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REVIEW ARTICLE

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Role of Donepezil in the Management of Neuropsychiatric Symptoms in Alzheimer's Disease and Dementia with Lewy Bodies

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SUMMARY

Alzheimer's disease (AD) is a progressive condition that affects cognition, function, and behavior. Approximately 60–90% of patients with AD develop neuropsychiatric symptoms (NPS) such as hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep disturbances, appetite and eating changes, or altered sexual behavior. These noncognitive behavior changes are thought to result from anatomical and biochemical changes within the brain, and have been linked, in part, to cholinergic deficiency. Cholinesterase inhibitors may reduce the emergence of NPS and have a role in their treatment. These agents may delay initiation of, or reduce the need for, other drugs such as antipsychotics. This article summarizes the effects of donepezil, a cholinesterase inhibitor, on the NPS of dementia with emphasis on AD and dementia with Lewy bodies.

Introduction

The natural course of neurodegenerative dementias, including Alzheimer's disease (AD), is one of progressive deterioration affecting cognition, function, and behavior [1]. AD starts with symptoms of forgetfulness, with patients ultimately losing their ability to perform routine activities of daily living [2]. Many patients also exhibit behavioral changes. As the illness progresses, patients with AD need increasing amounts of care and attention, and the dependence associated with progressive cognitive decline is distressing for patients and their families and caregivers [3].

Neurobiology of NPS

Neuropsychiatric symptoms (NPS) are a heterogeneous group of noncognitive symptoms and behaviors that are common in AD [4]. Approximately 60–90% of AD patients develop NPS. There is an emerging neurobiology of NPS. NPS result from pathological and biochemical changes within the brain [5]. Neurofibrillary tangles and amyloid plaques are thought to contribute to behavioral changes in AD, and tau pathology has been linked to agitation in AD [6]. Muscarinic M_2 receptors may contribute to NPS in AD [7]. NPS are associated with underlying neurotransmitter imbalances

encompassing acetylcholine, serotonin, dopamine, noradrenaline, glutamate, and γ-aminobutyric acid [8]. NPS have been linked, in part, to cholinergic deficits affecting the limbic system and frontal lobe [9–11]. Lemstra et al. [12] proposed a specific central cholinergic deficiency syndrome of NPS associated with the profuse thalamic cholinergic projections from the brain stem.

The neurobiological linkage between NPS and central cholinergic deficits suggests that cholinergic therapy may be of benefit for NPS. This article summarizes the effects of donepezil, a cholinesterase inhibitor (ChEI), on the NPS of dementia, including AD and dementia with Lewy bodies (DLB), in clinical and real-world settings.

Methodology of Review

For this literature review, data were collected from MEDLINE®/PubMed® and EMBASE® using specified search criteria based on efficacy and safety of donepezil in NPS in patients with dementia. The search terms were combinations of the following: "Alzheimer", "neuropsychiatric symptoms", "behavioral and psychological symptoms", "cholinesterase inhibitor", "donepezil", "dementia", "Lewy bodies", "efficacy", and "safety". Only articles published in English were considered for this review. If a title or abstract described a high-quality study that was likely to be eligible for inclusion, the full article was obtained and assessed for relevance according to predefined criteria. We reviewed the published randomized trials of donepezil for NPS, as well as any subanalyses. We also collated data for donepezil in NPS in real-world clinical practice.

Treatment of NPS

Symptom-Targeted Management

There is a diverse array of NPS in AD, and several clinical instruments have been developed to assess NPS, usually relying on an interview with the caregiver. The Neuropsychiatric Inventory (NPI) is one commonly used means of assessing the spectrum of NPS in AD using a caregiver-based interview. The 12 NPS of dementia assessed by the NPI are hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior changes, and appetite and eating change [13,14]. The NPI assists in the evaluation of these behaviors, enabling accurate diagnosis and treatment. Other commonly used assessments include the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale [15], Cohen-Mansfield Agitation Inventory (CMAI) [16], and Alzheimer's Disease Assessment Scale–Noncognitive (ADAS-Noncog) [17].

Fernández et al. [18] found that 92% of 1014 patients with AD had some NPS at baseline on the ADAS-Noncog. The most prevalent behaviors were lack of concentration (56%), tremors (56%), depression (44%), lack of cooperation (36%), delusions (32%), motor behavior (29%), and tearfulness (28%). Patients with higher ADAS-Noncog scores had more delusions ($P = 0.0417$), hallucinations ($P = 0.0451$), delirium ($P = 0.0233$), and tremors ($P < 0.001$), whereas those with lower ADAS-Noncog scores had more emotional symptoms of tearful mood ($P = 0.0170$) and apathy ($P = 0.0310$). These authors classified the behaviors into three groups of hyperactivity, psychosis, and affective abnormalities, and suggested an additional group of inattention that is characterized by frustration and lack of concentration, impatience, and poor cooperation. This syndrome was more common among patients with higher ADAS-Noncog scores (26–50).

Nonpharmacological treatments for NPS include behavioral therapy, cognitive stimulation therapy, and psychoeducation [19].

Pharmacologic Treatment of NPS

Pharmacological therapies include antipsychotics (e.g., aripiprazole, haloperidol, risperidone, quetiapine, olanzapine), antidepressants (e.g., fluoxetine, citalopram, paroxetine, sertraline, trazodone), anticonvulsant mood stabilizers (e.g., carbamazepine, valproate), and cognitive enhancers (e.g., donepezil, galantamine, rivastigmine, memantine).

Pharmacotherapy should target specific clinical symptoms, while minimizing adverse effects [19–21]. Antipsychotic agents may be used to treat psychosis and disruptive behaviors, including aggression (risperidone is the only antipsychotic licensed for NPS in AD in Canada and Europe, but it is not approved for NPS in the USA). Antidepressants may be given for apathy, anxiety, and agitation, and some psychotic symptoms. Anticonvulsant mood stabilizers may be given to treat aggression and agitation, although carbamazepine and valproate are associated with considerable adverse effects. Cognitive enhancers may be effective for treating several behaviors, including apathy, agitation, and psychosis, and may reduce NPS in late-stage AD [21]. Benzodiazepines should be avoided in patients with AD, but a single low dose of lorazepam or zopiclone may be helpful to prevent or reduce agitation in stressful situations.

Antipsychotics, anticonvulsants, and benzodiazepines are all associated with side effects and should be used with caution [19,22]. Antipsychotics adversely affect memory and cognition [23], and are not recommended for long-term use (more than 12 weeks) [24]. A meta-analysis found that antipsychotic use for relatively brief periods of less than 8–12 weeks is associated with a small increased risk for death compared with placebo (odds ratio [OR] 1.54; 95% confidence interval [CI], 1.06–2.23; $P = 0.02$) [25]. This is similar to the OR of 1.6–1.7 calculated by the US Food and Drug Administration (FDA) [26], and the risk is included as a black box warning in the package insert for these agents. Risperidone and olanzapine have been linked to increased cerebrovascular events compared with placebo in patients with dementia (relative risk, 2.7; 95% CI, 1.4–5.3) and warnings have been issued by the US FDA [26,27]. Physicians should carefully consider the risks and benefits for each patient when prescribing for NPS in AD [28].

Donepezil for NPS

Donepezil improves cognitive symptoms and delays cognitive decline in patients with AD and has a good safety profile [27,29]. There is evidence that donepezil improves the NPS of AD [27,30–32]. A study of 86 patients with AD treated with donepezil found that pretreatment behaviors might predict which patients are

likely to respond to treatment [33]. Compared with patients who did not respond to donepezil therapy, those who responded had significantly worse baseline delusions, agitation, depression, anxiety, apathy, disinhibition, and irritability (Table 1). Five behaviors significantly improved for patients who responded: delusions, agitation, anxiety, disinhibition, and irritability. Patients with these symptoms are more likely to respond to treatment with donepezil.

A randomized withdrawal trial showed that donepezil improved NPS [34]. NPI score was the primary outcome measure for this study. A total of 134 patients with mild-to-moderate AD and at least moderate NPS (NPI >11 points) were treated with donepezil 5 mg for 6 weeks, titrated to 10 mg for a further 6 weeks, after which they were randomized to either placebo or donepezil 10 mg for 6–12 weeks in the withdrawal portion of the study. During the initial open-label phase, the total NPI and NPI-Distress (NPI-D) scores were lower after treatment with donepezil than at baseline (Table 1). All domains of the NPI except euphoria were improved to some extent ($P < 0.05$). Following randomized discontinuation, donepezil-treated patients had improvements in total NPI score compared with the placebo group, who relapsed behaviorally, and in terms of the NPI-D score. This study provides evidence that donepezil is effective in the treatment of NPS. The results also demonstrate that behavioral worsening may follow donepezil withdrawal.

In a secondary analysis of patients with severe behavioral disturbances previously treated with donepezil and sertraline, Cummings et al. [32] hypothesized that donepezil would reduce behavioral changes, with the greatest effects on mood changes and apathy. The dataset comprised 120 patients with NPI total score >5, severity score ≥2 in ≥2 domains of the 12-item NPI, and Mini Mental State Examination (MMSE) scores of 8–23 who were treated with donepezil 5 or 10 mg for 20 weeks. The total 10-item and total 12-item NPI scores improved significantly from baseline to week 20 ($P < 0.001$) [Table 1]. Significant improvements were seen for the physically nonaggressive ($P < 0.001$) and verbally nonaggressive ($P < 0.05$) factors of the CMAI–Community from baseline to week 20. BEHAVE-AD scores improved significantly from baseline to week 20 in the intent-to-treat–observed cases (OC) analysis ($P < 0.005$) and last observation carried forward (LOCF; $P < 0.01$). These results suggest that donepezil reduces behavioral symptoms, particularly mood disturbances and delusions, in patients with AD with relatively severe psychopathology.

A subgroup analysis of the Donepezil in Moderate-to-Severe AD (MSAD) study [35] examined whether donepezil 10 mg was effective for patients with more severe AD (standardized MMSE score, 5–12) compared with placebo [36]. The NPI was used to evaluate NPS. NPS in donepezil-treated patients were significantly improved over placebo-treated patients at weeks 4 ($P = 0.0252$), 18 ($P = 0.0314$), and 24 ($P = 0.0198$) in the OC analysis and additionally at week 24 in the LOCF analysis ($P = 0.0062$) [Table 1]. At the week 24 LOCF analysis, benefits in 11 of the 12 NPI items were noted for donepezil, with significant differences observed for depression/dysphoria ($P = 0.0348$), anxiety ($P = 0.0380$), and apathy/indifference ($P = 0.0116$) compared with placebo. Nine of the 11 items showed improvement from baseline with donepezil and the other two items (agitation/aggression and irritability/lability) showed less decline for the donepezil-treated group than for the placebo group. In this analysis, donepezil had significant benefits over placebo for behavioral measures in a subgroup of patients with more severe AD.

Donepezil 5 mg plus perphenazine 8 mg (an antipsychotic) was compared with perphenazine 16 mg among patients with AD and psychotic symptoms [22]. The addition of donepezil to perphenazine improved symptoms of delusions/hallucinations over perphenazine alone (Positive and Negative Symptoms Scale, $P = 0.006$; Clinical Global Impression scale, $P = 0.028$) [Table 1].

Meta-analysis of ChEIs for NPS

Campbell et al. [37] performed a meta-analysis of nine randomized controlled trials (RCTs) to evaluate the effects of ChEIs (donepezil, rivastigmine, and galantamine) on NPS in patients with AD. Compared with placebo, ChEIs had beneficial effects on NPS, with standard and weighted mean differences in NPI points of −0.10 and −1.38, respectively (Table 1). Overall, ChEIs led to a statistically significant reduction in NPS among patients with mild to severe AD ($P = 0.003$). The standard mean differences in each ChEI compared with placebo were donepezil (six studies): −1.76 (95% CI, −3.37 to −0.15); galantamine (two studies), −1.65 (95% CI: −3.10 to −0.19); and rivastigmine (one study): −0.55 (95% CI, −2.31 to 1.21).

Tan et al. [38] evaluated the efficacy and safety of the three ChEIs (donepezil, galantamine, and rivastigmine) and memantine for the treatment of AD in 11 studies. This analysis found behavioral benefits only for donepezil 10 mg (−2.72 [95% CI, −4.92 to −0.52]) and galantamine 24 mg (−1.72 [95% CI, −3.12 to −0.33]).

Di Santo et al. [39] performed a meta-analysis on the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of AD. Of 40 RCTs included in the analysis, 18 involved behavioral outcomes. Although the results for donepezil lacked homogeneity, the overall composite size effects were significant for donepezil, galantamine, and memantine at −0.17, −0.14, and −0.21, respectively, but not for rivastigmine. There were fewer studies available for galantamine and rivastigmine than for donepezil; the overall results for the ChEIs may have been primarily attributable to donepezil.

One meta-analysis included four trials that directly compared donepezil with galantamine and rivastigmine (three open-label trials and one RCT) [40]. Adjusted indirect comparison did not find significant differences between the drugs for cognition, but the relative risk for global response was better with donepezil and with rivastigmine than with galantamine, and the effect of donepezil was better than that of galantamine for change in behavior (none of the rivastigmine trials included in the analysis assessed behavior). The pooled weighted mean difference in NPI score versus placebo for donepezil was −4.3 (95% CI, −5.95 to −2.65) and for galantamine was −1.44 (95% CI, −2.39 to −0.48).

Donepezil in Real-world Settings

Several RCTs have shown the benefits of donepezil for NPS in a clinical trial environment. Studies also support the efficacy of donepezil in real-world settings.

Patients with dementia who live in nursing homes are generally older, exhibit greater dementia severity and NPS and have more

Table 1 Trials of donepezil for NPS of AD

Study/design	Patients	AD/NPS severity	Intervention	Duration	Results
Mega et al. 1999 [33] Open-label	86	AD/NPI-10 scores varied	Donepezil 5 mg for 4 weeks and 10 mg for 4 weeks	8 weeks	Responders had worse baseline symptoms than nonresponders for: Delusions ($P = 0.04$); agitation ($P = 0.04$); depression ($P = 0.006$); anxiety ($P = 0.02$); apathy ($P = 0.003$); disinhibition ($P = 0.02$); irritability ($P < 0.001$) Symptoms that worsened for nonresponders and improved for responders: Delusions: $P = 0.003$ for nonresponders; $P = 0.004$ for responders Agitation: $P = 0.01$ for both nonresponders and responders Anxiety: $P = 0.006$ for nonresponders; $P = 0.004$ for responders Disinhibition: $P = 0.02$ for nonresponders; $P = 0.05$ for responders Irritability: $P = 0.003$ for nonresponders; $P = 0.001$ for responders
Holmes et al. 2004 [34] Randomized withdrawal study	134	Mild–moderate AD/NPI >11 points	Donepezil 5 mg titrated to 10 mg Placebo	Open label: 12 weeks Randomized: 6–12 weeks	Open-label phase: NPI-Total: 22 versus 13 points (ITT-LOCF $P < 0.0001$) NPI-Distress: 13.5 versus 7.9 points (ITT-LOCF $P < 0.0001$) Randomized phase: NPI-Total: mean change, −2.9 versus 3.3 (ITT-LOCF $P = 0.02$) NPI-Distress: median change, −2.0 versus 1.0 (ITT-LOCF $P = 0.01$)
Cummings et al. 2006 [32] Open-label (subanalysis)	120	Severe behavioral disturbances: NPI-Total >5 Severity score ≥2 in ≥2 domains of the 12-item NPI MMSE 8–23	Donepezil 5 or 10 mg	20 weeks	NPI-10: baseline 26.7 to week 20, −7.2 ($P < 0.001$) NPI-12: base line 31.4 to week 20, −8.2 ($P < 0.001$) Cohen-Mansfield Agitation Inventory–Community: Physically nonaggressive: baseline 15.1 to week 20, −2.8 ($P < 0.001$) Physically aggressive: baseline 1.6 to week 20, 0.0 (NS) Verbally nonaggressive: baseline 8.0 to week 20, −1.1 ($P < 0.05$) Verbally aggressive: baseline 4.5 to week 20, −0.1 (NS) Behavior Pathology in Alzheimer's Disease ITT-OC: mean change, −1.1 ($P < 0.005$)
Feldman et al. 2005 [36] RCT (subanalysis)	290	Moderate–severe AD (standardized MMSE score 5–17)	Donepezil 5 mg titrated to 10 mg Placebo	24 weeks	NPI: LS mean difference 6.86 LOCF ($P = 0.0062$) Significant differences for: Depression/dysphoria ($P = 0.0348$) Anxiety ($P = 0.0380$) Apathy/indifference ($P = 0.0116$)
Bergman et al. 2003 [22] Randomized	12			4 weeks	Improved symptoms of delusions/hallucinations compared with perphenazine alone on:

(continued)

Table 1 (Continued)

Study/design	Patients	AD/NPS severity	Intervention	Duration	Results
		Inpatients with AD with psychotic symptoms not responding to perphenazine	Donepezil 5 mg plus perphenazine 8 mg Perphenazine 16 mg		Positive and Negative Symptoms Scale ($P = 0.006$) CGI scale ($P = 0.028$)
Campbell et al. 2008 [37] Meta-analysis	9 RCTs	Mild–severe AD	Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) Placebo		NPI (all patients): Standard mean difference −0.10 (95% CI, −0.18 to −0.01) Weighted mean difference −1.38 (95% CI, −2.30 to −0.46) NPI (mild AD): Weighted mean difference −1.92 (95% CI, −3.18 to −0.66) NPI (mild-moderate AD): Standard mean difference −0.16 (95% CI, −0.28, −0.03) Weighted mean difference −1.92 (95% CI, −3.18, −0.66) NPI (moderate-severe AD): Standard mean difference −0.06 (95% CI, −0.17, 0.05) Weighted mean difference −0.77 (95% CI, −2.12, 0.57) NPI (severe AD): Weighted mean difference −0.06 (95% CI, −2.12 to 0.57)

AD, Alzheimer's disease; CGI, Clinical Global Impression; CI, confidence interval; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; NS, not significant; OC, observed cases; RCT, randomized controlled trial.

comorbidities than community-dwelling patients. A 24-week RCT evaluated the efficacy of donepezil 10 mg in the treatment of 208 patients with AD (mean MMSE score, 14.4; range, 5–26) in 27 nursing homes across the USA (Table 2) [41]. The primary endpoint of mean NPI-Nursing Home Version 12-item total scores improved from baseline for both the donepezil and placebo groups, with no significant differences. The secondary endpoint of categorical changes in behavior showed a significant difference for agitation/aggression in favor of donepezil ($P = 0.0442$). Rates of adverse events (AEs) were similar between the two groups (97% placebo, 96% donepezil); gastrointestinal AEs occurred more frequently in donepezil-treated patients. Most AEs were transient and mild or moderate in severity.

To ascertain whether community-dwelling patients with AD can benefit from donepezil, Carrasco et al. [27] evaluated the prevalence and treatment responsiveness of NPS in patients with mild to moderately severe AD in a community setting in Spain. After treatment with donepezil 10 mg for 18–20 weeks, NPI scores improved from a mean baseline score of 19.1–10.3 ($P < 0.0001$) [Table 2]. Donepezil was considered to be very well or well tolerated in 91.3% of patients by physicians and in 89.8% by caregivers. Overall, there was a low incidence of AEs (n = 65%; 12.3%), with the most frequent being diarrhea and agitation. Donepezil was observed to reduce caregiver burden.

Paleacu et al. [30] evaluated the effects of donepezil 5–10 mg as monotherapy for 28 AD patients with NPS treated at a health center in Israel for 6 months. The mean dose of donepezil was 9.10 mg/day. Twenty-four patients completed the study, five of whom needed rescue antipsychotic treatment due to incomplete response. The overall NPI score improved significantly ($P = 0.008$). When compared with patients who completed the study, the patients who discontinued had higher mean NPI scores on the irritability and agitation subscales at baseline [Table 2]. Patients completing the study had significant reductions in delusions ($P = 0.05$), hallucinations ($P = 0.01$), and agitation ($P = 0.08$). Donepezil reduced the severity of NPS in these patients reducing the likelihood that they would need psychotropic drugs.

Overall, donepezil is well tolerated, with most adverse events being cholinergic in nature and mild or moderate in severity [42]. Adverse events tend to be transient, occurring most often during the early treatment period [43,44]. Side effects tend to be dose related [45] and dose titration can be a useful strategy for minimizing adverse effects.

Treatment for DLB

DLB—most commonly a form of AD with both amyloid and Lewy body pathology—is strongly associated with NPS. Common features include fluctuating cognition, hallucinations, and delusions. However, treatment is difficult because of the risk for exacerbation of parkinsonism by antipsychotic agents [46]. In 2014, donepezil was approved for treatment of DLB in Japan, making it the first pharmacological agent to be approved for DLB [47].

Donepezil 3, 5, and 10 mg has been compared with placebo in 140 patients with DLB [46]. Using the NPI-plus (a 12-item NPI, with the addition to the 10-item NPI of "sleep" and "cognitive

Table 2 Studies of donepezil for NPS of AD in the real-world setting

Study/design	Patients	AD/NPS severity	Intervention(s)	Duration	Results
Tariot et al. 2001 [41] RCT	208 in 27 nursing homes	AD (MMSE score 14.4)	Donepezil 10 mg Placebo	24-week	Improvements in: NPI-NH 12-item total scores for both groups (NS) Categorical change in behavior for agitation/aggression: 45% donepezil, 28% placebo ($P = 0.0442$)
Carrasco et al. 2011 [27] Community setting	529	Mild to moderately severe AD/NPS	Donepezil 5 mg titrated to 10 mg	Up to 24 weeks	Improvements in: NPI scores by 34.4% (−8.81; 95% CI: −7.61 to −10.01) from 19.1 to 10.3 ($P < 0.0001$)
Paleacu et al. 2002 [30] (Health center)	28	AD/NPS	Donepezil 5 mg titrated to 10 mg	6 months	Improvements in: NPI score from 33.4 to 21.2 points ($P = 0.008$) Compared with completer patients, patients who discontinued had higher mean NPI scores for irritability (5.75 versus 2.80) and agitation (7.75 versus 3.75) Completer patients had reductions in: Delusions ($P = 0.05$) Hallucinations ($P = 0.01$) Agitation ($P = 0.08$)

AD, Alzheimer's disease; CI, confidence interval; MMSE, Mini Mental State Examination; NPI, neuropsychiatric inventory; NPI-NH, NPI-Nursing Home Version; NPS, neuropsychiatric symptoms; NS, not significant.

fluctuation" for DLB), NPI subscores for hallucinations and cognitive fluctuation (NPI-2), and for delusions, hallucinations, apathy, and depression (NPI-4) were significantly improved at the final evaluation with donepezil 10 mg compared with placebo ($P < 0.001$), and scores for hallucinations and cognitive fluctuation were significantly improved in the donepezil 5 mg group ($P < 0.001$), although the difference for the NPI-10 was not significant. There was a dose-dependent improvement for hallucinations and cognitive fluctuation ($P = 0.036$). For the NPI-12, the domains of delusion, hallucinations, and cognitive fluctuation improved in all treatment groups and worsened in the placebo group (5 mg, $P = 0.012$, 0.014, and 0.004; 10 mg, $P = 0.002$, <0.001, and <0.001, respectively, compared with placebo).

A 52-week open label extension study found that the improvement in NPS with donepezil continued throughout the study period, despite an interim washout period (≤8 weeks) [48]. However, deterioration was more likely for patients with a longer washout period (≥2 weeks).

A recent phase 3 study of 142 patients with DLB found improvements in NPI-2 (hallucinations and cognitive fluctuation) scores for donepezil 10 mg and 5 mg compared with baseline (−2.8 and −1.8, respectively), but these changes were not significantly different from placebo (−2.1) [49].

In patients with DLB and visual hallucinations treated with donepezil 5 mg, increasing the dose of donepezil to 10 mg can be effective for managing relapse after initial treatment at the lower dose. [50] An open label study of 24 patients with DLB who had relapse of NPS after treatment with donepezil 5 mg found that NPI scores improved significantly for six of 10 behaviors after a dose increase to donepezil 10 mg. Importantly, visual hallucinations were significantly improved at weeks 2 (mean score, 2.80; $P < 0.0001$) and 4 (mean score 2.85; $P < 0.0001$) from baseline (mean score, 8.23) [51].

Economic Evaluation

NPS in AD are one of the main causes of the decision to move a patient to residential care, a major cost of AD. [52] A study from Israel assessed the cost of NPS in AD in community-dwelling patients [52]. The total annual cost of AD was $14 420 (indirect cost of $10 520 and direct cost of $3900), of which approximately 30% ($4115) was for management of NPS (25% of the indirect costs of AD and 35% of the direct costs).

Murman et al. [53] found an annual increase of $247–409 in direct costs for each NPI score increase of 1 point in patients with AD. Payments for services (physician visits, home care) were $3162–5919 higher for patients with high NPI scores than for those with low NPI scores and total costs (including unpaid caregiving) were $10 670–16 141 higher.

While it is difficult to compare data across countries with different healthcare systems, a German study found that donepezil was cost-effective for treating patients with mild to moderately severe AD when compared with no treatment [54]. Donepezil increased the time that patients had MMSE scores >10 and NPI scores <28. Donepezil was also cost-effective compared with memantine for patients with moderate to moderately severe AD, although the savings were lower than for no treatment.

Conclusion

Cholinergic deficiency contributes to the behavioral and cognitive changes in AD. Donepezil has been found to be effective for treatment of the NPS of AD and DLB, both in RCTs and in real-world settings. Economic evaluation shows donepezil to be cost-effective for treatment of NPS in AD.

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Conflict of Interest

The authors have not published or submitted the manuscript elsewhere.

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