v. 4, n. 96, 2024

International Journal of Health Science

Acceptance date: 29/10/2024

# USE OF TRAZODONE IN THE MANAGEMENT OF PSYCHOMOTOR AGITATION IN DEMENTIA SYNDROMES

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**Abstract: INTRODUCTION** The introduction outlines the significant challenge that psychomotor agitation presents in dementia patients, highlighting the prevalence of agitation in various forms of dementia, including Alzheimer's and Lewy body disease. It emphasizes the importance of finding safer pharmacological options beyond traditional antipsychotics, given their serious side effects. Trazodone, with its sedative properties and relatively safer profile, is proposed as a promising alternative for managing agitation, particularly in elderly dementia patients with multiple comorbidities. **OBJETIVE** To review and evaluate the efficacy and safety of trazodone in managing psychomotor agitation in dementia syndromes, comparing it with other pharmacological agents, and analyzing its role in reducing caregiver burden and improving patient outcomes. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Trazodone" OR "Psychomotor Agitation" OR "Dementia Syndromes" OR "Pharmacological Management" OR "Neuropsychiatric Symptome" in the last years. **RESULTS AND DISCUSSION** The review discusses the efficacy of trazodone in reducing psychomotor agitation in dementia, particularly in Alzheimer's patients, where it has been shown to lower agitation scores without the risks posed by antipsychotics. Comparisons between trazodone and other pharmacological agents indicate that trazodone is effective with fewer side effects, especially in long-term management. Its benefits in improving sleep and reducing caregiver burden are also highlighted. However, the review notes that trazodone's slower onset of action limits its use in acute settings, and higher doses may pose risks of sedation and falls. Additionally, caution is advised in its use in Lewy body de-

mentia due to potential worsening of motor symptoms and hallucinations. **CONCLUSION** Trazodone emerges as a valuable treatment for psychomotor agitation in dementia, offering a safer alternative to antipsychotics, particularly in long-term care. While its benefits in controlling agitation and reducing caregiver burden are clear, careful titration and monitoring are necessary to minimize risks such as sedation and falls. Further large-scale studies are needed to establish clear dosing guidelines and to fully understand its long-term safety and efficacy in this population. Trazodone's role in the management of agitation in dementia, especially when combined with non-pharmacological interventions, warrants ongoing investigation to optimize patient outcomes.
**Keywords:** Trazodone; Dementia; Psychomotor Agitation; Neuropsychiatric Symptoms; Pharmacological Treatment.

## INTRODUCTION

The management of psychomotor agitation in dementia syndromes poses a significant clinical challenge for healthcare providers. Psychomotor agitation, characterized by excessive motor activity and emotional distress, is a common neuropsychiatric symptom observed in various types of dementia, including Alzheimer's disease, Lewy body dementia, and vascular dementia[1]. The pathophysiology underlying psychomotor agitation in dementia is multifactorial, involving complex interactions between neurodegeneration, neurotransmitter imbalances, and environmental stressors[1]. In particular, disruptions in the cholinergic, serotonergic, and dopaminergic systems have been implicated in the emergence of agitation, making pharmacological interventions targeting these pathways a cornerstone of treatment approaches[1].

The prevalence of psychomotor agitation among dementia patients varies depending on the stage of the disease, but it is estimated that up to 80% of patients with advanced dementia exhibit some form of agitation during their illness[2]. This behavioral disturbance not only affects the quality of life of patients but also places an immense burden on caregivers and healthcare systems[2]. Agitation can manifest as restlessness, pacing, verbal outbursts, or even aggressive behavior, complicating the management of dementia and often leading to the use of physical restraints or pharmacological sedation in institutional settings[2]. Therefore, effective management strategies are crucial to improve patient outcomes and reduce caregiver distress.

Pharmacological treatments for psychomotor agitation in dementia syndromes are diverse, ranging from antipsychotics to mood stabilizers and antidepressants[3]. However, many of these agents are associated with significant side effects, particularly in elderly populations, where polypharmacy and comorbid conditions are prevalent[3]. The use of antipsychotics, for instance, has been linked to an increased risk of cerebrovascular events and mortality in dementia patients[3]. As a result, there has been growing interest in alternative pharmacological agents with better safety profiles, such as trazodone, a serotonin antagonist and reuptake inhibitor initially developed as an antidepressant[3].

Trazodone has gained attention for its off-label use in managing agitation in dementia patients due to its sedative properties and relatively low risk of severe side effects[4]. Unlike antipsychotics, trazodone does not carry the same risk of cerebrovascular events, making it a potentially safer option for frail, elderly patients with multiple comorbidities[4]. Furthermore, trazodone's dual action on serotonin receptors and its mild alpha-adrenergic blocking effect contribute to its

calming properties, which can help reduce the intensity and frequency of agitation episodes[4]. Despite its widespread use in clinical practice, there is still a need for robust clinical trials to establish the efficacy and safety of trazodone for this indication[4].

The pharmacokinetics of trazodone in elderly patients with dementia is another important consideration for its use in this population[5]. Aging is associated with changes in drug metabolism and excretion, which can affect the pharmacodynamics of medications like trazodone[5]. In dementia patients, these alterations may be exacerbated by concurrent medications used to treat other comorbidities, leading to potential drug interactions and an increased risk of adverse effects[5]. However, trazodone's relatively short half-life and its metabolism through the liver's cytochrome P450 system make it a manageable option in terms of dose adjustments and monitoring[5].

The ethical implications of pharmacologically managing agitation in dementia should not be overlooked. While trazodone offers a pharmacological alternative to antipsychotics, the decision to use medication for behavioral disturbances in dementia patients must consider the principles of autonomy, beneficence, and non-maleficence[6]. The sedation associated with trazodone may improve agitation symptoms but could also lead to reduced alertness and potential impairments in functional status[6]. Therefore, clinicians must weigh the benefits of agitation control against the risks of potential oversedation, particularly in patients with advanced dementia who may already have limited cognitive function and mobility[6].

Moreover, the off-label use of trazodone for psychomotor agitation in dementia underscores the need for clinical guidelines that reflect current evidence-based practices[7]. While trazodone is widely prescribed in this context, its use is often guided by clinical experience rather than formal recommendations[7]. As such, the development of consensus guidelines that address the appropriate dosing, monitoring, and duration of trazodone therapy in dementia patients is essential for optimizing its use in clinical practice[7]. Furthermore, such guidelines should incorporate considerations for polypharmacy, as many dementia patients are already taking multiple medications for comorbid conditions, which increases the risk of drug interactions and adverse effects[7].

In addition to its pharmacological effects, trazodone's role in reducing caregiver burden is an important aspect of its use in dementia management[8]. Caregivers of dementia patients with psychomotor agitation often experience high levels of stress and burnout due to the unpredictable and disruptive nature of the symptoms[8]. By providing a pharmacological option that can effectively reduce agitation, trazodone may help alleviate some of the emotional and physical strain on caregivers, allowing for better patient-caregiver interactions and improved overall care[8]. However, it is important to note that pharmacological interventions should be used in conjunction with non-pharmacological strategies, such as environmental modifications and behavioral therapies, to achieve the best outcomes[8].

Research gaps in the use of trazodone for agitation management remain, despite its growing popularity in clinical settings[9]. Most studies on trazodone's efficacy in dementia have been small-scale or retrospective, limiting the generalizability of their findings[9]. Large, randomized controlled trials are needed to confirm the benefits and risks of trazodone in this population, particularly in comparison to other commonly used pharmacological agents like antipsychotics and benzodiazepines[9]. In addition, future research should explore the long-term effects of trazodone use, including its impact on cognitive function, physical mobility, and overall mortality in dementia patients[9].

Finally, the future of pharmacological management of psychomotor agitation in dementia is likely to evolve as more research is conducted into the underlying mechanisms of agitation and the role of neurotransmitters in its manifestation[10]. Trazodone's unique pharmacological profile makes it a promising candidate for further study, particularly in terms of its safety and tolerability in elderly, frail populations[10]. However, the ultimate goal should be to develop personalized treatment plans that combine pharmacological and non-pharmacological strategies to address the multifaceted nature of psychomotor agitation in dementia[10].

## OBJETIVES

To review and evaluate the efficacy and safety of trazodone in managing psychomotor agitation in dementia syndromes, comparing it with other pharmacological agents, and analyzing its role in reducing caregiver burden and improving patient outcomes.

### SECUNDARY OBJETIVES

1. To explore trazodone's pharmacological mechanisms and how they address agitation in dementia patients.
2. To compare the safety profile of trazodone with antipsychotics and benzodiazepines.
3. To analyze its role in improving sleep disturbances related to agitation.
4. To assess the impact of trazodone on different subtypes of dementia, including Alzheimer's disease and Lewy body dementia.
5. To identify research gaps and future directions for the use of trazodone in neuropsychiatric symptom management.

## METHODS

This is a narrative review, in which the main aspects of trazodone in managing psychomotor agitation in dementia syndromes, comparing it with other pharmacological agents, and analyzing its role in reducing caregiver burden and improving patient outcomes in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Trazodone" OR "Psychomotor Agitation" OR "Dementia Syndromes" OR "Pharmacological Management" OR "Neuropsychiatric Symptome" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case--control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

## RESULTS AND DISCUSSION

The efficacy of trazodone in managing psychomotor agitation in patients with dementia has been the subject of increasing clinical interest. Various studies have examined trazodone's ability to reduce agitation episodes, particularly in patients with Alzheimer's disease, where neuropsychiatric symptoms are common. In Alzheimer's patients, trazodone has demonstrated moderate success in reducing the severity of agitation episodes without the same risks associated with antipsychotics or benzodiazepines[11]. A retrospective study involving Alzheimer's patients with severe agitation showed that trazodone, administe-

red at low doses, led to a significant reduction in agitation scores over a period of four weeks[11]. These findings suggest that trazodone may serve as a safer alternative to antipsychotics in managing psychomotor agitation, especially in patients who cannot tolerate more aggressive pharmacological interventions[11].

In terms of comparative efficacy, trazodone has been evaluated alongside antipsychotics such as risperidone and quetiapine, which are commonly used for agitation management in dementia patients[12]. While antipsychotics remain a first-line treatment due to their potent sedative effects, they are associated with a high risk of adverse events, including cerebrovascular accidents and increased mortality in elderly patients[12]. Trazodone, on the other hand, presents a lower risk profile, particularly concerning cardiovascular events, making it a more attractive option for long-term management[12]. A randomized trial comparing trazodone and risperidone in a cohort of dementia patients found that both medications were equally effective in reducing agitation scores; however, patients on trazodone experienced fewer severe side effects such as somnolence, extrapyramidal symptoms, and orthostatic hypotension[12].

One area of particular interest is trazodone's impact on sleep disturbances, which are frequently co-morbid with agitation in dementia patients[13]. Sleep disruptions exacerbate neuropsychiatric symptoms, including agitation, creating a vicious cycle that worsens the overall clinical picture[13]. Trazodone, due to its sedative properties, has been shown to improve sleep quality in dementia patients, which in turn helps mitigate agitation episodes during waking hours[13]. In a study focusing on dementia patients with both agitation and sleep disorders, trazodone was found to significantly improve both parameters, suggesting that sleep stabilization plays a crucial role in controlling agitation[13]. This dual effect makes trazodone particularly beneficial in patients whose agitation is linked to sleep fragmentation or insomnia[13].

The safety profile of trazodone is another key factor driving its use in the management of agitation in dementia. While other psychotropic agents such as benzodiazepines or antipsychotics are often associated with a high risk of sedation, falls, and cognitive decline, trazodone's side effects appear to be more tolerable for elderly patients with dementia[14]. A meta-analysis of clinical trials assessing trazodone's use in geriatric populations highlighted its lower incidence of serious adverse events compared to traditional antipsychotics[14]. In particular, trazodone does not appear to exacerbate cognitive decline to the same extent as antipsychotics, making it a more suitable option for long-term management of agitation in dementia patients[14].

Trazodone's efficacy in different subtypes of dementia has also been explored, with varying results. In Alzheimer's disease, where agitation is often linked to cholinergic deficits and neurofibrillary tangles, trazodone's serotoninergic action appears to provide a balancing effect on neurotransmitter imbalances[15]. However, in patients with Lewy body dementia, who are more prone to hallucinations and motor disturbances, the use of trazodone must be approached with caution due to its potential to worsen hallucinations and exacerbate motor symptoms[15]. A study examining trazodone's effects in Lewy body dementia found that while it reduced agitation, a subset of patients experienced worsening of parkinsonism and visual hallucinations, necessitating dose adjustments or discontinuation of the drug[15].

The onset of action of trazodone in managing acute agitation episodes has been another focal point of clinical research. Unlike antipsychotics, which often have a rapid sedative effect, trazodone's calming effects may take longer to manifest, particularly at the low doses commonly used for agitation

in dementia[16]. In clinical practice, trazodone is often administered over several days to weeks, with gradual titration to achieve the desired therapeutic effect without causing excessive sedation[16]. This slower onset of action may be a limitation in managing acute, severe agitation episodes where rapid control of symptoms is necessary[16]. However, for chronic management, trazodone's delayed effect may be more appropriate, reducing the risk of oversedation and promoting a more stable behavioral profile[16].

Combining trazodone with non-pharmacological interventions has also been explored as a strategy to enhance its efficacy. Behavioral interventions such as environmental modifications, music therapy, and cognitive-behavioral techniques are often recommended as first-line treatments for agitation in dementia patients[17]. Trazodone, when used in conjunction with these strategies, may amplify the calming effects and reduce the overall need for higher pharmacological doses[17]. A systematic review of studies on non-pharmacological and pharmacological combination therapy in dementia patients found that those receiving trazodone alongside behavioral therapies demonstrated greater reductions in agitation scores compared to those receiving trazodone alone[17]. This synergistic effect supports a holistic approach to managing neuropsychiatric symptoms in dementia, combining the benefits of both pharmacological and non-pharmacological modalities[17].

Trazodone's role in palliative care for patients with advanced dementia also warrants attention, particularly as these patients often experience severe agitation during the terminal stages of the disease[18]. In palliative care settings, the goal is to alleviate distress without causing undue sedation or impairing remaining cognitive and functional abilities[18]. Trazodone's mild sedative effects, coupled with its relatively benign side effect profile, make it a viable option for symptom management in end-stage dementia patients who are no longer responsive to other treatments[18]. A retrospective cohort study of dementia patients in hospice care found that those receiving trazodone for agitation experienced improved symptom control without significant reductions in alertness or participation in care activities[18].

The impact of trazodone on caregiver burden is another crucial aspect of its use in dementia management[19]. Agitation in dementia patients is not only distressing for the patients themselves but also for caregivers, who often bear the emotional and physical toll of managing these behaviors[19]. By reducing the frequency and severity of agitation episodes, trazodone may help alleviate caregiver stress and burnout[19]. In a caregiver survey conducted as part of a clinical trial, caregivers of dementia patients receiving trazodone reported significant improvements in their ability to manage daily care tasks and felt more confident in handling agitation episodes, thereby enhancing overall quality of life for both the patient and the caregiver[19].

In terms of long-term outcomes, trazodone appears to offer a safer profile for chronic use compared to antipsychotics and benzodiazepines[20]. While long-term use of antipsychotics has been associated with increased mortality and cognitive decline, trazodone's safety data suggest that it does not significantly accelerate the progression of cognitive impairments in dementia patients[20]. However, as with any pharmacological intervention in the elderly, careful monitoring is essential to mitigate risks such as falls, sedation, and potential drug interactions[20]. A longitudinal study assessing long-term trazodone use in dementia patients found that while the incidence of falls was slightly higher in the trazodone group compared to a non-medicated control group, the overall benefit in agitation reduction outweighed the risks[20].

The issue of trazodone dosing and titration in dementia patients has been a topic of ongoing debate in the literature[21]. Low-dose trazodone is generally well-tolerated and effective for mild to moderate agitation, but higher doses may be necessary for more severe cases[21]. However, higher doses increase the risk of sedation and orthostatic hypotension, particularly in frail, elderly patients[21]. Clinicians are advised to start with low doses and titrate slowly, monitoring for signs of oversedation and adjusting the dose as needed to achieve a balance between symptom control and minimizing adverse effects[21]. Guidelines on the optimal dosing of trazodone in dementia-related agitation remain scarce, underscoring the need for more comprehensive clinical trials that establish clear dosing protocols[21].

Despite its benefits, trazodone is not without its limitations. In some patients, trazodone's sedative effects may interfere with daytime functioning, particularly in those with less severe cognitive impairments[22]. Excessive sedation can lead to reduced mobility, increasing the risk of falls and impairing the patient's ability to engage in daily activities[22]. This is especially concerning in patients who are still relatively active and independent, as trazodone-induced drowsiness may contribute to a decline in overall functional status[22]. Therefore, clinicians must carefully assess the risk-benefit ratio of trazodone in each patient, tailoring the dose to minimize sedation while still providing relief from agitation[22].

The potential for drug interactions is another factor that must be considered when prescribing trazodone to dementia patients[23]. Many dementia patients are on multiple medications for comorbid conditions such as hypertension, diabetes, and cardiovascular disease, increasing the likelihood of pharmacokinetic and pharmacodynamic interactions[23]. Trazodone is metabolized by the liver's cytochrome P450 system, which is also involved in the metabolism of many other drugs commonly prescribed to elderly patients[23]. As such, clinicians must be vigilant in monitoring for potential interactions, particularly with drugs that affect heart rate, blood pressure, or cognition[23]. Close collaboration with pharmacists and regular medication reviews are essential to ensure the safe use of trazodone in this population[23].

## CONCLUSION

In conclusion, trazodone represents a valuable pharmacological option for the management of psychomotor agitation in dementia patients, especially when compared to antipsychotics and benzodiazepines. Its dual action on serotonin receptors and sedative properties provide an effective means of reducing agitation without the heightened risk of cerebrovascular events, mortality, or cognitive decline often associated with other treatments. The existing clinical evidence supports its efficacy, although caution is warranted in specific subpopulations such as those with Lewy body dementia, where it may exacerbate certain symptoms. Thus, trazodone remains an important tool in managing neuropsychiatric symptoms in dementia when combined with non-pharmacological interventions.

Individualized dosing and careful titration are essential in ensuring trazodone's safety and effectiveness, particularly in elderly and frail patients. Risks such as sedation, falls, and orthostatic hypotension must be closely monitored. While trazodone has demonstrated benefits in reducing agitation and improving sleep, further research is necessary to evaluate its long-term safety and determine appropriate guidelines for chronic use. Currently, there is a lack of established protocols for dosing and monitoring trazodone in dementia patients, highlighting the need for more comprehensive studies.

Trazodone also plays an important role in reducing caregiver burden by controlling agitation and improving the overall well-being of both patients and caregivers. The emotional and physical toll of managing dementia-related behaviors can be substantial, and trazodone's ability to reduce agitation episodes can significantly enhance the quality of life for caregivers. However, it should be used as part of a broader, multimodal approach, incorporating behavioral therapies and environmental modifications to optimize patient outcomes.

While trazodone has shown promise, further large-scale, randomized clinical trials are needed to address the existing gaps in knowledge regarding its long-term efficacy and safety. Its use in clinical practice should be carefully tailored to each patient, with ongoing monitoring and the integration of non-pharmacological strategies. As the prevalence of dementia continues to rise, trazodone's role as a safer pharmacological alternative for the management of agitation warrants further investigation to solidify its place in long-term dementia care.

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