

Chapter 7

Treating the Behavioral Symptoms of Dementia



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Dementia is a term that includes multiple etiologies of cognitive impairment that significantly diminishes an individual's level of daily functioning. Alzheimer's disease (AD) is the most common form of dementia. AD is a progressive neurodegenerative disorder affecting memory and other cognitive domains interfering with daily functioning. Other dementias, such as vascular dementia, Lewy body dementia, and frontotemporal dementia, are less common but also cause considerable distress to patients and caregivers. With all dementias, behavior and mood changes often manifest as the neurodegenerative disorder progresses. These behavior and mood changes are either referred to as the behavioral and psychological symptoms of dementia (BPSD) or the neuropsychiatric symptoms of dementia (NPS). This chapter focuses on the treatment of BPSD, as these symptoms frequently facilitate caregiver stress and nursing home placement [1, 2].

There are three main categories of BPSD, including agitation/aggression, psychosis, and mood disorders. Greater than 90% of patients with dementia develop at least one of these behavioral symptoms in a 5-year period, with 85% of the symptoms rising to the level of clinical significance [3]. Thus, it is imperative that physicians who frequently diagnose and treat patients with dementia are aware of the non-pharmacological and pharmacological treatments available for BPSD. This chapter will first present data for non-pharmacologic treatments of BPSD, as they are the recommended first-line interventions [4–6] (Figs. 7.1 and 7.2). However, the majority of the chapter will review the pharmacological options available to treat BPSD that fail to respond to non-pharmacological interventions.

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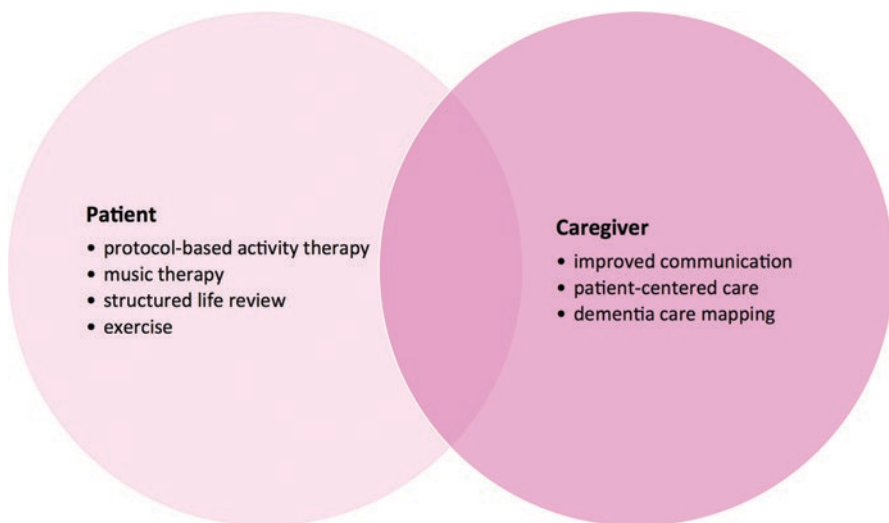


Fig. 7.1 Non-pharmacological interventions for BPSD

Treatment of Agitation in Dementia

Agitation in individuals with dementia manifests in a variety of ways including restlessness, pacing, fidgeting, repetitive motor activities, and abnormal vocalizations. Physicians should first consider the etiology of the agitation; for example, does the patient have an infection such as a UTI and is the patient in pain, delirious, and frustrated by apraxia or word-finding difficulties? Addressing the etiology of the agitation is the most useful first step. However, the symptom of agitation itself may require direct treatment, while the underlying etiology is under investigation.

Non-pharmacological Interventions

There are few randomized, controlled trials examining non-pharmacological treatments of agitation in settings other than care home placement. A recent systematic meta-analysis of non-pharmacological interventions for agitation [7] found significant improvement with caregiver training. Specifically, improving communication, person-centered care, and dementia care mapping within the care home each significantly reduced agitation. Follow-up showed that improvement continued 3–6 months after intervention, demonstrating efficacy with paid caregiver training even months after the intervention ceased. Protocol-based activity and music therapy were also beneficial interventions. However, the benefits persisted only during the therapeutic intervention, with no sustained benefit at follow-up [7–10]. In contrast, interventions such as touch therapy were not beneficial, even during the therapeutic

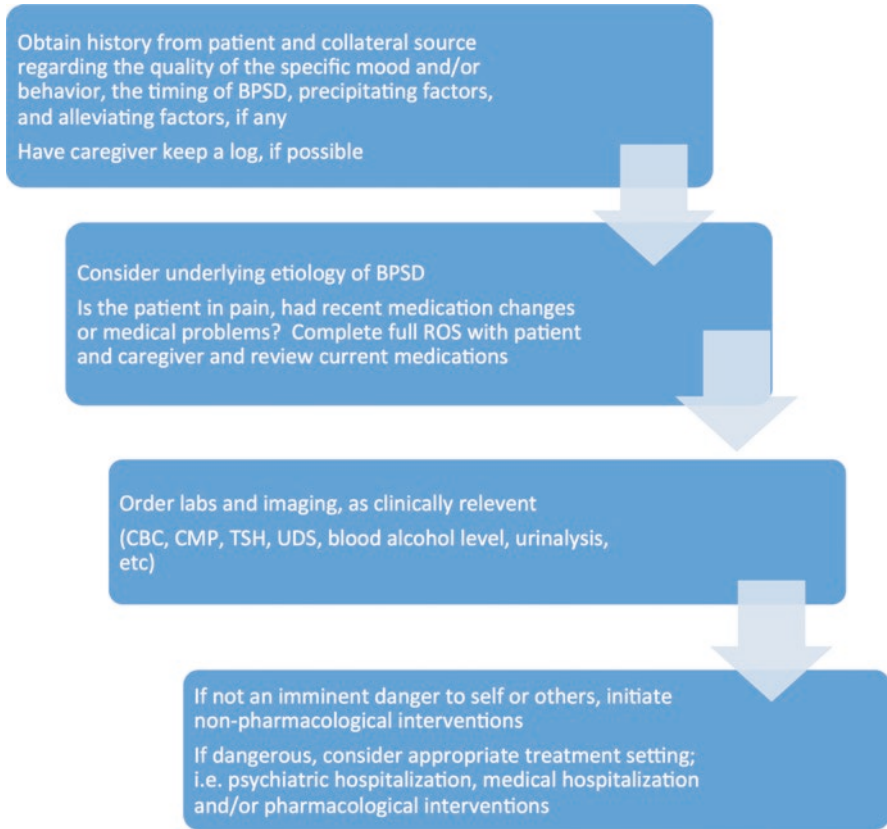


Fig. 7.2 Clinical evaluation of BPSD in dementia

intervention [7]. Aromatherapy has shown some benefit in select studies, but the benefits were not replicated in blinded trials [7, 11, 12]. Similarly, there is insufficient evidence regarding the efficacy of exercise for agitation in dementia [7].

Pharmacological Interventions

Pharmacological interventions for agitation and aggression in dementia are at times necessary based on potential danger to the patient and/or caregivers, despite the lack of FDA-approved medications for these indications. In these situations, treating physicians must delicately weigh the risks versus benefits of available pharmacological interventions. Antipsychotic medications are commonly used to treat agitation and aggression in the elderly with dementia [13]. In 2005, the US Food and Drug Administration (FDA) released a warning that both typical and atypical antipsychotics are associated with increased mortality in the elderly with dementia. The

FDA's announcement was based on 17 placebo-controlled trials (15 positive trials) showing a 1.6- to 1.7-fold mortality increase in the elderly with behavioral disturbances and dementia. Increased mortality was related to both cardiac and noncardiac causes of death [14]. Currently, the American Geriatrics Society (AGS) Beers Criteria 2015 recommends that physicians "avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others" [15].

Medication Selection

Once physicians, patients, and/or surrogate decision-makers have jointly decided that an antipsychotic is necessary, which one should the prescriber choose? There is a large body of literature examining this question. A recent systematic review of meta-analyses addressing antipsychotic use in dementia provides considerable guidance for prescribing physicians [6]. One meta-analysis of typical antipsychotics for the treatment of BPSD concluded that typical antipsychotics were significantly more effective than placebo at treating symptoms of agitation in dementia, with a modest effect size (0.18). There was no difference in efficacy comparing haloperidol, thioridazine, or other typical antipsychotics [16]. However, other side effects, such as the anticholinergic side effects of thioridazine, must be considered in medication choice.

The 2016 review of meta-analyses included ten studies examining atypical antipsychotics for BPSD. The authors concluded that risperidone, olanzapine, and aripiprazole have significant benefit in treating agitation and aggression in dementia, with a modest effect size. Quetiapine did not significantly improve BPSD in dementia when compared to placebo [6]. Table 7.1 provides guidance on initiation, titration, and dosage recommendations for antipsychotic use in individuals with dementia, adapted from the APA's practice guidelines for Alzheimer's disease and other dementias [17] and guideline watch update from 2014 [18].

Adverse Events/Side Effects

Prescribing physicians must also consider the potential adverse effects related to antipsychotic use. Side effects such as akathisia, Parkinsonism, sedation, anticholinergic effects, cardiac conduction abnormalities, postural hypotension, urinary incontinence and urinary tract infections, and falls must be monitored in the elderly treated with antipsychotic medications [6, 17]. As discussed previously, increased risk of death, as well as an increased risk of cerebrovascular events, in elderly with dementia who are treated with antipsychotics (typical or atypical) is a significant risk that limits their use. Other serious adverse events include tardive dyskinesia, neuroleptic malignant syndrome, and metabolic syndrome [17].

Table 7.1 Common medications for the behavioral and psychological symptoms of dementia

Medication	Formulations	Starting dose	Effective dose	Monitoring
Antipsychotics				
Risperidone	Tablet	0.25–0.5 mg	1–1.5 mg daily	AIMS
	Disintegrating tablet			Metabolic monitoring
	LAI			
Olanzapine	Tablet	2.5–5 mg daily	Up to 10 mg daily	AIMS
	Disintegrating tablet			Metabolic monitoring
	IM			
	LAI			
Aripiprazole	Tablet	2.5–5 mg daily	Up to 15 mg daily	AIMS
	LAI			
Haloperidol	Tablet	0.25–0.5 mg daily	Up to 2 mg daily	AIMS
	Liquid			*IV highest risk of prolonged QTc interval
	IM			
	IV			
	LAI			
Antidepressants				
Sertraline	Tablet	12.5–25 mg daily	50–200 mg daily	Electrolytes
	Liquid			
Citalopram	Tablet	5–10 mg daily	10–20 mg daily	*FDA max dose for age >60 is 20 mg daily
	Liquid			QTc interval
Venlafaxine	Immediate release tablet	IR: 25 mg daily	IR: up to 300 mg in divided doses	Blood pressure (specifically diastolic)
	Extended release tablet	XR: 37.5 mg daily	XR: up to 300 mg daily	
Mirtazapine	Tablet	7.5 mg daily	15–60 mg daily	Weight
	Disintegrating tablet			Falls with sedation
Bupropion	Immediate release	IR: 37.5 BID	IR: up to 100 mg TID	Seizures in anorexia or neurologic abnormalities
	Sustained release (SR)	SR: 100 mg daily	SR: 150 mg BID	
	Extended release (XL)	XL: 150 mg daily	XL: 300 mg daily	

AIMS Abnormal Involuntary Movement Scale, *IM* intramuscular, *IV* intravenous, *LAI* long-acting injectable

*Refers to the source 4, 5 & 6

Length of Treatment

How long should physicians prescribe an antipsychotic medication for agitation or aggression in individuals with dementia? Two meta-analyses [19, 20] are available to help guide this decision, as well as the American Psychiatric Association (APA) guideline on the use of antipsychotics for the treatment of agitation and psychosis in dementia [20]. Mortality rates were lower in individuals for whom antipsychotic discontinuation occurred, as opposed to those who continued treatment [20]. Discontinuation of antipsychotic medications can be well tolerated but has been shown to further aggravate BPSD in those with severe behavioral symptoms [6, 19, 20]. The APA recommends discontinuing antipsychotic medications after 4 weeks if there is limited efficacy at an adequate dose [21]. If there is clinically significant treatment efficacy, physicians should consider tapering and/or discontinuing the antipsychotic within 4 months of initiation, unless there has been a failed attempt at withdrawal. Symptoms should be monitored every month during the taper and for 4 months after discontinuing an antipsychotic medication. Another study looking specifically at subjects who had a significant clinical response to risperidone concluded that in those patients with dementia whose agitation and/or psychosis responded to risperidone which was continued for 4–8 months, discontinuation of the medication worsened relapse [22].

Are there other medication classes that are effective at treating agitation/aggression in individuals with dementia? Considering the increased risk of severe adverse events with antipsychotic medications, there is interest in identifying other medication classes with safer side-effect profiles for treatment of BPSD. Antidepressants have some data supporting their use. A Cochrane review of antidepressants for treating agitation and psychosis in dementia concluded that there is a paucity of high-quality data regarding efficacy of the antidepressants for this indication. They note that there is some evidence that sertraline, citalopram, and trazodone may help treat agitation and psychosis for some individuals with dementia [23]. The more recent Citalopram for Agitation in Alzheimer Disease Study (CitAD), a randomized, double-blind, placebo-controlled, parallel study, examined the use of citalopram (10 mg titrated to a max of 30 mg daily) for BPSD in probable AD individuals. The authors concluded that in combination with a psychosocial intervention, citalopram showed a significant benefit in the treatment of agitation and reduced caregiver distress. However, there were significant cognitive side effects and prolonged QT intervals in the citalopram-treated individuals [24]. It is important to note that the FDA revised prescribing recommendation for citalopram in March 2012 to include the maximum recommended dosage for patients 60 years and older is now 20 mg daily, while the maximum dosage prescribed in the CitAD study was 30 mg daily [25]. Other medications, such as acetylcholinesterase inhibitors (e.g., galantamine 24 mg/day) and the NMDA receptor antagonist memantine, show very modest benefits in the treatment of agitation in dementia [26, 27]. There are other novel treatment investigations ongoing but remain investigational at this time [28]. The use of medications such as carbamazepine, valproate, beta blockers, and lithium for the treatment of agitation in dementia is not recommended at this time by the APA [17, 18].

In conclusion, the most data exists for using antipsychotic medications for the treatment of agitation and aggression in dementia. However, physicians, in consultation with patients and/or surrogate decision-makers, must carefully weigh the following options when non-pharmacological interventions are ineffective: the risks of treatment, the risks of untreated agitation/aggression, and the potential modest benefits of medication treatment. During this deliberation, other less-studied options, such as antidepressants, acetylcholinesterase inhibitors, and memantine, may be considered based on individual clinical factors.

Treatment of Psychosis in Dementia

Psychotic symptoms are common in the course of dementia, with 75% of patients experiencing some form of psychosis during the disease process [29]. Psychotic symptoms are part of the neurodegenerative progression of dementing illnesses and include delusions and hallucinations.

Similar to recommendations for agitation and aggression in dementia, pharmacological treatment of psychosis is appropriate if the symptoms are causing clinically significant distress and/or impacting the patient's quality of life [21]. Although psychotic symptoms are common at some point in the course of dementia, if the symptoms are not causing significant consequences, they can be addressed with non-pharmacological interventions.

Medication Selection

It is helpful to consider the underlying type of dementia when tailoring interventions for individual patients. In patients with AD, antipsychotic medications are again the mainstay of treatment, with the most data supporting the use of risperidone for psychosis in dementia [6, 21]. Meta-analyses also demonstrate modest efficacy with the atypical antipsychotic medications, olanzapine and aripiprazole, with no significant efficacy seen with quetiapine [6]. Patients with Lewy body dementia or Parkinson's dementia are more sensitive to the adverse effects of antipsychotic medications, in particular, extrapyramidal symptoms [30, 31]. Clinically, physicians most often prescribe quetiapine or clozapine in individuals with these particular types of dementia; however, there is very little evidence supporting this practice [21, 31]. Pimavanserin, a selective serotonin_{2A} receptor inverse agonist, is a newer medication now FDA approved specifically for the treatment of hallucinations and delusions due to psychosis in patients with Parkinson's disease. Further research and clinical experience will provide more information on the utility of this medication for the behavioral disturbances with specific dementias.

Adverse events and length of treatment for psychosis with antipsychotic medications are the same as discussed previously for agitation and aggression. There is not

enough evidence supporting alternative medication classes for the treatment of psychosis in dementia [6, 32]. There is not sufficient evidence to support prescribing antidepressants specifically to address psychotic symptoms, despite the modest benefits noted when addressing agitation.

Treatment of Mood Disorders in Dementia

The relationship between mood disorders, specifically depression, and dementia is very complex. However, it is clear that depressive symptoms, which include mood changes, irritability, apathy, social isolation, thoughts of death, and suicidal ideation, are very common manifestations of neurodegenerative disorders. In the literature, rates of mood symptoms in individuals with dementia are between 10% and 86%, with 20–40% meeting full criteria for depression [33–36]. Thus, physicians commonly treating older adults with dementia must be familiar with the literature regarding current treatment for mood in this specific population.

Non-pharmacological Interventions

Non-pharmacological interventions for mood symptoms are also first line for patients with dementia. Unlike treatment of cognitively unimpaired older adults, beneficial therapeutic interventions require caregiver participation. Cognitive behavioral therapy (CBT) is an effective treatment modality for non-cognitively impaired older adults with depression and anxiety; however, adaptations are required for the cognitively impaired individual. For individuals with dementia, data support the efficacy of behavioral management techniques such as increased pleasant activities, behavioral problem-solving therapy, and structured life review [37–40]. For caregivers, CBT techniques targeting communication, caregiver stress, and reinforcement of the behavioral techniques helpful for the patient are effective psychosocial treatment modalities [7, 38, 40]. Thus, non-pharmacological interventions for mood disorders can be very effective, particularly when they incorporate caregivers into the treatment.

Pharmacological Interventions

Data for the efficacy of antidepressants in dementia show mixed results. However, SSRI antidepressants remain the mainstay of pharmacological treatment of depression in dementia with data supporting sertraline and citalopram [17, 41–43]. APA guidelines recommend avoiding cyclic antidepressants (such as

amitriptyline) in the elderly with dementia, as they are less effective than other antidepressant medications and/or have more intolerable side effects. There is some evidence that psychostimulants such as methylphenidate (20 mg/day) can be an effective treatment for apathy in patients with dementia [17, 43–45]. Modafinil was not effective in treating apathy in a randomized, double-blind placebo-controlled study [46]. Electroconvulsive therapy (ECT) is another effective treatment strategy for elderly patients with depression, but there are limited data specifically studying ECT in elderly individuals with dementia [47–49]. Clinically, individuals with dementia and depression receive ECT if he or she has life-threatening symptoms (i.e., not eating) or has refractory depression to multiple antidepressant trials.

Adverse Events/Side Effects

SSRI antidepressants are the first-line pharmacological treatment in depressed elderly as they have less side effects than other antidepressant categories, such as the cyclic antidepressants and monoamine oxidase inhibitors (MAOIs), which have significant anticholinergic and cardiovascular side effects. Physicians prescribing SSRI antidepressants to elderly with dementia need to monitor for side effects including gastrointestinal side effects (nausea/vomiting), neurological side effects (Parkinsonism, akathisia), and sexual side effects, weight loss, and hyponatremia. There is an increased risk for falls in elderly individuals treated with SSRI medications [50]. Also, SSRIs and other antidepressants are metabolized through the cytochrome P450 system; thus, the prescriber must consider possible drug-drug interactions when prescribing antidepressants in the elderly [17].

Other antidepressants with less data in the elderly with dementia have specific side effects. Mirtazapine, a noradrenergic/specific serotonergic antidepressant, causes weight gain (which may be desirable in older adults with dementia) and sedation, with rare but serious side effects of liver toxicity and neutropenia. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), can cause increased blood pressure during both treatment and discontinuation of the medication. Duloxetine, another SNRI, has no specific data supporting its use in the elderly population but is often used with depression and pain in older adults. Bupropion, a norepinephrine-dopamine reuptake inhibitor, lowers seizure threshold more than other antidepressants and would not be a good choice for older adults with known seizure disorder or other risk factors for seizures. Trazodone, a serotonin-2 antagonist/reuptake inhibitor, has common side effects of sedation and may be used at low doses for insomnia and/or agitation in this population; however, higher doses are required for depression and may cause sedation and orthostatic hypotension, increasing the risk of falls [17].

Length of Treatment

Based on the literature review while preparing this chapter, the recommendations were unclear regarding the length of treatment for depression in the elderly with dementia. According to the APA's guidelines for the treatment of major depressive disorder in the elderly, the same length of treatment for the general adult population is recommended. Specifically, treatment with an effective antidepressant, at the full therapeutic dose, should be continued for 4–9 months, up to 12 months, after remission. If the individual has had three or more recurrent depressive episodes, or other factors that would warrant long-term treatment, medication should be continued indefinitely at the same dose that got the patient well. In the elderly population with dementia, mood symptoms can fluctuate; thus, determining the length of treatment depends on the specific clinical situation [17].

Case Report

Ms. A was a 51-year-old female with no past psychiatric history that self-presented with increased anxiety, irritability, and memory concerns. She reported using no alcohol or other illicit substances. Her family history was notable only for her maternal grandmother having AD and her mother having an unknown dementia in her 60s. Mental status exam was notable for a well-groomed female, good eye contact, very cooperative, increased psychomotor activity, very mild word-finding difficulty, logical thought process, no suicidal ideation, but perseverative concern with her memory and change in mood. She was visibly anxious, but alert and oriented, with good attention but poor recall, some repeating within 5–10 min. Labs (TSH, CBC, CMP, vitamin B12, folate, RPR) were within normal limits. We decided to first treat mood symptoms and then look at memory if not improved. We initiated fluoxetine 20 mg and CBT.

Visit 2: Ms. A's anxiety and irritability were better but no change in memory. Her brain MRI was normal. We sent her for neuropsychological testing.

Visit 3: Ms. A developed myoclonic jerks while sleeping, possibly related to fluoxetine. Since she continued with some residual mood and anxiety symptoms, we changed fluoxetine to citalopram. Neuropsychological testing showed profound anterograde memory deficit, also visual memory and naming deficits. Her executive functioning was mildly impaired, though her anxiety did not fully account for the severity.

Ms. A was sent to a memory clinic, considering her very young age. PET imaging demonstrated biparietal hypometabolism, and CSF biomarkers were consistent with AD. She was diagnosed with Alzheimer's disease and started on donepezil 10 mg daily. She was also continued on citalopram 20 mg daily. Her memory decline slowed over the next few months, and her mood and anxiety improved significantly.

At her last psychiatric visit, her AD was in moderate stage, so memantine was added, donepezil was continued, and her surrogate decision-maker requested a trial off citalopram (tapered 10 mg for 2 weeks, then discontinued). Her neuropsychiatric symptoms remained stable with this regimen.

Clinical Pearls

- Behavioral and psychological symptoms of dementia occur in all dementia subtypes.
- Non-pharmacological interventions are first-line treatments for BPSD.
- Document a thorough risk/benefit discussion with the family in the patient's chart if antipsychotics are the best option and if time permits (not emergency situation).
- If medications are warranted, start at a low dose and titrate slowly, but the patient may require doses typical of other adults to have symptomatic relief.
- Monitor carefully for side effects which are seen more frequently in the elderly with dementia.
- At each visit, consider if the patient needs to continue BPSD medications.

Conclusion

Behavioral and psychological symptoms of dementia are common and part of the clinical presentation of any individual with dementia of any type. Physicians can best guide treatment strategies by considering the differential diagnosis of the emotion or behavior (i.e., is this agitation, aggression, psychosis, or a mood change?) and considering and treating any underlying etiology of that particular symptom. Non-pharmacological interventions should be first-line treatment for any BPSD. Pharmacological treatment initiation should ideally occur only after a full risk/benefit analysis is considered with the patient and/or surrogate decision-maker. When pharmacological treatment is warranted, close monitoring of side effects and regular consideration regarding the need for continued treatment are imperative.

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