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ORIGINAL RESEARCH

Neuropsychiatric Symptoms Predict Faster Cognitive Decline in Dementia Collaborative Care Than Antipsychotic Use

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Background: To compare short-term cognitive outcomes among groups with and without neuropsychiatric symptoms (NPSs) or antipsychotic prescription and to determine which disease status or treatment modality is associated with relatively faster cognitive decline.

Methods: We retrospectively analyzed a prospective cohort of patients diagnosed with dementia and mild cognitive impairment. All participants were evaluated using the Cognitive Abilities Screening Instrument (CASI) during their initial clinical assessments and at the annual follow-up. The dependent variable was annual delta CASI. Multivariate linear regression analysis was used to assess the degree of association between NPS, antipsychotic use, and cognitive decline after adjusting for confounding factors. Neuropsychiatric symptoms were examined individually to determine their predictive value for cognitive decline.

Results: A total of 407 (N = 407) patients were included in the study. NPSs, rather than antipsychotic use, led to faster cognitive decline. A higher baseline NPI total score predicted a significantly faster decline in CASI scores (1-year delta CASI = −0.22, 95% CI = −0.38~ −0.05, p = 0.010). Specific items (delusions, agitation, depression, anxiety, euphoria, and apathy) in the NPS significantly increased cognitive decline.

Conclusion: Certain neuropsychiatric symptoms, rather than antipsychotic use, lead to faster cognitive decline in a dementia collaborative care model. Checking for and providing appropriate interventions for NPS in people with dementia and their caregivers are highlighted.

Keywords: neuropsychiatric symptoms, antipsychotics, cognitive decline, cognitive abilities screening instrument, dementia collaborative care

Introduction

Neuropsychiatric symptoms (NPSs) are behavioral (eg aberrant motor behavior) and psychological (eg delusion or hallucination) symptoms. They hold a high prevalence in patients with dementia and occur frequently during the course of cognitive decline. In addition to dementia caused by Alzheimer's disease (AD), NPSs are common across various types of dementia.[1–3]

In our previous study on the institutionalization risks for patients with dementia in Taiwan, we found that the presence of NPSs at entry into dementia collaborative care is a significant predictor.[4] Institutionalization partially reflects dementia progression[5] and provides indirect evidence of the speed of progression. Surveillance of longitudinal changes in dementia severity are essential for providing individualized care plans. A longitudinal survey of neuropsychological functions predicts the prognosis of patients with cognitive impairment.[6] Factors associated with faster neurocognitive progression warrant further confirmation and may serve as a pivotal role for continuous care directions.

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A case management model in dementia care has been reported to reduce the prevalence of neuropsychiatric symptoms.[7,8] The use of psychotropic medications is significantly associated with a high severity of NPS.[9] Decreasing the severity of NPS can be achieved with both a cognitive-behavioral approach[10] and psychotropic use.[11]

Increasing evidence has shown that the conversion rate of mild cognitive impairment (MCI) to dementia is higher in patients with more severe NPS.[12,13] Certain types of NPSs are predictors of progression to AD.[14] The prevalence of NPSs is associated with an increased rate of cognitive decline, even in older adults without dementia.[15] Antipsychotic use has been postulated to predict cognitive decline;[16] however, confounding effect of the indication should be taken into account.

NPSs are significant factors for families to recognize the progression of dementia.[17] NPS severity is associated with caregiver stress and therapeutic outcomes.[18] Furthermore, neuropsychiatric symptoms are associated with healthcare utilization, including home personal care and assistive devices.[19] Dementia collaborative care has been implemented in our affiliation since 2015 and serves as an appropriate place for investigating patient-family dyads, neuropsychiatric symptoms, and psychotropic prescriptions.

This study aimed to compare short-term cognitive outcomes among groups with and without NPSs or antipsychotic prescription and determine the one associated with faster cognitive decline.

Materials and Methods

Participants

We retrospectively analyzed a prospective cohort diagnosed with dementia and MCI. The diagnosis was based on the Clinical Dementia Rating (CDR) scale[20] and confirmed by neurologists and psychiatrists. Their severities ranged from CDR 0.5 to 3. The dementia collaborative care model was established in October 2015. The inclusion criteria for this retrospective cohort were as follows: (1) patients diagnosed with MCI or dementia in an outpatient clinic setting; (2) entry between October 2015 and July 2022; (3) consent from patients and their families to join the care model; and (4) at least two annual neurocognitive tests for comparison: one at entry and the other during 1-year follow-up. The overall cohort was composed of 407 patients including 158 men and 249 women. Their mean age was 78.1 years and were all Taiwanese living in Central Taiwan.

After the diagnosis of dementia or MCI, patients and caregivers received an initial assessment, including functional and living status and NPSs by evaluating the Neuropsychiatric Inventory (NPI),[21,22] nutritional status, financial support, and medication reviews to determine their unmet needs.[23,24] Medication reviews by pharmacists were obtained from cloud drug lists registered at the National Health Insurance system. The antipsychotics included quetiapine, aripiprazole, risperidone, olanzapine, amisulpride, lurasidone, brexpiprazole, clozapine, paliperidone, zotepine, ziprasidone, haloperidol, and clotiapine. Risk-benefit documentation for antipsychotic use was obtained from the patients receiving antipsychotic treatment. Due to different receptor profiles and relevant potential adverse reactions, the above antipsychotics were also grouped as first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) for further analysis.

All data required for the present study were extracted from electronic charts after deleting personal information. This clinical study was approved by the Institutional Review Board of Changhua Christian Hospital (CCH IRB 220920). The requirement for informed consent from each participant was waived by the institutional review board because of the retrospective chart review design. Attentions were paid on minimal risk of patient data confidentiality and the study was in compliance with the Declaration of Helsinki.

Outcomes and Variables

The outcome measure of the cognitive screening test used in this study was the Cognitive Ability Screening Instrument (CASI).[25] The CASI evaluates memory, executive function, orientation, visuospatial function, and language cognitive domains, with a range of 0–100. Higher scores indicated better cognitive function. The dependent variable was annual delta CASI. All participants were evaluated using the CASI during their initial clinical assessment and at the subsequent annual follow-ups (baseline and 12 months). Higher decrease in CASI scores during the observed time period was regarded as faster cognitive decline.

Specific neuropsychiatric symptoms are associated with fast dementia progression; however, previous studies have reported heterogeneous results.[9,26] Each item of the NPI was examined individually to determine its distribution within the cohort.

Statistical Analysis

Data were analyzed using R software (R Foundation for Statistical Computing). For baseline demographics and clinical information, categorical variables are presented as numbers (percentages) and continuous variables as means (standard deviations). The variables were checked for deviations from normal distribution. Nominal variables among patients with or without antipsychotic use were compared using Pearson's chi-square test or Fisher's exact test, whereas continuous variables were compared using analysis of variance or the Kruskal–Wallis rank sum test.

Potential predictors of dementia progression, including age at dementia/MCI diagnosis, years of education, sex, dementia type, history of CVA, and walking capability,[27–31] were analyzed.

We categorized the patients into AD and non-AD groups according to the dementia type. Walking capability was categorized as fully ambulatory (free), ambulatory with assistance or holding a cane (needing assistance), or wheelchair bound (wheel-bound).

Multivariate linear regression analysis was used to assess the degree of association between NPS, antipsychotic use, and cognitive decline after adjusting for confounding factors. Variation inflation factors (VIFs) of the included variables were calculated for examination of collinearity. Since antipsychotic use were possibly in relation to severe NPSs, a mediation analysis with removing these two factors individually were performed.

Results

Table 1 shows the demographic information of our study cohort (N = 407) of patients with and without antipsychotic use at entry into dementia collaborative care. Significant differences were found between the groups in terms of age, walking

Table 1 Comparison of Covariates Among Groups with and without Antipsychotic Use

		No	Yes	p-value
N		300	107	
Age	Year	77.32 (7.91)	80.34 (7.28)	0.001
Male (%)		119 (39.7)	39 (36.4)	0.638
Education	Year	6.10 (4.62)	5.23 (4.53)	0.094
Dementia type (%)	AD	190 (63.3)	58 (54.2)	0.122
History of CVA (%)		33 (11.0)	10 (9.3)	0.768
Walking Capability(%)	Free	213 (71.0)	58 (54.2)	0.006
	Need-assistance	72 (24.0)	39 (36.4)	
	Wheel-bound	15 (5.0)	10 (9.3)	
NPI		6.65 (9.76)	14.93 (16.56)	<0.001
Any Psychosis(%)		78 (26.0)	65 (60.7)	<0.001
Moderate-severe psychosis(%)		41 (13.7)	39 (36.4)	<0.001
CASI interval	Year	1.11 (0.51)	1.12 (0.60)	0.887
Delta CASI		−6.30 (20.29)	−8.34 (20.20)	0.371

Notes: Psychosis was defined as the severity score multiplied by the frequency score of either delusion or hallucination > 0. Moderate-severe psychosis was defined as severity score multiply by frequency score of either delusion or hallucination ≥ 4.

Abbreviations: AD, Alzheimer's disease; CVA, cerebrovascular accident; NPI; Neuropsychiatric inventory; CASI, Cognitive abilities screening instrument.

capability, and NPI (in total, presence of delusions or hallucinations, and moderate-severe psychosis clusters). Psychosis was defined as the NPI severity score multiplied by the frequency score of either delusion or hallucination more than 0. Moderate-severe psychosis was defined as NPI severity score multiply by frequency score of either delusion or hallucination more or equal to 4. The mean CASI interval was 1.11 (0.53) years. The primary outcomes (annual delta CASI) for the two groups were −6.30 and −8.34 (p = 0.371, not significant).

Table 2 provides a multivariate linear regression model of cognitive decline using delta CASI. VIFs of the included variables ranged from 1.106 to 1.291. Minimal collinearity was considered. After adjusting for other confounders (age at dementia diagnosis, sex, education, dementia type, history of CVA, and walking capability), a higher baseline NPI total score predicted a significantly faster decline in CASI scores. The 1-year delta CASI was −0.22 with 95% confidence interval of −0.38 to −0.05 (p = 0.010).

As for the mediation analysis regarding NPSs and antipsychotic use, the NPI independently predicted fast cognitive decline in multivariate analysis, regardless of antipsychotic use putting into the model or not. In other words, NPSs, rather than antipsychotic use, leads to a faster cognitive decline. These findings are summarized in Table 3. Subgroup analysis according to antipsychotic drug classes (FGA and SGA) showed similar outcome and the results were presented in Supplemental Table 1.

A comparison of dementia progression using delta CASI among each item of the NPI (sub-score of each NPS in substitution of NPI total score) showed that specific items (delusion, agitation, depression, anxiety, euphoria, and apathy)

Table 2 Multivariate Linear Regression of Dementia Progression Using Delta CASI

Variable	Units	Coefficient [95% CI]	p-value
(Intercept)		32.66 [10.59;54.74]	0.004
Age	Year	−0.46 [−0.73;-0.18]	0.001
Sex	Male	−3.38 [−7.75;0.99]	0.130
Education	Year	−0.10 [−0.58;0.38]	0.694
Dementia type	AD	Ref	
	non-AD	−1.43 [−5.70;2.83]	0.511
CVA	Yes	−4.34 [−10.97;2.29]	0.201
Walking capability	Free	Ref	
	Need assistance	2.90 [−1.76;7.56]	0.224
	Wheel-bound	1.03 [−7.33;9.38]	0.810
NPI		−0.22 [−0.38;-0.05]	0.010
Antipsychotic use	Yes	0.59 [−4.13;5.32]	0.806

Abbreviations: CASI, Cognitive abilities screening instrument; AD, Alzheimer's disease; CVA, cerebrovascular accident; NPI, Neuropsychiatric Inventory.

Table 3 Multi-Variate Linear Regression of Dementia Progression Using Delta CASI Focusing on Antipsychotic Use and NPI

	Delta CASI [95% CI] p-value		
NPI	-	−0.21 [−0.37;-0.05] 0.009	−0.22 [−0.38;-0.05] 0.010
Antipsychotic use	−1.18 [−5.74;3.38] 0.612	-	0.59 [−4.13;5.32] 0.806

Note: All other factors included to adjustment are the same as those in Table 2.
Abbreviations: CASI, Cognitive abilities screening instrument; NPI; Neuropsychiatric inventory.

Table 4 Comparison of Dementia Progression Using Delta CASI Among Each Item of NPI

Variable	Delta CASI [95% CI]	p-value
Delusion	−7.87 [−12.11;-3.63]	<0.001
Hallucination	−2.66 [−8.58;3.26]	0.380
Psychosis cluster presence	−5.77 [−9.87;-1.67]	0.006
Moderate-high psychosis cluster	−6.79 [−11.71;-1.87]	0.007
Agitation	−5.79 [−10.41;-1.16]	0.015
Depression	−4.84 [−8.90;-0.79]	0.020
Anxiety	−7.08 [−12.10;-2.06]	0.006
Euphoria	−13.62 [−26.83;-0.42]	0.044
Apathy	−5.72 [−10.54;-0.90]	0.021
Disinhibition	1.34 [−5.26;7.94]	0.691
Irritability	−2.52 [−6.87;1.84]	0.258
Aberrant behavior	−1.19 [−6.65;4.26]	0.669
Sleep problem	−2.53 [−6.55;1.50]	0.219
Eating problem	−1.63 [−6.41;3.16]	0.506

Note: All other factors included to adjustment are the same as those in Table 2 except NPI total scores.
Abbreviations: CASI, Cognitive abilities screening instrument; NPI; Neuropsychiatric inventory.

of the NPS significantly increased the cognitive decline of the participants, as presented in Table 4. The presence of psychosis (delusions or hallucinations) or moderate-to-severe psychosis was also associated with faster cognitive decline.

Discussion

This study shows that neuropsychiatric symptoms at entry to dementia collaborative care predicted faster cognitive decline in patients with dementia or MCI in Taiwan. Antipsychotic use did not mediate or contribute to the faster rate of decline.

Regarding the predictors of disease progression, we found that age at dementia diagnosis was associated with a faster rate of cognitive decline. This is consistent with a cohort study of patients with AD receiving anti-dementia medication treatment.[32] This might possibly be due to more comorbidities in older populations.

In the era of boxed warnings of antipsychotic prescriptions for patients with dementia, both pharmacological agents and non-pharmacological techniques have shown some efficacy[33] in the management of NPSs. Antipsychotic use has been reported to lead to faster cognitive decline in other study context[34] but not in this cohort. We infer that this discrepancy may be due to the dementia collaborative team, particularly physicians and case managers paying attention to the safety and effectiveness of antipsychotics and caregiver support with proper education. Choosing to use antipsychotics in a similarly identifiable patient population may be based on clinical decisions and may differ within individualized levels including family factors.

The reason behind NPS being associated with faster cognitive decline can be discussed in several dimensions. Biologically, neuroanatomical correlates of persistent NPS have been proposed.[35] In addition, the four major types of dementia have different NPS profiles.[36] Psychologically, patients with NPSs have difficulty adhering to cognitive-enhancing activities and anti-dementia drugs. Certain NPSs have been shown to be associated with worse cognitive performance.[37] Socially, NPSs are associated with caregiver burden and treatment outcomes.

Neurodegenerative diseases inevitably decline, and strategies to assist people living with dementia and their caregivers are important. Because certain NPSs independently predict faster rates of cognitive decline, a dementia collaborative team should routinely identify and ascertain the NPS for each case. More trials should be conducted on the effect of ameliorating NPS in reducing the functional progression of dementia.[38]

The present study has some limitations. We derived the medication list at entry into dementia collaborative care to represent antipsychotic use. As the medication review in our study was obtained at entry only, we could not address the issue of duration of antipsychotic use and defined the daily dose in more detail.

Heterogeneity exists in the declining trajectory of serial cognitive testing for each participant. In addition, collaborative dementia care involves an interventional cohort, so the composition and longitudinal effects of the intervention should also be considered. However, these long-term effects warrant further investigation.

Conclusion

This study found that certain NPSs, rather than antipsychotic use, led to faster cognitive decline in a dementia collaborative care model. The present study highlighted that delusions and mood conditions in patients were associated with faster cognitive decline. Therefore, it is essential to check and provide appropriate interventions for NPSs in patients with dementia and their caregivers.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics Approval & Patient Consent Statement

This clinical study was approved by the Institutional Review Board of Changhua Christian Hospital (CCH IRB 220920). The requirement for informed consent from each participant was waived by the institutional review board because of the retrospective chart review design. Attentions were paid on minimal risk of patient data confidentiality and the study was in compliance with the Declaration of Helsinki.

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Disclosure

Yen-Jen Chen, Ming-Che Chang, Kai-Ming Jhang and Wen-Fu Wang contributed equally to this work and share first authorship. The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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