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REVIEW ARTICLE

Neuropsychiatric Symptoms in Dementia: Considerations for Pharmacotherapy in the USA

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Abstract

Dementia affects all domains of cognition. The relentless progression of the disease after diagnosis is associated with a 98% incidence of neuropsychiatric symptoms (NPS) at some point in the disease, including depression, psychosis, agitation, aggression, apathy, sleep disturbances, and disinhibition. These symptoms can be severe and lead to excess morbidity and mortality. The purpose of this article was to describe current literature on the medication management of NPS of dementia and highlight approaches to and concerns about the pharmacological treatment of NPS in the USA. Guidelines and expert opinion favor nonpharmacologic management of NPS as first-line management. Unfortunately, lack of adequate caregiver training and a high failure rate eventually result in the use of psychotropic agents in patients with dementia. Various psychotropic medications have been studied, although how they should be used in the management of NPS remains unclear. A systematic approach to evaluation, treatment, and monitoring, along with careful documentation and evidenced-based agent and dose selection, is likely to reduce risk and improve patient outcomes. Considerations should be given to the NPS presentation, including type, frequency, and severity, when weighing the risks and benefits of initiating, continuing, or discontinuing psychotropic management. Use of antidepressants, sedative/hypnotics, antipsychotics, and antiepileptic agents should include a clear and documented analysis of risk and benefit in a given patient with dementia.

1 Introduction

Despite a declining age-specific incidence of dementia in high-income countries, the absolute numbers of patients with cognitive decline continues to rise as the population ages [1]. Treatment with cognition-enhancing/preserving medication, including cholinesterase inhibitors and memantine, is typically pursued in all but the least and most severely afflicted [2]. Noncognitive symptoms of dementia occur in 98% of individuals at some point in their disease and are often the most distressing to caregivers and patients themselves [3]. Neuropsychiatric symptoms (NPS), including apathy, depression, sleep disorders, hallucinations, delusions, psychosis, agitation, and aggression, are exceedingly prevalent [4, 5]. The presence of depression in dementia has been shown to accelerate the rate of cognitive decline, even beyond education level and sex [6]. Dementia symptoms

Key Points

Neuropsychiatric symptoms of dementia are heterogeneous in clinical presentation and should not be viewed or treated as a collective syndrome.

Limited medications may be used to target very specific neuropsychiatric symptoms.

A small population of patients with neuropsychiatric symptoms of dementia may benefit from continued medication management, but all patients should be repeatedly assessed for appropriateness of discontinuation.

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will wax and wane as a natural course, according to both environmental factors and disease progression-related factors [7]. In their most severe manifestations, NPS can lead to worse patient outcomes, accelerated disease progression, institutionalization, morbidity and mortality, and significant caregiver stress and financial strain [4, 5, 8]. Studies have shown that determinants of nursing home placement in patients with dementia include difficult behaviors; patients scoring the highest on psychotic and behavioral symptoms are over two times more likely to be institutionalized [9, 10]. It is possible that caregivers may be willing to delay hospitalization or institutionalization if behaviors can be managed, though this theory has not yet been studied.

The presentations of NPS appear at different times during various types of dementia, and presentation frequencies may vary depending on setting. In early Alzheimer's disease (AD), depression, disinhibition, apathy, and sleep disorders are prevalent, and disease progression leads to an increase in delusions, hallucinations, and aggression [11–15]. A naturalistic study of patients in a geriatric psychiatry unit in Germany found aggression, including both verbal and physical, was the most frequent symptom, occurring in approximately 57% of patients. However, the authors noted that symptoms such as depression and apathy might not warrant acute treatment or hospitalization, except in severe cases [16]. Apathy, arising from primary amotivation, appears to be the most common and lasting NPS of AD, affecting up to 76% of patients with AD [11, 17]. A recent systematic review by Theleritis et al. [18] focused on describing apathy and management approaches, so we refer readers to this review for more comprehensive discussion. Conversely, in Parkinson's disease (PD), visual hallucinations appear earlier, and disease progression results in the gradual appearance of Parkinson's disease dementia (PDD), intertwined commonly with depression, anxiety, and sleep disorders [19]. In vascular dementia, sleep disorders, agitation, depression, and anxiety are not associated with a specific stage of the disease [20]. Similar to PDD, dementia with Lewy bodies (DLB) is most often accompanied by nonthreatening visual hallucinations, sleep disorders, and anxiety [12, 13]. In a population-based study evaluating the frequency of symptoms in people with dementia, apathy was the most frequent symptom, followed by depression and agitation/aggression [21]. The majority of patients had AD, although people with vascular dementia, PDD, and others were also represented.

While it is clear that NPS can cause increased disease burden for both patients and caregivers, less clear guidelines regarding the appropriate management of NPS have been published. The American Association for Geriatric Psychiatry (AAGP), the Alzheimer's Association, the American Geriatrics (AGS) Society, the National Institute for Health and Care Excellence (NICE), the American Psychiatric Association (APA) and the Detroit Expert Panel on the Assessment and Management of the NPS of Dementia agree and emphasize that nonpharmacologic treatment should be implemented as first-line management of NPS [3, 22–26]. Nonpharmacologic management is similar among guidelines, suggesting the use of techniques including but not limited to the removal or avoidance of triggers, environmental modifications, treatment of precipitating medical conditions, discontinuation of offending pharmacologic agents, aromatherapy, animal-assisted therapy, and exercise, music, art, and reminiscence therapies [3, 22–25, 27, 28].

However, even when nonpharmacologic approaches are effectively employed, a high percentage of patients with dementia are eventually treated with psychotropic medications, recently demonstrated to be 84% of nursing home and 29% of community-dwelling elders residing in the USA [29]. It is important to use all available evidence to select agents and doses of psychotropic medications to minimize risk and maximize the potential for benefit in these vulnerable patients.

Certain guidelines suggest that pharmacologic management may be considered first line after a thorough risk/benefit assessment in the following situations: significant risk of harm to patient or others due to psychosis or aggression, severely distressed patient or caregivers, and major depression with or without suicidal ideation [3, 22–25]. A noted difference among guidelines appears in those provided by the APA, in which only the patients are discussed in situations that may warrant pharmacologic treatment, and the feelings/distress of caregivers are omitted [25]. If nonpharmacologic interventions prove ineffective or if any of the aforementioned situations exist, recommendations from various groups, including the AAGP, AGS, and Alzheimer's Association, as well as the APA and NICE, are that the use of pharmacologic therapy may be warranted [3, 22–25].

Recommendations regarding the choice of pharmacologic treatment vary greatly regarding the agents used for specific NPS, but a common theme does exist: pharmacologics should be used judiciously in the elderly [3, 22, 24–26]. Recommendations about the duration of treatment appear only in reference to the use of psychotropics and suggest that medications should be tapered and withdrawn if no clinically significant response to therapy occurs after a 4-week trial of adequate doses [25]. Furthermore, it is recommended that attempts to taper antipsychotics occur within 4 months of initiation [25]. In general, pharmacologic agents used for the management of NPS should be initiated at the lowest dose and titrated up to the minimum effective dose as tolerated. These agents should not be continued indefinitely, and their use should be continually reassessed [3, 22, 24–26]. The purpose of this article was to describe the current literature on medication management of NPS of dementia and highlight approaches to and concerns about the treatment of NPS to assist the practicing clinician. We sought to

give perspectives as to why an individualized approach is imperative and to provide suggestions for why psychotropics may be perceived as having minimal and variable efficacy across patients with dementia-related NPS. If a clinician has a low threshold for starting a given psychotropic for any NPS, has expectations for nonspecific or global improvement of NPS, and has an unclear threshold for discontinuing the given psychotropic, the patient can ultimately be at risk for intolerabilities in addition to inefficacy. Thus, this review is a practical, yet detailed discussion with highlights from recently published randomized controlled trials aimed at any clinician who may care for patients with dementia and NPS. Selected common symptoms were identified for further discussion. We avoided elaboration where a specific symptom had recently been the subject of a comprehensive, systematic review, instead referring readers to that publication. Specific information regarding clinical trials designed to assess the use of pharmacologic agents for NPS in patients with dementia is included in Tables 1 and 2, which we revisit throughout this article.

2 Concerns Associated with the Use of Psychotropic Medication in Patients with Dementia

Justification for hesitation in using psychotropic medication in patients with dementia stems from the fact that all of the agents have significant toxicity and mostly weak evidence of efficacy in this population [30]. Antidepressants, sedatives/hypnotics, and antipsychotics are all associated with high rates of worsening of cognition, falls, and serious cardiovascular adverse effects [31]. In the case of antipsychotic use, large databases have revealed a significant association with increased mortality in patients with dementia, leading to a "black box warning" from the US FDA in 2005 [32]. Similar warnings have been issued to providers in other countries, including Canada, France, Germany, and other European countries. The excess mortality with antipsychotic use was approximately 1.5 times on average and attributed to cardiovascular events (stroke and myocardial events) and infection [32].

Medication toxicities include both short- and long-term adverse effects, some of which can cause complications affecting morbidity or mortality. One such example is dizziness or hypotension that leads to a fall, subsequently resulting in impaired functioning or reduced survival. Even interactions between multiple medications can lead to toxicities. Published lists of medications that are potentially inappropriate for older populations include many of the psychotropic medications used off-label for managing NPS of dementia [33, 34]. Medications considered "potentially inappropriate" may contribute to confusion and increased fall risk, such as anticholinergic effects, worsened cognitive impairment, extrapyramidal symptoms, orthostatic hypotension, sedation, or risk of delirium [33, 34]. A study of patients newly started on an acetylcholinesterase inhibitor for dementia showed that the anticholinergic drug burden increased with the number of physicians providing care [35]. Ruxton et al. [36] found that certain medications with anticholinergic effects and overall exposure increased not only the risk of cognitive impairment and falls in older adults but also all-cause mortality. Thus, providers should evaluate psychotropic utility in the context of the overall patient, with various symptoms, comorbidities, and concurrent medications. In patients with NPS receiving psychotropics who subsequently exhibit negative sequelae, providers should evaluate the severity and consider dose reduction or discontinuation of the offending agent. A switch to an alternative agent can be considered if pharmacotherapy is thought to provide symptomatic benefit. Only as a last resort, when the psychotropic has demonstrated clear benefit for NPS, should additional medications to target the side effects cautiously be added. Keep in mind that the additional agent will have its own side effects, will increase drug burden, and can put the patient at risk for more drug interactions.

Atypical antipsychotic medications are considered one of the most robustly studied classes in the management of NPS in patients with dementia [37]. These medications have been associated with several adverse effects, such as metabolic syndrome (which includes hyperlipidemia, weight gain, hyperglycemia, and increased diabetic risk), akathisia, drug-induced parkinsonism, and tardive dyskinesia/dystonia [38, 39]. In patients who have been treated with antipsychotic medications for several months or years, increases in the risk of death, pneumonia, cardiovascular events, parkinsonism, cognitive disturbance, gait problems including falls, and sedation have been observed [40, 41].

Although atypical antipsychotic medications have been found to help in decreasing agitation in patients with dementia, they have also been found to worsen cognitive symptoms, including confusion in this group of patients, even after the effect of sedation has been accounted for [42]. Aripiprazole and olanzapine were more likely to cause somnolence, whereas quetiapine accounted more for cognitive disturbance than did placebo [39, 40, 43]. Risperidone and olanzapine appeared to account more for the risk of cardiovascular adverse events, gait disturbance, and extrapyramidal side effects [39, 40, 44]. Among commonly used atypical antipsychotic medications, risperidone has been found to have more extrapyramidal side effects than the others, whereas olanzapine is more responsible for weight gain in the general population [45, 46]. In general, the use of antipsychotic medications has been associated with weight gain,

Table 1 Randomized, blinded, controlled trials of agents (available in the USA) for neuropsychiatric symptoms of dementia since 2004

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Antidepressants							
Finkel et al. [56]; Pfizer Inc.	MC, DB, PC, PG (*N* = 245); 12 wk	SER (in pts on DON)	Outpatients	Probable or possible AD per NINCDS/ADRDA criteria and MMSE 8–23, Rosen-modified Hachinski Ischemia scale score ≤ 4, Clinical Dementia Rating scale score ≤ 2	ND between groups in scores on primary outcome measure NPI total score, CGI-I, CGI-S	ND on various rating scales, including HAMD, CMAI-C	ND in changes in vital signs, weight, ECG measure, or laboratory values. Common AE in SER group: diarrhea
Weintraub et al. [55]; NIMH; Pfizer Inc. provided medication only	RAN, DB, PC, MC (*N* = 131); 24 wk (12-wk efficacy trial and 12 wk extension phase of responders)	SER	Unspecified but required pts with caregivers	Dementia due to AD per DSM-IV and MMSE scores 10–26	ND between groups at wk 24 in scores on primary outcome measure mADCS-CGIC score	ND between groups in CSDD scores at wk 24	Pts on SER had higher rates of pulmonary SAEs. Common AEs in SER group: diarrhea, dizziness, dry mouth
Porsteinsson et al. [54]; NIA and NIMH, and in part by NIH	RAN, PC, DB, MC, PG (*N* = 186); 9 wk	CIT	Unspecified, but required caregiver who spent at least several h/wk with the pt	Probable AD per NINCDS criteria and MMSE scores 5–28 with clinically significant agitation	Scores on primary outcome measures NBRS-A and mADCS-CGIC scores showed improvement in CIT arm	Improvement on CMAI, total NPI, and caregiver distress scores but not NPI agitation subscale or ADCS-ADL scale	Worsening of cognition, increased fall frequency, increased risk of URTI, and QT interval prolongation observed with CIT. Common AE with CIT: diarrhea, fever
Mood stabilizers (anticonvulsants)							
Tariot et al. [90]; The National Institute on Aging and Abbot Laboratories Inc.	RAN, DB, PC, parallel-arm multisite (*N* = 153); 6 wk	DS	Nursing homes	Probable or possible AD according to NINCDS-ADRDA criteria; MMSE score 4–24	ND between groups in scores on primary outcome measure of change in agitation factor of BPRS	ND between groups on CMAI	More diarrhea with DS than PL. Common side effects (> 10% incidence) in both groups: GI disorders, general disorders (falls), infections/infestations, injury/poisoning/procedural complications, abnormal laboratory values, musculoskeletal and connective tissue disorders, nervous system disorders, psychiatric disorders, and skin/subcutaneous tissue disorders
Herrmann et al. [91]; Alzheimer's Society of Canada	RAN, MC, DB, PC, CO (*N* = 14); 6 wk	VAL	LTC facilities	Probable AD of at least 1 year per NINCDS-ADRDA criteria and primary degenerative dementia per DSM-IV criteria; MMSE < 15	ND between groups in scores on primary outcome measure NPI agitation/aggression subscale score	ND in CMAI score between groups	No statistically significant difference. Pts on VAL had more falls, sedation, loss of appetite, loose stools, thrombocytopenia

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Sommer et al. [92]; Norwegian Research Council, Health East Hospital Trust, and Innlandet Hospital Trust; Novartis provided medication only	MC, RAN, DB, PC ($N=103$); 8 wk	OXC	Nursing homes	Diagnosis of AD or vascular dementia according to ICD-10 diagnostic criteria for research; MMSE score 0–20	ND between groups in scores on primary outcome measure change in agitation and aggression subscore of NPI-NH	ND between groups on BARS	Significantly more pts had "some AEs" with OXC. Common AEs included sedation and falls
Antipsychotics							
Suh et al. [93]; Janssen Korea	RAN, DB, CO ($N=120$); 18 wk	RIS, HAL	Semi-hospitalized LTC institution	Dementia of Alzheimer type, vascular dementia, or combination of both according to DSM-IV; FAST score of 4+	Pts on RIS had greater improvement on BEHAVE-AD-K total score vs. pts on HAL. CGI-C scores also in favor of RIS treatment	ND between groups on BEHAVE-AD-K score items: psychosis, activity disturbances, affective disturbance, and anxieties and phobias. Pts on RIS had more improvement on aggressiveness and diurnal rhythm disturbances than pts on HAL. Pts on RIS also improved more on CMAI-K total score (including subscale items: aggressive behavior, physical nonaggressive behavior, and verbally agitated behavior)	HAL associated with worsening of EPS (based on ESRS total score and parkinsonism) vs. RIS. Pts on HAL also had more somnolence, insomnia, and sialorrhea than pts on RIS
De Deyn et al. [94]; Bristol-Myers Squibb and Otsuka Pharmaceutical Co., Ltd.	RAN, DB, PC, MC ($N=208$); 10 wk	ARI	Noninstitutional (e.g., ALF or adult communities, or living with a caregiver)	AD per DSM-IV; MMSE score 6–24	ND between groups in primary outcome measure of mean change in caregiver-assessed NPI psychosis subscale. ND in CGI-I or CGI-S between groups. Pts with baseline NPI ≥ 12 had greater improvement on CGI-S scores and CGI-I responder rates (post hoc)	Greater improvement in ARI pts on BPRS psychosis subscale vs. PL pts	Statistically significant differences in AE NR. ND in movement-type AE between groups. Four deaths (ARI arm) unrelated to study drug. Common side effects included accidental injury, somnolence, UTI, bronchitis, hypertension

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Deberdt et al. [95]; Eli Lilly and Company	MC, DB, PC (*N* = 494); 10 wk	OLA, RIS	Outpatient or residential setting (nursing homes or ALFs)	Dementia diagnoses defined by NINCDS-ADRDA or DSM-IV criteria; MMSE score 5–24	No significant differences between groups in changes in any efficacy measure, including primary outcome measures of NPI psychosis total or CGI severity of psychosis	ND between groups in mean change on the scale scores CSDD, CMAI aggression	More somnolence and dyspnea with OLA vs. PL, abnormal gait, flu syndrome, asthenia in RIS vs. PL, urinary incontinence and hostility with active treatment vs. PL
Tariot et al. [96]; AstraZeneca Pharmaceuticals LP	RAN, MC, DB, PC (*N* = 284); 10 wk	QUE, HAL	Nursing homes (not bedridden)	Probable AD by DSM-IV criteria or possible AD per NINCDS-ADRDA criteria; MMSE ≥ 5	Mean total BPRS and CGI-S scores improved for all pts; ND between groups in degree of improvement	Pts on QUE had improved BPRS agitation vs. pts on PL. ND between groups on NPI-NH agitation or BPRS thought disturbance scores. Pts on QUE had improved BPRS anergia vs. HAL	Higher SAS scores for HAL vs. QUE. More somnolence and urinary incontinence with QUE vs. PL. More infections and convulsion with QUE vs. HAL or PL. Fewer instances of agitation with QUE vs. PL. More dyspepsia, pallor, fever, insomnia with HAL vs. QUE
Schneider et al. [97]; NIMH; Astra Zeneca Pharmaceuticals, Forest Pharmaceuticals, Janssen Pharmaceutical, and Eli Lilly provided medications only	RAN, MC, DB, PC (*N* = 421); 36 wk	OLA, QUE, RIS	Ambulatory and living at home or in ALF	Dementia of AD type per DSM-IV or probable AD on basis of history, physical exam, structural brain imaging; MMSE score 5–26	No significant differences in primary outcome measure of time until all-cause discontinuation between groups (median time 5.3–8.1 wk). Longer median time to discontinuation due to lack of efficacy in OLA and RIS groups vs. PL. Discontinuation due to intolerance, AE, or death favored PL vs. active treatment	Specific symptom scores NR	No significant differences between groups with proportion of pts with at least one SAE or any AE, though pts discontinued antipsychotic treatment at greater rates than PL due to intolerance, AE, or death. More pts on OLA and RIS experienced EPS and weight/BMI change, pts on antipsychotics experienced more sedation, and more pts on OLA had cognitive disturbance and confusion/mental status changes. RIS pts had higher rates of prolactin elevation

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Verhey et al. [98]; unspecified	RAN, MC, DB, two-arm (*N* = 58); 5 wk	OLA, HAL	Nursing homes and outpatients living in own home	Dementia according to DSM-IV criteria but, excluded other neurological conditions contributing to dementia, including Parkinson's disease, Lewy body disease	ND between groups in primary outcome measure of reduction in mean total sum score from baseline to endpoint on CMAI. Both treatments improved CMAI scores at endpoint vs. baseline	ND between groups in terms of NPI and NPI items, including distress, psychosis, hyperactivity, mood. Reductions in both groups on change in scores over 5 wk on NPI and NPI items: hyperactivity, mood/apathy. No improvement in NPI psychosis in either group	ND between groups on AIMS, SAS, or UKU
Kurlan et al. [99]; National Institute on Aging; AstraZeneca, LP provided medication only	MC RAN, DB, PC, PG (*N* = 40); 10 wk	QUE	Own residence or supervised care setting (e.g., nursing homes)	Dementia defined by DSM-IV, probable AD per NINCDS-ADRDA criteria or Consortium diagnostic criteria for DLB or UK Brain Bank criteria for PD; MMSE score ≥ 8	ND between groups in primary outcome measure of BPRS score. ND in secondary outcome measures of NPI, ADCS-CGIC, UPDRS, R-MDS-D, parkinsonism	No particular symptoms analyzed separately	ND between groups with any particular AE
Mintzer et al. [100]; Bristol-Myers Squibb company and Otsuka Pharmaceutical Development & Commercialization	MC, RAN, DB, PC (*N* = 487); 10 wk	ARI	Nursing homes or residential ALF	AD defined by DSM-IV criteria; MMSE score 6–22	Primary outcome measure of mean change from baseline in NPI-NH psychosis subscale improved and differed for ARI 10 mg but not 2 or 5 mg vs. PL arm. BPRS core scores improved for all ARI arms from baseline to endpoint; only ARI 10 mg improved BPRS total scores at 10 wk	Individual items on NPI-NH showing improvement with ARI 10 mg vs. PL: delusions, agitation/aggression, anxiety, irritability. CMAI scores improved on ARI 5 and 10 mg	ND between groups on deaths, cerebrovascular AE, EPS, or other common AE
Rainer et al. [101]; AstraZeneca Pharmaceuticals	Rater-blinded, RAN, PG, MC (*N* = 72); 8 wk	QUE, RIS	Living with someone or daily contact with caregiver	Dementia of AD, vascular, mixed, or frontotemporal lobe type according to DSM-IV and ICD-10 criteria; MMSE score 10–26	ND between groups on primary outcome measure of change from baseline to endpoint in NPI part 1 and 2 (caregiver burden/distress), though both medications showed overall improvement in symptoms using NPI	CMAI scores improved in each arm (not statistically significant), but ND between groups in change in scores	ND between groups on any particular AE. Sedation occurred more frequently (at least 10%) in QUE arm. AEs occurring more frequently (at least 10%) in RIS arm: diarrhea, muscle rigidity

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Zhong et al. [102]; AstraZeneca Pharmaceuticals	RAN, DB, MC, PC, fixed dose ($N=333$); 10 wk	QUE	Nursing homes or ALF	Probable or possible AD or vascular dementia according to DISM-IV or NINCDS-ADRDA criteria	Primary outcome measure was change from baseline to endpoint on PANSS-EC score, which was superior with QUE 200 mg/day (using OC, but not LOCF analysis) vs. PL, but no better for QUE 100 mg/day vs. PL. Pts improved on QUE 200 mg/day on CGI-C vs. PL. In AD subgroup, pts receiving QUE 200 mg/day had greater reduction in PANSS-EC vs. PL	ND between any QUE groups vs. PL on the following scores: NPI-NH, NPI-NH items (agitation, depression, psychosis), CMAI, and CMAI items (physically aggressive behavior, non-aggressive physical behavior, and verbal aggression). In AD subgroup, ND on NPI-NH and CMAI between groups	ND between groups in pts withdrawing due to AE. Common AEs (> 10%) reported among groups included falls, lethargy, skin laceration, UTI. Statistical significance unknown
Paleacu et al. [103]; AstraZeneca	DB, RAN, PC ($N=40$); 6 wk	QUE	Unspecified	AD defined by DSM-IV; MMSE score < 24	Coprimary endpoints included change in NPI score and CGI-C, but statistical significance (p value) NR for comparisons between QUE vs. PL, only for changes within treatments from endpoint vs. baseline scores. Authors appear to conclude ND on NPI score	Items on NPI with significant improvement in PL arm only: agitation, apathy. Items on NPI with significant improvement in both arms at endpoint vs. baseline: delusions, hallucinations, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior, night-time behavior, appetite, and depression	ND in AEs between groups
Streim et al. [104]; Bristol-Myers Squibb company and Otsuka Pharmaceutical Company, Ltd	RAN, PG, DB, PC ($N=256$); 10 wk	ARI	Institutional (nursing home or residential ALF)	AD per DSM-IV; MMSE score 6–22	Coprimary endpoints were mean change from baseline on NPI-NH Psychosis subscale and CGI-S scores, which showed improvement in both groups, but were not significantly different between groups. ND between groups on NPI-NH total scores but BPRS scale scores improved	ND between groups on BPRS Psychosis subscale scores or Core scores. Pts on ARI showed more improvement than PL on Cornell Depression Scale and CMAI	Somnolence more frequent with ARI (14%) vs. PL (4%), statistical significance unknown. Statistical differences in body weight changes and weight gain ≥ 7% from baseline with ARI (decreased/less) and PL (increase/more)

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
De Deyn et al. [105]; AstraZeneca	RAN, DB, double-dummy, multisite, PG ($N=100$); 6 wk	QUE IR and XR	Nursing homes or equivalent institutions	Dementia of AD type defined by DSM-IV or dementia in AD according to ICD-10; MMSE score of ≤ 23	Primary outcome variable of incidence/type of AE was 69.1% in QUE XR group and 71.9% in QUE IR group; AE types were similar. Common (> 10%) AE in either group included somnolence, vomiting, sedation. Pts gaining $\geq 7\%$ of baseline weight was 6.3% (QUE XR) and 15.6% (QUE IR). Statistical significance NR for any outcome measures	Improvements in CMAI and NPI disruption score, though statistical significance unknown	See "Outcomes" column (as this was a tolerability study)
Cholinesterase inhibitors and memantine							
Holmes et al. [106]; Pfizer/Eisai	RAN, DB, PC, MC, withdrawal ($N=134$); 24 wk (including 12 wk of open-label treatment)	DON	Unspecified	Probable AD per NINCDS-ADRDA criteria; MMSE score 10–27	Primary outcome measure of NPI differed and improved in pts on DON vs. PL	During open-label phase, pts on DON improved at wk 12 vs. baseline on NPI items: agitation, anxiety, apathy, delusions, depression, disinhibition, hallucinations, irritability, and motor activity	NR
Cummings et al. [107]; National Institute on Aging	MC, RAN, DB, PC, PG, fixed dose ($N=404$); 24 wk	MEM (in pts on DON)	In the community	Probable AD according to NINCDS-ADRDA criteria; MMSE score 5–14	Primary outcome measure change from baseline on SIB and ADCS-ADL, reported in a previous paper. Scores on NPI significantly different for pts on MEM (improved) vs. PL	Significant differences in favor of MEM in NPI items: agitation/aggression, irritability/lability, appetite/eating changes. Fewer pts on MEM displayed emergence of agitation, irritability, and night-time behavior in pts with no behavioral symptoms in certain domains at baseline	Reported in previous trial paper

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Howard et al. [108]; Medical Research Council and the Alzheimer's Society	MC, blinded, RAN, PG (*N* = 272); 12 wk	DON	Residential care facility or with a caregiver in the community	Probable or possible AD per NINCDS-ADRDA criteria	Primary outcome measure of mean reduction in CMAI score from baseline to endpoint was not different between DON and PL groups. ND between groups on NPI	No specific symptom reported	Statistical significance NR, but AEs were similar with DON and PL. No AE occurred in > 5% of pts in either arm
Fox et al. [109]; Lundbeck	DB, RAN, PC (*N* = 149); 12 wk	MEM	Nursing or residential care homes and acute psychiatric wards	Probable AD; SMMSE score of ≤ 19, Hachinski Score ≤ 4	ND between groups in primary outcome measure (change in CMAI score). NPI scores also differed in favor of MEM. Significant reductions at endpoint vs. baseline with MEM for SIB but not CGI-C (statistical significance between groups unknown)	No significant reduction in either group on CMAI scores	Statistical significance unknown, but AEs appeared similar. Common AEs (> 10%) in either group: fatigue, somnolence, confusion, hallucinations, abnormal gait
Multiple agents							
Pollock et al. [110]; US Public Health Service and the Sandra A. Rotman Program in Neuropsychiatry	RAN, DB, controlled (*N* = 103); 12 wk	CIT, RIS	Admitted to geropsychiatric ward of hospital with possible discharge to nursing homes, personal care homes, or residential homes	Dementia of AD type, vascular dementia, DLB, mixed dementia, or dementia not otherwise specified	No significant difference between changes in NBRS agitation or psychosis scores. Psychosis scores reduced with both CIT and RIS. Agitation scores reduced with CIT but not RIS	See "outcomes" column	UKU Total and psychic subscale scores were significantly different between groups and worse for RIS vs. CIT. ND on other UKU subscales: neurologic, autonomic, or other
Culo et al. [111]; US Public Health Service and the Sandra A. Rotman Program in Neuropsychiatry	RAN, DB, controlled (subanalysis of previous trial by Pollock et al. [110]) (*N* = 97); 12 wk	CIT, RIS	Admitted to geropsychiatric ward of hospital with possible discharge to nursing homes, personal care homes, or residential homes	DLB and AD only	DLB pts improved less than AD pts based on NPI changes. No significant difference at endpoint vs. baseline between groups in pts with DLB. CGI-C showed pts with DLB did not improve or worsened vs. pts with AD (improved)	Specific symptom outcomes NR	No significant differences on discontinuations, and UKU scores between groups among AD vs. DLB. Pts with DLB displayed greater mean change (higher) in UKU scores on RIS vs. CIT

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Freund-Levi et al. [112]; Janssen Pharmaceuticals	RAN, PG, controlled, fixed-dose, single-center ($N=100$); 12 wk	GAL, RIS	Unspecified	Dementia according to DSM-IV or presence of mild cognitive impairment	CMAI scores declined with both groups; change statistically significantly improved with RIS vs. GAL	CMAI subscore item aggressive physical behavior differed between groups using LOCF but not OC	ND observed on SAS. Statistical significance NR for other common AE
Other agents							
Peskind et al. [113]; Department of Veterans Affairs and the Joan C. Alhadeff Research Foundation	RAN, DB ($N=31$); 6 wk	PRO	Nursing home	Probable or possible AD per NINCDS-ADRDA criteria	Primary outcome measure of NPI Total score and CGI-C mean score showed greater improvement for pts on PRO vs. PL	On individual NPI subscore items, PRO ND vs. PL	Blood pressure and heart rate decreases not significantly different between groups
Wang et al. [114]; NIA, the Joan Alhadeff Alzheimer's disease Research Fund, and the VA Mental Illness Research, Education, and Clinical Center Special Fellowship in Advanced Psychiatry	RAN, DB, PC, single-site, PG ($N=22$); 8 wk	PRA	Nursing home or community dwelling	Probable or possible AD by NINCDS-ADRDA criteria	Primary outcome measures of CGI-C and change from baseline on NPI and BPRS all showed greater improvement or positive changes in pts on PRA vs. PL	NPI subscores for specific items were displayed; PL scores and statistical significance NR	Statistical significance NR for AE list, though differences in blood pressure changes no different for PRA vs. PL
Rosenberg et al. [115]; National Institute on Aging	RAN, DB, PC, MC ($N=60$); 6 wk	MET	Unspecified	Possible or probable AD per NINCDS-ADRDA criteria; MMSE ≥ 10	Primary outcome measure of differences in change in AES showed ND with MET vs. PL. A second primary outcome measure of ADCS-CGI-C change in apathy showed improvement in favor of MET over PL	NPI apathy scores were in favor of MET	Pts on PL had more arthralgia. ND between groups in other reported AEs

Table 1 (continued)

Study; funding sponsor	Study design (*N*); study length	Medication	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Cummings et al. [78]; Avanir Pharmaceuticals Inc.	RAN, MC, DB, PC, sequential parallel comparison design (*N* = 220); 10 wk	DXQ	Outpatient, ALF, and nursing homes	Probable AD based on 2011 National Institute on Aging–Alzheimer Association criteria; MMSE score of 8–28	Primary outcome measure (change from baseline in NPI agitation/aggression domain) improved for DXQ group vs. PL	Using sequential parallel comparison design, improvements were seen in favor of DXQ for CGI-C and ADCS-CGI-C, CSDD, NPI Total score (and aberrant motor behavior and irritability/lability domains and other selected groupings of NPI domains)	Statistical significance NR, though TEAE occurred in 61.2 and 43.3% of pts receiving DXQ or PL, respectively. Common TEAEs: falls, diarrhea, UTI, dizziness
van den Elsen et al. [116]; European Regional Development Fund and the Province of Gelderland; Echo Pharmaceuticals provided medical product only	RAN, DB, PC, MC (*N* = 50); 3 wk	THC	Nursing homes and outpatient	AD or vascular or mixed dementia per NINCDS-ADRDA or NINCDS-AIREN criteria	Primary outcome measure of change in NPI no different between THC and PL groups. NPI scores decreased in both groups. ND between groups on CGI-C	ND between groups on NPI subscale scores: agitation, aberrant motor behavior. ND between groups observed on CMAI	ND between groups on reported metabolic AE. Statistical significance not shown for common specific (not by organ class) AE (> 10%) reported in either group: dizziness, somnolence, cognitive disorder, fall
van den Elsen et al. [117]; European Regional Development Fund and the Province of Gelderland; Echo Pharmaceuticals provided medical product only	RAN, DB, PC, repeated CO, MC trial (*N* = 22); 12 wk	THC	Unspecified	Dementia type AD, vascular or mixed. According to NINCDS-ADRDA or NINCDS-AIREN criteria; CDR scores 0.5–3	ND between groups on primary outcome of NPI	ND between groups on NPI subscale agitation/aggression or CMAI	Statistical significance between groups NR for reported AE. Psychiatric disorders > 10% for AE of either THC or PL at various time periods

AD Alzheimer's disease, *ADCS-ADL* Alzheimer Disease Cooperative Study-activities of daily living, *ADCS-CGIC* Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change, *AE* adverse effect, *AES* Apathy Evaluation Scale, *AIMS* Abnormal Involuntary Movement Scale, *ALF* assisted-living facilities, *ARI* aripiprazole, *BARS* Brief Agitation Rating Scale, *BEHAVE-AD* Behavioral Pathology in Alzheimer's Disease Rating Scale, *BEHAVE-AD-K* Korean version of the Behavioral Pathology in Alzheimer's Disease Rating Scale, *BMI* body mass index, *BPRS* Brief Psychiatric Rating Scale, *CDR* Clinical Dementia Rating Scale, *CGI-C* Clinical Global Impression of Change, *CGI-I* Clinical Global Impression – Improvement, *CGI-S* Clinical Global Impression – Severity, *CIT* citalopram, *CMAI* Cohen-Mansfield Agitation Inventory, *CMAI-C* Cohen-Mansfield Agitation Inventory-Community, *CMAI-K* Korean version of the Cohen-Mansfield Agitation Inventory, *CO* crossover, *CSDD* Cornell Scale for Depression in Dementia, *DB* double blind, *DLB* dementia with Lewy bodies, *DON* donepezil, *DS* divalproex sodium, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, *DXQ* dextromethorphan-quinidine, *ECG* electrocardiogram, *EPS* extrapyramidal symptoms, *ESRS* Extrapyramidal Symptoms Rating Scale, *FAST* Functional Assessment Staging Test, *GAL* galantamine, *GI* gastrointestinal, *h* hour(s), *HAL* haloperidol, *HAMD* Hamilton Depression Rating Scale, *ICD-10* International Statistical Classification of Diseases – tenth revision, *IR* immediate release, *LOCF* last observation carried forward, *LTC* long-term care, *mADCS-CGIC* modified Alzheimer Disease Cooperative Study – Clinical Global Impression of Change, *MC* multicenter, *MEM* memantine, *MET* methylphenidate, *MMSE* Mini-Mental State Examination, *NBRS* Neurobehavioral Rating Scale, *NBRS-A* Neurobehavioral Rating Scale, agitation subscale, *ND* no difference(s), *NIA* National Institute on Aging, *NIH* National Institutes of Health, *NIMH* National Institute of Mental Health, *NINCDS* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria, *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria, *NINCDS-AIREN* National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche en l'Enseignement en Neurosciences, *NPI* neuropsychiatric inventory, *NPI-NH* neuropsychiatric inventory nursing

Table 1 (continued)

home version, *NR* not reported, *OC* observed cases, *OLA* olanzapine, *OXC* oxcarbazepine, *PANSS-EC* Positive and Negative Syndrome Scale – Excitement Component, *PC* placebo controlled, *PD* Parkinson's disease, *PG* parallel group, *PL* placebo, *PRA* prazosin, *PRO* propranolol, *pt(s)* patient(s), *QUE* quetiapine, *RAN* randomized, *RIS* risperidone, *R-MDS-D* Rochester Movement Disorders Scale for Dementia, *SAE* serious adverse event, *SAS* Simpson Angus scale, *SER* sertraline, *SIB* Severe Impairment Battery, *SMMSE* Standardized Mini-Mental State Examination, *TEAE* treatment-emergent adverse event, *THC* tetrahydrocannabinol, *UKU* Udvalg for Kliniske UndersØgelser side-effect rating scale, *UPDRS* Unified Parkinson's Disease Rating Scale, *URTI* upper respiratory tract infection, *UTI* urinary tract infection, *VAL* valproate, *wk* week, *XR* extended release

but lower doses of these medications have not been associated with any weight gain in elderly patients with dementia [46, 47].

Some studies have found no increased diabetic risk in elderly patients with dementia who are being treated with antipsychotic medications even though the reverse is true in younger age groups [48]. Some atypical antipsychotic medications, such as risperidone, aripiprazole, and ziprasidone, as well high-potency typical antipsychotic medications such as haloperidol, appear to be associated with a decreased risk of hyperlipidemia, whereas other atypical antipsychotic medications such as olanzapine, quetiapine, and clozapine, as well as lower-potency typical antipsychotic medications such as chlorpromazine and thioridazine, appear to incur a higher risk of hyperlipidemia [49].

Based on a large meta-analysis, the odds ratio for the risk of death when using antipsychotic medications in patients with dementia was estimated to be 1.54, but no evidence was found for differential risk according to dementia severity, specific diagnoses, or individual drugs [32, 40]. Even though the risk of death was not associated with any particular group, it was more appreciated when all the atypical antipsychotic medications were considered together as a group [40]. Changing from one antipsychotic agent to the other while treating patients with dementia with NPS has also been associated with changes in mental status, a condition that has been identified as a crossover effect of antipsychotic medication [42].

3 General Approach to the Patient with Neuropsychiatric Symptoms (NPS)

Given the slim therapeutic index for psychotropic medication in patients with dementia, it is exceedingly important to carefully evaluate the symptoms and identify a compelling need for intervention. Kales et al. [3] recommended the DICE approach: Describe (context, environment, patient and caregiver perspective, degree of distress); Investigate (potential iatrogenic causes, pain, fear, boredom); Create (a plan for intervention with discrete follow-up time), and Evaluate (evaluate the intervention and plan continuation or withdrawal). In a busy neurology practice, the use of interview tools can be an efficient way to identify behaviors and symptoms to be addressed and quantify the degree of distress associated with each symptom. The Memory and Behavior Checklist, developed in 1992 by Teri et al. [50] and subsequently validated and circulated by the Alzheimer's Association, is a 24-item list completed by the caregiver before the clinician's examination, that allows rapid identification of severely problematic issues that should be addressed. Additional benefits of the checklist include allowing the caregiver to highlight problems that may be uncomfortable

to verbalize in front of the patient and providing documentation of symptom severity if included in the medical record.

In our experience, patients presenting to a memory clinic are receiving, on average, eight medications, many of which have central nervous system adverse effects. Before any new medication is initiated, the prescribed and nonprescription agents should be optimized to reduce anticholinergic burden. Evidence also shows that switching cholinesterase inhibitors [51] can reduce NPS and the use of psychotropic medications. In the naturalistic study by Quante et al. [16], all patients admitted to the geriatric psychiatry unit for management of NPS showed improvement, regardless of whether pharmacotherapy treatment was prescribed.

Given the sheer number of publications related to NPS of dementia, we created Table 1 to highlight psychotropic medications that have been used in various studies. However, making definitive recommendations is difficult because of the heterogeneity of the studies in terms of patient population, type and severity of neuropsychiatric symptom, intervention, and outcome measures. We included studies published since 2004 in Table 1, because another publication reports on studies up to 2004 [52]. To align with selected criteria from the Sink et al. [52] review, we included only randomized controlled trials of agents available in the USA. The literature search was not limited to any particular type of dementia, though specific outcomes for NPS had to be reported. The following discussion highlights relevant secondary literature and selected key trials as it pertains to the medication management of specific symptoms. Selected symptoms were included in the following discussion if there was evidence or data to support changes to that specific symptom construct (e.g., agitation/aggression). We did not discuss symptoms for which comprehensive reviews existed highlighting the specific symptom (e.g., apathy).

4 Depression

Depression is one of the most common NPS, occurring in > 20% of individuals with dementia [29]. The symptoms can vary and include persistent sadness and anhedonia, accompanied by disturbed sleep/appetite, fatigue, and even suicidal ideation [53]. However, the relationship between depression and dementia is complicated. Not only has depression been shown to increase the risk of incident dementia, but uncontrolled depression can be associated with cognitive complaints and impairment (pseudodementia). In addition, antidepressants can worsen cognition, and depression can be a component of the dementing illness [31]. The evidence supporting the efficacy of antidepressants for managing depression in patients with dementia is mixed. Some clinical trials have shown no benefit, and most show significant adverse effects, including worsened cognition (Table 1) [54–56].

A 2011 meta-analysis reviewed seven placebo-controlled studies of antidepressants in patients with dementia and depression published between 1989 and 2010 [57]. The authors found inconclusive evidence of efficacy, as the included trials had variable designs and were underpowered. Of the seven studies, two found significantly beneficial effects of antidepressant versus placebo [57]. Of these two, the first studied clomipramine at a target dose of 100 mg/day for 6 weeks in 24 patients with probable AD. Patients receiving clomipramine showed significantly lower Hamilton Depressive Rating Scale (HDRS) scores over placebo in the first 6 weeks. The second evaluated sertraline at a mean dose of 95 mg/day in 44 patients for 12 weeks. Sertraline-treated patients showed greater improvements in scores on both the Cornell Scale for Depression in Dementia (CSDD) and the HDRS than did the placebo group. Five studies included in this meta-analysis did not demonstrate significant effects from an intervention with an antidepressant, including imipramine, sertraline, fluoxetine, and venlafaxine. The largest of the studies evaluated sertraline at a target dose of 100 mg/day in 131 patients for 12 weeks and found no demonstration of efficacy versus placebo [57].

It is clear that depression worsens the quality of life of patients with dementia, and the presence of major depression (with or without suicidal ideation) warrants pharmacologic treatment. However, most of the included randomized clinical trials were underpowered, and clinical judgment has led to the recommendation of a trial of a low-dose selective serotonin reuptake inhibitor (SSRI) (sertraline 25–50 mg, fluoxetine 10 mg, or citalopram 10 mg daily to start) in affected patients [58]. Tricyclic antidepressants and other agents with significant anticholinergic effects, such as paroxetine, should be avoided [31].

5 Sleep Disorders

Sleep disorders, consisting of disruption in sleep, is a common complaint of patients with dementia and their caregivers, with > 50% of patients affected at the more severe stages of the disease [59]. Implementation of improved sleep hygiene is often helpful in reducing the need for pharmacologic intervention. Reduction in caffeine-containing foods and beverages, reducing night-time fluid intake, increased daytime activity and exercise, and creation of an optimal environment for sleep (lighting, temperature), along with a more structured daily and evening routine, should be attempted [58]. If these tactics fail, pharmacologic intervention with the least offensive agents could be tried. First, cholinesterase inhibitors, usually already prescribed in patients with memory complaints, when given at bedtime,

Table 2 Randomized, controlled withdrawal trials of agents for neuropsychiatric symptoms as of 2004

Study; funding sponsor	Study design (*N*); study length	Drug	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Ruths et al. [118]; NR	RAN, PC, DB trial (*N* = 30); 4 wk	HAL, RIS, or OLA	Nursing homes	Dementia diagnosis per ICD-10	Effects of antipsychotic withdrawal assessed with NPI-Q, which showed ND between groups, and actigraphy. Antipsychotic discontinuation associated with reduced average sleep efficiency	On individual items of the NPI-Q, differences between groups observed in restlessness (aberrant motor behavior)	AE associated with antipsychotic discontinuation: one pt restarted antipsychotic due to increased leg movements. AE for pts remaining on antipsychotics NR
Ballard et al. [82]; The Alzheimer's Research Trust	RAN, blinded, PC, 2-group discontinuation (*N* = 128); 12 months	THI, CHL, HAL, TRI, or RIS	Nursing or residential home	Possible or probable AD per NINCDS-ADRDA; MMSE score > 6 or SIB > 30	ND between discontinuation and continuation groups on primary outcome measure of total SIB score change from baseline to 6 months. ND between groups in NPI or M-UPDRS estimated mean changes and CGI-C over 6 months. Analysis at 12 months limited due to missing data but show no significant difference between groups in SIB score changes at 12 months. NPI estimated mean change in scores showed differences between groups in favor of continuation though a test of interaction was not statistically significant	Specific symptom outcomes NR	ND in cognitive function changes as measured by SMMSE
Ruths et al. [88]; NR	RAN, MC, DB, controlled (*N* = 55); 4 wk	HAL, RIS, or OLA	Nursing home	Dementia per ICD-10	Primary outcome measure of successful antipsychotic discontinuation, which was described as 23 of 27 pts remaining off antipsychotics at wk 4	ND on individual items or total NPI scores between antipsychotic discontinuation and continuation group	NR
Bergh et al. [86]; Innlandet Hospital Trust, the Research Council of Norway, and the South-Eastern Norway Regional Health Authority	DB, RAN, PG, MC, PC (*N* = 128); 25 wk	SSRIs (ESC, CIT, SER, or PAR)	Nursing homes	AD, dementia, or vascular dementia per ICD-10 criteria	ND observed in primary efficacy endpoint was CSDD and NPI scores between groups	No particular subscale of the CSDD (e.g., mood or non-mood) or NPI (e.g., agitation, psychotic, apathy) showed differences between groups	ND between groups on UPDRS. More pts in discontinuation (20%) vs. PL group (6%) withdrew from study due to increased depressive or neuropsychiatric symptoms

Table 2 (continued)

Study; funding sponsor	Study design (*N*); study length	Drug	Pt residence	Dementia type and severity	Outcomes	Outcomes related to specific symptoms	AEs
Devanand et al. [80]; NIH and the Department of Veterans Affairs; Jannsen provided medication only	RAN, DB (*N* = 110); 32 wk	RIS	Outpatients and nursing home/ALF	Dementia criteria per DSM-IV and probable AD per NINCDS-ADRDA criteria; MMSE score 5–26 in outpatients or 2–30 in nursing home residents	Primary outcome measure was time to relapse during wk 0–16 of phase B (pts responding to RIS during phase A); pts receiving PL had increased risk of relapse at 16 wk. Pts discontinuing RIS at 16 wk and switched to PL had an increased risk of relapse vs. PL	Specific symptom outcome NR	No significant differences in reported AE rating scales
Ballard et al. [84]; Lundbeck pharmaceutical company and National Institute for Health Research	RAN, DB, PC, MC, double-dummy, PG (*N* = 199); 24 wk	MEM, antipsychotics	Care facilities	Probable or possible AD according to NINCDS-ADRDA criteria	ND between groups on primary outcome measure of agitation on the CMAI and function using BADLS. ND between groups on NPI or CGI-C	Specific symptom outcomes NR	Statistical significance NR. In antipsychotic group, 193 pts had AE (25 SAE) and in MEM group, 167 pts had AE (18 SAE)

AD Alzheimer's disease, *AE* adverse event, *ALF* assisted living facility, BADLS Bristol Activities of Daily Living Scale, *CGI-C* Clinical Global Impression of Change, *CHL* chlorpromazine, *CIT* citalopram, *CMAI* Cohen-Mansfield Agitation Inventory, *CSDD* Cornell Scale for Depression in Dementia, *DB* double blind, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, ESC escitalopram, *HAL* haloperidol, *ICD-10* International Statistical Classification of Diseases – tenth revision, *MC* multicenter, *MEM* memantine, *MMSE* Mini-Mental State Examination, *M-UPDRS* Modified Unified Parkinson's Disease Rating Scale, *ND* no difference(s), *NIH* National Institutes of Health, *NINCDS-ADRDA* National Institute of Neurological and Communication Disorders and Stroke-Alzheimer Disease and Related Disorders Association criteria, *NPI* neuropsychiatric inventory, *NPI-Q* neuropsychiatric inventory Questionnaire, *NR* not reported, *OLA* olanzapine, *PAR* paroxetine, *PC* placebo controlled, *PG* parallel group, *PL* placebo, *RAN* randomized, *RIS* risperidone, *SAE* serious adverse event, *SER* sertraline, SIB Severe Impairment Battery, *SMMSE* Standardized Mini-Mental State Examination, *THI* thioridazine, *TRI* trifluoperazine, *UPDRS* Unified Parkinson's disease rating scale, *wk* week

can improve sleep latency [60]. Second, trazodone 50 mg at bedtime has been shown to improve sleep metrics in individuals with dementia [61]. In a Cochrane review published in November 2016, authors analyzed four randomized controlled trials of melatonin with doses up to 10 mg and found no demonstration of efficacy over placebo in any sleep parameter, including efficiency of sleep and number of night-time awakenings. Results of this Cochrane review included one phase II trial of ramelteon 8 mg nightly in patients with mild to moderate AD. No significant differences from placebo were reported. The one positive study of trazodone, involving only 30 patients, was cited previously [61] and was considered low quality [62]. Benzodiazepines and benzodiazepine receptor agonists (zolpidem and zopiclone) should be avoided in elderly patients with dementia because they may induce falls and worsen cognition [31].

6 Psychosis

Psychotic episodes, which may consist of hallucinations or delusions are experienced by patients with dementia at much lower rates than that of depression and sleep disorders but can be a source of extreme distress for both the patient and their caregivers [63], which can lead to increased rates of nursing home placement [5, 64]. Though psychosis can persist and worsen over time, it may also fluctuate and resolve [5, 65]. It is estimated that between 16 and 75% of patients with PD and approximately 40% of patients with AD have psychosis at some point in their disease course [65, 66]. This rate is higher in patients with DLB as visual hallucinations are a key feature of this condition [64]. In multiple types of dementia, delirium may also present with psychotic symptoms, further clouding the clinical picture of NPS [67].

The presence of hallucinations does not automatically warrant the use of antipsychotic medication. In many cases, the hallucinations and/or delusions can be of minor consequence, and the caregiver can manage with only reassurance and redirection [58]. If possible, reducing the doses of or discontinuing concurrent medications that may contribute to NPS, such as sedatives or anticholinergics, may be considered [64]. In cases of DLB, donepezil can improve psychotic symptoms, including hallucinations and delusions [68]. However, if the patient, the caregiver, or both are severely affected by the symptoms, a low-dose antipsychotic agent can be trialed. The efficacy of antipsychotics for treating psychotic symptoms, specifically, in AD is unclear because many studies appear to group behavioral disturbances with psychotic symptoms in evaluating medication efficacy in patients with dementia [11, 69]. While most antipsychotics have been shown to be ineffective or intolerable secondary to worsened motor function, low-dose clozapine appears effective for PD psychosis [64]. Unfortunately, frequent blood monitoring (weekly evolving to bi-weekly) for agranulocytosis significantly limits the use of clozapine. In April 2016, pimavanserin was the first antipsychotic to receive approval for the treatment of hallucinations and delusions associated with PD psychosis [70, 71]. Pimavanserin is an inverse agonist at 5-HT2a (and less so at 5-HT2c) receptors in the brain and was not shown to worsen parkinsonism over 6 weeks in one study [71].

Documented adverse effects of atypical antipsychotics include increased risk of stroke, myocardial infarction and other cardiovascular events, pulmonary-related adverse effects, cognitive changes, sedation, drug-induced parkinsonism, tardive dyskinesia/dystonia, falls and hip fractures, and metabolic adverse effects [72]. Since all of the available antipsychotics carry the boxed warning for increased risk of death in patients with dementia-related psychosis, a documented discussion of the risks and benefits of the treatment should occur prior to the prescription [58]. A careful case-controlled analysis of the mortality risk of individual antipsychotic medication was performed on a large database of 46,008 veterans aged > 65 years with a diagnosis of dementia and a recent prescription for an antipsychotic, valproic acid, or an antidepressant [73]. The investigators reported increased mortality (from highest to lowest risk) with haloperidol, risperidone, olanzapine, and quetiapine, with numbers need to harm of 26, 27, 40, and 50, respectively. It was also noted that the mortality risk was dose dependent, reinforcing the need to use the lowest possible dose for the shortest possible duration in patients with dementia requiring these agents. Since the increased mortality is attributed to mostly cardiovascular events, patients with dementia with vascular risk factors may be particularly vulnerable. According to the APA practice guideline on using antipsychotics in the treatment of agitation or psychosis in patients with dementia, published in May 2016, antipsychotics should only be used when symptoms are severe, dangerous, or cause significant patient distress, and haloperidol should not be used as first-line treatment [25].

7 Agitation/Aggression

Agitation is used to describe a wide range of behaviors that include verbal outbursts, physical aggression, intense anxiety and crying, and persistent perambulation and wandering [3]. Agitation can happen at any stage of the disease and affects up to 20% of community-dwelling patients with AD [11]. It is exceedingly important to identify the triggers and context for the agitation and try to remove the cause. Possible causes of agitation include pain, infection, or other exacerbations of medical illness, loneliness, boredom, medication side effects, environmental changes, and fatigue [11]. Pharmacologic treatment should only be considered when measures to remove triggers are ineffective, the behavior is

severe, and the agitation is persistent. Citalopram, an antidepressant, has been shown to be effective in combination with psychosocial intervention for reducing agitation in patients with dementia [54] but at the cost of impaired cognition and cardiac adverse effects (QTc prolongation). It was subsequently reported that patients with lower levels of cognitive impairment and only moderate agitation were most likely to benefit from citalopram and that restricting doses to ≤ 20 mg daily may reduce the chance of adverse effects [74].

Antipsychotic agents have modest benefits for agitation/aggression but are associated with increased mortality, as discussed in Sects. 2 and 6 [3]. They should only be employed when the patient demonstrates aggression with risk of harm to self or others and, even then, the intervention should be at the lowest possible dose (quetiapine 25 mg daily to start) and for a short duration (re-evaluate at 8 weeks). Quetiapine is recommended over risperidone or haloperidol because evidence exists of a lower mortality risk [73].

Some antiepileptic agents have been promoted as "mood stabilizers" and have been tried in patients with dementia and agitation [75]. In a recent review, valproic acid was not effective and caused significant side effects. Carbamazepine was effective in several small studies, but the medication must be titrated slowly over 6–8 weeks to avoid central nervous system side effects and has many drug interactions [75]. It is possible that some of the newer agents, such as levetiracetam and lamotrigine may have some benefits, but clinical trial evidence is lacking.

Benzodiazepines are used extensively in patients with dementia, particularly those in nursing homes, despite very little evidence of efficacy in managing NPS. A recent systematic review revealed usage data in up to 20% of patients and a clear association with accelerated cognitive decline and falls [76]. There is evidence that single doses of lorazepam can be effective for acute agitation, but little evidence supports chronic dosing for agitation or sleep disturbances [76, 77].

The development of additional, and safer, pharmacologic agents to manage agitation and aggression in patients with dementia is necessary. In a recent randomized clinical trial, patients with dementia and clinically significant agitation received either placebo or the combination of dextromethorphan and quinidine for 10 weeks. The treatment successfully reduced agitation, and the main adverse effects were falls and urinary tract infections [78]. This product is currently marketed for pseudobulbar affect and could be a safer alternative to antipsychotics for the management of agitation/aggression in dementia.

8 Medication Withdrawal

It has been suggested that discontinuing acetylcholinesterase inhibitors in patients with AD could be deleterious because of both worsened cognition and NPS [79]. Additionally, the effects of psychotropic withdrawal or discontinuation on adverse effects and symptom management are unclear. Table 2 summarizes the discontinuation studies. Even if the psychotropic is considered effective, providers may be wary of continuing them and quick to consider discontinuing treatment in light of adverse effects and federal regulations dictating discontinuation [80]. Devanand et al. [80] investigated patients with AD (both outpatients and residential) with psychosis and agitation–aggression who had responded to 16 weeks of risperidone treatment and the effects of discontinuation. At baseline, almost half of patients lived in an assisted-living facility or nursing home, 80% had psychosis, and 81% had agitation–aggression. Of the patients who responded to risperidone and were discontinued after the first 16 weeks, 60% relapsed compared with 33% of those randomized to continue risperidone. Another intervention arm included patients who continued risperidone for an additional 16 weeks (total of 32 weeks of treatment) and were discontinued. These patients were also more likely to relapse than those continuing risperidone treatment (48 vs. 15%, respectively; $p = 0.02$). Despite patients being at higher risk of relapse with discontinuation, the effect of risperidone on addressed psychosis and agitation was not robust. Furthermore, this study did not find that more severe symptoms were associated with a higher likelihood of relapse. Overall, it appears that, in patients who respond (characterized as ≥ 30% reduction on the neuropsychiatric inventory and 1 or 2 on the Clinical Global Impression of Change [CGI-C]) to risperidone, patients who discontinue medication should be closely monitored for relapse. Subsequently, Patel et al. [81] classified neuropsychiatric inventory symptoms in the previous study into absent, mild/moderate, and severe symptoms to identify that severe hallucinations were associated with relapse after 32 weeks. Auditory, but not visual, hallucinations were significantly predictive of relapse. Findings led authors to suggest that the initial severity of NPS, not just current or final presentation, should be included when considering appropriateness of antipsychotic discontinuation. Prior to this, the cognitive decline of patients with AD living in a nursing home or assisted-living facility and continuing or discontinuing risperidone, chlorpromazine, trifluoperazine, or haloperidol were evaluated [82]. Of note, 12% of patients had visual hallucinations and 33% of patients had delusions at baseline. There was no difference based on the Severe Impairment Battery over 6 months, nor were there any notable global differences based on loss of function and CGI scores, indicating that withdrawing antipsychotics does not lead to cognitive and functional decline. A longer-term follow-up to this study identified greater mortality with continued antipsychotic use, especially beyond the first year [83]. Another study found no differences between patients with AD who received antipsychotics for at least 3 months and then switched to memantine and those who

continued on antipsychotics in terms of agitation, activities of daily living, or overall NPS [84]. A 2018 Cochrane review of long-term (≥ 3 months) antipsychotic withdrawal or discontinuation concluded that antipsychotics could be discontinued in patients with dementia, though the supportive evidence was low quality. Importantly, authors stated that antipsychotic continuation could be beneficial in patients with psychotic symptoms, agitation, or aggression, or who had demonstrated response [85].

In the 25-week DESEP study evaluating depressive symptoms in nursing home residents with AD and/or vascular dementia, patients who discontinued prespecified SSRIs (escitalopram, citalopram, sertraline, and paroxetine) experienced a significant increase in depressive symptoms compared with patients continuing their SSRI [86]. Of note, the authors sought to identify the effects of antidepressant discontinuation in patients where the medication yielded unclear or questionable benefits. Patients had been on the antidepressant for ≥ 3 months and those randomized to the discontinuation arm were prescribed a taper over 1 week. Though there were no differences between groups on the total neuropsychiatric inventory scores, there was a statistically significant difference on the affective subscore of the neuropsychiatric inventory. Though patients with a current documentation or history of depressive disorder were excluded, included patients could have had undiagnosed depression, as indicated by high scores on the depression rating scale. A further limitation was that patients could have been receiving other psychotropics [86]. Thus, it appears that, in patients who exhibit minimal benefit from SSRIs, discontinuation could lead to an increase in depressive symptoms.

Higher doses of psychotropic medications prior to withdrawal or discontinuation may be an indication of the severity of NPS, as these medications are generally started at low doses and slowly titrated to a balance of efficacy and tolerability, especially in the geriatric population. Overall, it might appear that patients with specific symptoms or more severe NPS (e.g., neuropsychiatric inventory scores of ≥ 14) may obtain greater benefit from psychotropic intervention than patients with milder symptoms [87, 88].

9 Additional Considerations for the Treating Clinician

Caregiver training, as one example of a nonpharmacologic technique, has been shown to significantly reduce the impact of NPS in patients with dementia [89]. Many patients respond positively to the use of nonpharmacological interventions, but it is important to note that some may find these interventions upsetting, further potentiating NPS [25]. Nonpharmacologic management techniques must be individualized and developed with input from healthcare providers and caregivers to increase their success [25]. When effective, nonpharmacologic strategies reduce the need for pharmacologic therapy, avoiding the use of potentially harmful medications [25].

Some studies allowed for inclusion of medications used for dementia, without specific attention to their possible effects on NPS. Alternatively, the clinical trial evidence supporting the efficacy or even the toxicity of psychotropic medication for patients with dementia usually excludes patients receiving multiple psychotropic medications or with important comorbid conditions. In practice, most patients do not meet these criteria and receive multiple medications with similar adverse effects and have age-induced impaired organ function (renal, hepatic), leading to additive risk in this vulnerable population. For example, it is common for a patient to receive trazodone for sleep and citalopram for agitation, both of which can increase risk of QTc prolongation. Opportunities to reduce pill burden and polypharmacy should be embraced whenever possible.

The mechanism by which various NPS present is unclear. For example, even within the realm of hallucinations, certain types may be more likely to present in one dementia than in another, and, subsequently, the response to medications directed towards visual versus auditory hallucinations among different dementias may also differ. Many presentations and nuances of symptoms may be characterized under categories such as "depressive symptoms" or "agitation and aggression." To make it more difficult, some symptoms under each of these categories may respond readily to medication management, and others are fairly resistant. Improvements in specific symptoms may be significant during the study but then nonsignificant by study endpoint, further highlighting the variability in response over time. One evaluation of the CitAD study, highlighting individual items on the neuropsychiatric inventory, found that delusions, anxiety, and irritability/lability differed significantly between patients receiving citalopram and those receiving placebo [8]. In general, all patients had agitation/aggression, but the degrees of irritability/lability, anxiety, apathy/indifference, aberrant motor behavior, disinhibition, and depression/euphoria varied [8]. Given these findings, the application in clinical practice remains unclear. Questions may include whether patients in whom symptoms initially respond would most benefit from citalopram or whether citalopram would be efficacious in more severe psychosis. In addition, some studies look at the total score on a neuropsychiatric inventory, which may not yield any meaningful benefit until specific symptoms are analyzed. The identification of these individual symptom improvements helps identify the most appropriate candidate for medication therapy. The psychosocial or environmental context is not generally described in studies and may differ from a patient's surroundings. It is also unclear how a

co-occurring psychiatric illness, such as depression, may impact the overall treatment and response of a patient with dementia. How a patient, who has been carefully selected for medication management based on targeted symptoms with clearly defined goals, responds to the medication can also influence its continued use in NPS management. Thus, the management of NPS truly becomes individualized medicine as providers seek to understand the etiology and pathophysiology of specific symptoms, identify and apply relevant literature, observe the effects of medication management, and determine the appropriateness of continuation versus discontinuation according to response or remission and relapse risk in caring for their patients.

10 Conclusions

NPS occur in virtually all patients with dementia and can have dire consequences, including institutionalization and caregiver morbidity. Nonpharmacologic interventions can be quite effective but are difficult to implement and often fail to provide satisfactory resolution. Pharmacologic intervention should be pursued in only the most severely afflicted, with careful documentation of the indication and the risk and benefit discussion with the patient and caregiver. Careful consideration should be given to not only the initial presentation of the NPS but also the evidence of medication efficacy directed towards specific symptomatology and the overall risks of the "untreated" symptom compared with those of the medication. If a medication is initiated for NPS, the persistence of symptoms should be assessed thorough evaluation to ascertain which patients might be the best candidates for continued medication versus drug discontinuation while weighing the risks of symptomatic relapse and possible subsequent decline.

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Compliance with Ethical Standards

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