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EXPERT OPINION

Trazodone in the Management of Major Depression Among Elderly Patients with Dementia: A Narrative Review and Clinical Insights

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Objective: Major depressive disorder (MDD) often co-occurs with dementia and other neurological disorders, and treatment with antidepressants can improve symptoms, quality of life, and survival in these patients. This narrative review provides an expert opinion about the role and effectiveness of trazodone in the treatment of older adults with MDD and cognitive impairment due to physical illnesses, such as dementia.

Results: Because of its mechanism of action, trazodone can treat several depression symptoms often seen in people with dementia, including insomnia, agitation, anxiety, cognitive impairment, and irritability.

Conclusion: Trazodone may be beneficial for patients with dementia or other neurological disorders comorbid with MDD, especially when the clinical picture of depression includes or is comorbid to symptoms of insomnia, irritability, inner tension, anxiety, or psychomotor agitation.

Keywords: major depressive disorder, depression, dementia, cognitive impairment, trazodone

Introduction

About 9% of older adults living in the community have a major depressive disorder, while the incidence rises to 25% among older adults who are institutionalized or have been recently hospitalized.[1–3] Despite its severity, prevalence and potential negative consequences, major depressive disorder (MDD) in older adults (elderly-MDD) is often under-diagnosed and undertreated. Comorbid depression with dementia or other neurological conditions is common, occurring in 40% of Parkinson's disease cases, 20 to 30% of Alzheimer's disease cases and 30 to 60% of stroke patients, and treatment with antidepressants can lead to improvements in symptoms, quality of life and survival rates for these patients with neurological disorders.[3] Secondary depression in patients with neurological conditions such as dementia, stroke and Parkinson's disease is often associated with depressive symptoms such as insomnia, irritability or psychomotor agitation, and medications such as trazodone may be particularly effective in treating these specific symptoms.[4]

Trazodone has a dual mechanism of action that involves inhibiting the serotonin transporter (SERT) and antagonizing both the 5-HT2A and 5-HT2C receptors of the serotonin type 2 (5-HT2) receptor.[5,6] Trazodone has antagonistic effects on α1- and α2-adrenergic receptors and histamine H1 receptors, and has minimal anticholinergic effects. It is also widely recognized that

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trazodone has therapeutic benefits as a hypnotic at low doses (25–100 mg).[5,7] The mechanisms of arousal are known to involve several neurotransmitter systems, including serotonin, noradrenaline, dopamine, acetylcholine, and histamine.[4,8–10]

Inhibiting multiple neurotransmitter systems can effectively reduce arousal and induce sleep. Trazodone's effectiveness in this regard may be due to its ability to inhibit H1 receptors. The sleep-inducing effect of H1 receptor blockade may be strengthened by simultaneous antagonism of 5-HT2A and α-adrenergic receptors.[8–10] Preclinical studies suggest that the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are primarily due to SERT blockade, which allows serotonin to exert its agonistic actions on the 5-HT1A receptor.[9,11] However, the agonistic effect of serotonin also affects other serotonin receptor subtypes, specifically the 5-HT2A and 5-HT2C receptors, which are believed to be the cause of the negative effects commonly linked to SSRI and SNRI treatment, such as insomnia, sexual dysfunction, and anxiety.[5] Serotonin antagonist and reuptake inhibitors (SARIs) like trazodone differ from SSRIs and SNRIs in that they offer both SERT inhibition and 5-HT2A/5-HT2C receptor antagonism simultaneously. This characteristic helps to avoid the typical issues associated with 5-HT2A/2C stimulation. Additionally, the combined effect of 5-HT2A/2C antagonism and SERT inhibition may enhance the antidepressant properties of SARIs and improve treatment tolerability.[5,9,11–14]

The aim of this expert opinion is to provide a clinical evaluation and opinion about the role and effectiveness of trazodone in the treatment of older adults with MDD and cognitive impairment due to physical illnesses, such as dementia. The focus is on the most pertinent and practical clinical considerations, based on the pharmacological properties of trazodone and results from clinical trials. An illustrative case report is presented.

Materials and Methods

A search of PubMed was conducted using the search terms "trazodone", "dementia", and "cognitive impairment", covering the period from 1974 to 2023. Search criteria were as follows: (((trazodone)) AND (dementia or cognitive impairment)). The search yielded 200 papers, and the full text of the 54 manuscripts that were considered consistent with the topic of this paper (trazodone in patients with cognitive impairment or dementia and depression) were retrieved from PubMed or other databases, analyzed, and the information deemed useful for this manuscript was included, along with information from an additional 30 papers retrieved from their references, while the remaining references came from the personal knowledge of the authors. The search and preliminary selection of papers was performed by one of the authors (AF). Subsequently, all authors reviewed and checked the inclusion and exclusion criteria and the data of the resulting manuscripts, which all authors agreed to include in this paper.

Results

Diagnosing Depression in Patients with Dementia or Other Non-Psychiatric Conditions Marked by Cognitive Impairment

To be diagnosed with depression, an individual must experience at least five of the common symptoms of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Box 1) for a period of at least two weeks, and at least one of the symptoms must be either depressed mood, or loss of interest or pleasure.

Box 1 Common Symptoms of Depression in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

1. Depressed mood
2. Loss of interest or pleasure in nearly all activities
3. Significant weight loss or gain, or changes in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt, or a specific plan for committing suicide.

The symptoms should not be attributable to the physiological effects of substance use or another medical condition. In older adults with dementia, it may be quite challenging to determine whether possible symptoms of elderly-MDD such as anhedonia, insomnia, psychomotor changes, irritability, lack of energy, or changes in weight and appetite, are caused primarily by dementia or are instead linked more to a concurrent episode of depression. Likewise, it is often difficult to determine if and to what extent depression may contribute to key symptoms of dementia, such as cognitive impairment. Cognitive changes that occur prior to depressive symptoms and persist after successful treatment of elderly-MDD are more likely to result from underlying dementia as the root cause. However, for other symptoms, it may not be straightforward or even possible to definitively determine whether the symptom is more closely associated with elderly-MDD or dementia.

Dementia is usually diagnosed when acquired cognitive impairment reaches a level of severity that interferes with social and/or occupational functioning. Mild cognitive impairment (MCI) represents a transitional stage between normal cognition and dementia, characterized by predominantly intact functional abilities.[15]

In the presence of dementia, symptoms of insomnia, agitation, anxiety, and irritability are relatively frequent[16] and hence the use of trazodone may be particularly beneficial. However, those and other neuropsychiatric symptoms may be present also in patients with MCI[17] and therefore trazodone can be beneficial in these patients too.

Different subtypes of dementia may present with different patterns of neuropsychiatric symptoms, even in the early stages. For example, non-amnestic MCI, which is more likely to progress to non-Alzheimer's dementia, has been associated with a higher prevalence of hallucinations and sleep disturbances than amnestic MCI. However, studies comparing neuropsychiatric symptom profiles in Alzheimer's disease and non-Alzheimer's dementia have not yielded entirely consistent results.[16]

Unfortunately, there has not been a comprehensive study specifically assessing the variations in trazodone efficacy among patients with different types of dementia. Nevertheless, we remain hopeful that this aspect will be thoroughly investigated in the future.

When assessing depressive symptoms and cognitive changes, a thorough history and physical examination is crucial. Additionally, a comprehensive neurological examination is necessary to identify, for example, focal deficits or parkinsonism. If a non-psychiatric condition such as dementia has not yet been identified, it is recommended that laboratory tests for anemia, thyroid disease, B12 deficiency and renal impairment are carried out to rule out an underlying medical condition. In addition, an interview with the patient's close family or friends can be very helpful in determining whether the patient's symptoms are primarily caused by depression, an underlying physical illness such as dementia, or both.[18]

Several screening tools, such as the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Geriatric Depression Scale (GDS), are useful for detecting depressive symptoms in older adults. The PHQ-9 is a reliable and valid screening tool designed for primary care settings.[19] It covers all nine DSM criteria for major depression and has been proven to be effective in measuring depression treatment outcomes in older adults. Additionally, it can be utilized to evaluate individual patient care response to treatment. The CES-D is frequently employed in primary care settings to evaluate depressive symptoms.[20] The GDS has been studied in various settings and was created with the older adult population in mind.[21] Individuals with positive results on any of these screening tools should undergo additional clinical evaluations and interviews to determine if they meet the diagnostic criteria for depression. Use of cognitive screening tools such as the Mini-Mental State Exam is advised to assess cognitive performance. However, it is important to not depend solely on these tools to identify cognitive impairment. Additionally, the presence of cognitive impairment caused by known dementia should not automatically exclude the possibility of additional cognitive impairment caused by depression. These tools can also be useful in tracking cognitive performance before, during, and after depression treatment.[3] If cognitive impairment continues after depressive symptoms improve, and there is no prior diagnosis of dementia, further evaluations should be conducted to rule out underlying or coexisting dementia. These evaluations should encompass brain imaging to exclude stroke, tumors, and normal pressure hydrocephalus. Patients with comorbid depression and dementia should receive treatment for both conditions.

Trazodone for the Treatment of Depression in the Elderly Patients with Cognitive Impairment or Dementia

A recent review about the treatment of depression and agitation in the elderly found that trazodone was clinically useful not only in the treatment of depression in the elderly, but also in the case of serious comorbidity with dementia or agitated behaviour, due to its special anxiolytic and sleep normalising effect and well-tolerated side effect profile.[22]

A study conducted on depressed patients in a stroke rehabilitation program randomly assigned 22 subjects to receive either a placebo or 300 mg/day of trazodone-HCl, starting 30 days after the stroke.[23] Individuals who received antidepressant therapy showed a consistent trend towards greater improvement in the Barthel Index for Activities of Daily Living, compared to those who received placebo. Similarly positive results were found in elderly patients with mild to moderate dementia and depression, the Hamilton Depression Rating Scale (HDRS) score was reduced from 23 ± 3 to 21 ± 4 in the trazodone group ($p < 0.05$ vs baseline), after 4 weeks of treatment.[24]

Psychomotor agitation is one of the symptoms of depression and trazodone is also known for its calming properties. Research conducted on trazodone in individuals diagnosed with Alzheimer's disease, mixed type dementia, or fronto-temporal dementia has demonstrated the effectiveness of this medication in alleviating a range of symptoms including irritability, anxiety, psychomotor instability, emotional disorders, and delirium.[25,26]

A review focused on the efficacy and tolerability of antidepressants for the treatment of Behavioral and Psychological Symptoms of Dementia (BPSD), concluded that antidepressants can be effective in managing BPSD and are generally well tolerated among elderly patients with dementia.[27] In the trazodone trials included in this paper, two studies (including one re-analysis of a previous trial) compared trazodone with haloperidol in dementia patients. The original trial and its reanalysis both demonstrated the beneficial effects of trazodone in treating BPSD, while also indicating that trazodone was better tolerated compared to haloperidol in both studies. Another trial compared trazodone with haloperidol, Behavioral Management Techniques (BMT), and placebo in Alzheimer's disease (AD) patients. In this trial, trazodone showed no superiority over the other active treatment groups, but it had more side effects than the placebo group, although it was comparable to the other active treatment groups. Also, a trial compared trazodone with placebo in patients with Frontotemporal Dementia (FTD), and trazodone was found to be beneficial.[27] A randomized, double-blind, parallel-group, 9-week treatment trial found that depressive symptoms in patients with dementia and agitated behavior were associated with greater behavioral improvement by trazodone-treated patients compared to haloperidol treated patients[28] while a randomized, controlled trial with trazodone in patients with FTD, concluded that trazodone is an effective treatment for the behavioural symptoms of FTD.[29] In this study, the administration of trazodone resulted in a noteworthy reduction in the total score of the Neuropsychiatry Inventory (NPI) among the 26 assessed patients ($p = 0.028$). Specifically, 10 patients experienced a decrease of over 50% in their NPI score, primarily attributed to enhancements in four specific scale items: irritability, agitation, depressive symptoms, and eating disorders. A 10-week pilot study about trazodone in 13 patients with dementia of the Alzheimer's type (DAT), showed that irritability, anxiety, restlessness, and affective disturbance were all decreased ($p < 0.05$) at the end of the 10-week observation period. No side effects were observed and mean Mini Mental State scores were unaffected by treatment.[30] A Cochrane review to evaluate agitation in patients with dementia concluded that long-term randomized controlled trials, involving large samples of participants with a wide variety of types and severities of dementia are necessary before trazodone can be recommended as a treatment for behavioural and psychological manifestations of dementia.[31] However, the review specifically excluded people with dementia and an additional diagnosis of depression.[32] Of interest, in a longitudinal and descriptive analysis which was conducted using data from patients aged >65 years with a first prescription of trazodone during the period 2002–2011, the most common therapeutic indications for trazodone were: depression (21.41%), Alzheimer/dementia (20.36%), sleep disorders (16.22%), and anxiety disorder (8.91%). The median dose was 100 mg/day. The use of trazodone concomitantly with potentially interacting medicines was frequent: anti-hypertensives (53.60%), and CNS depressors (59.32%).[33]

Mueller et al described three patients with dementia with Lewy bodies, who presented with major visual hallucinations, delusion, and an orbitofrontal syndrome including disinhibition, agitation, and irritability. The 3 patients were intolerant of low-dose clozapine (neutropenia for one, somnolence for the other and Pisa syndrome and falls for the last

one). Given their psychotic and frontal symptoms, they used pimavanserin and trazodone simultaneously. After 4 to 6 weeks of treatment, a marked improvement was observed in all 3 patients, with a decrease of the neuropsychiatric inventory scores from a mean of 88 to 38.[34] Kitamura et al conducted a study in which they assessed the behavioral and BPSD, such as depression, anxiety, delusions, hallucinations, irritability, agitation, aggression, and wandering. The researchers retrospectively analyzed the medical records of 13 patients with Alzheimer's dementia who exhibited aggression and negativism in caregiving situations and were administered trazodone as treatment. The study revealed that trazodone led to an improvement in BPSD symptoms in 9 patients, with 6 patients experiencing a reduction in aggression and negativism during caregiving. Based on these findings, the authors concluded that trazodone may be an effective treatment option for addressing specific types of BPSD, particularly aggression and negativism in caregiving situations.[35] Leng et al examined 1234 community-dwelling women (mean age 83.2 years) from the Study of Osteoporotic Fractures and assessed cognitive status (normal, mild cognitive impairment, or dementia) 5 years later, finding that the use of antidepressants, especially SSRIs and trazodone, was associated with an increased risk of cognitive impairment 5 years later among the oldest women. However, the study could not establish if the use of antidepressant contributed, or was rather the effect of the earliest and unrecognized symptoms of the following cognitive impairment.[36]

Regarding the cognitive impairments and increased risk of cognitive decline associated with elderly-MDD,[37,38] other studies have suggested that trazodone may be beneficial. Improvement in the cognitive disturbance factor of the Hamilton depression rating scale was significantly greater for adult patients with MDD receiving ER trazodone in the randomized placebo-controlled study of conducted by Sheehan et al,[39] and this effect was similar to that of venlafaxine XR in the randomized, double-blind study comparing the efficacy and safety of trazodone ER and venlafaxine XR.[40] However, it is important to note that medications such as amitriptyline, dothiepin, mianserin and trazodone may impair attention and ability to concentrate in elderly patients, possibly due to their sedative action.[41–43] On the other hand, the lack of anticholinergic properties and the low risk of abuse support the safety and efficacy of trazodone for insomnia, especially in elderly patients with depression, Alzheimer's disease, history of alcohol or substance abuse, or patients with organic brain syndrome.[44–49] Of interest, trazodone was also suggested as a medication to treat insomnia in patients with mild cognitive impairment and depression, whose behavioral, cognitive, and functional decline was associated with COVID-19 stay-home.[50]

In a retrospective cohort study of new admissions to nursing homes in Ontario, Canada, he initiation of antipsychotic and trazodone use was compared by year of admission using discrete time survival analysis and stratified by history of dementia. Relative to residents admitted in 2014, antipsychotic initiation significantly decreased in later years, while trazodone initiation modestly increased. The relative increase in trazodone initiation was larger among residents with dementia, this suggesting trazodone may have been initiated in lieu of antipsychotics.[51] In a recent review aimed at offering consultation-liaison psychiatrists an updated tool for guiding the treatment and care of elderly patients, it was found that although the evidence supporting the use of trazodone is limited, it is generally well tolerated. Therefore, trazodone can be considered as a viable option, on an as-needed basis, for managing irritability and agitation in patients with Alzheimer's disease and mixed dementia.[52]

In a 12 week trial in patients with dementia and neuropsychiatric symptoms (BPDS), trazodone, but not buspirone, was effective for BPSD.[53] However, in a larger 16-week trial of trazodone, haloperidol and placebo, no significant differences were found between study arms.[54,55] Of course, the use of trazodone is not completely without risks, such as the risk of falls or even delirium[56] compared with no antidepressant use. Therefore, the use of trazodone should always follow a careful evaluation of the balance of risks and benefits of trazodone versus other treatments or versus no treatment.[32,57,58]

The Psychopharmacology Algorithm Project at the Harvard South Shore Program introduced three algorithms designed to address BPSD in distinct contexts: emergent, urgent, and non-urgent. In emergent situations necessitating intramuscular (IM) administration, the primary recommendation is olanzapine, given that IM aripiprazole, previously favored, is no longer available. Haloperidol injection is the secondary choice, with potential consideration of an IM benzodiazepine thereafter. In urgent scenarios, the initial approach includes oral second-generation antipsychotics such as aripiprazole and risperidone. For non-emergent situations, the proposed medication sequence encompasses trazodone, donepezil, and memantine, followed by antidepressants like escitalopram and sertraline, second-generation antipsychotics, prazosin, and carbamazepine.[59] According to a systematic review about the Effectiveness of Pharmacological Interventions for Symptoms of Behavioral Variant Frontotemporal Dementia, trazodone was one of the medications

that had the greatest significant reductive effect on the symptoms of behavioral variant frontotemporal dementia.[60] Similarly, a study on the Effects of Psychotropic Medications on Cognition, Caregiver Burden, and Neuropsychiatric Symptoms in Alzheimer's Disease over 12 Months, concluded that that trazodone might be helpful in the treatment of behavioral symptoms.[61]

A research investigation into the use of trazodone among the older adults in Spain, observed that 11,766 patients were administered an initial prescription of trazodone and reported a notable upward trajectory in trazodone utilization, with a fivefold increase in 2011 compared to 2002. The median daily dose was 100 mg.[33] Likewise, in a study involving individuals aged 66 years and older in Ontario, Canada, the distribution of trazodone and quetiapine showed a gradual rise over time, aligning with a concurrent decline in the distribution of benzodiazepines. This trend was especially noticeable in the oldest age group and among individuals with dementia. High rates of psychotropic polypharmacy were linked to benzodiazepines, trazodone, and quetiapine, and overall trends exhibited similarities in both long-term care and community settings.[62]

In a recent study, actigraphy was used to assess sleep parameters in 30 patients with Alzheimer's disease before and after a two-week course of trazodone. The results showed a significant improvement in relative rhythm amplitude, indicating a more consistent daytime behavioral pattern and suggesting that trazodone may contribute to the stabilization of circadian rhythms in individuals with Alzheimer's disease.[63] Similarly, in a double-blind, randomized, and controlled trial involving individuals with Alzheimer's and sleep issues, those using trazodone exhibited significant improvements compared to the placebo group. According to actigraphic data post-treatment, trazodone users experienced an additional 42.5 minutes of sleep per night, and their nighttime percent sleep increased by 8.5 percentage points. Importantly, neither trazodone nor the placebo induced notable daytime sleepiness or an increase in nap frequency, and there were no discernible differences in the frequency or severity rating of adverse events between the two groups.[64]

In a study focusing on the utilization of antidepressants in nursing homes in Belgium, the overall prevalence of antidepressant use was 39.5%. Among individuals using a single antidepressant (n = 551), the primary indications were depression (66.2%), insomnia (13.4%), anxiety (6.2%), and neuropathic pain (1.6%). Notably, when trazodone, amitriptyline, or mirtazapine were prescribed for depression, 92.3%, 55.5%, and 44.5% of the prescribed dosages fell below the minimum effective antidepressant levels. This suggests that these medications were predominantly employed for indications other than depression, such as insomnia. Specifically, in cases of insomnia, trazodone (90.5%) or mirtazapine (5.4%) were commonly used, often at lower dosages than required for depression treatment.[65] A one-year study conducted in a geriatric care center assessed sleep disorders among 178 older adult patients with dementias, of which 114 with Alzheimer's disease (64%). During the study period, 68 patients (38.2%) had sleep disorders and approximately 85% of patients with sleep disorders received hypnosedative drugs. Trazodone was the most frequently prescribed medication (n = 35), and had an efficacy rate of 65.7%.[66]

According to a systematic review conducted by McCleery et al[67] about the pharmacotherapies for sleep disturbances in dementia, there is still a dearth of evidence to guide the drug treatment of sleep problems in individuals with dementia. Notably, the review found no randomized controlled trials investigating several commonly prescribed drugs, including benzodiazepine and non-benzodiazepine hypnotics, for sleep problems in dementia. Consequently, there remains considerable uncertainty regarding the balance of benefits and risks associated with these widely used treatments. Among the studies analyzed, there was some evidence suggesting the potential benefit of a low dose (50 mg) of trazodone, although further larger-scale trials are necessary to draw a more definitive conclusion on the risks and benefits.[67] Lopez Pausa et al conducted a naturalistic, prospective, observational study of 396 patients with probable Alzheimer's disease. Trazodone was prescribed to 6.1% of patients, particularly those with irritability, agitation, and disinhibition. After 6 months, patients treated with trazodone showed no increase in the frequency or severity of behavioral and psychological symptoms of dementia, nor was there an increase in caregiver burden.[68]

In a 2009 study, the objective was to gather expert opinions on the management of BPSD and examine prevailing prescription practices in the UK. The findings indicated that experts identified quetiapine as the most suitable agent for all BPSD, with acetylcholinesterase inhibitors being rated next for psychotic symptoms, benzodiazepines for agitation or aggression, and trazodone for behavioral symptoms like disinhibition.[69]

Kitamura et al conducted a retrospective analysis of the medical records of 13 patients with Alzheimer's Disease who were identified as exhibiting aggression and negativism in caregiving situations and were treated with trazodone. The BPSD during the pre-treatment stage were evaluated using the Neuropsychiatric Inventory (NPI). Following trazodone treatment, improvement in BPSD was observed in 9 patients, and specifically, aggression and negativism in caregiving situations showed improvement in 6 patients. Trazodone was considered effective for addressing a specific subtype of BPSD, particularly aggression and negativism in caregiving situations.[35] Within the context of a nursing home, a group of patients underwent assessment using the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale, and a systematic approach was employed to choose pharmacotherapy. Eleven patients underwent evaluation and were treated with different psychotropic medications. The predominant drug administered was trazodone, with an average dosage of 70 mg/day (ranging from 50 to 100 mg/day). Nine of the patients exhibited favorable responses to the treatment, evident in a reduction of the BEHAVE-AD score by 30% or more, and no clinical side effects were observed.[70]

In a nine-week double-blind comparison study evaluating trazodone and haloperidol for the treatment of agitation in dementia patients, 28 elderly individuals exhibiting agitated behaviors were randomly assigned to receive either trazodone (50–250 mg/day) or haloperidol (1–5 mg/day). The study found no significant difference in improvement between the two medication groups. However, adverse effects were more prevalent in the haloperidol-treated group. Analysis of improvements in specific areas suggested that repetitive, verbally aggressive, and oppositional behaviors tended to respond better to trazodone, while symptoms of excessive motor activity and unwarranted accusations showed a preference for haloperidol. These findings indicate that moderate doses of trazodone and haloperidol are equally effective in addressing overall agitated behaviors in dementia patients, but individual symptoms may exhibit a preference for a particular agent.[71]

Tolerability and Pharmacological Interactions

In general, trazodone is well-tolerated for treating MDD, with the most common side effects being drowsiness, headache, dizziness, and dry mouth.[72,73] Trazodone may be associated with an increased risk of orthostatic hypotension caused by the blockade of adrenergic α1-receptors,[74] especially in older adult patients or those with pre-existing heart disease,[75,76] so caution should be exercised when prescribing this medication to patients with dementia. In a retrospective study of the comparative risk of harm associated with the use of zopiclone or trazodone in nursing home residents more than 80% of whom had dementia, 1403 residents received trazodone and 1599 residents received zopiclone. Zopiclone use was associated with similar rates of injurious falls and major osteoporotic fractures and all-cause mortality compared with trazodone.[77]

Interestingly, in a study of a total of 31,055 patients receiving maintenance hemodialysis, of whom 18,941 were zolpidem initiators (61%) and 12,114 were trazodone initiators (39%), 101 fall-related fractures occurred. Zolpidem versus trazodone initiation associated with higher risk of hospitalized fall-related fracture.[78]

Trazodone has been linked to infrequent cases of priapism.[79–82] Men with conditions that may increase the risk of priapism, such as sickle cell anemia, multiple myeloma, leukemia, autonomic nervous system dysfunctions, and hypercoagulable states, as well as those with anatomical deformities of the penis, such as angulation, cavernosal fibrosis, or Peyronie's disease, should exercise caution when using trazodone.[5,83]

Clinical and preclinical studies have reported cases of life-threatening cardiac arrhythmias, including ventricular tachycardia, even with therapeutic doses.[74,84–86] Trazodone may cause prolongation of the corrected QT interval (QTc) and torsade de pointes at toxic plasma concentrations from overdose.[87] Data suggest a correlation between the interaction of trazodone with hERG potassium channels and prolongation of the QT interval.[75,88] In patients with dementia, as in most other patients, it is recommended to avoid concomitant use of trazodone with drugs known to be cardiotoxic or to prolong the QT interval, as this may increase the likelihood of ventricular arrhythmias, including torsade de pointes. Trazodone has been found to have drug-drug interactions with cytochrome P450 3A4 enzyme inhibitors, including erythromycin, ketoconazole, and ritonavir, which can increase the plasma concentration of trazodone. On the other hand, carbamazepine may decrease trazodone plasma concentrations. However, trazodone does not significantly inhibit or induce the metabolism of other medications. A number of patients with dementia are treated with cognitive enhancers

like acetylcholinesterase inhibitors (AChEIs) and memantine. The US Food and Drug Administration (FDA) has approved galantamine and rivastigmine for mild-to-moderate dementia, memantine for moderate-to-severe dementia, and donepezil for mild-to-severe dementia. Considering that donepezil and galantamine are metabolized in the liver through CYP2D6 and CYP3A4, their hepatic metabolism may be affected by specific substrates, inhibitors, or enhancers of the same enzymes.[89]

Trazodone is primarily metabolized to meta-chlorophenylpiperazine (mCPP) by the isoenzyme 3A4 of the cytochrome P450.[4,90] Hence, trazodone may compete for the catalytic site of the cytochrome P450 3A4, which is one of the isoenzymes involved in the metabolism of donepezil. However, given that donepezil may be metabolized by two cytochromes (CYP3A4 and CYP2D6), the competitive inhibition with trazodone, may not be clinically relevant. It is noteworthy that rivastigmine, another AChEI, is least likely among the cognitive enhancers to have pharmacokinetic interactions with other medications since it does not undergo hepatic metabolism.[91]

Memantine is predominantly excreted unchanged by the kidneys and is unlikely to have pharmacokinetic interactions with trazodone.

Regarding pharmacodynamic interactions, it is important to highlight that trazodone exhibits minimal anticholinergic activity. This characteristic has made it particularly favorable for addressing the needs of elderly patients with dementia who are concurrently using acetylcholinesterase inhibitors to enhance cholinergic transmission.[11]

When trazodone is prescribed, it is recommended that concomitant use with other antidepressants such as tricyclic antidepressants, MAOs, or fluoxetine be avoided because of the potential risk of developing serotonin syndrome and cardiovascular adverse effects.[83] However, trazodone is often prescribed at low doses as an augmentation to SSRIs, SNRIs, or other serotonergic medications such as vortioxetine, without a major risk of serotonin syndrome because of its relatively low affinity for the serotonin transporter. A study investigated possible interactions between trazodone, citalopram, and fluoxetine conducted on 97 patients with depressive syndrome over a period of one year.[92] The findings indicated that the use of citalopram and fluoxetine along with trazodone did not have a significant effect on trazodone serum concentrations. Furthermore, no instances of headache, daytime sedation, fatigue, or serotonin syndrome were reported during the study.

Simulated Case Example

This case example is a simulation of a real-life clinical scenario based on the authors' clinical experience. It intentionally does not refer to any specific patient in order to better protect patient confidentiality. However, the clinical case summarizes and reflects the many similar cases we see in our daily clinical practice.

Patient Information: FN

Age: 78 years old

Gender: Male

Medical History: Alzheimer's Dementia, Hypertension, Type 2 Diabetes, Hyperlipidemia, Prostate hypertrophy, Depression.

Current Medications: lisinopril, metformin, atorvastatin, tamsulosin, memantine

Chief Complaint: FN is a 78-year-old male who used to work as a surgeon. He currently lives in an assisted living facility and has been brought to the clinic by a nurse assistant due to complaints of worsening memory loss, mild agitation, and insomnia. During the visit, he also reports feeling empty, sad, and hopeless most of the time, and has lost interest in activities he used to enjoy. He also expressed feelings of worthlessness and excessive guilt related to the loss of his wife 5 years ago due to cancer, which he believes he diagnosed too late. The nursing assistant explains that the patient has difficulty sleeping, low energy, and increased appetite, although he no longer seems to enjoy any food presented to him. The nurse has also observed a further decline in his memory, ability to concentrate, and ability to perform daily activities. FN has expressed a desire to die, but indicated that, for religious reasons, he would not take his own life.

History of Present Illness

FN has a history of Alzheimer's Dementia. Over the past few months, his symptoms have been worsening. He has been experiencing memory loss and difficulty with daily activities such as dressing and grooming, sadness, low energy, insomnia, increased appetite, anxiety, agitation. Family members report that he has become more withdrawn and less interested in social activities.

Past Medical History

FN has a history of hypertension, type 2 diabetes, prostate hypertrophy and hyperlipidemia. He has been taking lisinopril, metformin, tamsulosin, and atorvastatin for these conditions. He has a history of one episode of depression, which occurred after the loss of his wife and remitted without any treatment. He was diagnosed with dementia 2 years ago.

Physical Examination

On physical examination, FN appears sad, mildly anxious and agitated, and withdrawn. He is oriented to person but not to place and has a clear difficulty with time and with recalling recent events. His affect is blunted, and his speech is slow and hesitant. There are no signs of focal neurological deficits.

Assessment and Plan

FN was diagnosed with major depressive disorder and dementia. The plan is to start trazodone once-a-day ER at 75 mg at night and refer him to a neurologist for further evaluation and management of his dementia. The assisted living facility staff and family members will be educated on how to manage his symptoms and provide him with support. A follow-up appointment is scheduled for the following week, to monitor his progress and adjust his treatment plan as needed.

Outcome

The patient responded well to trazodone once-a-day ER, with noticeable improvements in sleep and agitation. However, his other symptoms remained unchanged. As a result, the dosage was increased to 150 mg administered at night. He continued to improve in the following weeks. After approximately one month, his mood had significantly improved, and he had resumed enjoying food and attending church services at the assisted living facility. He also exhibited happiness when visited by family members and was no longer fixated on feelings of guilt related to his wife's passing. While cognitive functions remained impaired, there was a moderate improvement in this area as well.

Discussion

Trazodone has mechanisms of action that allow it to treat various symptoms associated with depression, including the symptoms of insomnia, agitation, and irritability that are commonly seen in people with dementia. Clinical trials of trazodone have shown that it has a beneficial effect on sleep measures in patients with depression, improving measures of sleep quality compared to the placebo in controlled studies.[93,94] Trazodone's hypnotic effect is usually obtained at lower doses than those used for depression, and is believed to be mainly due to the blocking of 5-HT2A receptors, H1 receptors, and α1-adrenergic receptors.[5,95–99] Of interest, sleep disorders are a common occurrence in patients with dementia and trazodone has proven to be an effective treatment option for older adult patients with dementia and associated primary or secondary sleep disorders.

The various trazodone formulations, including IR (immediate release), SR (slow release, sometime referred to as delayed release) and once-a-day ER (sometimes referred to as XR or COAD), may offer a possibility to personalize the treatment in patients with late-life depression and physical conditions such as dementia. For instance, Trazodone IR appears to be an ideal therapeutic option for the treatment of patients with mild or moderate major depression who have initial insomnia (difficulty falling asleep) and/or agitation or irritability at certain times of the day and who may therefore benefit from achieving higher blood concentration peaks at certain times of the day or night. Trazodone SR is indicated for patients with mild to moderate major depression, initial (difficulty falling asleep) and central (difficulty staying asleep) insomnia and/or moderate to severe daytime or nighttime anxiety. It provides lower but longer lasting peaks in blood concentration than the IR formulation and higher but more rapidly declining peaks than the once-a-day ER formulation. Trazodone ER is suitable for the treatment of major depression with early, central, or late insomnia and/or daytime or nocturnal anxiety, including severe depression

requiring continuous maintenance of therapeutic blood levels. The ER formulation provides consistent release of trazodone over 24 hours, with a smooth pharmacokinetic curve that lacks the peaks and troughs seen with immediate-release trazodone.[83] It allows starting at an effective dose of 150 mg, which can be increased by 75 mg/day every three days (ie, starting at 225 mg on day 4 of therapy), up to 300 mg taken once daily in the evening, simplifying treatment, and improving adherence. However, in elderly patients, we usually start with lower doses (ie, 75 mg) and often do not find it necessary to reach the full 300 mg dose. This formulation is effective for mild to moderate insomnia and anxiety, maintains constant levels the next day, and has reduced peak concentration side effects such as orthostatic hypotension or sedation. In the pivotal clinical trial, only 9 of the 202 patients treated with trazodone ER were over 65 years of age.[83] Although the clinical literature and experience with trazodone have not shown strong differences in response between older and younger patients, caution should be exercised when using the drug in geriatric patients due to limited experience. A lower starting dose is recommended in this population to assess tolerability more safely. This caution applies even more strongly to the immediate-release formulation, because of the higher peak blood concentrations. When prescribing trazodone for older adult patients in our practice, we often start the IR, SR, or ER formulations at an initial dose of no more than 50, 50, or 75 mg respectively, if given as a single dose at night, and no more than 100, 100, or 150 mg per day respectively, if administered in divided doses.

Like most medications, trazodone has disadvantages and potential risks along with its benefits. For example, trazodone may not be effective in subtypes of depression characterized by hypersomnia, low energy, and psychomotor retardation, which are less common in patients with dementia than the forms of agitated depression, but are still possible. Trazodone also has a relatively common risk of orthostatic hypotension or sedation, although this is less common with the SR and ER formulations than with the IR formulation and may be mitigated by a slow titration rate. Caution should also be exercised in patients at high risk for arrhythmias.[4] In summary, we believe that the main benefits of trazodone in patients with dementia include:

1. Trazodone is effective in treating depression with symptoms of insomnia, anxiety, irritability, or agitation, as often seen in patients with elderly MDD and conditions such as dementia.
2. Compared with benzodiazepines, trazodone is less likely to be abused or to cause dependence/tolerance.
3. Trazodone usually does not cause the anticholinergic side effects commonly seen with tricyclic antidepressants, such as dry mouth, constipation, urinary retention, or worsening of cognitive dysfunction.
4. Unlike mirtazapine,[100] trazodone does not usually cause increased appetite and weight gain.[83,93,94,97]
5. Trazodone is unlikely to increase blood levels of other drugs due to pharmacokinetic interactions at the cytochrome P450 level.[83]

However, trazodone also has potential drawbacks, such as:

1. Trazodone may cause dizziness or orthostatic hypotension and increase the risk of falls or cardiovascular ischemia.
2. Trazodone may cause drowsiness, which may further worsen cognitive function, contribute to hypersomnia, and decrease participation and interest in daily activities.
3. Trazodone may cause cardiac arrhythmias.

Several limitations of this paper should be acknowledged. We recognize that narrative reviews do not require a rigorous and reproducible search strategy across multiple databases and do not allow for systematic comparison of selected studies with tables, graphs, and appropriate statistical methods. In narrative reviews, the authors rely on their knowledge, expertise, and familiarity with the field to evaluate and selectively select studies with the goal of reporting and commenting on those parts of the existing literature that they consider more relevant for a qualitative summary and interpretation of a clinical question or practice, focusing on their personal knowledge, experience, and perspective. We therefore acknowledge the risk that a narrative review may be subject to selection bias, as narrative reviews select papers based on the authors' experience, knowledge and personal perspective. Systematic reviews are generally considered the gold standard of evidence synthesis. Narrative reviews are not intended to replace systematic reviews, but can provide

opinions and guidance on clinically relevant issues for those clinicians who are interested in the authors' views that may be applicable to their practice. Other limitations include the limited amount of published literature on the benefits and potential harms of trazodone use in older people with depression and cognitive impairment.

Conclusions

Patients with neurological disorders, such as mild cognitive impairment, Alzheimer's disease, stroke, and Parkinson's disease, often experience comorbid major depressive disorder (MDD), which may typically be characterized by symptoms such as insomnia, irritability, agitation, anxiety, and changes in appetite. Trazodone is a well-established treatment for depression that is generally well tolerated and may be beneficial in patients with dementia or other neurological disorders comorbid with MDD, especially when the clinical picture includes symptoms of insomnia, irritability, internal tension, anxiety, or psychomotor agitation.

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