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RESEARCH ARTICLE

Real-World Use of Trazodone in Older Persons in Long Term Care Setting: A Retrospective Study

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ABSTRACT

Background: Trazodone, an antidepressant drug is also largely used in several medical contexts. Insomnia, behavioral disorders, and anxiety may be underlying symptoms for prescribing trazodone. This cross-sectional study aims to identify reasons for trazodone prescription, assess the efficacy, as well as identify any related side effects in older persons living in long term care facilities (LTCFs).

Methods: Older adults aged ≥ 60 years, at risk of or affected with Covid-19 and enrolled in the GeroCovid Observational study from LTCFs, and using trazodone were included. A structured questionnaire was administered to treating physicians regarding reasons for trazodone prescription, discontinuation, possible adverse events and benefits.

Results: Thirty-seven out 74 LTCFs participating in both the GeroCovid and GeroCovid Vax studies completed the questionnaire regarding trazodone use. Of the 427 participants included in this study analysis, we found that 43% had diagnoses of dementia and depression, 33% had dementia, no behavioral and psychological symptoms of dementia (BPSD) and no depression, 14% had dementia with BPSD and no depression, and < 11% had only depression. The main reasons for trazodone prescription included agitation, insomnia, depression and anxiety. Trazodone use was reported as partially or totally effective in more than 90% of participants using the drug. Falls were the most frequent adverse event (30% of participants).

Conclusions: Our data suggest that trazodone behaves as an eclectic antidepressant that, in the clinical practice, may also be used for BPSD and insomnia, especially in older people with dementia.

A full list of the working group members is provided in Acknowledgements section.

Summary

- Our study sought to evaluate the reasons for using trazodone in long term care facilities, its effectiveness and its main side effects in this setting.
- The main reasons for trazodone prescription in long term care facilities include agitation, insomnia, depression and anxiety. Trazodone was reported effective in 43%–58% of participants, partially effective in 30%–45% and totally ineffective in 7%–12% of cases; the main adverse effects related to trazodone assumption are falls, reported by more than 30% of participants, while all the others adverse events were reported in < 4% of individuals.
- Our data suggest that trazodone is used in the clinical practice also for behavioral and psychological symptoms of dementia and insomnia, mainly in older people with dementia.

1 | Introduction

Trazodone, a licensed antidepressant drug is largely used in several medical contexts (i.e., acute care hospitals, clinics, nursing homes, and at-home [1–3], at low dosages up to 100 mg [1], which are unlikely to exert an antidepressant effect). Interestingly, trazodone use is frequent even in other clinical symptoms such as, insomnia, behavioral and psychological symptoms of dementia (BPSD), and anxiety. Studies have underlined that low or very low doses of trazodone have been proven effective for these noncanonical indications [1–3]. In Spain, Macías Saint-Gerons et al. demonstrated a frequent use of trazodone in patients with Alzheimer's dementia (20.4%), sleep disorders (16.2%), and anxiety disorders (8.9%), as the most common off label therapeutic indications [3]. A systematic review analyzing few and heterogeneous studies regarding trazodone prescription for insomnia concluded that it is a generally safe drug, particularly for patients with comorbid depression, across different populations [4]. In addition, Cuomo et al. suggested neuroprotective properties of trazodone in improving depressive symptoms in older adults and managing behavioral disturbances in patients affected by Alzheimer's disease or frontotemporal dementia [5].

However, due to the largely growing use of trazodone use in older persons living in long term care facilities (LTCFs), there is a need to investigate the clinical symptoms and characteristics of trazodone prescription use in this setting of older adults.

Older persons living in LTCFs are generally frail and often characterized by multimorbidity, polypharmacy, disability and dementia which excludes them from clinical trials. However, LTCFs provide a unique setting due to the residents' characteristics and allow to carefully monitor the effects of a given medication. Therefore, this population may represent a pivotal advantage for research regarding real-life responses in older, frail, and multimorbid patients generally excluded from clinical trials. This study aimed to identify the reasons for trazodone prescription in LTCFs and to assess the efficacy, as well as any side effects in this setting.

2 | Methods

2.1 | Study Design and Population

This retrospective study included 427 residents of LTCF enrolled in GeroCovid Observational and GeroCovid Vax studies. Details on these initiatives can be found elsewhere [6, 7]. Briefly, GeroCovid Observational is a longitudinal multiscope and multisetting study (also including long term care [LTC] settings) promoted by the Italian Society of Gerontology and Geriatrics (SIGG; Florence, Italy) and was performed from March to December 2020. This study explored the impact of COVID-19 pandemic and SARS-CoV-2 infection in different health domains of individuals over 60 years. GeroCovid Vax is a prospective study implemented only in LTCFs between February and May 2021. This study was promoted by the SIGG and the Istituto Superiore di Sanità (ISS, Rome, Italy), and sponsored by the Italian Medicines Agency (AIFA). GeroCovid Vax aimed to assess the efficacy and safety of vaccinations against SARS-CoV-2 in residents older than 60, some of whom had been previously involved in GeroCovid Observational. In both studies, data was collected regarding ongoing chronic drug treatments for each participant. For the present analysis we included residents undergoing trazodone therapy at the time of data collection. In August 2022, LTFCs physicians were asked to respond to an additional questionnaire regarding trazodone use. LTCFs physicians from 37 out 74 LTCFs participating in the GeroCovid and GeroCovid Vax studies provided such additional information regarding trazodone use, corresponding to data in 507 patients. However, 80 participants did not have complete information. Thus, our present study provides data on 427 trazodone users.

Data were recorded in a dedicated electronic register developed by Bluecompanion (London, United Kingdom) in an anonymous way. The GeroCovid Observational study protocol was approved by the Campus Bio-Medico University Ethical Committee in April 2020. The GeroCovid Vax study protocol was approved by the Italian National Ethical Committee in January 2021. All participating investigational centers received approval of the study protocol from their local Ethical Committee and institutional review boards. All investigators agreed to work according to the Good Clinical Practice (GCP) (ICH E6-R2). Each participant or their next of kin (for those with severe cognitive impairment) provided written or dematerialized informed consent. Alternatively, the local investigator provided a written declaration, according to the derogations granted during the COVID-19 pandemic.

2.2 | Data Collection

For the purpose of this study, trained researchers collected the following data from each participant: age, sex, the presence of chronic diseases coded based on Medical Dictionary for Regulatory Activities [8] (i.e., hypertension, stroke, cardiovascular diseases, diabetes mellitus, osteoarthrosis, chronic obstructive pulmonary disease, obesity, undernutrition, chronic kidney disease, respiratory disease, chronic liver disease, cancer, and

anxiety), with special attention to the clinical diagnosis of depression and dementia (according to the DSM-V criteria or on clinical evaluation and administration of validated scales). For depression, also depressive symptoms were considered.

In addition to the above information, a structured questionnaire (for details, see Supporting Information S2) was developed by a team of geriatricians and administered to physicians at LTCFs to explore the following aspects related to trazodone treatment:

- Reasons for prescribing trazodone including agitation, insomnia, wandering, depression, apathy, physical aggression, verbal aggression, anxiety, echolalia, grumble, delusions, hallucinations, and opposing attitudes;
- Possible adverse events linked to trazodone assumption including headache, nausea, vomiting, diarrhea, constipation, change in appetite or weight, weakness, nervousness, dizziness, instability, falls, delirium, muscle aches, rash, sweats, tremors, coordination problems, tired/itchy/red eyes, chest pain, heartbeat, coma, fainting, convulsions, short breath, and bleeding or bruising (according to technical sheet);
- Overall benefit of the therapy, classified as total, partial, or no benefit; and
- Possible reasons for therapy discontinuation, including the following: new unrelated conditions, inefficacy, adverse reaction, drug effective but no longer necessary, and fear of drug interactions.

In relation to falls, the questionnaire included information regarding whether falls occurred since treatment with trazodone, or if falls occurred before trazodone use.

2.3 | Statistical Analyses

Summary statistics are expressed as means ± standard deviation (SD) for quantitative measures and counts and percentages for categorical variables. Missing values were not imputed.

Participants were grouped according to the following diagnoses: (1) dementia and depression; (2) depression only; (3) dementia with BPSD (no depression); (4) dementia only (no BPSD, no depression); and (5) other (including those with neither dementia nor depression diagnosis). Groups were compared according to sociodemographic characteristics, main chronic conditions, reasons for trazodone prescription and discontinuation by using the Chi-square or Fisher exact tests for categorical variables, and Kruskal–Wallis test or Wilcoxon rank sum test for quantitative ones; Bonferroni adjustment for multiple comparisons was considered.

Since falls were the most frequently reported adverse events, we compared the characteristics of participants who fell after trazodone assumption (but with no falls before prescription) versus those with no falls. Moreover, a multivariable logistic regression model with a stepwise selection (p-value to entry 0.15; p-value to stay 0.20) was performed among variables associated with the outcome with $p \leq 0.20$ at the univariable level, forcing age and sex into the model.

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).

3 | Results

Table 1 shows the main demographics and clinical characteristics of the entire sample population and according to groups.

Individuals with dementia, with or without BPSD, were older than those with depression, with or without dementia (85.3 ± 5.0 and 85.6 ± 6.2 years vs. 83.5 ± 7.1 and 81.1 ± 10.6 years, respectively), even if differences were not statistically significant (Wilcoxon sum rank test with Bonferroni adjustment, $p > 0.005$). In relation to comorbidities, significant differences among groups were found for diabetes mellitus (more prevalent among participants with depression only compared to those with dementia only, 45% vs. 13%, respectively; Chi-square test 16.20, DF 1, $p < 0.0001$) and osteoarthrosis (more frequent among individuals with dementia and depression than among those with dementia and BPSD, 59% vs. 35%, respectively; Chi-square test 10.43, DF 1, $p = 0.0012$). A borderline significant difference for stroke among participants with depression only, with respect to those with dementia and BPSD, was also found (21% vs. 1.8%, respectively; Fisher Exact test 9.22, DF 1, $p = 0.0053$).

Table 1 reports the main reasons for trazodone prescription including agitation (reported in all groups, with frequencies between 50% and 60%), insomnia (reported by 30%–50% of study participants and by 80% of individuals in "other" group), depression (referred by 83% and 57% of individuals with depression, without or with dementia, respectively) and anxiety (reported by more than 30% of individuals with depression only, or with dementia BPSD).

Trazodone was reported effective in 43%–58% of participants (100% in "other" group), partially effective in 30%–45% and totally ineffective in 7%–12% of cases (Table 2). A small percentage reported a discontinued use of trazodone because it was considered no longer necessary (3%–7%). The main adverse effects related to trazodone assumption are presented in Figure 1: falls, reported by more than 30% of participants (about 30% of individuals with dementia, and 18% of those with depression), were the most frequent adverse events. Falls were also reported before trazodone assumption, but in a lower percentage (21% among participants with dementia and BPSD, 24% among those with dementia only, 19% among those with dementia and depression, and 15% for participants with depression only). All the others adverse events were reported in < 4% of individuals, with no significant differences among groups.

Fifty-eight participants reported falls after treatment with trazodone, and clinical characteristics are described in Supporting

TABLE 1 | Main clinical characteristics.

	All (n = 427)	Dementia and depression (n = 182)	Depression only (n = 29)	Dementia with BPSD (n = 58)	Dementia, no BPSD (n = 143)	Other (n = 15)	p-value
Age, mean ± SD	84.2 ± 7.0	83.5 ± 7.1	81.1 ± 10.6	85.3 ± 5.0	85.6 ± 6.2	81.2 ± 8.7	0.040
Female sex, n (%)	316 (74.0)	143 (78.6)	21 (72.4)	39 (67.2)	105 (73.4)	8 (53.3)	0.15
Main chronic diseases, n (%)							
Hypertension	311 (73.2)	137 (75.3)	23 (79.3)	44 (75.9)	98 (68.5)	9 (69.2)	0.58
Stroke	54 (12.8)	28 (15.4)	6 (20.7)	1 (1.8)	18 (12.9)	1 (7.7)	0.06
Diabetes mellitus	93 (22.1)	45 (24.9)	13 (44.8)	14 (24.1)	18 (12.9)	3 (23.1)	0.003
Osteoarthrosis	218 (51.5)	107 (58.8)	14 (48.3)	20 (34.5)	71 (50.4)	6 (46.2)	0.027
COPD	55 (13.1)	22 (12.2)	5 (17.2)	6 (10.3)	21 (15.0)	1 (7.7)	0.78
Obesity	20 (4.8)	9 (5.0)	1 (3.4)	4 (6.9)	5 (3.6)	1 (7.7)	0.85
Undernutrition	34 (8.3)	18 (10.3)	1 (3.4)	4 (6.9)	10 (7.5)	1 (7.7)	0.71
Chronic kidney disease	74 (17.3)	33 (18.1)	5 (17.2)	10 (17.2)	23 (16.1)	3 (20.0)	0.99
Cardiovascular disease	284 (66.5)	129 (70.9)	17 (58.6)	32 (55.2)	96 (67.1)	10 (66.7)	0.22
Respiratory disease	61 (14.3)	25 (13.7)	5 (17.2)	6 (10.3)	24 (16.8)	1 (6.7)	0.66
Chronic liver disease	47 (11.0)	21 (11.5)	2 (6.9)	9 (15.5)	13 (9.1)	2 (13.3)	0.67
Cancer	65 (15.2)	30 (16.5)	2 (6.9)	3 (5.2)	27 (18.9)	3 (20.0)	0.09
Anxiety	47 (11.0)	0 (0.0)	0 (0.0)	19 (32.8)	27 (18.9)	1 (6.7)	< 0.001
BPSD	90 (21.1)	32 (17.6)	0 (0.0)	58 (100.0)	0 (0.0)	0 (0.0)	< 0.001
Reason for prescription[a], n (%)							
Agitation	241 (56.4)	89 (48.9)	18 (62.1)	33 (56.9)	92 (64.3)	9 (60.0)	0.08
Insomnia	184 (43.1)	72 (39.6)	9 (31.0)	31 (53.4)	60 (42.0)	12 (80.0)	0.009
Wandering	47 (11.0)	18 (9.9)	0 (0.0)	6 (10.3)	23 (16.1)	0 (0.0)	0.05
Depression	127 (29.7)	103 (56.6)	24 (82.8)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
Apathy	45 (10.5)	30 (16.5)	2 (6.9)	6 (10.3)	7 (4.9)	0 (0.0)	0.008
Physical aggression	36 (8.4)	9 (4.9)	1 (3.4)	11 (19.0)	13 (9.1)	2 (13.3)	0.015
Verbal aggression	82 (19.2)	26 (14.3)	0 (0.0)	18 (31.0)	36 (25.2)	2 (13.3)	0.001
Anxiety	124 (29.0)	66 (36.3)	11 (37.9)	19 (32.8)	27 (18.9)	1 (6.7)	0.002
Echolalia	8 (1.9)	2 (1.1)	0 (0.0)	0 (0.0)	6 (4.2)	0 (0.0)	0.26
Grumble	25 (5.9)	6 (3.3)	1 (3.4)	7 (12.1)	11 (7.7)	0 (0.0)	0.10
Delusions	40 (9.4)	14 (7.7)	1 (3.4)	15 (25.9)	10 (7.0)	0 (0.0)	< 0.001
Hallucinations	55 (12.9)	19 (10.4)	2 (6.9)	17 (29.3)	17 (11.9)	0 (0.0)	0.001
Opposing attitudes	82 (19.2)	26 (14.3)	2 (6.9)	19 (32.8)	35 (24.5)	0 (0.0)	0.001
At least one symptom among BPSD list	395 (92.5)	156 (85.7)	23 (79.3)	58 (100.0)	143 (100.0)	15 (100.0)	< 0.001

Abbreviations: BPSD, behavioral and psychological symptoms of dementia; COPD, chronic obstructive pulmonary disease; SD, standard deviation.
[a]It was possible to report more than one reason for the prescription.

Information S1: Table S1. Compared to participants with no falls (n = 274), no significant differences by age, gender and main chronic diseases were found with respect to individuals with falls, except cancer was found to be more frequent in those experiencing falls (40% vs. 16%, Fisher Exact test 8.33, DF 1, p = 0.0104). At the multivariable level (Supporting Information S1: Table S2), characteristics associated with falls were cancer (OR = 2.50, 95% CI 1.18–5.27; Wald Chi-square 5.77, DF 1, p = 0.0163) and physical aggression as reason for prescription (OR = 3.68, 95% CI 1.46–9.25; Wald Chi-square 7.65, DF 1, p = 0.0163); borderline

TABLE 2 | Outcomes of trazodone therapy in terms of efficacy (upper panel) and reasons for discontinuation (lower panel).

	All (n = 427)	Dementia and depression (n = 182)	Depression only (n = 29)	Dementia with BPSD (n = 58)	Dementia, no BPSD (n = 143)	Other (n = 15)	p-value
Benefit							0.019
No	40 (9.4)	13 (7.2)	3 (10.3)	7 (12.1)	17 (11.9)	0 (0.0)	
Partial	143 (33.6)	63 (35.0)	10 (34.5)	26 (44.8)	44 (30.8)	0 (0.0)	
Yes	242 (56.9)	104 (57.8)	16 (55.2)	25 (43.1)	82 (57.3)	15 (100.0)	
New unrelated conditions	16 (3.8)	7 (3.9)	0 (0.0)	2 (3.4)	6 (4.2)	1 (6.7)	0.81
Inefficacy	47 (11.1)	19 (10.6)	5 (17.2)	8 (13.8)	15 (10.5)	0 (0.0)	0.48
Adverse reaction	9 (2.1)	5 (2.8)	0 (0.0)	1 (1.7)	3 (2.1)	0 (0.0)	1.00
Effective, but no longer necessary	21 (5.0)	12 (6.7)	1 (3.4)	0 (0.0)	7 (4.9)	1 (6.7)	0.24
Fear of drug interactions	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0.58

Abbreviation: BPSD, behavioral and psychological symptoms of dementia.

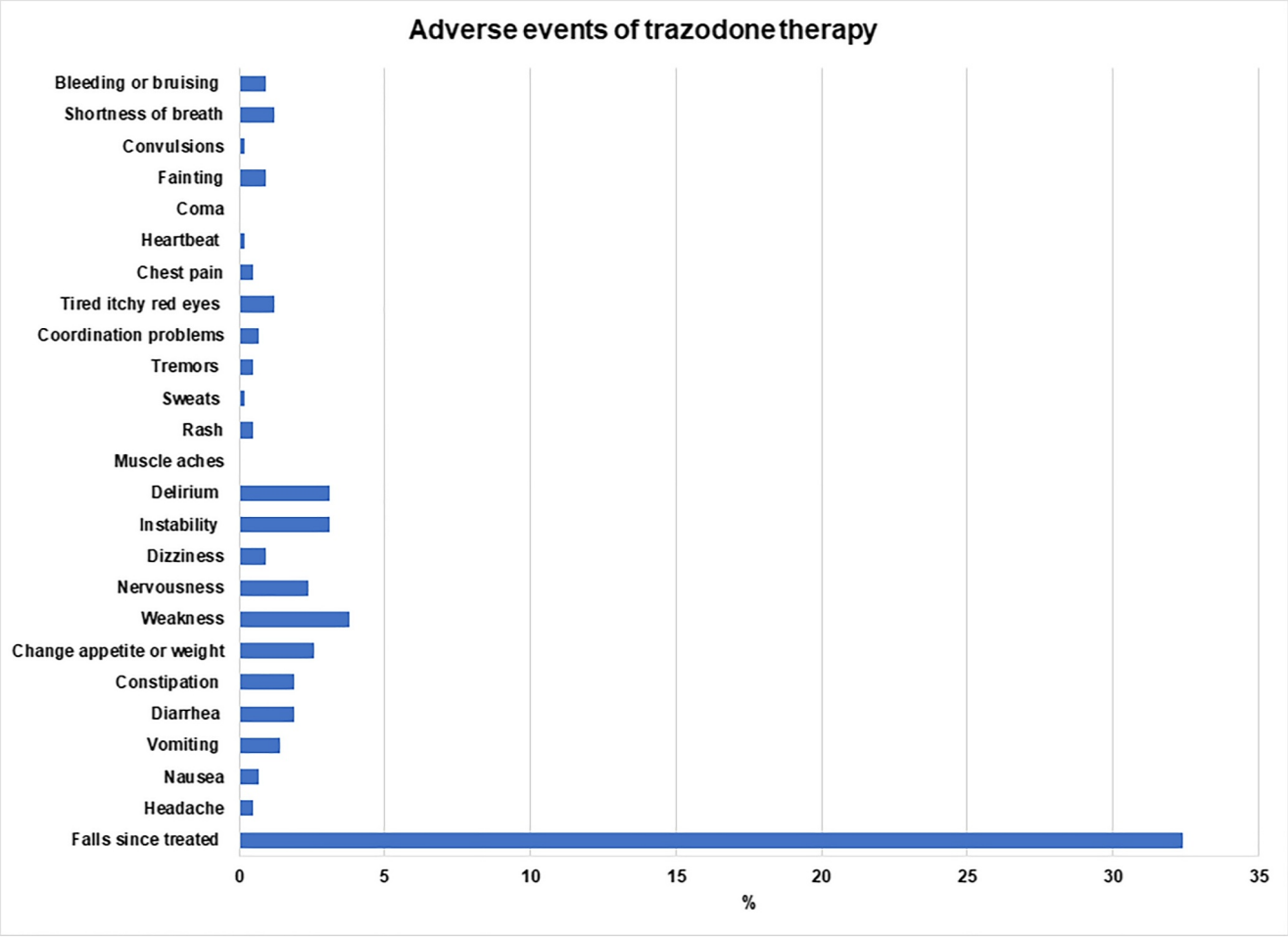

FIGURE 1 | Adverse events of trazodone therapy.

significance was found also for apathy and grumbling as reasons for prescription (OR = 2.24, 95% CI 0.94–5.35, Wald Chi-square 3.33, DF 1, p = 0.0680; and OR = 2.82, 95% CI 0.98–8.19, Wald Chi-square 3.65, DF 1, p = 0.0561, respectively).

4 | Discussion

This is the first study to explicitly test trazodone use in LTCFs older residents. We found that the need for trazodone

prescription was frequent in agitation, anxiety, and insomnia in residents with dementia and depression, while wandering, delusions, opposing attitudes, and hallucinations were more common in those with dementia only.

Trazodone is an antidepressant with multiple therapeutic mechanisms. In addition to inhibiting serotonin reuptake, trazodone is an antagonist of 5-HT2 receptor whose activation is commonly associated with insomnia, anxiety, and agitation [9, 10]. The different effects related to trazodone use may be explained by the dose used. At low doses, trazodone acts on the 5-HT2A, alpha-1, and H1 receptors inducing a hypnotic effect, and at higher doses (at least 150 mg/day in adult patients), combining 5-HT2A antagonism and SERT blockade, contributes to its antidepressant role [11, 12].

Trazodone is licensed for major depressive disorders and prescribed for insomnia in depression. The rising use of trazodone in LTCFs is consistent with increasing diagnosis and treatment of depression as well as, reducing neuropsychiatric symptoms in patients affected by various types and degrees of dementia [13, 14]. Functional serotonergic deficits may contribute to the onset of behavioral disturbances in dementia such as insomnia, depression, and anxiety [15, 16]. For these symptoms, trazodone may represent a sedating atypical serotonergic antidepressant with a lower rate of adverse effects respect to other psychotropic drugs [17–19].

Our data highlighted that the use of trazodone was associated with a higher incidence of falls in 32.4%. However, falls were also reported before trazodone assumption in 20.6%, especially in participants with dementia (24.1%). In literature the risk of falls in older adults seemed comparable for different antidepressant classes: selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and trazodone [20]. A recent retrospective matched cohort study conducted among older adults, aged 70–89 years, concluded that the risk of fall-related injuries was significantly increased by the use of antidepressants, duloxetine, escitalopram, paroxetine, amitriptyline, imipramine, and trazodone, particularly in the context of polypharmacy [21]. A meta-analysis in 2018 showed that in older adults, SSRIs were systematically associated with a higher risk of falls and fractures compared with TCAs. Moreover, the risk of falls and fractures associated with trazodone, bupropion, and mirtazapine appears to be equivalent to or lesser than that observed for SSRIs [22, 23]. The risk of falls with low-doses trazodone, moreover, was demonstrated similar to risk of falls associated with benzodiazepines (OR: 1.5–2.0) [24, 25].

Consensus panels on dementia treatment have concluded that there is not clear evidence regarding recommendations for a low-dose use of trazodone in BPSD due to evidence that low-dose trazodone use has also been correlated with an increased risk of falls [26].

Interestingly, we found that significant clinical characteristics associated with falls in trazodone users were cancer and physical aggression. Indeed, falls may be explained by the loss of physical function and frailty in older adults with cancer caused by sarcopenia and cachexia [27, 28]. The association between falls and agitation or verbal/physically/aggressive behaviors, is common in residents with moderate-severe dementia [29]. Falls in dementia patients are associated with multiple intrinsic and extrinsic risk factors, some shared with aging, while others unique to the disease. These latter factors include verbally disruptive and attention-seeking behavior, cortical changes on imaging studies, visual perception problems, balance and gait impairments and caregiver burden [30]. Due to numerous confounders, the difficulty of establishing the correlation between trazodone and falls remains difficult.

Our findings suggest that trazodone is safe at low doses in older residents, however it remains important to be aware of the high risk of falls, similarly to other antidepressants and benzodiazepines, and to understand those potential adverse events when managing trazodone toxicity.

The strengths of our study include the collection of data from a large sample of older LTCFs residents in the "real world"; therefore, our results are representative of everyday clinical practice in the vulnerable population living in institutions. Real-life data analyses are particularly useful for the evaluation of new treatment options and may provide healthcare professionals and public health policy makers with additional information to those obtained from randomized controlled trials.

On the other hand, our study had some limitations. First, although the DSM-V criteria are the reference standard for neuropsychological diagnosis in current clinical practice in LTCFs, the retrospective nature of our study could not rely on a scheduled diagnostic procedure. Second, the available information was limited to about half of the LTCFs involved in the GeroCovid study.

Finally, even though the clinical effects of trazodone could not be rated through a standardized scale, assessments were performed by physicians with specialized clinical training in residential care, mostly geriatricians.

5 | Conclusions and Implications

Our data suggest that trazodone behaves as an eclectic antidepressant that, in the clinical practice, is also used also for BPSD and insomnia, mainly in older people with dementia. Attempts should be made to assess the cost/benefit ratio of off-label trazodone use by balancing its efficacy and side effects at different doses. We strongly believe that the present data provide an important basis for testing off-label uses of trazodone in specifically designed large randomized clinical trials in older adults.

Author Contributions

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Ethics Statement

The GeroCovid Observational study protocol was approved by the Campus Bio-Medico University Ethical Committee in April 2020. The GeroCovid Vax study protocol was approved by the Italian National Ethical Committee in January 2021. All participating investigational centers received approval of the study protocol from their local Ethical Committee and institutional review boards.

Consent

Each participant or their next of kin (for those with severe cognitive impairment) provided written or dematerialized informed consent. Alternatively, the local investigator provided a written declaration, according to the derogations granted during the COVID-19 pandemic.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be made available on reasonable request to the study's supervisors (Prof. Raffaele Antonelli Incalzi; Dr. Alessandra Coin).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.