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# Impact of DL-3-n-Butylphthalide on Progression in Alzheimer's Disease: A Retrospective Cohort Analysis

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**Objective:** To evaluate the efficacy of DL-3-n-butylphthalide (NBP), a synthetic compound that has shown neuroprotective effects, on cognitive function, psychiatric–behavioral symptoms, and daily activities in patients with Alzheimer's disease (AD).

**Methods:** This retrospective cohort study included patients with AD treated with or without NBP. Disease deterioration and decline were defined by changes in Clinical Dementia Rating–Sum of Boxes (CDR-SB) over six months. Multivariate logistic regression, inverse probability of treatment weighting (IPTW) and overlap-weighted propensity score matching (PSM) were used to adjust for confounding.

**Results:** Totally 100 were included in this study, with 39 classified as the NBP group and 61 as the non-NBP group. NBP was associated with lower odds of deterioration (adjusted odds ratio [OR] = 0.19, 95% confidence interval [CI]: 0.04–0.88, $p = 0.034$) and decline (adjusted OR = 0.10, 95% CI: 0.03–0.49, $p = 0.001$). In IPTW and PSM analyses, deterioration occurred in 4.31% vs 22.10% and 4.06% vs 24.27%, and decline in 4.31% vs 39.38% and 4.06% vs 44.28% for the NBP and non-NBP groups, respectively.

**Conclusion:** NBP was associated with reduced risks of clinical worsening and helped preserve cognitive and behavioral functions in patients with AD. These results highlight the potential of NBP as a promising therapeutic option in AD management. Future randomized controlled trials are necessary to validate these findings and assess the long-term efficacy of NBP in clinical settings.

**Significance:** This real-world study suggests that NBP may slow disease progression and preserve cognitive and behavioral function in AD.

**Keywords:** Alzheimer's disease, cognitive impairment, DL-3-n-butylphthalide, CDR-SB

## Introduction

Dementia is characterized by a profound decline in cognitive function, behavioral and psychological symptoms, and a marked impairment in daily life abilities,[1] in which Alzheimer's disease (AD) stands as the most prevalent form in the elderly,[2] constituting 50% to 70% of all cases.[3,4] Currently, 55.2 million people are living with dementia worldwide,[5] a figure expected to reach approximately 139 million by 2050.[6] Among the Group of Twenty (G20) members, China carries the highest burden of Alzheimer's disease and other dementias (ADOD).[7] The prevalence of AD is steadily increasing, posing a significant threat to the health and quality of life of elderly individuals, with mortality risk continuously rising, thereby placing a substantial burden on families and society.[2,8] However, unfortunately, the current

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clinical treatments for AD primarily involve symptomatic therapeutic agents, such as cognitive enhancers targeting neurotransmitters and medications aimed at alleviating neuropsychiatric symptoms.[9] These medications can partially manage the symptoms in AD patients but do not affect the pathological progression of the disease.[9]

The pathogenesis and pathological mechanisms of AD are highly complex, involving abnormal amyloid-beta deposition,[10,11] hyperphosphorylation of tau protein,[10,11] cholinergic dysfunction,[12] genetic abnormalities,[13] neuroinflammation,[14,15] neuronal excitotoxicity,[16] mitochondrial damage,[17] brain-gut-microbiota axis,[18] blood-brain barrier impairment,[19] and vascular dysfunctions.[20] Medications developed for a single target (such as acetylcholinesterase inhibitors and NMDA receptor antagonists) in the mechanism achieve limited clinical efficacy, more adverse effects, and a failure to improve the course of the disease fundamentally.[21,22] Studies have shown that these drugs can only temporarily improve clinical symptoms and have limited effectiveness, especially in the late stages of the disease.[23,24] The treatment model of "single compound, single target" has failed in the treatment of Alzheimer's disease. Therefore, focusing on the complexity of the above pathophysiological mechanisms, multi-target therapy is an exploratory direction in dementia treatment.[22,25]

DL-3-n-Butylphthalide (NBP) is a synthetically derived chiral compound modeled on L-3-n-butylphthalide, which was first isolated from *Apium graveolens* seeds in 1978,[26] and approved by the Food and Drug Administration (FDA).[27] Preclinical studies have demonstrated that NBP exerts multiple neuroprotective effects by synergistically suppressing inflammation and oxidative stress,[28] protecting microvasculature and maintaining the integrity of the blood-brain barrier,[29] reducing hippocampal neuronal apoptosis,[30] and decreasing tau phosphorylation and kinase activation,[31] with clinical studies showing cognitive benefits in patients with vascular cognitive impairment (VCI),[26] and those with ischemic stroke.[32] Building on the findings, NBP, with its multi-target mechanisms of action and the potential to intervene in key pathways implicated in AD pathogenesis, holds significant promise as a neuroprotective agent for therapeutic benefits in AD.[33,34] We hypothesized that NBP may reduce the risk of disease deterioration and disease decline. Therefore, the objective of our study was to evaluate the therapeutic efficacy of NBP in individuals with cognitive impairment due to AD, either as monotherapy or in combination with other cognitive enhancers.

# Methods

## Study Design and Data Retrieve

This study is a retrospective cohort analysis. Data from AD patients who visited the Neurology Memory Clinic of The First Affiliated Hospital of Kunming Medical University between January 2019 and December 2022 were consecutively included. All relevant data were retrieved from the Hospital's Medicine Information Database. This is an electronic health record (EHR) system that systematically collects and stores patient data for clinical and research purposes. For this study, we extracted relevant data elements, including demographic characteristics (eg, age, sex), medical history, laboratory test results, medication prescriptions, and treatment regimens. These data were retrieved through structured queries designed to ensure accuracy and completeness in alignment with the study objectives. The study was conducted in strict accordance with relevant guidelines and regulations to ensure data security and patient privacy.[35,36]

## Participants

All the patients fulfilled the criteria for probable AD according to the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA) 2011 version.[37,38] The diagnosis was predominantly established using a comprehensive clinical history provided by caregivers, neuropsychological assessments (Montreal Cognitive Assessment and Clinical Dementia Rating, etc)., brain magnetic resonance imaging (MRI) including T1-weighted images for anatomical assessment, T2-weighted and FLAIR images for detecting structural abnormalities, and blood tests (complete blood count, thyroid function tests, vitamin B12 levels, HIV, TPPA, etc.) for differential diagnosis.

The inclusion criteria were: (1) 18 or above years old; (2) With a chief complaint of memory loss and a gradual onset developing over months to years; (3) Fulfilled the NIA-AA 2011 criteria for probable AD;[37,38] (4) Patients with Clinical Dementia Rating - Global Score (CDR-GS) $\geq$ 0.5; (5) showing no evident abnormalities during the neurological examination; (6) The total score on the Hachinski Ischemic Scale (HIS)[39] is $\leq$4 points; (7) Brain MRI scan indicating

a medial temporal lobe atrophy[40] and a Fazekas scale[41] score of ≤2; (8) Dependable and consistent caregivers, capable of being reached regularly (a minimum of once every three months, completed all follow-up scale; (9) Clinical Dementia Rating Scale (CDR) and Montreal Cognitive Assessment Scale (MoCA) assessments were conducted at baseline and after six months of treatment; (10) At the time of the final neuropsychological assessment following six months of treatment, each patient had consistently been receiving the same medication and dosage.

Exclusion criteria were: (1) Suffering from severe systemic disease(s); (2) Severe physical conditions leading to an inability to cooperate in completing neuropsychological assessments; (3) Any kinds of haemorrhagic disorders within the cranial region, as visualized in cranial CT/MRI imaging; (4) Underwent non-pharmacological treatment for cognitive function or behavioral and psychological symptoms of dementia (BPSD) involved cognitive rehabilitation, cognitive training, psychosocial interventions, behavioral interventions, or environmental interventions; (5) Presence of any malignant tumors or ongoing anti-neoplastic therapy; (6) Participated in any other prospective or cross-sectional studies within nine months prior to the study's end date; (7) Did not complete the 6 month treatment; (8) Did not maintain the same treatment strategy over 6 month period; (9) Psychiatric disorders such as schizophrenia, bipolar disorders, major depression disorders, anxiety disorders, post-traumatic stress disorders, obsessive-compulsive disorders, borderline personality disorders, etc.

All the above conditions were diagnosed by licensed physicians and documented in relevant medical records, regardless of whether they were active or not.

## Pharmacologic Management

Patients who received treatment with NBP either alone or in combination with one or more pharmacologic therapies for AD, such as Donepezil, and Memantine, were categorized as the NBP group. Patients who received one or more cognitive-enhancing medications, including Donepezil and/or Memantine, without NBP were categorized as the non-NBP group.

Each cognitive-enhancing medication was administered at the following oral doses: NBP 100 mg three times daily as monotherapy, Donepezil 5 mg daily, and/or Memantine 20 mg daily. All treatment regimens were maintained for six months, with dosages kept consistent across all patients to ensure the validity of the findings.

## Study Endpoints and Neuropsychological Assessment

The primary endpoints were the proposition of disease deterioration and disease decline between the two groups measured by the change of CDR-Sum of Boxes (CDR-SB). The CDR is used for dementia severity grading and follow-up, which evaluates six areas of cognition (memory, orientation, judgment, problem-solving abilities, community affairs, home and hobbies, and personal care),[42] CDR-SB is a scoring method that scored 0–18 scores with higher scores indicating more significant impairment.[43]

Disease deterioration was defined as a change in CDR-SB score of ≥ 0.98 for MCI, ≥ 1.63 for mild AD, and ≥2.30 for moderate to severe AD.[44] Disease decline was defined as a change in CDR-SB score of ≥ 0.5 for MCI and ≥ 1.0 for AD.[45]

Secondary endpoints were the change of CDR-SB and change of MoCA,[46] Neuropsychiatric Inventory (NPI)[47] and AD cooperative study - activities of daily living (ADCS-ADL)[48] from the baseline to the end of 6 months. The MoCA can assess seven cognitive fields, including executive, naming, attention, language, abstraction, memory and delayed recall, and orientation, with scores ranging from 0 to 30, and a score of < 23 is considered to be cognitively impaired.[49–52] The MoCA scale score was corrected for the subject's education level, and those with ≤12 years were added to the total score by 1 point (the score should not exceed 30 points), and the score was the MoCA scale corrected score.[53] The NPI consists of 10 items on behavior and two on the autonomic nervous system. The total score ranges from 0 to 144, with the higher scores representing more severe damage. The ADCS-ADL is a standardized questionnaire composed of 23 items that assess the actual performance of specific actions and behaviors observed by the caregivers in the past four weeks. Scores range from 0 to 54; the lower the score, the more severe the dysfunction.

To ensure the authenticity and reliability of all assessments, all scales are administered by neurologists who have received uniform training.

The above scales were assessed prior to the medication being initialed and at the end of the six-month administration. Safety evaluation indicators included vital signs changes and subjective reports of adverse events in the course of drug administration.

For detailed information on the scales mentioned above and safety evaluation, please refer to Appendix.

## Statistical Analysis

### Descriptive Statistics and Univariate Testing

The analysis presented continuous variables as the mean with standard deviation (SD) for normally distributed data or as the median with interquartile range (IQR) presented as the 1st quartile to the 3rd quartile (Q1-Q3) for non-normally distributed data. The Student's *t*-test was applied for normally distributed data, while the Mann–Whitney test was employed for data with non-normal distributions. Categorical variables were represented as counts and percentages. The statistical significance of categorical variables was assessed using Pearson's chi-square test or Fisher's exact test.

### Analyses of the Primary Endpoints

Multivariate logistic regression was conducted to evaluate the two treatment groups concerning the primary endpoints. Based on established statistical suggestions[54,55] variables with a univariate analysis *p*-value of <0.1 were included in the multivariate logistic regression model to avoid potential omission of relevant predictors. Those variates with clinical meanings related to the primary endpoint were adjusted, ignoring the *p* - value. Baseline CDR-SB and MoCA scores were included in all models as clinically relevant covariates to adjust for baseline disease severity. The results were expressed as adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs).

The propensity data set generated the Inverse Probability of Treatment Weighting (IPTW) dataset were used as sensitivity analysis on the primary endpoints. To balance those observable characteristics, each patient was weighted by the inverse probability of being in the NBP group to compare to the non-NBP group. Overlap-Weighted Propensity Score Matching (PSM) was a propensity score method developed to emulate essential features of clinical studies. It assigned weights to patients according to their probability of belonging to each treatment group, thereby including all patients and achieving an exact balance in the mean of all covariates within the model.[56]

### Hochberg Multiple Testing Procedure

To control the family-wise error rate at 0.05, the Hochberg multiple test procedure[57] was used and described as follows:

1. Starts by examining the largest *p*-value $P_{(m)}$. If $P_{(m)} \leq \alpha$, all null hypotheses are rejected.
2. If not, then the null hypothesis of $H_{(m)}$ cannot be rejected, and one goes on to compare $P_{(m-1)}$ with 50% of $\alpha$. If smaller, then all null hypotheses of $H_{(i)}$ (i=m - l., l) are rejected.
3. If not, then H(m) cannot be rejected, and one proceeds to compare $P_{(m-2)}$ with one-third of $\alpha$...etc.

### Analysis of Secondary Endpoints

The changes in CDR-SB and MoCA were assessed using a linear regression model. Variables with a univariate analysis p-value <0.1 were included in the multivariate linear regression. Comparisons between the two groups for other variables were conducted using the *t*-test or Mann–Whitney *U*-test, and the chi-square test or Fisher's exact test, as appropriate. All reported p-values for the secondary endpoints are nominal and should not be considered as statistical inference.

### Sample Size Calculation

The sample size calculation was conducted using a significance level of 0.05 and a power of 0.8. Based on our clinical experience, the disease deterioration rate was assumed to be 3.5% in the NBP group and 30% in the non-NBP group, and 30 samples were needed in each group. The disease decline rate was assumed to be 7% in the NBP group, and 40% in the non-NBP group, and 31 samples were needed in each group.

### Statistical Software

Stata SE 13 (Serial number 401306302851), R software version 4.2.0 (http://cran.r-project.org/), and easy-R (www.empowerstats.com) were used for statistical analysis. GraphPad 10.1.2 was used to generate figures.

For further information, please check the Statistical section in Appendix.

# Results

## Study Participants

A total of 100 patients' data met the inclusion criteria and were enrolled in our study, with 39 classified as the NBP group and 61 as the non-NBP group (Figure 1).

## Demographic and Baseline Characters of All the Participants

In the original dataset, the proportion of females was 67.21% in the non-NBP group and 41.03% in the NBP group ($p$ =0.010). Smoking prevalence was 16.39% in the non-NBP group and 33.33% in the NBP group ($p$ =0.050). There were no significant differences observed across age, education, nature of work, night sleep duration, hypertension, diabetes, hyperlipidemia, stroke, trauma, alcohol consumption, baseline MoCA, and CDR-SB scores. In the IPTW and Overlap-Weighted datasets, no variables exhibited significant differences, reflecting the successful adjustment of baseline characteristics (Table 1). The usage of intelligence-enhancers and Apolipoprotein E (APOE) statuses are listed in sTables 1 and 2 in the Appendix.

## The Analysis of the Primary Endpoint

### Disease Deterioration

Disease deterioration was observed in 11 participants (18.03%) in the non-NBP group and 3 participants (7.69%) in the NBP group (sTable 2 in the Appendix). In the univariate logistic analysis for clinical deterioration, education exceeding nine years demonstrated a significant association with increased risk, with an odds ratio of 3.64 (95% CI: 1.06 to 12.55) and a $p$-value of 0.041. However, this association lost significance in the multivariate model (OR=3.04, 95% CI: 0.55 to 16.73, $p$ =0.200). Notably, using NBP was significantly associated with a reduced risk of disease deterioration in the multivariate analysis, with an odds ratio of 0.19 (95% CI: 0.04 to 0.88) and a $p$-value of 0.034. Other variables, including sex, age, and baseline cognitive assessments, exhibited no significant associations, with $p$ -values exceeding 0.05 (Table 2).

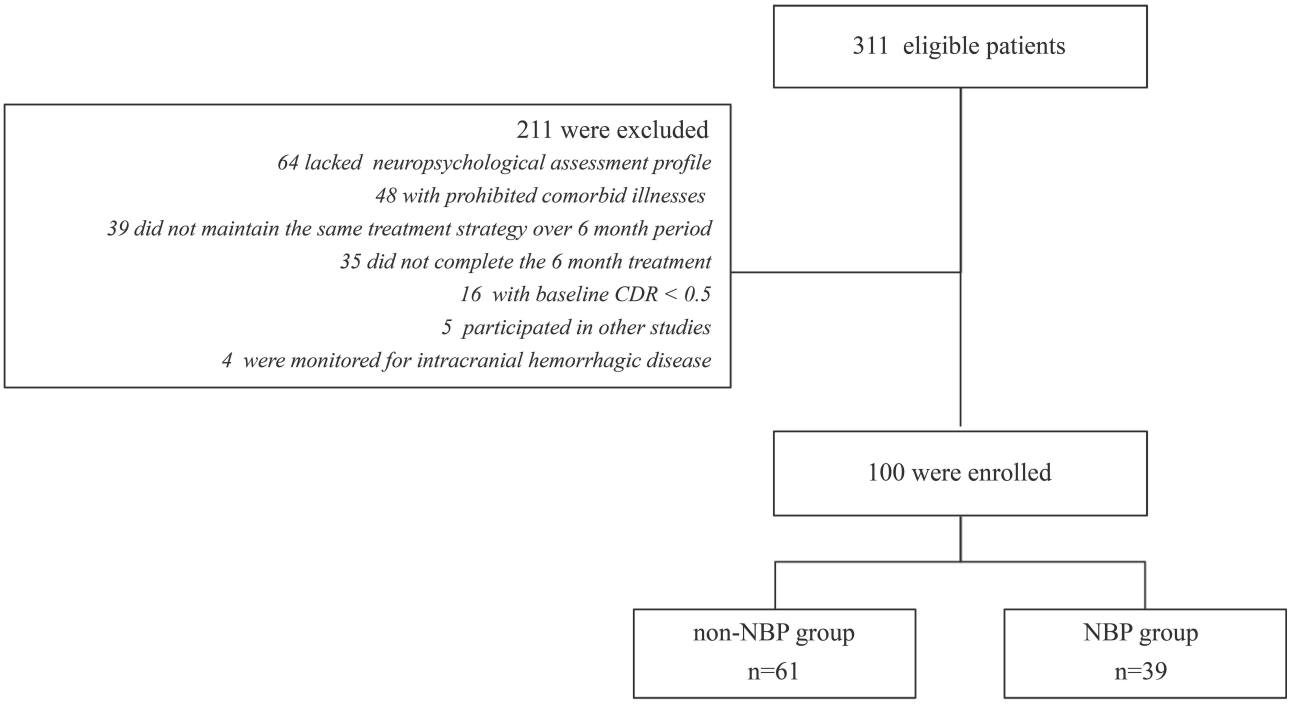


**Figure 1** Flow Diagram of Screening and Enrollment of AD Patients' Data.

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**Table 1** Demographic and Baseline Characteristics of All the Participants

| | Original Dataset | | | | IPTW Dataset | | | | Overlap-Weighted PSM Dataset | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Non-NBP (n=61)** | **NBP (n=39)** | **Statistics** | **p-value** | **Non-NBP (n=97.03)** | **NBP (n=91.76)** | **p-value** | **SMD** | **non-NBP (n=17.7)** | **NBP (n=17.7)** | **p-value** | **SMD** |
| Sex (female) [n (%)] | 41 (67.21) | 16 (41.03) | $\chi^2$ = 6.66 | 0.010 | 59.7 (61.57) | 50 (54.46) | 0.531 | 0.144 | 10.0 (56.31) | 10.0 (56.31) | >0.999 | <0.001 |
| Age [mean (SD)] | 72.46 (12.16) | 72.33 (9.37) | t = 0.055 | 0.956 | 72 (12.24) | 71.8 (9.19) | 0.940 | 0.017 | 72.0 (12.45) | 72.0 (8.84) | >0.999 | <0.001 |
| Education (year) [median (Q1-Q3)] | 9 (6, 12) | 11(8.5, 13.5) | z = −0.983 | 0.325 | 9.0 (6, 15) | 9.0 (7.23, 15) | 0.742 | 0.078 | 10.4 (4.57) | 10.4 (4.38) | >0.999 | <0.001 |
| Nature of work (mental) [n (%)] | 32 (52.46) | 25 (64.10) | $\chi^2$ = 1.316 | 0.251 | 56.8 (58.51) | 54.0 (58.90) | 0.973 | 0.008 | 10.7 (60.22) | 10.7 (60.22) | >0.999 | <0.001 |
| Night sleep (hours) [mean (SD)] | 7.44 (2.17) | 7.59 (1.64) | t = −0.362 | 0.718 | 7.5 (2.05) | 7.5 (1.49) | 0.951 | 0.012 | 7.4 (2.05) | 7.4 (1.49) | >0.999 | <0.001 |
| Hypertension [n (%)] | 27 (44.26) | 19 (48.72) | $\chi^2$ = 0.190 | 0.663 | 49.3 (50.78) | 49.4 (53.78) | 0.792 | 0.060 | 9.2 (51.83) | 9.2 (51.83) | >0.999 | <0.001 |
| Diabetes [n (%)] | 10 (16.39) | 9 (23.08) | $\chi^2$ = 0.691 | 0.406 | 14.9 (15.37) | 15.9 (17.29) | 0.802 | 0.052 | 2.9 (16.24) | 2.9 (16.24) | >0.999 | <0.001 |
| Hyperlipemia [n (%)] | 15 (24.59) | 10 (25.64) | $\chi^2$ = 0.014 | 0.906 | 25.9 (26.70) | 25.1 (27.39) | 0.947 | 0.016 | 4.8 (26.78) | 4.8 (26.78) | >0.999 | <0.001 |
| Stroke [n (%)] | 9 (14.75) | 6 (15.38) | $\chi^2$ = 0.007 | 0.931 | 11.8 (12.16) | 11.6 (12.63) | 0.945 | 0.014 | 2.0 (11.50) | 2.0 (11.50) | >0.999 | <0.001 |
| Trauma [n (%)] | 2 (3.28) | 1 (2.56) | Fisher | 1.000 | 2.2 (2.26) | 1.2 (1.30) | 0.653 | 0.072 | 0.2 (0.93) | 0.2 (0.93) | >0.999 | <0.001 |
| Smoke [n (%)] | 10 (16.39) | 13 (33.33) | $\chi^2$ = 3.855 | 0.050 | 17.4 (17.96) | 19.6 (21.38) | 0.685 | 0.086 | 3.4 (19.30) | 3.4 (19.30) | >0.999 | <0.001 |
| Alcohol [n (%)] | 6 (9.84) | 6 (15.38) | $\chi^2$ = 0.694 | 0.405 | 11.3 (11.67) | 11.1 (12.05) | 0.958 | 0.012 | 2.2 (12.17) | 2.2 (12.17) | >0.999 | <0.001 |
| Cognitive impairment [n (%)] | | | | | | | | | | | | |
| MCI | 3 (4.92) | 3 (7.69) | Fisher | 0.176 | 6.1 (6.23) | 7.5 (8.15) | 0.880 | 0.117 | 1.5 (8.20) | 1.5 (8.20) | >0.999 | <0.001 |
| Mild AD | 26 (42.62) | 23 (58.97) | | | 45.9 (47.28) | 46.4 (50.58) | | | 9.0 (50.47) | 9.0 (50.47) | | |
| Moderate and Severe AD | 32 (52.46) | 13 (33.33) | | | 45.1 (46.49) | 37.9 (41.27) | | | 7.3 (41.33) | 7.3 (41.33) | | |
| Donepezil [n (%)] | 38 (62.30) | 25 (64.10) | $\chi^2$ = 0.033 | 0.855 | 59.8 (61.62) | 57.3 (62.40) | 0.944 | 0.016 | 11.1 (62.62) | 11.1 (62.62) | >0.999 | <0.001 |
| Memantine [n (%)] | 23 (37.70) | 12 (30.77) | $\chi^2$ = 0.503 | 0.478 | 37.5 (38.67) | 32.4 (35.31) | 0.771 | 0.070 | 6.0 (33.62) | 6.0 (33.62) | >0.999 | <0.001 |
| Baseline MoCA [median (Q1-Q3)] | 14(9, 18) | 12 (8.5, 15) | z = 1.348 | 0.178 | 13 (7, 18) | 13 (8.70, 16.33) | 0.823 | 0.016 | 13.3 (6.13) | 13.3 (5.82) | >0.999 | <0.001 |
| Baseline CDR-SB [median (Q1-Q3)] | 8 (4.5, 11) | 7 (4.5, 9.5) | z = 1.207 | 0.227 | 7 (4, 10.77) | 7 (4, 9.88) | 0.690 | 0.091 | 7.3 (3.77) | 7.3 (4.20) | >0.999 | <0.001 |
| APOE carriers | | | | | | | | | | | | |
| No | 30 (49.18%) | 26 (66.67%) | Fisher | 0.109 | 54.1 (55.80) | 60.7 (66.13) | 0.365 | 0.316 | 11.5 (64.76) | 11.5 (64.76) | >0.999 | <0.001 |
| Yes | 20 (32.79%) | 11 (28.21%) | | | 30.9 (31.83) | 27.1 (29.58) | | | 5.4 (30.25) | 5.4 (30.25) | | |
| Un-known | 11 (18.03%) | 2 (5.13%) | | | 12.0 (12.36) | 3.9 (4.30) | | | 0.9 (4.98) | 0.9 (4.98) | | |

**Abbreviations**: AD, Alzheimer's disease; APOE, Apolipoprotein E; CDR-SB, Clinical dementia rating scale-sum of boxes; IPTW, Inverse probability of treatment weighting; MCI, Mild cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide; PSM, Propensity matching scores; Q1, the 1st quartile; Q3, the 3rd quartile; SD, standard deviation; SMD, standard mean difference.

**Table 2** Univariate and Multivariate Logistic Regression Analysis of Disease Deterioration in the Original Dataset

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Sex (female) | 1.01 (0.32, 3.15) | 0.991 | | |
| Age (>60) | 1.48 (0.30, 7.24) | 0.630 | | |
| Education (more than 9 years) | 3.64 (1.06, 12.55) | 0.041 | 3.04 (0.55, 16.73) | 0.200 |
| Nature of work (mental) | 3.19 (0.83, 12.24) | 0.091 | 2.30 (0.36, 14.73) | 0.380 |
| Sleeping length (more than 9 hour) | 0.75 (0.09, 6.50) | 0.794 | | |
| Hypertension | 1.21 (0.39, 3.73) | 0.746 | | |
| Diabetes | 1.19 (0.30, 4.78) | 0.803 | | |
| Hyperlipidemia | 0.20 (0.02, 1.60) | 0.129 | | |
| Stroke | 0.40 (0.05, 3.27) | 0.390 | | |
| Trauma | 3.23 (0.27, 38.22) | 0.352 | | |
| Smoke | 0.90 (0.23, 3.55) | 0.880 | | |
| Alcohol | 0.52 (0.06, 4.41) | 0.553 | | |
| Cognitive impairment severity (MCI as ref.) | | | | |
| Mild AD | 0.83 (0.08, 8.24) | 0.876 | | |
| Moderate and Severe AD | 0.77 (0.08, 7.77) | 0.824 | | |
| Donepezil | 1.07 (0.33, 3.46) | 0.914 | | |
| Memantine | 1.04 (0.32, 3.37) | 0.952 | | |
| NBP | 0.38 (0.10, 1.46) | 0.158 | 0.19 (0.04, 0.88) | 0.034 |
| Baseline MoCA score | 0.98 (0.89, 1.08) | 0.669 | 0.91 (0.79, 1.05) | 0.216 |
| Baseline CDR-SB | 1.01 (0.88, 1.17) | 0.840 | 0.94 (0.75, 1.18) | 0.596 |
| APOE Carriers (no is ref.) | | | | |
| Yes | 1.00 (0.30, 3.31) | 0.994 | 1.07 (0.28, 4.14) | 0.922 |
| Un-known | 0.00 (0.00, Inf) | 0.993 | 1.00 (Not Available) | |

**Abbreviations**: AD, Alzheimer's disease; APOE, Apolipoprotein E; CDR-SB, Clinical dementia rating scale-sum of boxes; CI, confidence interval; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide; OR, odds ratio.

Sensitivity analysis on disease deterioration was performed in the IPTW and Overlap-Weighted PSM Datasets. In the IPTW dataset, the NBP group exhibited a significantly lower rate of disease deterioration (4.31%) compared to the non-NBP group (22.10%), with a *p*-value of 0.005. Similarly, in the Overlap-Weighted dataset, the disease deterioration rate was significantly reduced in the NBP group (4.06%) relative to the non-NBP group (24.27%), with a *p*-value of 0.002 (Table 3).

**Table 3** Analysis of Disease Deterioration in the IPTW and Overlap-Weighted PSM Datasets

| | IPTW Dataset | | | Overlap Weighted PSM Dataset | | |
|---|---|---|---|---|---|---|
| | **Non-NBP (n=94.4)** | **NBP (n=103.3)** | **p-value** | **Non-NBP (n=17.4)** | **NBP (n=17.4)** | **p-value** |
| Number of Disease Deterioration | 21.44 (22.10%) | 3.95 (4.31%) | 0.005 | 4.30 (24.27%) | 0.72 (4.06%) | 0.002 |

**Abbreviations**: CDR-SB, Clinical dementia rating scale-sum of boxes; IPTW, Inverse probability of treatment weighting; NBP, DL-3-n-Butylphthalide; PSM, Propensity matching scores.

## Disease Decline

Disease decline was observed in 22 participants (36.07%) in the non-NBP group and 3 participants (7.69%) in the NBP group (sTable 2 in the Appendix). In the analysis of disease decline, the univariate logistic model identified a significant association between NBP use and reduced risk of decline, with an odds ratio of 0.15 (95% CI: 0.04 to 0.54, $p$ =0.004). This association remained robust in the multivariate model, where NBP use demonstrated an odds ratio of 0.10 (95% CI: 0.03 to 0.49, $p$ =0.001). Other factors, including sex, age, education level, and baseline MoCA and CDR-SB scores, showed no significant associations with disease decline, with $p$-value exceeding 0.05 (Table 4).

Sensitivity analysis on disease decline was performed in the IPTW and Overlap-Weighted PSM Datasets. In the IPTW dataset, the rate of disease decline was markedly lower in the NBP group (4.31%) compared to the non-NBP group (39.38%), with a $p$-value of <0.001. A similar trend was observed in the Overlap-Weighted dataset, where the NBP group exhibited a decline rate of 4.06%, significantly lower than the 44.28% observed in the non-NBP group, with a $p$-value of <0.001 (Table 5).

**Table 4** Univariate and Multivariate Logistic Regression Analysis of Disease Decline in the Original Dataset

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Sex (female) | 0.95 (0.38, 2.36) | 0.907 | | |
| Age (>60) | 0.66 (0.22, 1.99) | 0.464 | | |
| Education (more than 9 years) | 1.46 (0.59, 3.61) | 0.418 | | |
| Nature of work (mental) | 1.47 (0.58, 3.75) | 0.416 | | |
| Sleeping length (more than 9 hour) | 0.84 (0.16, 4.36) | 0.840 | | |
| Hypertension | 1.38 (0.56, 3.42) | 0.488 | | |
| Diabetes | 0.76 (0.23, 2.55) | 0.660 | | |
| Hyperlipidemia | 0.69 (0.23, 2.08) | 0.507 | | |
| Stroke | 1.62 (0.50, 5.31) | 0.422 | | |
| Trauma | 1.52 (0.13, 17.53) | 0.737 | | |
| Smoke | 1.08 (0.37, 3.13) | 0.891 | | |
| Alcohol | 1.00 (0.25, 4.03) | 1.000 | | |
| Cognitive impairment severity (MCI as ref.) | | | | |
| Mild AD | 0.45 (0.07, 2.85) | 0.396 | | |
| Moderate and Severe AD | 0.90 (0.15, 5.52) | 0.912 | | |
| Donepezil | 1.06 (0.41, 2.71) | 0.905 | | |
| Memantine | 0.84 (0.32, 2.19) | 0.717 | | |
| NBP | 0.15 (0.04, 0.54) | 0.004 | 0.10 (0.03, 0.49) | 0.001 |
| Baseline MoCA score | 0.96 (0.89, 1.04) | 0.353 | 0.93 (0.83, 1.05) | 0.251 |
| Baseline CDR-SB | 1.06 (0.95, 1.19) | 0.293 | 1.01 (0.85, 1.21) | 0.908 |
| APOE Carriers (no is ref.) | | | | |
| Yes | 1.30 (0.50, 3.39) | 0.590 | 1.15 (0.39, 3.36) | 0.804 |
| Un-known | 0.00 (0.00, Inf) | 0.992 | 1.00 (not available) | |

**Abbreviations**: AD, Alzheimer's disease; APOE, Apolipoprotein E; CDR-SB, Clinical dementia rating scale-sum of boxes; CI, confidence interval; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide; OR, odds ratio.

**Table 5** Analysis of Disease Decline in IPTW and Overlap-Weighted PSM Datasets

| | IPTW Dataset | | | Overlap Weighted PSM Dataset | | |
|---|---|---|---|---|---|---|
| | **Non-NBP (n=97.0)** | **NBP (n=91.8)** | **p-value** | **Non-NBP (n=17.4)** | **NBP (n=17.4)** | **p-value** |
| Number of Disease Decline | 38.2 (39.38%) | 4.0 (4.31%) | <0.001 | 7.9 (44.28%) | 0.7 (4.06%) | <0.001 |

**Abbreviations**: CDR-SB, Clinical dementia rating scale-sum of boxes; IPTW, Inverse probability of treatment weighting; NBP, DL-3-n-Butylphthalide; PSM, Propensity matching scores.

## The Analysis of the Secondary Endpoints

Detailed information on the evaluation of CDR-SB change (Figure 2) and MoCA were listed in Table 6.

In the univariate linear regression analysis of CDR-SB change, NBP demonstrated a significant association with a reduction in CDR-SB, with a coefficient of −1.22 (95% CI: −1.87 to −0.56) and a *p*-value of 0.001. This association was further supported in the multivariate model, where NBP showed a coefficient of −1.77 (95% CI: −2.51 to −1.02) with a *p*-value of <0.001. Baseline MoCA scores were also significant in the multivariate analysis, with a coefficient of −0.08 (95% CI: −0.16 to −0.01) and a *p*-value of 0.036, indicating an inverse relationship with CDR-SB change. Additionally, the "unknown" category of APOE carriers showed a significant association with reduced CDR-SB in both univariate (Coef. = −1.18, 95% CI: −2.20 to −0.15, $p$ =0.027) and multivariate models (Coef. = −1.52, 95% CI: −2.54 to −0.51, $p$ =0.004). Other variables, including sex, age, and cognitive impairment severity, exhibited no significant associations, with $p$ -values exceeding 0.05 (Table 7).

In the univariate linear regression analysis of MoCA change, NBP was significantly associated with an increase in MoCA scores, with a coefficient of 2.42 (95% CI: 1.34 to 3.50, $p$ <0.001). This association remained robust in the multivariate model, where NBP exhibited a coefficient of 2.34 (95% CI: 1.07 to 3.61, $p$ <0.001). Other variables, including sex, age, education level, baseline cognitive impairment severity, and APOE carrier status, did not demonstrate significant associations, as their $p$ -values exceeded 0.05 in both univariate and multivariate analyses (Table 8).

The evaluation of NPI and ADCS-ADL is listed in Table 9. The change in the NPI scores from baseline to the end of the 6 months demonstrated a significant reduction in the NBP group, with a mean change of −4.59 (SD 17.31) compared to an increase of 4.92 (SD 18.59) in the non-NBP group ($p$ =0.030). The median changes, however, did not reach

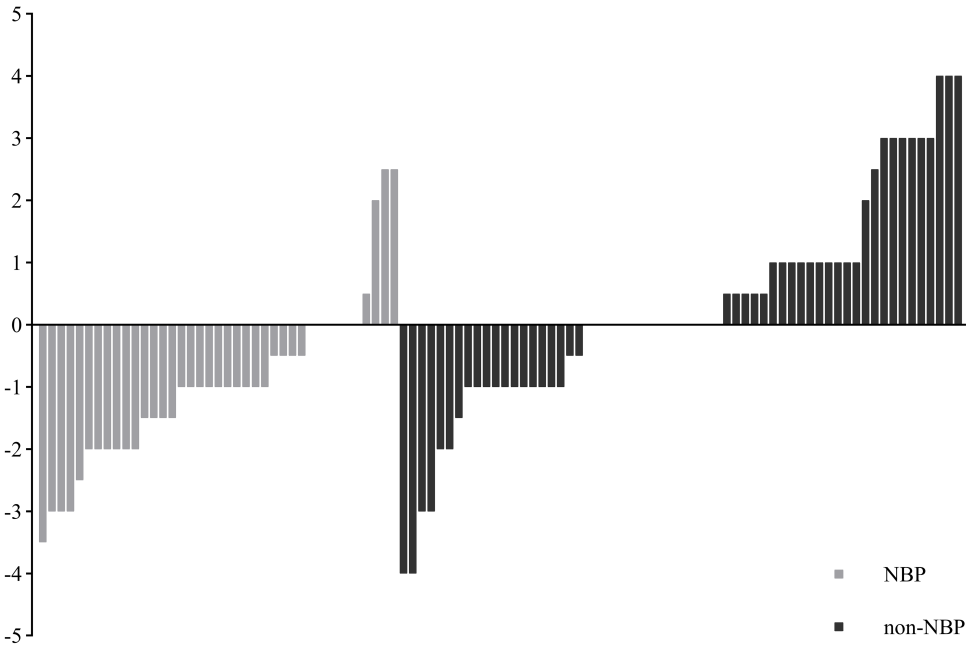


**Figure 2** The CDR-SB change for each individualEach bar represents one participant in either the NBP or non-NBP group. Bars above and below zero indicate improvement or worsening, respectively. The absence of a bar denotes no change in CDR-SB scores before and after treatment for that participant.


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**Table 6** Evaluation of CDR-SB and MoCA

| | | Non-NBP (n=61) | NBP (n=39) | Statistics | p-value |
|---|---|---|---|---|---|
| Baseline CDR-SB | Mean (SD) | 8.16(3.89) | 7.24(3.97) | t=1.15 | 0.255 |
| | Median (Q1-Q3) | 8(4.50–11.00) | 7(4.50–9.50) | z=1.21 | 0.227 |
| | Min-max | 1.50–18.00 | 0.50–18.00 | | |
| End CDR-SB | Mean (SD) | 8.42(4.48) | 6.28(3.73) | t=2.48 | 0.015 |
| | Median (Q1-Q3) | 7(5.00–11.00) | 6(3.25–8.25) | z=2.26 | 0.024 |
| | Min-max | 1.00–18.00 | 0.50–16.00 | | |
| Change CDR-SB | Mean (SD) | 0.25(1.79) | −0.96(1.36) | t=3.63 | <0.001 |
| | Median (Q1-Q3) | 0 (−1.00–1.00) | −1(−2.00 - −0.25) | z=4.01 | <0.001 |
| | Min-max | −4.00–4.00 | −3.50–2.50 | | |
| Baseline MoCA | Mean (SD) | 13.46(6.05) | 12.05(5.68) | t=1.16 | 0.248 |
| | Median (Q1-Q3) | 14(9.00–18.00) | 12(8.50–15.00) | z=1.35 | 0.178 |
| | Min-max | 2.00–25.00 | 2.00–25.00 | | |
| End MoCA | Mean (SD) | 12.93(6.45) | 13.95(6.39) | t=−0.77 | 0.443 |
| | Median (Q1-Q3) | 14(8.00–18.00) | 14(9.00–17.50) | z=−0.44 | 0.663 |
| | Min-max | 2.00–27.00 | 4.00–28.00 | | |
| Change MoCA | Mean (SD) | −0.52(2.59) | 1.90 (2.84) | t=−4.39 | <0.001 |
| | Median (Q1-Q3) | 0 (−2.00–1.00) | 2(0.00–3.50) | z=−4.06 | <0.001 |
| | Min-max | −7.00–5.00 | −5.00–9.00 | | |

**Abbreviations**: CDR-SB, Clinical dementia rating scale-sum of boxes; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide.

**Table 7** Linear Regression Analysis of CDR-SB Change in the Original Dataset

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Coef. | 95% CI | p-value | Coef. | 95% CI | p-value |
| Sex (female) | 0.00 | −0.69, 0.69 | 0.996 | −0.50 | −1.35, 0.35 | 0.243 |
| Age (>60) | 0.15 | −0.72, 1.02 | 0.735 | 0.58 | −0.28, 1.44 | 0.185 |
| Education (more than 9 years) | 0.02 | −0.67, 0.70 | 0.963 | 0.11 | −0.55, 0.78 | 0.736 |
| Smoke | −0.22 | −1.03, 0.59 | 0.591 | −0.34 | −1.35, 0.66 | 0.497 |
| Alcohol | −0.18 | −1.22, 0.87 | 0.743 | 0.08 | −0.32, 0.48 | 0.706 |
| Cognitive impairment (MCI as ref.) | | | | | | |
| Mild AD | −0.36 | −1.84, 1.12 | 0.637 | −0.53 | −2.00, 0.94 | 0.476 |
| Moderate and Severe AD | −0.10 | −1.59, 1.39 | 0.895 | −0.61 | −2.52, 1.30 | 0.529 |
| Baseline MoCA | −0.02 | −0.07, 0.04 | 0.585 | −0.08 | −0.16, −0.01 | 0.036 |
| Baseline CDR-SB | 0.01 | −0.08, 0.09 | 0.884 | −0.06 | −0.21, 0.10 | 0.461 |
| APOE Carriers (no is ref.) | | | | | | |
| Yes | −0.04 | −0.79, 0.70 | 0.910 | −0.12 | −0.87, 0.62 | 0.741 |
| Un-known | −1.18 | −2.20, −0.15 | 0.027 | −1.52 | −2.54, −0.51 | 0.004 |
| NBP | −1.22 | −1.87, −0.56 | 0.001 | −1.77 | −2.51, −1.02 | <0.001 |

**Abbreviations**: AD, Alzheimer's disease; APOE, Apolipoprotein E; CDR-SB, Clinical dementia rating scale-sum of boxes; CI, confidence interval; Coef., coefficients; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide.

statistical significance, with values of 0 (Q1-Q3: −4.00 to1.50) in the NBP group and 0 (Q1-Q3: −3.25 to 7.00) in the non-NBP group ($p$ =0.168). The results for change of appetite and eating abnormalities in NPI showed that the median score was 12 (IQR 3.75–26) in the non-NBP group and 4 (IQR 0.5–11.5) in the NBP group, with statistical analysis indicating a significant difference between the groups (p = 0.006). The change in the ADCS-ADL scores from baseline to the end of the 6 months did not show a statistically significant difference between the two groups. The mean change in

**Table 8** Linear Regression Analysis of MoCA Change in the Original Dataset

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | **Coef.** | **95% CI** | **p-value** | **Coef.** | **95% CI** | **p-value** |
| Sex (female) | −0.24 | −1.41, 0.92 | 0.684 | 0.37 | −1.07, 1.81 | 0.609 |
| Age (>60) | −0.78 | −2.24, 0.68 | 0.298 | −0.82 | −2.28, 0.64 | 0.268 |
| Education (more than 9 years) | 0.77 | −0.38, 1.92 | 0.191 | 0.64 | −0.49, 1.78 | 0.262 |
| Smoke | 0.19 | −1.18, 1.56 | 0.788 | −0.61 | −2.33, 1.10 | 0.479 |
| Alcohol | 1.42 | −0.34, 3.17 | 0.116 | 1.38 | −0.59, 3.34 | 0.167 |
| Cognitive impairment (MCI as ref.) | | | | | | |
| Mild AD | −0.56 | −3.00, 1.88 | 0.654 | −0.44 | −2.94, 2.05 | 0.725 |
| Moderate and Severe AD | −1.79 | −4.24, 0.67 | 0.156 | −1.39 | −4.66, 1.87 | 0.398 |
| Baseline MoCA | −0.03 | −0.13, 0.06 | 0.488 | −0.06 | −0.19, 0.07 | 0.375 |
| Baseline CDR-SB | −0.09 | −0.24, 0.05 | 0.218 | 0.01 | −0.26, 0.27 | 0.952 |
| APOE Carriers (no is ref.) | | | | | | |
| Yes | 0.02 | −1.28, 1.32 | 0.976 | 0.33 | −0.94, 1.59 | 0.610 |
| Un-known | −0.39 | −2.17, 1.40 | 0.671 | 0.24 | −1.49, 1.98 | 0.782 |
| NBP | 2.42 | 1.34, 3.50 | <0.001 | 2.34 | 1.07, 3.61 | <0.001 |

**Abbreviations**: AD, Alzheimer's disease; APOE, Apolipoprotein E; CDR-SB, Clinical dementia rating scale-sum of boxes; CI, confidence interval; Coef., coefficients; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; NBP, DL-3-n-Butylphthalide.

**Table 9** Evaluation of NPI and ADCS-ADL

| | | **Non-NBP n=52** | **NBP n=27** | **Statistics** | **p-value** |
|---|---|---|---|---|---|
| Change NPI | Mean (SD) | 4.92 (18.59) | −4.59 (17.31) | t=2.21 | 0.030 |
| | Median (IQR) | 0 (−3.25, 7) | 0 (−4, 1.5) | z=1.38 | 0.168 |
| | Min-max | −26, 76 | −78, 16 | | |
| Change NPI Delusions | Median (IQR) | 0 (−2.25, 0) | 0 (0, 0) | z=−0.83 | 0.409 |
| Change NPI Hallucination | Median (IQR) | 0 (0, 0) | 0 (0, 0) | z=1.03 | 0.301 |
| Change NPI Agitation/Aggression | Median (IQR) | 0 (0, 0) | 0 (0, 0) | z=1.22 | 0.224 |
| Change NPI Depression/Dysphoria | Median (IQR) | 0 (0, 4) | 0 (0, 2) | z=0.23 | 0.817 |
| Change NPI Anxiety | Median (IQR) | 0 (−1, 0) | 0 (−1, 0) | z=0.83 | 0.408 |
| Change NPI Euphoria/Elation | Median (IQR) | 0 (0, 0.25) | 0 (0, 0) | z=1.22 | 0.224 |
| Change NPI Apathy/Indifference | Median (IQR) | 0 (0, 0) | 0 (0, 0) | z=−0.44 | 0.661 |
| Change NPI Disinhibition | Median (IQR) | 0 (0, 2) | 0 (0, 1) | z=1.28 | 0.199 |
| Change NPI Irritability/Lability | Median (IQR) | 0 (−1, 0.25) | 0 (0, 0) | z=0.36 | 0.723 |
| Change NPI Aberrant Motor Behavior | Median (IQR) | 0 (−1, 0) | 0 (−0.5, 0) | z=0.68 | 0.496 |
| Change NPI Sleep and Nighttime Behavior Disorders | Median (IQR) | 0 (0, 0) | 0 (0, 0) | z=−0.51 | 0.608 |
| Change NPI Appetite and Eating Abnormalities | Median (IQR) | 12 (3.75, 26) n=48 | 4 (0.5, 11.5) n=23 | z=2.74 | 0.006 |
| Change ADCS-ADL | Mean (SD) | −1.40 (7.27) | −2.22 (12.49) | t=0.35 | 0.727 |
| | Median (Q1-Q3) | −0.5 (−4, 2.25) | −2 (−4, 0.5) | z=0.65 | 0.514 |
| | Min-max | −27.00, 10.00 | −49.00, 24.00 | | |

**Abbreviations**: ADCS-ADL, AD cooperative study - activities of daily living; NBP, DL-3-n-Butylphthalide; NPI, Neuropsychiatric Inventory.

the non-NBP group was −1.40 (SD 7.27), while in the NBP group, it was −2.22 (SD 12.49), with a *p*-value of 0.727. The median change was −0.50 (Q1-Q3: −4.00 to 2.25) in the non-NBP group and −2.00 (Q1-Q3: −4.00 to 0.50) in the NBP group, with a *p*-value of 0.514.

## Subgroup Analyses

In the monotherapy subgroup (NBP, n=4; non-NBP, n=39), NBP showed a significant improvement in MoCA scores with a mean change of 2.50 ($p$ =0.009), while non-NBP showed a decrease of −0.77. No significant differences were found in CDR-SB scores ($p$=0.243) or disease deterioration ($p$ =0.564).

In the combination therapy subgroup (NBP, n=35; non-NBP, n=22), NBP showed a significant improvement in MoCA scores with a mean change of 1.83 ($p$ =0.022) and a greater reduction in CDR-SB scores (−0.99 vs −0.07, $p$ =0.020). No significant difference in disease deterioration was observed between the groups ($p$ =0.239). Detailed results are provided in sTable 4 (Monotherapy Group) and sTable 5 (Combination Therapy Group) in the Appendix.

## Safety Issues

Overall, the total incidence of adverse events was low. In the non-NBP group, adverse events such as abdominal distension, abnormal liver enzymes, diarrhea, dizziness, ischemic stroke, and ovarian cancer were reported, with frequencies ranging from 1.00% to 4.92%. In contrast, the NBP group reported no occurrences of these events, except for fatigue, which was observed in 2.56% of participants. This suggests a potential difference in the safety profile between the two groups (sTable 3 in Appendix).

# Discussion

This study evaluated the efficacy of NBP as monotherapy or in combination with other pharmacological treatments for AD in a real-world setting. After six months, patients receiving NBP showed slower cognitive decline and a trend toward improvement in neuropsychiatric symptoms. Notably, NBP alleviated appetite and eating disturbances, with adverse event rates below 3% in the NBP group and 5% in the non-NBP group.

The CDR-SB has been shown to distinguish between very mild and mild AD and predict its progression,[58] and its wide scoring range supports its use in monitoring disease course.[59] It has been widely adopted as a primary outcome in large AD trials.[60–64] In this study, disease deterioration and decline on the CDR-SB were used as co-primary endpoints. After six months, disease deterioration occurred in 14 patients (14.00%) overall, including three (7.69%) in the NBP group and 11 (18.03%) in the non-NBP group. Disease decline was observed in 25 patients (25.00%), with three (7.69%) in the NBP group and 22 (36.07%) in the non-NBP group. Multivariate analysis confirmed that NBP reduced the odds of disease deterioration (OR=0.19, 95% CI: 0.04 to 0.88) and disease decline (OR=0.10, 95% CI: 0.03 to 0.49). Findings were consistent in IPTW and Overlap-Weighted PSM analyses. Using the Hochberg procedure,[57] $p$=0.034 for deterioration and $p$=0.001 for t decline, supporting the efficacy of NBP. Beyond the primary endpoints, NBP was associated with a greater reduction in CDR-SB score (coef. −1.22, 95% CI: −2.51 to −1.02) and an increase in MoCA score (coef. 2.42, 95% CI: 1.07 to 3.61) suggesting both slower functional decline and enhanced cognitive performance.[65]

Although NPI changes did not reach statistical significance, patients in the NBP group showed a greater reduction, particularly in appetite and eating abnormalities (Table 7). The lack of significance may be related to the limited sample size, but the findings indicate a potential benefit of NBP in alleviating neuropsychiatric symptoms. Patients' daily living abilities were assessed using the ADCS-ADL, with no significant differences observed between groups. Evidence from meta-analysis indicates that both pharmacological and non-pharmacological treatments yield modest cognitive benefits, while functional improvements are limited.[66,67] In moderate to severe dementia, agents such as cholinesterase inhibitors or memantine enhance cognition and global clinical impression, though functional gains remain modest. Since instrumental and the basic activities of daily living represent the most vulnerable domains compared with cognition and the BPSD, early intervention is critical. Preserving function at the earliest stages offers greater potential for favorable outcomes and improved patient experiences.

Previous studies have shown that NBP can improve cognition, either as monotherapy in non-demented patients with VCI[26] or in combination with donepezil in mild to moderate AD.[68] Distinct from these trials, our real-world study incorporated patient across the full spectrum of cognitive impairment, systematically assessed activities of daily living, behavior, and cognition,[69] and adopted disease deterioration and decline as co-primary endpoints to capture treatment effects across the disease stages. Robust statistical methods, including multifactorial analyses, IPTW, and Overlap-

Weighted PSM, were used to reduce confounding and strengthen validity. The inclusion of both NBP monotherapy and combination therapy reflects clinical prescribing patterns and ensured adequate statistical power; although this may introduce heterogeneity, sensitivity analyses showed consistent benefits across subgroups, supporting the robustness and clinical relevance of the findings.

In the AD drug development pipeline, the majority of investigational therapies are designed as disease-modifying treatments (DMTs), targeting the complex mechanisms of dementia and offering renewed therapeutic prospects.[70] Given the multifactorial pathology of AD, repurposed drugs and combination strategies may be more effective than monotherapies in addressing both the symptoms and underlying disease processes.[71] NBP shows therapeutic promise through multi-target mechanisms: it reduces neuroinflammation by inhibiting microglial activation and cytokine release, ameliorates mitochondrial dysfunction by enhancing oxidative phosphorylation and limiting ROS, mitigates excitotoxicity via NMDA receptor modulation, and preserves blood–brain barrier integrity by suppressing MMP-9 and endothelial inflammation. Preclinical evidence further suggests that NBP may attenuate amyloid-β accumulation and tau hyperphosphorylation,[28,29] supporting its potential as a disease-modifying therapy. Together with the present findings, which demonstrate clinical benefits of NBP in both monotherapy and combination settings across disease stages, these data underscore the need for rigorously designed randomized controlled trials (RCTs) validate its role in delaying AD progression.

As a retrospective cohort analysis, this study has several limitations. Selection bias is an inherent concern,[72] though we minimized this risk through multivariate logistic regression, IPTW analysis, and Overlap-Weighted dataset analyses, which yielded consistent results supporting the effect of NBP on disease progression. Similar to other reports,[73–75] biomarkers were not employed for diagnosis;[76] however, the use of NIA-AA clinical criteria ensured diagnostic validity in routine practice and provides a valuable reference for clinicians. The relatively short six-month follow-up and modest sample size may limit the ability to detect slower disease changes, reduce statistical power for subgroup analyses, constrain generalizability. Furthermore, the initial sample size assumptions were based on preliminary clinical observations rather than published data, reflecting the absence of prior studies using similar endpoints for NBP in AD; post hoc analyses nevertheless confirmed adequate power for the primary endpoint of disease decline. Combining NBP monotherapy and combination therapy could also introduce heterogeneity, yet subgroup analyses showed consistent benefits across both groups, supporting the robustness of the findings. Despite these limitations, this study is the first real-world retrospective cohort study to apply deterioration and decline as co-primary endpoints in China, offering valuable clinical insights. Previous studies have used ADAS Cog[77] or ADCS-ADL[68] changes as primary outcomes, while other evidence[44] indicates that a 1–2 points annual increase in CDR-SB reflects clinically meaningful decline. Accordingly, a six-month increase in CDR-SB can be considered a clinically relevant unfavorable endpoint, reinforcing the validity of our co-primary measures A prospective study is now underway with extended follow-up and larger sample size to provide more robust evidence. Importantly, as a real-world study, medication dosages, adherence, and treatment regimens were not protocol-driven but determined by treating physicians, reflecting clinical practice variability and enhancing the relevance of these findings to routine care.

## Conclusion

In this real-world retrospective cohort, patients receiving NBP in routine treatment had a significantly lower risk of clinical deterioration and disease decline compared with those not receiving NBP. NBP also led to more favorable CDR-SB outcomes, including both slower progression and clinical improvement, and was associated with higher MoCA scores and potential benefits for neuropsychiatric symptoms. These findings support the role of NBP in delaying AD progression, although the retrospective design and limited sample size warrant cautious interpretation. Prospective randomized studies are required to confirm these observations.

## Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to polish the sentences in our manuscript and ensure that the English is clear and understandable. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors, Dr. Xiaolei Liu (ring@vip.163.com), upon reasonable request.

## Ethics

This study followed the ethnic and scientific principles of Helsinki's Declaration and regulation of Chinese law for Chinese Good Clinical Practice. The study protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University (2023L108). A neurologist initiated telephone calls to all participants and their relatives to obtain informed consent. In cases where participants or their relatives could not be reached, the Ethics Committee of The First Affiliated Hospital of Kunming Medical University granted a waiver of informed consent for this study.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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