

Pharmacologic management of behavioral and psychological symptoms of major neurocognitive disorder

Monica Mathys, PharmD, BCPP, BCGP¹

How to cite: Mathys M. Pharmacologic management of behavioral and psychological symptoms of major neurocognitive disorder. Ment Health Clin [Internet]. 2018;8(6):284-93. DOI: 10.9740/mhc.2018.11.284.

Abstract

Behavioral and psychological symptoms of dementia (BPSD) occur in approximately 80% of patients who receive a diagnosis of major neurocognitive disorder. Nonpharmacologic strategies are the first-line treatment for BPSD. However, psychotropic medications are often necessary when nonpharmacologic methods are not effective in treating symptoms that are distressing or are causing behaviors that are dangerous to the patient or the patient's caregivers. The article provides a review of evidence-based recommendations for the use of antipsychotics, cognitive enhancers, and serotonin reuptake inhibitors for the treatment of BPSD. Different pharmacologic approaches are demonstrated through 2 patient cases in which nonpharmacologic management was not effective. The severity of BPSD must be weighed against the risks and benefits of pharmacologic intervention in order to implement an optimal medication regimen.

Keywords: dementia, neurocognitive disorders, psychological symptoms, behavioral symptoms, antipsychotics, selective serotonin reuptake inhibitors, cholinesterase inhibitors, memantine

¹ (Corresponding author) Associate Professor of Pharmacy Practice, Clinical Pharmacy Specialist-Mental Health, Texas Tech University Health Sciences Center, Dallas, Texas, monica.mathys@ttuhsc.edu, ORCID: <http://orcid.org/0000-0002-6907-1996>

Disclosures: I have nothing personal to disclose. Psychopharmacology Pearls are review articles intended to highlight both the evidence base available and/or controversial areas of clinical care for psychiatric and neurologic conditions as well as strategies of clinical decision-making used by expert clinicians. As pearls, articles reflect the views and practice of each author as substantiated with evidence-based facts as well as opinion and experience. Articles are edited by members of the Psychopharmacology Pearls Editorial Board as well as peer reviewed by MHC reviewers. This article was developed as part of the 2018 Psychopharmacology Pearls product for BCPP recertification credit. The course information and testing center is at cnp.org/353267.

Introduction

With publication of the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders*, the terms *dementia*, *amnesic*, and *cognitive disorders* were included under the umbrella of neurocognitive disorders (NCDs). The term *NCD* covers a broad list of diagnoses that can affect both younger individuals and older adults. Neurocognitive disorders are labeled as either mild or major followed by their etiologic subtypes. Diagnoses considered to be NCDs

include vascular NCD; frontotemporal NCD (Pick disease); and NCD due to Alzheimer disease, Lewy bodies, traumatic brain injury, human immunodeficiency virus infection, prion disease (eg, mad cow disease), Parkinson disease, or Huntington disease. The most prevalent types of NCDs are Alzheimer disease (70% of NCDs), vascular disease (10%-20% of NCDs), and Lewy bodies (3%-7% of NCDs).¹ It is estimated that 50% of the NCD population has mixed dementia, which usually includes both an Alzheimer and a vascular presentation.^{2,3}

Behavioral and psychological symptoms of dementia (BPSD) occur in approximately 80% of patients with major NCD.^{4,5} These symptoms lead to increased caregiver burden and early nursing home placement.⁶⁻⁸ In addition, patients with BPSD have faster cognitive and functional decline and increased morbidity and mortality compared with dementia patients without these symptoms.^{6,9}

BPSD is a broad term with a wide spectrum of possible symptoms, which are illustrated in Table 1.¹⁰ These noncognitive symptoms are divided into 4 clusters: hyperactivity, psychosis, affective symptoms, and eu-

TABLE 1: Behavioral and psychological symptoms of dementia¹⁰

Symptom	Prevalence, %
Disinhibition	9-35
Psychosis	10-35
Sleep disturbance	12-42
Anxiety	17-45
Irritability	20-55
Depression	20-57
Agitation/aggression	22-52
Apathy	29-76

phoria. Common hyperactivity symptoms are agitation, aggression, and irritability. Psychosis symptoms include hallucinations and delusions, and affective symptoms include depression, dysphoria, and anxiety. Symptoms that have been more difficult to categorize throughout the literature include aberrant motor behaviors, disinhibition, decreased appetite, sleep disturbances, and apathy.¹¹

Most patients with dementia will experience one or more BPSDs, which can cause distress for the patient and/or caregivers. Therefore, treatment of these symptoms is essential in community and institutional settings. Appropriate assessment of BPSD should involve noting the type, frequency, severity, pattern, and timing of the symptoms. Modifiable contributors, such as pain, constipation, infection, and medications, should be addressed. Non-pharmacologic methods should always be implemented first for BPSD, and these methods should be continued even if medication therapy is warranted.^{12,13} A few examples of nonpharmacologic interventions include gently redirecting the patient, providing structured activities during the day, creating a calm, quiet environment, and providing music therapy.¹⁴⁻¹⁶ This article does not intend to dismiss the importance of nonpharmacologic treatments. Behavioral interventions have been shown to decrease medication use significantly among nursing home residents.¹⁷ However, the scope of this article is to review the medication options available when nonpharmacologic therapies are not effective.

Patient Case 1

A 70-year-old with a diagnosis of major vascular NCD and history of significant alcohol use (currently in remission) is admitted to an inpatient psychiatric unit. The patient was transferred from the nursing home after experiencing increased aggressiveness toward various staff members and the spouse. The patient recently punched a nurse in the jaw and jumped up to strangle the spouse during a family visit. The nursing home refuses to readmit until the

Take Home Points:

1. Nonpharmacologic methods are the first-line recommendation when treating disruptive behaviors associated with dementia. However, psychotropic medications may be warranted if the behaviors are dangerous or cause distress to the patient. Despite their risks, antipsychotics are the most prescribed medications for treatment of dementia-related behaviors. When antipsychotic use is clinically warranted, dosing and subsequent titration should be approached conservatively. Once the disruptive behaviors are managed, an attempt to taper and discontinue the antipsychotic should be considered within 4 to 6 months.
2. The risks associated with antipsychotics are concerning; therefore, clinicians often look for other pharmacologic treatments for dementia-related behaviors when nonpharmacologic therapies fail. Other medications that have demonstrated small to moderate effects for reducing psychologic symptoms include cholinesterase inhibitors, memantine, and selective serotonin reuptake inhibitors.
3. The use of benzodiazepines and mood stabilizers cannot be recommended for treatment of behavioral and psychological symptoms of dementia because the published data demonstrate a high risk of adverse effects, with a low probability of being effective.

aggressive behaviors are under control. Upon admission, the patient is unresponsive to behavioral interventions and continues to be highly intrusive, irritable, and physically aggressive. The patient takes medications for hypertension and diabetes, but none of these medications appears to be a precipitant to the aggressive behavior. All laboratory exams, urinalysis, and vital signs are within normal limits, and the patient was noted to be otherwise healthy on physical exam.

Antipsychotics

Antipsychotics are the most widely studied medications for the treatment of BPSD and appear to have modest efficacy.¹⁸⁻²⁰ The target symptoms for antipsychotic therapy are agitation, aggression, and psychosis, and the medications should only be initiated when these symptoms are assessed as dangerous or distressing for the patient.¹³ Second-generation antipsychotics (SGAs) with efficacy data include risperidone, olanzapine, quetiapine, and aripiprazole.¹⁸⁻²⁶ Based on meta-analyses, effect sizes for risperidone, olanzapine, and aripiprazole appeared to be small but statistically significant compared with placebo. Quetiapine was found to have a lower effect size.²⁰ Overall, the SGAs have demonstrated a 35%

improvement in Neuropsychiatric Inventory (NPI) scores, which is above the minimum number of 30% to be considered a clinical observable change. However, mean total improvement in NPI scores was 3.41 points, which is below the threshold of 4 points to be considered clinically significant.¹⁹ Haloperidol is the most studied first-generation antipsychotic (FGA).²⁷⁻²⁹ However, recent treatment guidelines¹³ recommend against the use of haloperidol and other FGAs as first-line agents because of several studies showing a higher risk of mortality compared with SGA.³⁰⁻³³

For patients who respond to antipsychotics, symptom improvement is usually seen within 1 to 4 weeks. Despite being effective, there are several concerns with antipsychotics in the dementia population. A US Food and Drug Administration (FDA) boxed warning exists for all antipsychotics regarding an increased risk of mortality in elderly patients with dementia-related psychosis. This warning was added after the FDA found SGA to be associated with an increased risk of death in a meta-analysis of 17 trials comparing risperidone, quetiapine, olanzapine, or aripiprazole to placebo for treatment of BPSD.³⁴ In addition to the FDA review, a 2005 meta-analysis that included 15 SGA studies found incidence of death to be 3.5% in the SGA group compared with 2.3% in the placebo group ($P=.02$).³⁵ Overall, these studies showed the risk of mortality was 1.5 to 1.7 times higher for dementia patients prescribed SGA compared with placebo, with the most common causes of death being stroke, myocardial infarction, and infection. First-generation antipsychotics were later studied and found to have equal or higher risk of mortality compared with SGAs.³⁰⁻³³

Accelerated cognitive decline and increased thromboembolic risk have been associated with antipsychotic use in addition to the other common class effects, such as weight gain, hyperglycemia and dyslipidemia, extrapyramidal side effects, and orthostatic hypotension.³⁶⁻⁴³ Additionally, several antipsychotics, such as olanzapine, clozapine, and chlorpromazine, antagonize muscarinic receptors, which can potentially worsen cognition and BPSD.⁴⁴ One of the largest antipsychotic trials²⁶ ($n = 421$), Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer’s Disease (CATIE-AD), found SGA modestly effective for BPSD (mean NPI improvement of 15 points), but 82% of the study participants stopped the antipsychotic before the 9-month study ended. Risperidone, olanzapine, and quetiapine had higher rates of discontinuation because of adverse effects compared with placebo ($P=.009$). Overall, time to discontinuation of treatment for any reason was no different for patients taking an antipsychotic versus those assigned to placebo. Rates of discontinuation were 77% for risperidone, 80% for olanzapine, 82% for quetiapine, and 85% for placebo.²⁶

Because of the risks of adverse effects and mortality, antipsychotics should be used cautiously for the treatment of BPSD following failure of behavioral interventions.⁴⁴ Interdisciplinary teams should consider alternative treatments, such as additional nonpharmacologic methods and safer medication regimens that target the specific behavioral symptoms. However, the benefits of antipsychotics outweigh the risks in cases where patients’ behaviors are dangerous or impede needed medical care, as noted in case 1.

When choosing an antipsychotic, FGAs are generally avoided because of a higher risk of extrapyramidal side effects and mortality compared with SGA. Traditionally, clinicians decide between risperidone, olanzapine, and quetiapine when choosing an antipsychotic because these medications are the most studied for treatment of BPSD. The use of aripiprazole is limited in practice because of its longer half-life (75 hours) and titration schedule, but these factors should not prevent clinicians from using the drug completely. A patient’s concurrent disease states and medications should be taken into consideration when choosing an initial agent. For example, dopamine antagonism can worsen neurologic symptoms for patients with NCD due to Lewy bodies or Parkinson disease; therefore, an antipsychotic such as quetiapine would be considered ahead of risperidone or olanzapine because of its lower affinity for dopamine receptors. Risperidone and aripiprazole would likely be considered before olanzapine and quetiapine for patients who are obese or have diabetes because these medications are associated with a lower incidence of hyperglycemia and weight gain.

Antipsychotics should be dosed and titrated conservatively to the minimum effective dose (Table 2). Signs of medication effectiveness include decreased aggression and agitation to where nursing staff can allow the patient to roam safely on the unit, the patient is not resisting medical care, or there is a decreased need for emergency medications. If benefit is not seen within 4 weeks, the medication should be tapered and discontinued. For antipsychotic responders, an attempt to taper and discontinue the medication should be considered within 4 to 6 months of starting therapy.¹³ Antipsychotic dose reduction attempts are mandated by the Centers for Medicare & Medicaid Services for patients residing in long-term care facilities. A minimum of 2 gradual dose reductions should be tried during the first year of therapy, with each attempt being 3 to 6 months apart.⁴⁵

Evidence suggests antipsychotic discontinuation can be done successfully. A medication withdrawal study led by Ruths and colleagues⁴⁶ found no difference in neuropsychiatric scale scores 4 weeks after patients were tapered off their antipsychotic compared with those who continued antipsychotic therapy. In addition, 85% of patients

TABLE 2: Antipsychotics dosing recommendations for behavioral and psychological symptoms of dementia

Antipsychotic	Starting Dose, mg	Titration Recommendations, mg
Risperidone	0.25-0.5 at bedtime	Increase by 0.25-0.5 every 5 d up to 2 per d
Quetiapine	12.5-25 at bedtime	Increase by 25 every 3 d up to 200 per d
Olanzapine	2.5 at bedtime	Increase by 2.5 every 5 d up to 10 per d
Aripiprazole	2 daily	Increase to 5 after 2 wk, then increase by 2.5-5 every 2 wk up to 15 per d

tapered off their antipsychotic remained medication free 4 weeks later.⁴⁶ In another study published the same year, Ballard et al⁴⁷ observed no serious effects on behavior or cognition for most patients who tapered and discontinued their antipsychotic. However, a 2012 study by Devanand and colleagues⁴⁸ found BPSD to worsen and relapse of symptoms to occur more frequently in patients tapered off risperidone (60%) compared with patients who continued taking the antipsychotic (33%).

Patient case 1 is an example of a patient with dementia who is dangerously aggressive despite the implementation of nonpharmacologic treatments. In order to return to the nursing home, the aggression must be treated to where nursing staff and other patients will be safe. An antipsychotic is warranted in this situation. Based on treatment guidelines, SGAs are preferred over FGAs, such as haloperidol. Because of the patient's history of diabetes, risperidone and aripiprazole are safer options because they are less likely to worsen hyperglycemia compared with olanzapine and quetiapine. As noted earlier, aripiprazole's long half-life and titration schedule make it less practical in an acute clinical scenario; therefore, risperidone would be the antipsychotic of first choice for this patient case.

Patient Case 2

A 73-year-old with a diagnosis of Alzheimer disease (moderate severity) was admitted to a nursing home 6 months ago. The geriatric psychiatry team has been asked to assess the patient because of concerns about increased depression, delusional thinking, and agitation. No physical or verbal aggression has been noted. The nurses report decreased appetite and refusal to participate in daily activities (which the patient usually enjoys) for the last 3 weeks. Recently, the patient has become more irritable and delusional. It appears the patient thinks the nursing home is their old home and the other residents are intruders. Vital signs and a full laboratory workup plus urinalysis were within normal limits, and the patient denies having any pain. A physical exam notes a thin-appearing person but is otherwise normal. Nonpharmacologic strategies were implemented to target behavioral symptoms as the initial intervention, but these have yielded minimal clinical improvement. The patient is

currently prescribed donepezil 5 mg daily for cognitive decline. Sertraline 25 mg daily was added to the medication regimen within the last week to target depressive symptoms.

Cognitive Enhancers

Cholinesterase inhibitors and memantine are primarily used in dementias to help slow cognitive decline. Cholinesterase inhibitors are recommended for neurocognitive disorders due to Parkinson disease, Lewy body disease, and Alzheimer disease, whereas memantine is indicated only for moderate to severe Alzheimer disease.¹² Cognitive enhancers may be useful in mixed dementia because many of these patients have an Alzheimer component to their disease.⁴⁹ Most large, well-designed trials of cholinesterase inhibitors and memantine studied BPSDs as secondary outcomes. Statistical improvements in neuropsychiatric assessment scores have been observed (mean improvement of 2 points on the NPI), but the clinical significance is questionable.⁵⁰⁻⁵² Two additional studies^{53,54} where behavioral symptoms were the primary measurement found 5 to 6 months of donepezil use improved moderate to severe BPSD for patients with Alzheimer dementia, and the results also appeared to be clinically significant (mean NPI improvement of 12 points).

Overall, studies^{50,53,54} suggest cholinesterase inhibitors are more effective for depression, dysphoria, apathy, and anxiety symptoms than for agitation or aggression. Memantine has been shown to improve agitation, aggression, and delusions.^{51,52} The benefit of cognitive enhancers may not be seen until 3 to 6 months after initiation; therefore, these medications will not have clinical utility in acute treatment of BPSD. However, clinicians can consider prescribing cholinesterase inhibitors and memantine to help slow cognitive decline, and eventually these medications may also assist with controlling disruptive behaviors. Memantine is usually well tolerated, with the most common adverse effects being headache, dizziness, and constipation.⁵⁵ Cholinesterase inhibitors are associated with more concerning side effects, such as gastrointestinal upset, anorexia and weight loss, bradycardia, sleep disruption, and urinary incontinence. Recent studies⁵⁵⁻⁵⁷ have concluded cholin-

esterase inhibitors may also increase risk of falls and hip fractures. In addition, withdrawal of cholinesterase inhibitors may lead to faster cognitive and functional decline.^{58,59}

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have also been studied for treatment of BPSD. Several trials that included sertraline (50-200 mg/d), citalopram (20-30 mg/d), or escitalopram (10 mg/d) have found these medications to be more effective than placebo or just as effective as antipsychotics for agitation and irritability.⁶⁰⁻⁶⁵ Most studies were 6 to 12 weeks in duration. However, 1 small study (n=85) comparing citalopram to perphenazine found BPSD to significantly improve by 17 days with both medications, and there was no difference in efficacy between the 2 drugs.⁶³ The results from this study suggest SSRIs may be helpful for treating BPSD within a few weeks of initiation. Overall, authors conclude that antipsychotics have a quicker onset treating symptoms compared with SSRIs, but SSRIs are better tolerated. Even when antipsychotic therapy is warranted in cases of extreme aggression, the treatment team can consider starting an SSRI with the antipsychotic. The rationale for combination therapy is to increase the patient's chances of improvement and to allow eventual discontinuation of the antipsychotic. More literature is needed to determine the overall risk of mortality of SSRIs compared with antipsychotics. There are data to suggest SSRIs increase risk of mortality in older adults compared with nonusers.⁶⁶ However, a large retrospective study comparing number needed to harm among patients with dementia prescribed antipsychotics, valproic acid, and antidepressants found mortality risk to be higher for antipsychotics and valproic acid compared with antidepressants.³²

Risks associated with SSRIs include gastrointestinal upset, hyponatremia, tremor and akathisia, risk of falls, and bone density loss. Patients should also be monitored for signs and symptoms of bleeding, especially if nonsteroidal anti-inflammatory drugs, antiplatelet drugs, or anticoagulants are concurrently prescribed.^{66,67} In addition, citalopram was found to prolong QT interval and was associated with a small but statistically significant decline in cognition (-1.05 on the Mini Mental State Examination) in the Citalopram for Agitation in Alzheimer's Disease (CitAD) study.⁶² Based on the literature,^{68,69} QTc interval increases have ranged from 5 ms with low doses of citalopram up to 35 ms for maximum doses. The CitAD study⁶² observed a mean increase of 18 ms in QTc interval from baseline to week 3 with citalopram 30 mg daily, and more patients in the citalopram group had an increase of 30 ms or more in QTc interval compared with the placebo group. However, few patients actually met criteria for prolonged QTc

interval (450 ms for males and 470 ms for females).⁷⁰ Currently, citalopram labeling recommends patients 60 years and older not exceed 20 mg daily because of a risk of QTc prolongation.⁶⁸

When choosing an SSRI, sertraline is often selected first because of a number of factors. Citalopram and escitalopram are associated with a dose-related risk of prolonged QTc,⁶⁸⁻⁷² and clinicians are able to titrate sertraline to higher doses in older adults if clinically warranted rather than being limited to low doses of citalopram and escitalopram. However, citalopram and escitalopram can remain a safe and efficacious choice when dosed conservatively in older patients without cardiac risk factors or ECG abnormalities. Due to lack of data, paroxetine and fluoxetine are not usually prescribed for BPSD. In addition, these 2 SSRIs are often not preferred for elderly patients because of their lower tolerability. Paroxetine has moderate antimuscarinic activity, and fluoxetine is associated with higher incidences of anxiety and agitation compared with the other SSRI.^{44,67} Both paroxetine and fluoxetine are significant inhibitors of P450 enzymes, which increases risk of drug-drug interactions in older adults.⁶⁷

Based on studies, SSRIs should be initiated at low doses (eg, sertraline 25 mg daily) and titrated every 1 to 2 weeks. Symptom improvement will often be seen within 2 to 3 weeks of initiating therapy. There are currently no data to suggest how long to use an SSRI for BPSD after initiation. However, it is assumed these medications are not needed indefinitely for all patients. Gradual dose reductions of all psychotropic medications are required by the Centers for Medicare & Medicaid Services in the long-term care setting when being prescribed for BPSD. A minimum of 2 gradual dose reductions should be tried during the first year of therapy, with each attempt being 3 to 6 months apart. If a patient continues to require the SSRI after 1 year, then dose reductions should be attempted at least once yearly.⁴⁵ These same recommendations can also be applied to community-dwelling patients.

Regarding patient case 2, the delusions are distressing for the patient, despite the nursing home staff trying nonpharmacologic strategies. Therefore, medication intervention may be needed. An antipsychotic will likely treat the patient's delusional symptoms. However, the risks may outweigh the benefits in this scenario given the absence of dangerous behavioral symptoms, so alternative pharmacologic strategies should be attempted first. Clinicians may consider increasing the donepezil to 10 mg daily if tolerated and/or adding memantine to the regimen. Maximizing cognitive enhancers may provide more optimal long-term control of behavioral symptoms. However, the small effect observed in the current

literature must be weighed against the risks of additional polypharmacy and adverse effects. Another option for this patient is to increase the sertraline to 50 mg daily to more optimally target depressive symptoms while potentially improving agitation and delusional thinking.

For this particular patient, optimizing the sertraline dose is a good first choice because the patient is already taking a therapeutic dose of donepezil. The effects of sertraline are likely to be observed sooner than the effects of increasing the donepezil. To minimize the risk of adverse effects, one medication change should be made at a time. Therefore, the treatment team should avoid increasing the donepezil or adding memantine until the effects of the sertraline titration are assessed. Clinicians can consider increasing the donepezil and/or adding memantine if further symptom control is needed after optimizing the sertraline (6-12 weeks later). In addition, increasing the cholinesterase inhibitor or adding memantine will always be a future option as the patient's cognition continues to decline. For patients who cannot tolerate SSRIs, optimizing the donepezil or adding memantine would be the recommended treatment.

Additional Agents With Limited Evidence

Medications with limited evidence for the treatment of BPSD include trazodone, carbamazepine, and valproate (divalproex or valproic acid). One double-blind study showed trazodone 50 to 250 mg/d to be as effective as haloperidol 1 to 5 mg/d for agitation and verbal aggression.⁷³ Trazodone 50 mg was also shown to increase sleep time for patients with Alzheimer disease and sleep disturbances.⁷⁴ Carbamazepine was significantly better than placebo for improving agitation, aggression, and hostility in 2 randomized, controlled studies.^{75,76} Valproate was not found to be more efficacious than placebo for most BPSD symptoms in 5 randomized, controlled studies and a Cochrane review/meta-analysis.⁷⁷ The authors of the meta-analysis⁷⁷ concluded that valproate's risk of adverse effects outweighed any benefits of the medication. Observed adverse effects of valproate and their associated risk included sedation (odds ratio [OR] 2.48; confidence interval [CI] 1.37-4.47), gastrointestinal upset (OR 7.09; CI 1.73-29.02), urinary tract infections (OR 3.02; CI 1.04-8.08), and thrombocytopenia (OR 7.91; CI 1.92-32.57). A more recent study led by Tariot et al⁷⁸ did not find valproate effective for treatment of BPSD compared with placebo, and patients taking valproate experienced more adverse effects, such as somnolence, gait disturbances, tremor, and gastrointestinal upset. Additionally, studies have found valproate to have a mortality risk similar to that of antipsychotics in the dementia population,^{79,80} and it has been associated

with accelerated brain volume loss and further cognitive decline.^{78,81}

Dextromethorphan/quinidine, which is FDA approved for treatment of pseudobulbar affect, was studied in 1 randomized, placebo-controlled trial of patients with Alzheimer disease and agitation. Neuropsychiatric Inventory agitation/aggression domain scores improved significantly in the treatment group (mean improvement of 2-3.3 points) compared with the placebo group ($P < .001$). The most common adverse effects observed with dextromethorphan/quinidine compared with placebo included falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), and urinary tract infections (5.3% vs 3.9%).⁸²

Data on the use of methylphenidate in dementia patients continue to emerge specifically for the treatment of apathy. Two studies,^{83,84} which each included 60 patients, compared methylphenidate to placebo for the treatment of apathy. Most patients had mild Alzheimer disease at baseline and randomized to methylphenidate or placebo for 6 to 12 weeks. The Apathy Evaluation Scale was used to evaluate the primary outcome in both studies. The 6-week study did not find methylphenidate 10 mg/d to statistically improve Apathy Evaluation Scale scores compared with placebo. However, there were statistically more methylphenidate patients assessed as having moderate or marked improvement based on the Clinical Global Impression of Change scale (21% vs 3%).⁸³ Apathy Evaluation Scale scores did statistically improve compared with placebo in the 12-week trial, in which patients were titrated to methylphenidate 20 mg/d.⁸⁴ Adverse events did not reach statistical significance in either study. A recent Cochrane review and meta-analysis concluded that methylphenidate may be useful for treatment of apathy, but there are limited data to predict how clinically meaningful its effect will be.⁸⁵

Benzodiazepines are prescribed among the general population for anxiety, agitation, and sleep. However, these medications have not been shown to be consistently effective in treating agitation or sleep disturbances in dementia patients, and some studies have found benzodiazepines to be associated with cognitive decline.⁸⁶ Additionally, benzodiazepines are known to be a high-risk drug class for older adults because of a risk of falls, orthostasis, oversedation, delirium, and respiratory depression.⁴⁴

Conclusion

When presented with a patient with disruptive behaviors due to NCD, clinicians should first search for any modifiable contributors, such as infection, pain, constipation, and medications. Nonpharmacologic methods

TABLE 3: Summary of benefits and risks of treatment options for behavioral and psychological symptoms of dementia (BPSD)

Medication	Target Symptoms	Benefits	Risks
Antipsychotics			
Risperidone Olanzapine Quetiapine Aripiprazole Haloperidol (not recommended as first-line)	Severe agitation Aggression Psychosis	Small to moderate efficacy Onset of efficacy is usually observed within the first 1-2 wk	Increased risk of mortality Extrapyramidal side effects Metabolic adverse effects Risk of thromboembolism Possible cognitive decline Risk of falls
Cholinesterase inhibitors			
Donepezil Galantamine Rivastigmine	Depression Dysphoria Anxiety	Small improvements in BPSD Medications may already be appropriate to help slow cognitive decline	Gastrointestinal upset Anorexia/weight loss Bradycardia Risk of falls
Memantine	Agitation Aggression Delusions	Small improvements in BPSD Medication may already be appropriate to help slow cognitive decline	Minimal risk of adverse effects <ul style="list-style-type: none"> • Headache • Dizziness • Constipation
Selective serotonin reuptake inhibitors			
Sertraline Citalopram Escitalopram	Agitation Depression Irritability	Some studies show selective serotonin reuptake inhibitors work as well as an antipsychotic Tolerability is often better compared with antipsychotics	Gastrointestinal upset Hyponatremia Risk of bleeds Tremor/akathisia Risk of bone loss Risk of falls Possible cognitive decline (Citalopram for Agitation in Alzheimer's Disease study)

should be implemented and continued even if medication therapy is needed. If a patient's behavioral symptoms, such as agitation and aggression, become dangerous, then SGA may be warranted. The goal should be to use the antipsychotic temporarily and to attempt a taper and discontinuation within 4 to 6 months of initiation.

Maximizing the use of cholinesterase inhibitors and memantine may help reduce BPSD in the long term. Selective serotonin reuptake inhibitors can also be tried for agitation and irritability. Treatment onset of SSRIs appears to be slower than that of antipsychotics, but studies suggest SSRIs are better tolerated (Table 3). Based on the current published data available, methylphenidate is recommended over cholinesterase inhibitors and antidepressants for treatment of apathy, but methylphenidate's clinical impact is still questionable.

Medications not recommended for the treatment of BPSD include benzodiazepines and anticonvulsants. Little evidence exists to support the use benzodiazepines for BPSD, but the risks of the medications in older adults have been well established. Valproate is associated with higher rates of adverse effects and does not appear more effective for BPSD compared with placebo. Because of limited data in

the dementia population, carbamazepine should only be used as a last-line pharmacologic option.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
2. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol*. 2007;62(4):406-13. DOI: [10.1002/ana.21208](https://doi.org/10.1002/ana.21208). PubMed PMID: [17879383](https://pubmed.ncbi.nlm.nih.gov/17879383/).
3. White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, et al. Recent clinical-pathologic research on the causes of dementia in late life: update from the Honolulu-Asia Aging Study. *J Geriatr Psychiatry Neurol*. 2005;18(4):224-7. DOI: [10.1177/0891988705281872](https://doi.org/10.1177/0891988705281872). PubMed PMID: [16306244](https://pubmed.ncbi.nlm.nih.gov/16306244/).
4. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement*. 2011;7(5):532-9. DOI: [10.1016/j.jalz.2011.05.2410](https://doi.org/10.1016/j.jalz.2011.05.2410). PubMed PMID: [21889116](https://pubmed.ncbi.nlm.nih.gov/21889116/); PubMed Central PMCID: [PMC3299979](https://pubmed.ncbi.nlm.nih.gov/PMC3299979/).
5. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol*. 2012;3:73. DOI: [10.3389/fneur.2012.00073](https://doi.org/10.3389/fneur.2012.00073). PubMed PMID: [22586419](https://pubmed.ncbi.nlm.nih.gov/22586419/); PubMed Central PMCID: [PMC3345875](https://pubmed.ncbi.nlm.nih.gov/PMC3345875/).
6. Kales HC, Chen P, Blow FC, Welsh DE, Mellow AM. Rates of clinical depression diagnosis, functional impairment, and nursing home placement in coexisting dementia and depression. *Am J Geriatr Psychiatry*. 2005;13(6):441-9. DOI: [10.1176/appi.ajgp.13.6.441](https://doi.org/10.1176/appi.ajgp.13.6.441). PubMed PMID: [15956263](https://pubmed.ncbi.nlm.nih.gov/15956263/).

7. Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA*. 2002;287(16):2090-7. PubMed PMID: [11966383](#).
8. Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci*. 2000;55(1):S2-13. PubMed PMID: [10728125](#).
9. Wancata J, Windhaber J, Krautgartner M, Alexandrowicz R. The consequences of non-cognitive symptoms of dementia in medical hospital departments. *Int J Psychiatry Med*. 2003;33(3):257-71. DOI: [10.2190/ABXK-FMWG-98YP-D1CU](#). PubMed PMID: [15089007](#).
10. Fauth EB, Gibbons A. Which behavioral and psychological symptoms of dementia are the most problematic? Variability by prevalence, intensity, distress ratings, and associations with caregiver depressive symptoms. *Int J Geriatr Psychiatry*. 2013;29(3):263-71. DOI: [10.1002/gps.4002](#). PubMed PMID: [23846797](#).
11. van der Linde RM, Dening T, Matthews FE, Brayne C. Grouping of behavioural and psychological symptoms of dementia. *Int J Geriatr Psychiatry*. 2013;29(6):562-8. DOI: [10.1002/gps.4037](#). PubMed PMID: [24677112](#); PubMed Central PMCID: [PMC4255309](#).
12. Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Guideline watch (October 2014): practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Arlington (VA): American Psychiatric Association [cited 2018 Jan 7]. Available from: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf
13. American Psychiatric Association. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Arlington (VA): American Psychiatric Association; 2016.
14. Lesser JM, Hughes S. Psychosis-related disturbances: psychosis, agitation, and disinhibition in Alzheimer's disease: definitions and treatment options. *Geriatrics*. 2006;61(12):14-20. PubMed PMID: [17184138](#).
15. Smith AG. Behavioral problems in dementia: strategies for pharmacologic and nonpharmacologic management. *Postgrad Med*. 2004;115(6):47-52, 55-6. PubMed PMID: [15216573](#).
16. Kales HC, Gitlin LN, Lyketsos CG. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762-9. DOI: [10.1111/jgs.12730](#). PubMed PMID: [24635665](#).
17. Centers for Medicare & Medicaid Services. National partnership to improve dementia care in nursing homes [cited 2018 Feb 21]. Available from: <https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/National-Partnership-to-Improve-Dementia-Care-in-Nursing-Homes.html>
18. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;(1):CD003476. DOI: [10.1002/14651858.CD003476.pub2](#). PubMed PMID: [16437455](#).
19. Maher AR, Maglione M, Bagley S, Suttorp M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359-69. DOI: [10.1001/jama.2011.1360](#). PubMed PMID: [21954480](#).
20. Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. *Ther Adv Chronic Dis*. 2016;7(5):229-45. DOI: [10.1177/2040622316658463](#). PubMed PMID: [27583123](#); PubMed Central PMCID: [PMC4994396](#).
21. Rabinowitz J, Katz I, De Deyn PP, Greenspan A, Brodaty H. Treating behavioral and psychological symptoms in patients with psychosis of Alzheimer's disease using risperidone. *Int Psychogeriatr*. 2007;19(2):227-40. DOI: [10.1017/S1041610206003942](#). PubMed PMID: [16879763](#).
22. Rainer M, Haushofer M, Pfolz H, Struhel C, Wick W. Quetiapine versus risperidone in elderly patients with behavioural and psychological symptoms of dementia: efficacy, safety and cognitive function. *Eur Psychiatry*. 2007;22(6):395-403. DOI: [10.1016/j.eurpsy.2007.03.001](#). PubMed PMID: [17482432](#).
23. Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry*. 2000;57(10):968-76. PubMed PMID: [11015815](#).
24. Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. *Curr Alzheimer Res*. 2007;4(1):81-93. PubMed PMID: [17316169](#).
25. Fujikawa T, Takahashi T, Kinoshita A, Kajiyama H, Kurata A, Yamashita H, et al. Quetiapine treatment for behavioral and psychological symptoms in patients with senile dementia of Alzheimer type. *Neuropsychobiology*. 2004;49(4):201-4. DOI: [10.1159/000077367](#). PubMed PMID: [15118358](#).
26. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525-38. DOI: [10.1056/NEJMoa061240](#). PubMed PMID: [17035647](#).
27. Lonergan E, Luxenberg J, Colford JM, Birks J. Haloperidol for agitation in dementia. *Cochrane Database Syst Rev*. 2002;148(2):CD002852. DOI: [10.1002/14651858.CD002852](#). PubMed PMID: [12076456](#).
28. Devanand DP, Marder K, Michaels KS, Sackeim HA, Bell K, Sullivan MA, et al. A randomized, placebo-controlled dose-comparison trial of haloperidol for psychosis and disruptive behaviors in Alzheimer's disease. *Am J Psychiatry*. 1998;155(11):1512-20. DOI: [10.1176/ajp.155.11.1512](#). PubMed PMID: [9812111](#).
29. Verhey FRJ, Verkaaik M, Lousberg R. Olanzapine versus haloperidol in the treatment of agitation in elderly patients with dementia: results of a randomized controlled double-blind trial. *Dement Geriatr Cogn Disord*. 2005;21(1):1-8. DOI: [10.1159/000089136](#). PubMed PMID: [16244481](#).
30. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-41. DOI: [10.1056/NEJMoa052827](#). PubMed PMID: [16319382](#).
31. Sahlberg M, Holm E, Gislason GH, Køber L, Torp-Pedersen C, Andersson C. Association of selected antipsychotic agents with major adverse cardiovascular events and noncardiovascular mortality in elderly persons. *J Am Heart Assoc*. 2015;4(9):e001666. DOI: [10.1161/JAHA.114.001666](#). PubMed PMID: [26330335](#); PubMed Central PMCID: [PMC4599488](#).
32. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-45. DOI: [10.1001/jamapsychiatry.2014.3018](#). PubMed PMID: [25786075](#); PubMed Central PMCID: [PMC4439579](#).
33. Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *Can Med Assoc J*. 2007;176(5):627-32. DOI: [10.1503/cmaj.061250](#). PubMed PMID: [17325327](#); PubMed Central PMCID: [PMC1800321](#).
34. Centers for Medicare & Medicaid Services. Atypical antipsychotics medications: use in adults [updated 2013 Aug; cited 2018 July 18]. Available from: <https://www.cms.gov/medicare-medicaid->

[coordination/fraud-prevention/medicaid-integrity-education/pharmacy-education-materials/downloads/atyp-antipsych-adult-factsheet.pdf](#)

35. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-43. DOI: [10.1001/jama.294.15.1934](#). PubMed PMID: [16234500](#).
36. Ballard C, Margallo-Lana M, Juszcak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ*. 2005;330(7496):874. DOI: [10.1136/bmj.38369.459988.8F](#). PubMed PMID: [15722369](#).
37. Vigen CLP, Mack WJ, Keefe RSE, Sano M, Sultzer DL, Stroup TS, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry*. 2011;168(8):831-9. DOI: [10.1176/appi.ajp.2011.08121844](#). PubMed PMID: [21572163](#); PubMed Central PMCID: [PMC3310182](#).
38. Deberdt WG, Siegal A, Ahl J, Meyers AL, Landbloom R. Effect of olanzapine on cognition during treatment of behavioral and psychiatric symptoms in patients with dementia: a post-hoc analysis. *Int J Geriatr Psychiatry*. 2008;23(4):364-9. DOI: [10.1002/gps.1885](#). PubMed PMID: [17708584](#).
39. Kennedy J, Deberdt W, Siegal A, Micca J, Degenhardt E, Ahl J, et al. Olanzapine does not enhance cognition in non-agitated and non-psychotic patients with mild to moderate Alzheimer's dementia. *Int J Geriatr Psychiatry*. 2005;20(11):1020-7. DOI: [10.1002/gps.1397](#). PubMed PMID: [16250069](#).
40. Zheng L, Mack WJ, Dagerman KS, Hsiao JK, Lebowitz BD, Lyketsos CG, et al. Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study. *Am J Psychiatry*. 2009;166(5):583-90. DOI: [10.1176/appi.ajp.2008.08081218](#). PubMed PMID: [19369318](#); PubMed Central PMCID: [PMC2891018](#).
41. Schmedt N, Garbe E. Antipsychotic drug use and the risk of venous thromboembolism in elderly patients with dementia. *J Clin Psychopharmacol*. 2013;33(6):753-8. DOI: [10.1097/JCP.0b013e3182a412d5](#). PubMed PMID: [24052055](#).
42. Dennis M, Shine L, John A, Marchant A, McGregor J, Lyons RA, et al. Correction to: risk of adverse outcomes for older people with dementia prescribed antipsychotic medication: a population based e-cohort study. *Neurol Ther*. 2018;7(1):169. DOI: [10.1007/s40120-018-0093-0](#). PubMed PMID: [29524109](#); PubMed Central PMCID: [PMC5990499](#).
43. Barbui C, Conti V, Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. *Drug Saf*. 2014;37(2):79-90. DOI: [10.1007/s40264-013-0127-6](#). PubMed PMID: [24403009](#).
44. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227-46. DOI: [10.1111/jgs.13702](#). PubMed PMID: [26446832](#).
45. Centers for Medicare & Medicaid Services. National partnership to improve dementia care in nursing homes & Quality Assurance and Performance Improvement (OAPI) [cited 2018 Mar 30]. Available from: [www.cms.gov/Outreach-and-Education/Outreach/NPC/Downloads/2017-12-14-Dementia-Care-Presentation.pdf](#)
46. Ruths S, Straand J, Nygaard HA, Aarsland D. Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study—the Bergen District Nursing Home Study (BEDNURS). *Int J Geriatr Psychiatry*. 2008;23(9):889-95. DOI: [10.1002/gps.1998](#). PubMed PMID: [18306150](#).
47. Ballard C, Lana MM, Theodoulou M, Douglas S, McShane R, Jacoby R, et al. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med*. 2008;5(4):e76. DOI: [10.1371/journal.pmed.0050076](#). PubMed PMID: [18384230](#); PubMed Central PMCID: [PMC2276521](#).
48. Devanand DP, Mintzer J, Schultz SK, Andrews HF, Sultzer DL, de la Pena D, et al. Relapse risk after discontinuation of risperidone in Alzheimer's disease. *N Engl J Med*. 2012;367(16):1497-507. DOI: [10.1056/NEJMoa1114058](#). PubMed PMID: [23075176](#); PubMed Central PMCID: [PMC3490406](#).
49. Herrmann N, Lanctôt KL, Hogan DB. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. *Alzheimers Res Ther*. 2013;5 Suppl 1:S5. DOI: [10.1186/alzrt201](#). PubMed PMID: [24565367](#); PubMed Central PMCID: [PMC3980908](#).
50. Trinh N-H, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*. 2003;289(2):210-6. PubMed PMID: [12517232](#).
51. Maidment ID, Fox CG, Boustani M, Rodriguez J, Brown RC, Katona CL. Efficacy of memantine on behavioral and psychological symptoms related to dementia: a systematic meta-analysis. *Ann Pharmacother*. 2008;42(1):32-8. DOI: [10.1345/aph.1K372](#). PubMed PMID: [18056833](#).
52. Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry*. 2008;23(5):537-45. DOI: [10.1002/gps.1949](#). PubMed PMID: [18058838](#).
53. Paleacu D, Mazeh D, Mirecki I, Even M, Barak Y. Donepezil for the treatment of behavioral symptoms in patients with Alzheimer's disease. *Clin Neuropharmacol*. 2002;25(6):313-7. PubMed PMID: [12469005](#).
54. Cummings JL, McRae T, Zhang R. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *Am J Geriatr Psychiatry*. 2006;14(7):605-12. DOI: [10.1097/01.JGP.0000221293.91312.d3](#). PubMed PMID: [16816014](#).
55. Allergan Inc. Namzaric (memantine hydrochloride and donepezil hydrochloride) capsule 2014 [updated 2017 Jun; cited 2018 Jan 7]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: [https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9ofedc32-19e5-480c-afc6-f35a5cf4b9aa](#)
56. Schneider LS. Treatment of Alzheimer's disease with cholinesterase inhibitors. *Clin Geriatr Med*. 2001;17(2):337-58. PubMed PMID: [11375139](#).
57. Gill SS, Anderson GM, Fischer HD, Bell CM, Li P, Normand SLT, et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors. *Arch Intern Med*. 2009;169(9):867. DOI: [10.1001/archinternmed.2009.43](#). PubMed PMID: [19433698](#).
58. Scarpini E, Bruno G, Zappalà G, Adami M, Richarz U, Gaudig M, et al. Cessation versus continuation of galantamine treatment after 12 months of therapy in patients with Alzheimer's disease: a randomized, double blind, placebo controlled withdrawal trial. *J Alzheimers Dis*. 2011;26(2):211-20. DOI: [10.3233/JAD-2011-110134](#). PubMed PMID: [21606568](#).
59. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893-903. DOI: [10.1056/NEJMoa1106668](#). PubMed PMID: [22397651](#).
60. Gaber S, Ronzoli S, Bruno A, Biagi A. Sertraline versus small doses of haloperidol in the treatment of agitated behavior in patients with dementia. *Arch Gerontol Geriatr*. 2001;33 Suppl 1:159-62. DOI: [10.1016/S0167-4943\(01\)00135-2](#).

61. Finkel SI, Mintzer JE, Dysken M, Krishnan KRR, Burt T, McRae T. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psychiatry*. 2004;19(1):9-18. DOI: [10.1002/gps.998](https://doi.org/10.1002/gps.998). PubMed PMID: [14716694](https://pubmed.ncbi.nlm.nih.gov/14716694/).
62. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014;311(7):682-91. DOI: [10.1001/jama.2014.93](https://doi.org/10.1001/jama.2014.93). PubMed PMID: [24549548](https://pubmed.ncbi.nlm.nih.gov/24549548/).
63. Pollock BG, Mulsant BH, Rosen J, Sweet RA, Mazumdar S, Bharucha A, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *Am J Psychiatry*. 2002;159(3):460-5. DOI: [10.1176/appi.ajp.159.3.460](https://doi.org/10.1176/appi.ajp.159.3.460). PubMed PMID: [11870012](https://pubmed.ncbi.nlm.nih.gov/11870012/).
64. Pollock BG, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, et al. A double-blind comparison of citalopram and risperidone for the treatment of behavioral and psychotic symptoms associated with dementia. *Am J Geriatr Psychiatry*. 2007;15(11):942-52. DOI: [10.1097/JGP.0b013e3180cc1ff5](https://doi.org/10.1097/JGP.0b013e3180cc1ff5). PubMed PMID: [17846102](https://pubmed.ncbi.nlm.nih.gov/17846102/).
65. Barak Y, Plopsi I, Tadger S, Paleacu D. Escitalopram versus risperidone for the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease: a randomized double-blind pilot study. *Int Psychogeriatr*. 2011;23(9):1515-9. DOI: [10.1017/S1041610211000743](https://doi.org/10.1017/S1041610211000743). PubMed PMID: [21492498](https://pubmed.ncbi.nlm.nih.gov/21492498/).
66. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ*. 2011;343:d4551. DOI: [10.1136/bmj.d4551](https://doi.org/10.1136/bmj.d4551). PubMed PMID: [21810886](https://pubmed.ncbi.nlm.nih.gov/21810886/); PubMed Central PMCID: [PMC3149102](https://pubmed.ncbi.nlm.nih.gov/PMC3149102/).
67. Lotrich FE, Pollock BG. Aging and clinical pharmacology: implications for antidepressants. *J Clin Pharmacol*. 2013;45(10):1106-122. DOI: [10.1177/0091270005280297](https://doi.org/10.1177/0091270005280297). PubMed PMID: [16172176](https://pubmed.ncbi.nlm.nih.gov/16172176/).
68. FDA Drug Safety Communication. Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses [2012 Mar 28; cited 2018 Feb 19]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm>
69. McClelland J, Mathys M. Evaluation of QTc prolongation and dosage effect with citalopram. *Ment Health Clin [Internet]*. 2016;6(4):165-70. DOI: [10.9740/mhc.2016.07.165](https://doi.org/10.9740/mhc.2016.07.165). PubMed PMID: [29955465](https://pubmed.ncbi.nlm.nih.gov/29955465/); PubMed Central PMCID: [PMC6007721](https://pubmed.ncbi.nlm.nih.gov/PMC6007721/).
70. Drye LT, Spragg D, Devanand DP, Frangakis C, Marano C, Meinert CL, et al. Changes in QTc interval in the citalopram for agitation in Alzheimer's disease (CitAD) randomized trial. *PLoS One*. 2014;9(6):e98426. DOI: [10.1371/journal.pone.0098426](https://doi.org/10.1371/journal.pone.0098426). PubMed PMID: [24914549](https://pubmed.ncbi.nlm.nih.gov/24914549/); PubMed Central PMCID: [PMC4051660](https://pubmed.ncbi.nlm.nih.gov/PMC4051660/).
71. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ*. 2013;346:f288. DOI: [10.1136/bmj.f288](https://doi.org/10.1136/bmj.f288). PubMed PMID: [23360890](https://pubmed.ncbi.nlm.nih.gov/23360890/); PubMed Central PMCID: [PMC3558546](https://pubmed.ncbi.nlm.nih.gov/PMC3558546/).
72. Kim A, Lim KS, Lee H, Chung H, Yoon SH, Yu KS, et al. A thorough QT study to evaluate the QTc prolongation potential of two neuropsychiatric drugs, quetiapine and escitalopram, in healthy volunteers. *Int Clin Psychopharmacol*. 2016;31(4):210-7. DOI: [10.1097/YIC.000000000000124](https://doi.org/10.1097/YIC.000000000000124). PubMed PMID: [26950553](https://pubmed.ncbi.nlm.nih.gov/26950553/).
73. Sultzer DL, Gray KF, Gunay I, Berisford MA, Mahler ME. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry*. 1997;5(1):60-9. PubMed PMID: [9169246](https://pubmed.ncbi.nlm.nih.gov/9169246/).
74. Camargos EF, Louzada LL, Quintas JL, Naves JOS, Louzada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. *Am J Geriatr Psychiatry*. 2014;22(12):1565-74. DOI: [10.1016/j.jagp.2013.12.174](https://doi.org/10.1016/j.jagp.2013.12.174). PubMed PMID: [24495406](https://pubmed.ncbi.nlm.nih.gov/24495406/).
75. Tariot PN, Erb R, Podgorski CA, Cox C, Patel S, Jakimovich L, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry*. 1998;155(1):54-61. DOI: [10.1176/ajp.155.1.54](https://doi.org/10.1176/ajp.155.1.54). PubMed PMID: [9433339](https://pubmed.ncbi.nlm.nih.gov/9433339/).
76. Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS. A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. *Am J Geriatr Psychiatry*. 2001;9(4):400-5. PubMed PMID: [11739066](https://pubmed.ncbi.nlm.nih.gov/11739066/).
77. Loneragan E, Luxenberg J. Valproate preparations for agitation in dementia. *Cochrane Database Syst Rev*. 2009;(3):CD003945. DOI: [10.1002/14651858.CD003945.pub3](https://doi.org/10.1002/14651858.CD003945.pub3). PubMed PMID: [19588348](https://pubmed.ncbi.nlm.nih.gov/19588348/).
78. Tariot PN, Schneider LS, Cummings J, Thomas RG, Raman R, Jakimovich LJ, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry*. 2011;68(8):853-61. DOI: [10.1001/archgenpsychiatry.2011.72](https://doi.org/10.1001/archgenpsychiatry.2011.72). PubMed PMID: [21810649](https://pubmed.ncbi.nlm.nih.gov/21810649/).
79. Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *Am J Psychiatry*. 2007;164(10):1568-76; quiz 1623. DOI: [10.1176/appi.ajp.2007.06101710](https://doi.org/10.1176/appi.ajp.2007.06101710). PubMed PMID: [17898349](https://pubmed.ncbi.nlm.nih.gov/17898349/).
80. Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, et al. Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry*. 2012;169(1):71-9. DOI: [10.1176/appi.ajp.2011.11030347](https://doi.org/10.1176/appi.ajp.2011.11030347). PubMed PMID: [22193526](https://pubmed.ncbi.nlm.nih.gov/22193526/).
81. Fleisher AS, Truran D, Mai JT, Langbaum JBS, Aisen PS, Cummings JL, et al. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. *Neurology*. 2011;77(13):1263-71. DOI: [10.1212/WNL.0b013e318230a16c](https://doi.org/10.1212/WNL.0b013e318230a16c). PubMed PMID: [21917762](https://pubmed.ncbi.nlm.nih.gov/21917762/); PubMed Central PMCID: [PMC3179645](https://pubmed.ncbi.nlm.nih.gov/PMC3179645/).
82. Cummings JL, Lyketsos CG, Peskind ER, Porsteinsson AP, Mintzer JE, Scharre DW, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA*. 2015;314(12):1242-54. DOI: [10.1001/jama.2015.10214](https://doi.org/10.1001/jama.2015.10214). PubMed PMID: [26393847](https://pubmed.ncbi.nlm.nih.gov/26393847/).
83. Rosenberg PB, Lanctôt KL, Drye LT, Herrmann N, Scherer RW, Bachman DL, et al. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(8):810-6. DOI: [10.4088/JCP.12mo08099](https://doi.org/10.4088/JCP.12mo08099). PubMed PMID: [24021498](https://pubmed.ncbi.nlm.nih.gov/24021498/).
84. Padala PR, Padala KP, Lensing SY, Ramirez D, Monga V, Bopp MM, et al. Methylphenidate for apathy in community-dwelling older veterans with mild Alzheimer's disease: a double-blind, randomized, placebo-controlled trial. *Am J Psychiatry*. 2018;175(2):159-68. DOI: [10.1176/appi.ajp.2017.17030316](https://doi.org/10.1176/appi.ajp.2017.17030316). PubMed PMID: [28945120](https://pubmed.ncbi.nlm.nih.gov/28945120/).
85. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctôt KL. Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database Syst Rev*. 2018;5:CD012197. DOI: [10.1002/14651858.CD012197.pub2](https://doi.org/10.1002/14651858.CD012197.pub2). PubMed PMID: [29727467](https://pubmed.ncbi.nlm.nih.gov/29727467/).
86. Defrancesco M, Marksteiner J, Fleischacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: a systematic review of literature. *Int J Neuropsychopharmacol*. 2015;18(10):pyv055. DOI: [10.1093/ijnp/pyv055](https://doi.org/10.1093/ijnp/pyv055). PubMed PMID: [25991652](https://pubmed.ncbi.nlm.nih.gov/25991652/); PubMed Central PMCID: [PMC4648159](https://pubmed.ncbi.nlm.nih.gov/PMC4648159/).