0.6681	0.77	0.40–1.49	0.4401
Mild cognitive impairment	1.67	0.87–3.20	0.1207	0.96	0.45–2.03	0.9094	1.75	0.70–4.36	0.2324
Study participants with depression									
Dementia with no BPSD vs no dementia	2.29	1.26–4.16	0.0066	1.53	0.92–2.56	0.1037	1.50	0.78–2.89	0.2305
Dementia with BPSD vs no dementia	4.97	2.52–9.80	< 0.0001	1.96	0.99–3.78	0.0560	2.54	1.22–5.29	0.0128
Dementia with BPSD vs dementia with no BPSD	2.17	1.05–4.49	0.0365	1.28	0.63–2.60	0.4988	1.70	0.78–3.68	0.1797
Study participants without depression									
Dementia with no BPSD vs no dementia	3.87	2.66–5.62	< 0.0001	3.25	2.12–4.98	< 0.0001	1.19	0.70–2.03	0.5254
Dementia with BPSD vs no dementia	28.4	18.0–44.7	< 0.0001	5.68	2.94–10.9	< 0.0001	5.00	2.48–10.1	< 0.0001
Dementia with BPSD vs dementia with no BPSD	7.34	4.72–11.4	< 0.0001	1.75	0.90–3.38	0.0974	4.20	2.12–8.32	< 0.0001

Block entering of independent variables

OR, odds ratio; 95% CI, 95% confidence interval; TRAZ, participants on trazodone; AnDep, participants taking other antidepressants; No AnDep, participants not taking antidepressants; BPSD, behavioral and psychological symptoms of dementia

antidepressants). We also found that the use of trazodone was associated with clinical conditions other than depression. The frequency of antidepressant use in our sample was similar to the available literature [18], although lower in comparison with data from LTCF studies [19, 20]. Moreover, our study showed a higher use of trazodone than those reported in other studies [13, 21]. This may be explained by the fact that our study included multiple care settings with diverse clinical characteristics. The GeroCovid study includes a large data collection from diverse care settings, which extends clinical knowledge from previous population-based cohort or LTCF studies [13, 21].

We found that participants using trazodone were more likely to be functionally dependent and to have several comorbidities and a higher prevalence of cardiovascular

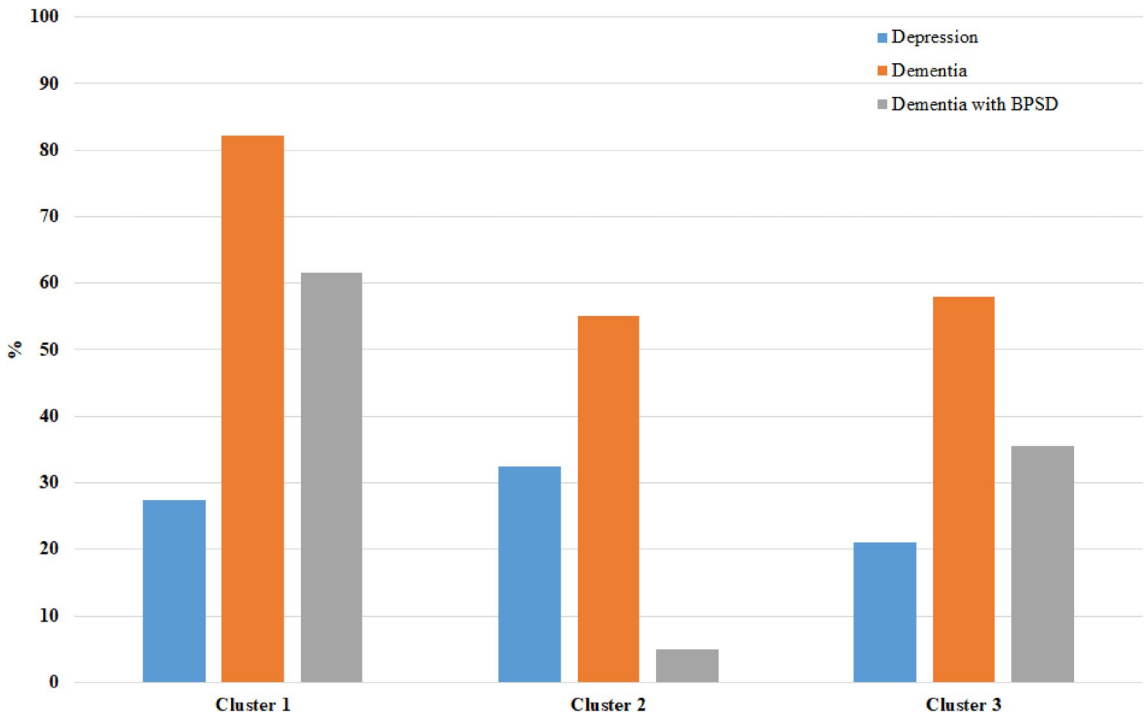

Fig. 1 Depression, dementia, and BPSD prevalence by clusters identified among TRAZ users

	Cluster 1	Cluster 2	Cluster 3
Demographic characteristics	Female dominance	Female dominance	Male dominance
	Older participants	Older participants	Younger participants
Mobility	Walk with help	Bed-rest conditions	Walk independently
Social determinants	Living at home	Institutionalized	Living at home with family
Chronic conditions	Multimorbidity (in particular hypertension, dementia and BPSD)	Multimorbidity (in particular hypertension, osteoarthrosis, diabetes mellitus, chronic obstructive pulmonary disease, obesity)	Fewer chronic diseases

Fig. 2 Summary of participants' characteristics among clusters

diseases or osteoarthritis. Furthermore, 28% of the participants in the TRAZ group had a formal diagnosis of depression (vs. 54% among participants treated with other antidepressants and 12% among participants not receiving antidepressants), while two-thirds of TRAZ group participants suffered from dementia (vs. 49% of those treated with other antidepressants and 22% of those not receiving antidepressant treatment), and one-third of TRAZ group had BPSD (vs. 14% in the AnDep and 4% in the No AnDep groups). Analyses underlined that independent of a depression diagnosis, BPSD was associated with an increased use of trazodone compared to other antidepressants. The association was the strongest among participants without depression, but still statistically significant in those with depression. Indeed, this antidepressant has been shown to be used off-label for insomnia [22, 23] and hold anxiolytic [24, 25] effects, as well as control aggression [26] and other BPSD [27, 28].

The cluster analysis provides some further insights regarding the prescription of trazodone. In particular, clusters 1 and 3 included older community-dwelling adults with a high prevalence of BPSD. However, cluster 3 included mainly those with better general clinical conditions, even if affected by dementia and BPSD and often not needing direct assistance at home. Furthermore, the dosage of trazodone in clusters 1 and cluster 3 was lower than 75 mg/day, a dosage which has been reported for treating BPSD, such as wandering, agitation, delusions [29], and treating psychotic symptoms in depression and dementia [30]. Interestingly, antipsychotics were used in 40–50% of individuals using trazodone. Trazodone has also been reported to be effective in neuroleptic-induced akathisia [31].

Cluster 2 identified institutionalized individuals and inpatients with disabilities and chronic pathologies, among which about one-third had depression and less than half dementia, but very few had BPSD.

Regardless of diagnosed dementia, antidepressants other than trazodone were prescribed in participants with depression. On the other hand, in those with dementia, there was a vast use of antidepressants regardless of depression or BPSD [32]. Dementia is often accompanied by affective disorders, including anxiety and emotional lability, which are widely treated with antidepressants even if clinical evidence regarding their efficacy remains conflicting [33]. Moreover, antidepressants such as sertraline and citalopram have also shown to reduce agitation and psychosis in dementia, which may partially explain their increased use among non-depressed participants with dementia [33]. Nevertheless, cardiovascular side effects might limit their off-label use in frail older individuals without depression. Psychiatric reactions to SSRI use, including anxiety, irritability and, more rarely, mania and psychosis, may also limit their use in older patients [34].

Another interesting finding from our study was that more than half of the participants suffering from depression were not treated with any antidepressant agent, which confirms other reports [35, 36], suggesting that the stigma of using psychiatric drugs in old people has not yet been overcome [37–39].

The strength of the present study relies on the large sample size and on the extensive clinical assessment in a real-life older population from different care settings.

The main limitations are represented by the cross-sectional analysis, the lack of information regarding the purpose of prescription, duration, effectiveness, as well as the tolerability of the prescribed drugs. Diagnoses were collected by medical records and we did not collect data regarding pain.

In conclusion, this study underlined a high prevalence of trazodone prescription in a large, multiset sample of older Italian participants with, or at risk of, COVID-19. The present data suggest an off-label use of this drug at doses ≤ 100 mg/day for the treatment of dementia with BPSD with or without depression. Further studies assessing reason of prescription, effectiveness and tolerability of different antidepressants in frail older adults, with and without dementia are necessary to design. Then, dedicated clinical trials trazodone on behavioral and psychological disturbances in the rapidly growing number of older adults with dementia.

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Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval The GeroCovid Observational study protocol was approved by the Campus Bio-Medico University Ethical Committee in April 2020. All participating investigational sites further submitted relevant sub-protocols to their competent local ethical committee and institutional review boards, as applicable according to Italian regulations. All investigators accepted to work according to the Good Clinical Practice (GCP) (ICH E6-R2).

Informed consent Written or dematerialized informed consent was obtained from each participant. Alternatively, a written declaration was kept on file by the local investigator, which responded to applicable derogations during the pandemic.

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