

## Pharmacological management of behavioral symptoms associated with dementia

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**Core tip:** Dementia may present with neuropsychiatric symptoms that may require pharmacological interventions. Medications used for the behavioral symptoms associated with dementia are not Food and Drug Administration-approved and hence are being used off-label in the United States. The decision to start medications is based on a judicious consideration of risks and benefits. The choice of the agent should be guided by a thorough understanding of its pharmacologic properties and safety profiles, concomitant medications, and concurrent medical conditions. This article reviews the current evidence for psychotropic medications and presents recommendations with an algorithm for the treatment of neuropsychiatric symptoms associated with dementia.

### Abstract

Dementia is a clinical syndrome with features of neurocognitive decline. Subtypes of dementia include Alzheimer's, frontotemporal, Parkinson's, Lewy body disease, and vascular type. Dementia is associated with a variety of neuropsychiatric symptoms that may include agitation, psychosis, depression, and apathy. These symptoms can lead to dangerousness to self or others and are the main source for caregiver burnout. Treatment of these symptoms consists of nonpharmacological and pharmacological interventions. However, there are no Food and Drug Administration-approved medications for the treatment of behavioral and psychological symptoms of dementia. Pharmacological interventions are used off-label. This article reviews the current evidence supporting or negating the use of psychotropic medications along with safety concerns, monitoring, regulations, and recommendations.

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### INTRODUCTION

Dementia is a clinical syndrome which includes a heterogeneous group of disorders that lead to cognitive decline in the absence of delirium<sup>[1]</sup>. Although the cognitive decline is a core feature of dementia, this may be associated with a variety of neuropsychiatric symptoms<sup>[1]</sup>. These symptoms are as follows: (1) affective and motivational symptoms; (2) perceptual disturbances; (3) delusions; (4) disturbances of basic drives; and (5) disinhibition and inappropriate behaviors<sup>[1]</sup>. A five-year study on the

prevalence of these symptoms by Steinberg shows that 97% experienced at least one symptom, with depression, apathy, or anxiety being the most frequent among these symptoms<sup>[2]</sup>. Although dementia is a heterogeneous group with subsyndromes including Alzheimer's, frontotemporal, Parkinson's, Lewy body disease, and vascular type, and involving distinct pathologies and symptoms, this article will focus on Alzheimer's disease (AD) and its pharmacological management. The pharmacological management does not differ significantly except that in Lewy body disease and Parkinson's disease, the use of antipsychotic medications can lead to worsening of the Parkinsonian symptoms. These medications are generally not advised in these conditions.

AD is a major cause of neurocognitive decline with gradual progression of cognitive and behavioral symptoms. Neuropsychiatric symptoms fluctuate throughout the course and may be distressing to the patient and caregiver<sup>[2]</sup>. This disease was first described in 1906 by Dr. Alzheimer<sup>[3]</sup>, as a cluster of symptoms that included cognitive impairment and psychosis. Apathy was consistently rated highest in symptom severity<sup>[2]</sup>. Additionally, psychosis of AD, featuring symptoms of delusions and hallucinations, agitation, and aggression may be a distinct clinical entity with poor outcome<sup>[4]</sup>. Jeste *et al*<sup>[5]</sup> published the diagnostic criteria for psychosis of AD, which are: (1) delusions and/or hallucinations (auditory or visual) of 1 mo duration or longer and are severe enough to cause disruption in patients' and/or others' functioning; (2) criteria for dementia of Alzheimer type are met; (3) these symptoms have not been present continuously prior to the onset of symptoms of dementia; (4) criteria for schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features have never been met; and (5) symptoms do not occur exclusively during the course of delirium and are not better accounted for by another general medical condition or direct physiological effects of a substance.

This is a clinically-oriented review meant for the practicing clinician. We selected studies based on their relevance to the topic.

## MANAGEMENT

Management of the behavioral and psychological symptoms of AD includes both nonpharmacological and pharmacological interventions (Figure 1). Without treatment, these symptoms can lead to a potential for harm to self or others. Depression and apathy can lead to poor self-care, and excitement and agitation may lead to altercations or injuries. Paranoia may lead to seclusive behavior and refusal of care.

Initial assessment includes a thorough history and physical examination to identify antecedents and any underlying medical conditions such as infections, neurological insults, or medication changes which can cause delirium. The target symptoms should be identified. The justification for treatment will depend upon whether

the benefits outweigh the risks.

Although this article does not cover the nonpharmacological interventions, it is important to note that these interventions should be employed as first-line in the management of behavioral and psychological symptoms of AD. When these measures fail, pharmacological treatment may be considered.

## PHARMACOLOGICAL INTERVENTIONS

Pharmacological interventions are necessary when nonpharmacological interventions are unsuccessful, symptoms are severe, or when patients present with symptoms that meet the criteria for psychosis of AD.

### Antidepressants

A meta-analysis of antidepressants for treatment of agitation and psychosis in dementia showed reduction in symptoms compared with placebo, with two studies favoring sertraline and citalopram<sup>[6]</sup>. A comparative study of citalopram and risperidone did not show any statistical difference in the treatment of agitation or psychosis of dementia<sup>[7]</sup>. A more recent study of citalopram for agitation in dementia again showed significant improvement compared to placebo. However, this study also revealed that patients in the citalopram group had no significant improvement in activities of daily living or use of rescue medication lorazepam, and was associated with worsening of cognition and prolongation of QT interval<sup>[8]</sup>. Although these medications have been shown to be tolerated reasonably well, concerns include risk of bleeding and vasospasm due to the blockade of serotonin uptake in platelets and pulmonary endothelial metabolism of serotonin<sup>[9]</sup>.

Trazodone has been useful in the management of agitation in dementia with partial success<sup>[6]</sup>. Two open label studies on buspirone for agitation and aggression in dementia suggested some benefit<sup>[10,11]</sup>. The first showed significant decrease in agitation scores at an average dose of 35 mg/d. The second involved 16 dementia patients with severe agitation and aggression and showed significant improvement for 6 patients. A pilot placebo-controlled study on trazodone and buspirone suggested benefits for trazodone but not buspirone in behaviorally disturbed AD patients<sup>[12]</sup>. In a 12-wk open label prospective study for efficacy of mirtazapine in 16 agitated patients with AD, Cakir *et al*<sup>[13]</sup> found significant reduction in the Cohen-Mansfield Agitation Inventory-Short form and Clinical Global Impression-Severity scales ( $P < 0.001$ ) between pre- and post-treatment. There were no significant side effects or cognitive worsening. The authors suggested that mirtazapine may be an effective alternate for treatment of patients with AD and agitation. However, there are no controlled studies or other studies to support or negate mirtazapine use for this purpose<sup>[13-15]</sup>.

### Sedative-hypnotics

Benzodiazepines can be used for acute agitation. A

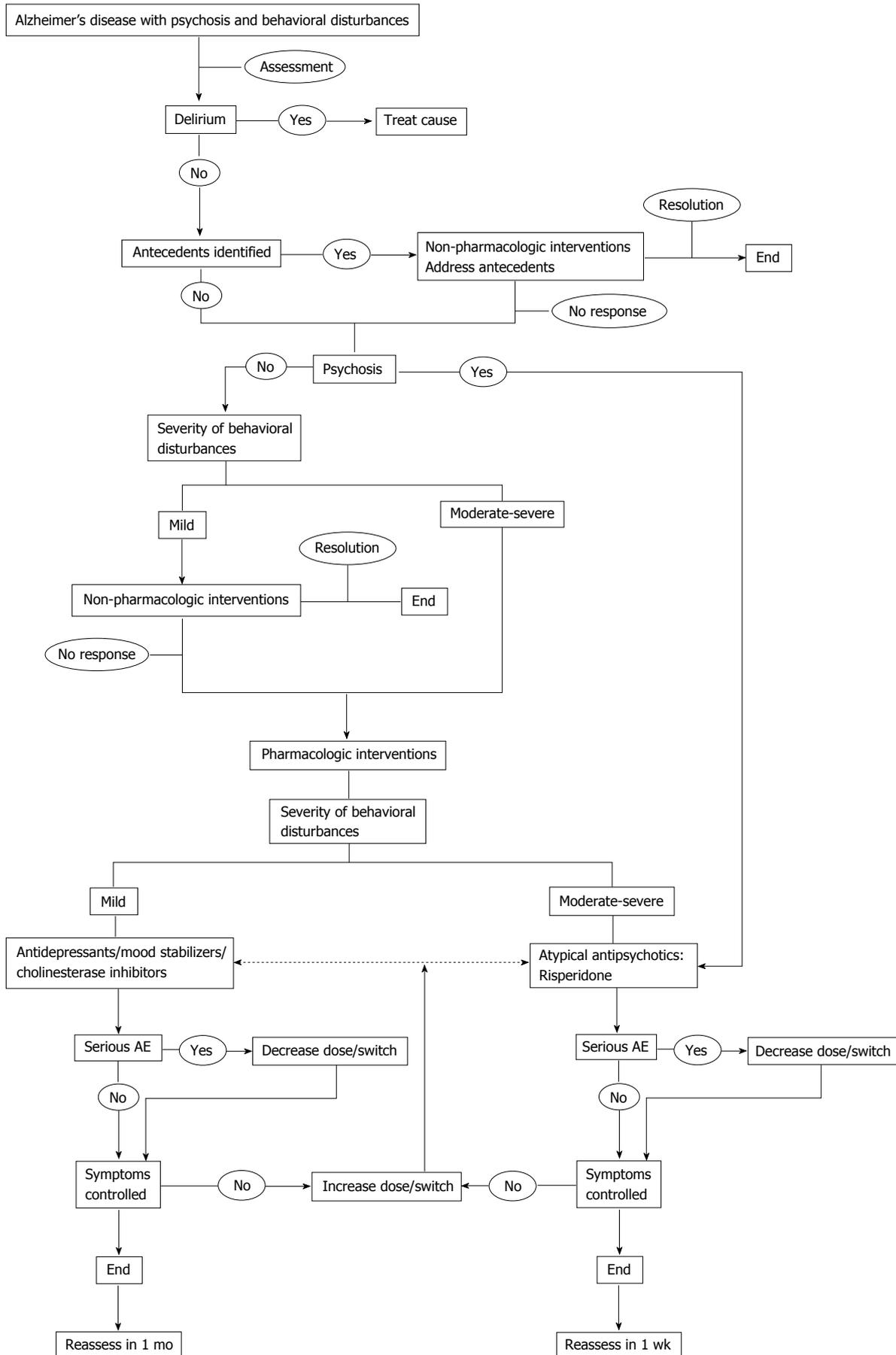


Figure 1 Algorithm for the treatment of behavioral and psychological symptoms of Alzheimer's disease<sup>[49]</sup>. Reproduced with minor changes, with permission from Psychiatric Times ©2014. AE: Adverse effect.

systematic review showed no significant differences between oxazepam, lorazepam, and alprazolam and other psychotropics including thioridazine, haloperidol, and olanzapine<sup>[16]</sup>. However, benzodiazepines are associated with sedation and increased risk for falls. Madhusoodanan *et al.*<sup>[17]</sup> have addressed the safety concerns of benzodiazepine use in the elderly in a previous publication.

### **Cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists**

Studies on cholinesterase inhibitors including donepezil, rivastigmine, and galantamine have shown modest improvements for behavioral symptoms. However, the patient population in these studies generally had low baseline Neuropsychiatric inventory (NPI) scores<sup>[18]</sup>. Memantine did not achieve significant improvement in agitation in a recent study among patients with moderate to severe AD. However, it improved the cognition compared to placebo<sup>[19]</sup>.

### **Mood stabilizers**

There are mixed results regarding the use of divalproex in the treatment of behavioral symptoms of dementia. An initial study showed efficacy in treating aggressive behaviors and agitation<sup>[20]</sup>. However, this was not replicated in a subsequent double-blind, placebo-controlled study<sup>[21]</sup>. A recent review confirms that it is ineffective in the treatment of agitation, and is associated with adverse effects, such as sedation, falls, infection, and gastrointestinal side effects<sup>[22]</sup>.

A systematic review that included carbamazepine, valproate, gabapentin, lamotrigine, topiramate, and oxcarbazepine, showed that only carbamazepine had efficacy in behavioral and psychological symptoms in controlled trials. Carbamazepine, however, is associated with significant adverse effects including sedation, hyponatremia, and leukopenia. It is also a strong inducer of the enzyme CYP450 3A4<sup>[23]</sup>.

Gabapentin showed improvement in several case reports and open studies and was well-tolerated. However, there are no controlled studies regarding the efficacy of gabapentin<sup>[23]</sup>.

There is insufficient data regarding lamotrigine and oxcarbazepine use in dementia. Lamotrigine can cause Stevens-Johnson syndrome, and the risk of this side effect may be potentiated by combination with valproate. Topiramate may have adverse effects on cognition and is not recommended<sup>[23]</sup>.

### **Antipsychotics**

Conventional antipsychotics were widely used for managing the behavioral and psychological symptoms of dementia until the advent of second-generation antipsychotics.

Efficacy of conventional antipsychotics had been established by controlled studies<sup>[24]</sup>. Unfortunately, these are also associated with serious cardiovascular and anticholinergic adverse effects, extrapyramidal symptoms, and tardive dyskinesia. The occurrence of extrapyramidal

symptoms may lead to decreased mobility, increased risk for infections, falls, the need for personal care, nursing home admission, and increased mortality risk<sup>[25,26]</sup>. Atypical antipsychotics are the most widely used class of psychotropic medications in the treatment of behavioral and psychological symptoms of dementia. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer Disease study (CATIE-AD) showed benefits of risperidone and olanzapine on the NPI total score. However, there was high rate of discontinuation due to adverse effects<sup>[27]</sup>. Quetiapine was shown to have limited efficacy on symptoms which may have been related to the low doses prescribed. Overall, treatment in the CATIE-AD study did not result in improvement in functioning, care needs, or quality of life. Atypical antipsychotics were also associated with worsening of cognitive function compared to placebo<sup>[28]</sup>. A meta-analysis of atypical antipsychotics for aggression and psychosis in AD showed improvement in aggression with risperidone and olanzapine. Risperidone also improved psychosis. However, both risperidone and olanzapine had higher rates of serious cardiovascular events, and extrapyramidal symptoms<sup>[29]</sup>.

Risperidone is the best studied of all the atypical antipsychotics used for behavioral and psychological symptoms of dementia and its efficacy has been established. It has minimal sedation, less weight gain, and fewer metabolic and anticholinergic effects compared with olanzapine and clozapine<sup>[30]</sup>. Adverse effects include dose-related extrapyramidal symptoms, hyperprolactinemia, osteoporosis, orthostatic hypotension and its attendant fall risk, and metabolic adverse effects. A long-acting injectable formulation is available. A study on relapse risk showed that discontinuation of risperidone among AD patients with psychosis or agitation was associated with increased risk of relapse<sup>[31]</sup>.

Olanzapine was shown to decrease psychosis and behavioral symptoms but is associated with significant adverse effects which include sedation, weight gain, metabolic syndrome, orthostatic hypotension, extrapyramidal symptoms, and anticholinergic effects<sup>[29]</sup>. Olanzapine is also available in both short-acting and long-acting intramuscular formulations. The long-acting injectable preparation may be associated with post-injection delirium sedation syndrome; hence it is advised that the patient be monitored for 3 h post-administration<sup>[32]</sup>.

A placebo-controlled study did not establish the efficacy of quetiapine at mean daily dose of 100 mg/d for psychotic symptoms, though it showed improvement in secondary measures of agitation<sup>[33]</sup>. A more recent placebo-controlled study suggests efficacy at 200 mg/d in the treatment of agitation; and the 100 mg/d group did not differentiate from placebo<sup>[34]</sup>. Another study comparing quetiapine to risperidone showed that low doses (mean doses quetiapine  $77 \pm 40$  mg/d, risperidone  $0.9 \pm 0.3$  mg/d) are equally effective<sup>[35]</sup>. Quetiapine has negligible extrapyramidal symptom risk, minimal anticholinergic effects, and fewer metabolic adverse effects<sup>[36]</sup>. The main concerns include sedation and orthostatic hypotension. Quetiapine is also available in

extended-release formulation. A study comparing the tolerability of immediate and extended release formulations for dementia patients with psychosis or agitation showed similar results for doses up to 300 mg/d<sup>[37]</sup>.

Aripiprazole showed modest improvements in psychosis and agitation in placebo-controlled clinical trials<sup>[38]</sup>. It is generally well-tolerated with the most reported adverse event being mild somnolence. This was not associated with falls or accidental injury. No clinically significant electrocardiogram abnormalities or weight changes were seen<sup>[39]</sup>. It is available in both short-acting and long-acting intramuscular formulations. A placebo-controlled study of the short-acting formulation of 10 mg to 15 mg in divided doses in dementia patients suggests that it is efficacious for acute agitation<sup>[40]</sup>. There are no studies regarding the long-acting preparation in this connection.

There are no controlled trials of clozapine for patients with behavioral and psychological symptoms of AD. It has a lesser risk of extrapyramidal symptoms and tardive dyskinesia<sup>[36]</sup>. Adverse effects include serious agranulocytosis, decreased seizure threshold, myocarditis, metabolic effects, weight gain, and orthostatic hypotension.

The efficacy of the newer atypical antipsychotics including ziprasidone, paliperidone, asenapine, and lurasidone has not been established in controlled trials for patients with behavioral and psychological symptoms of AD. These medications have been used for mood and psychotic disorders in the elderly, and may be associated with more favorable metabolic profile. Adverse effects include extra pyramidal symptoms, akathisia, sedation, and prolongation of the QT interval. Further studies are needed to establish the efficacy of these drugs in the treatment of behavioral and psychological symptoms of AD.

## DISCUSSION

AD with behavioral and psychological symptoms can be difficult to manage, often leading to caregiver burnout. A study on institutional placement of dementia patients shows that the predictive factors include caregiver's depression and patient's behavioral change<sup>[41]</sup>. The severity of symptoms in institutionalized patients is higher than those in the community, based on our clinical experience. Pharmacological interventions are frequently used in the institutional settings.

Management of behavioral and psychological symptoms of AD involves a complex interplay of factors that include severity of acute symptomatology, medical comorbidities, concurrent medications, and even caregiver interactions. Further compounding this dilemma is the non-approval status of any medication by the Food and Drug Administration (FDA) for the treatment of these symptoms. Therefore, medications are used off-label, and each one carries its own risk and benefits. In the United Kingdom, Australia, and Canada, risperidone has been approved for psychosis and dementia by their administrative agencies for drug use<sup>[42-44]</sup>.

In April 2005, an analysis of 17 placebo-controlled

studies in dementia patients led to the FDA black box warning of increased mortality risk and cerebrovascular accidents in elderly patients treated with atypical antipsychotics for behavioral disturbances associated with dementia<sup>[45]</sup>. The analysis showed a mortality rate of 1.6 to 1.7 times that of placebo. The causes of death were varied. Use of these medications for dementia-related symptoms decreased especially in the nursing homes as the federal regulations require appropriate documentation, minimal effective dose, and attempts at gradual dose reduction. The residents should be free from unnecessary medications, excessive dosages, and duration. Further studies on antipsychotics and mortality have provided additional information. Some studies confirmed an increased mortality risk, and others did not (Table 1). Of note, additional studies have focused on specific factors that may be confounding variables for the mortality risk as detailed below.

Kales *et al*<sup>[46]</sup> in an outpatient study comparing the mortality risk of different psychotropics suggested that haloperidol had the highest risk in the first 30 d and quetiapine the lowest. Additionally, the highest mortality risk for risperidone, olanzapine, quetiapine, and valproate is in the first 120 d of use. Lopez *et al*<sup>[26]</sup> in a long-term study adjusted the covariates and found that neither the nursing home admission nor mortality were linked to the use of antipsychotic medications. However, the presence of the psychiatric symptoms-including psychosis and agitation, was associated with increased mortality and nursing home admission. A study by Gardette *et al*<sup>[47]</sup> suggests that dementia severity played an important role, and antipsychotic use was not an independent risk factor for mortality when cognitive status was included in the multivariate analyses. In a large prospective study, Arai *et al*<sup>[48]</sup> presented their initial findings which showed no statistical difference on mortality among patients receiving antipsychotics and not receiving antipsychotics. Studies which either support or negate the mortality risk of antipsychotics are included in the table (Table 1).

An algorithm based on the recommendations below has been included (Figure 1). The algorithm describes the critical elements in the diagnostic assessment of Alzheimer's disease with psychosis and behavioral disturbances, through various interventions, and facilitates understanding of the management of this condition.

As discussed, the decision to start a patient on medication for behavioral and psychological symptoms of AD is based on a judicious consideration of risks and benefits. Although, not a scope of this article, we must emphasize that nonpharmacological interventions must be attempted first, and medications be used only if these measures are unsuccessful or the symptoms are too severe. Potential benefits have to be weighed against the risk of serious adverse effects. Appropriate documentation of the potential danger to self or others helps in the decision to start psychotropic medications. Moreover, it is also important to discuss with the patients and/or family, when possible, about the risks, benefits,

**Table 1 Comparison of studies supporting or negating the mortality risk of antipsychotic medications<sup>[49]</sup>**

Ref.	Type	Population	Comment
Schneider <i>et al</i> <sup>[50]</sup>	Meta-analysis; n = 5110	Mixed	Analyses of survival and causes of death needed; MR increased
Suh <i>et al</i> <sup>[51]</sup>	Prospective 1-yr study; n = 273	NH patients	MR not increased
Raivio <i>et al</i> <sup>[52]</sup>	Prospective 2-yr study; n = 254	NH patients	Very frail patients; restraints increased risk of mortality; MR not increased
Ballard <i>et al</i> <sup>[53]</sup>	Randomized, placebo-controlled, 1-yr study; n = 165	NH patients	MR increased
Gardette <i>et al</i> <sup>[47]</sup>	Prospective cohort 3.5-yr study; n = 534	Outpatients	Medications not independent predictor for mortality when adjusted for dementia severity; MR increased
Gisev <i>et al</i> <sup>[54]</sup>	Population-based cohort 9-yr study; n = 332	Outpatients	Highest risk in patients with baseline respiratory disease; MR increased
Huybrechts <i>et al</i> <sup>[55]</sup>	Population-based cohort 180-d study; n = 75445	NH patients	MR increased
Kales <i>et al</i> <sup>[46]</sup>	Retrospective cohort 180-d study; n = 33604	Outpatients	Highest risk with haloperidol; MR increased
Langballe <i>et al</i> <sup>[56]</sup>	Retrospective cohort 6-yr study; n = 26940	Outpatients	Limited adjustment in analysis; diagnosis based on prescription of antedementia drugs; MR increased
Lopez <i>et al</i> <sup>[26]</sup>	Prospective cohort 22-yr study with 4.3-yr follow-up; n = 957	Outpatients	Psychiatric symptoms increases risk of mortality; MR not increased
Arai <i>et al</i> <sup>[48]</sup>	Prospective cohort 10-wk study; n = 6000	Mixed	Preliminary finding; MR not increased

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goals, and alternatives of treatment. It is useful to document this discussion along with any comments or apprehensions. Medications should be started at low doses and titrated slowly and carefully.

For mild to moderate symptoms in the absence of psychosis, we recommend a trial of antidepressants (citalopram or sertraline) or cholinesterase inhibitors (donepezil, rivastigmine, galantamine). Mirtazapine and gabapentin have lesser degree of evidence, with positive results based on open-label studies and case reports. Though carbamazepine has shown efficacy, it is not recommended as a first line treatment because of its tolerability profile. Valproate has conflicting data supporting its efficacy and comes with significant side effects, though it remains widely used.

For moderate to severe symptoms, or in the presence of psychosis, antipsychotics may be used. Atypical antipsychotics are preferred as the initial choice. Risperidone is the most studied option, studies also support the use of olanzapine, quetiapine, and aripiprazole.

The choice of the agent should be guided by a thorough understanding of its pharmacologic properties and safety profiles, concomitant medications, and concurrent medical conditions. Drug interactions should be carefully considered. Parameters should be monitored, including chemistry panel, lipid profile, glycosylated hemoglobin, body mass index and waist measurements, electrocardiogram, and therapeutic blood levels when appropriate. Patients may be followed within a week to a month of starting treatment in the nursing home setting, or more often as needed.

Behavioral and psychological symptoms of AD typically wax and wane and attempts to taper medications is recommended. However, in patients with severe symptoms who responded to antipsychotics, withdrawal

of medications should be done with careful consideration as it may associated with the risk of relapse<sup>[31]</sup>.

## CONCLUSION

Behavioral and psychological symptoms are common in patients with AD. These symptoms can be difficult to manage. Thorough assessment is needed with careful consideration of the risks and benefits of medication treatment. Nonpharmacological intervention should be attempted first. Where symptoms are mild to moderate, antidepressants, cholinesterase inhibitors, and mood stabilizers may be used. For severe symptoms or with psychosis, atypical antipsychotics are preferred. Medications come with significant potential for adverse effects. Regular assessments for possible tapering and discontinuation are recommended. Further studies are needed for investigating better options in the pharmacological management of these symptoms and the safety concerns.

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