Relations Between Four Assessment Scales and Improved Medication Adherence in Alzheimer's Disease Population

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Research Article

Keywords: Alzheimer's disease, Alzheimer's diseases Assessment Scales, medication adherence, Neuropsychological scales

Posted Date: March 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1429156/v1

Abstract

Background and Objectives

This study aimed to investigate whether Alzheimer's disease (AD) assessment scales, which are widely being used in clinic, had relation with the improved medication adherence of AD patients.

Methods

In this prospective study, fifty-eight participants were recruited and thirty-one finally finished the procedures. Four neuropsychological scales (Alzheimer’s diseases Assessment Scale-Cognitive Subscale, Activity of Daily Living Scale, Neuropsychiatric Inventory, and The Clinician Interview-based Impression of Change, plus carer interview) were implemented and medication adherence rate were improved by multiple subjective methods (involving healthcare providers and caregivers), from June 2014 to June 2018. Statistical methods included bivariate and partial correlations controlled by the clinical factors of multiple patients. Correlation analysis were carried out for each item in the cognitive part of the Alzheimer's Disease Rating scale and medication adherence.

Results

The median adherence rate was 98.04%. No correlation between the four scales and the medication adherence of patients with AD was identified ($P > 0.05$). Partial correlation analysis also failed to reveal the correlation after excluding medication adherence–related factors ($P > 0.05$). But in Alzheimer's diseases Assessment Scale-Cognitive Subscale, scores of Commands and Constructional Praxis had a weak correlation with medication adherence ($P = 0.015$ and $P = 0.033$; correlation coefficients were 0.201 and 0.177, respectively).

Conclusions

Existing AD neuropsychological scales showed no relation with medication adherence rate elevated by multiple methods in AD patients, while performance, language, and visuospatial ability might be related to medication adherence in these population.

Trial registration

ClinicalTrials.gov Identifier: NCT02293915

Background

Alzheimer's disease (AD) is a chronic neurodegenerative disease and the main cause of dementia in patients aged more than 65 years [1]. Cholinesterase inhibitors, antagonist of the N-methyl-D-aspartate receptor, and latest new drugs (such as GV-971) that has provided significant cognitive benefit [2], are

suggested to be applied in the early stage of the disease. Patients with early symptoms of AD in 2025 will be treated substantially differently from how they are treated now [3].

The adherence of patients with AD was globally low at 50% [4]; prior studies reported rates ranging from 26–59% [5]. Nonadherence can aggravate bad health leading to an increase in hospitalization and cost for patients [6]. In the United States, medication nonadherence costed more than $100 billion per year in 2000 [7]. Overused drugs increase toxicity, and underadherent medications lead to a decrease in therapeutic effect. It is particularly detrimental to the health of older adults because of the increase in comorbidities and fragile physical environment [6]. Cognitive impairment is one of the most important risk factors for medication nonadherence in older adults [8]. A previous study reported an odds ratio of 9.0 for nonadherence among patients with dementia [9] and nearly three times as high for cognitively impaired persons, compared with those without dementia [10]. Which cognitive domains contribute to medication adherence are still in debating. Memory and executive functions have been implicated in maintaining the intention to take medication and implement a plan to adherence [11, 12], but some researcher could not reach the agreement [13].

A cheap, convenient, and simple method for early detection on AD is the application of neuropsychological scales. At present, several mature and widely accepted neuropsychological scales can be used to evaluate the various functions of patients with AD, including Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [14], Activity of Daily Living Scale (ADL)[15], Neuropsychiatric Inventory (NPI) [16], Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) [17]. They were widely used in various clinical drug trials [18] to evaluate the cognitive domains, daily life function, mental and behavior disorders, and overall function of patients separately [2]. In particular, the ADAS-Cog scale is considered to be the most important therapeutic index for evaluating the efficacy of drugs [18]. ADAS-Cog is gold standard for assessing the efficacy of antidementia treatments but lacks the ability to evaluate daily living, social interaction, and mental behavior [19]. CIBIC-Plus is used to evaluate the general cognition of patients with AD in clinical practice, while ADL and NPI are used to evaluate the social daily activity impairment, psychological and behavioral abnormalities, respectively. Previous studies suggested that a rapid decline in cognitive function, increase in behavioral abnormalities [20], and heavy stress on caregivers [21] could lead to a decline in medication adherence.

A good adherence assessment tool is needed for finding out an effective intervention. At present, Morisky scales and some other scales have been widely used to measure medication adherence. Because patients with AD are characterized by advanced age, cognitive decline, and dependency on caregivers for medication [22], the existing general medication adherence assessment tools had poor efficacy in patients with dementia [23]. Hayes et al. [13] evaluated the ability of independently living healthy adults in medication adherence using ADAS-Cog. The low cognitive function groups had a 4.1 relative risk of non-adherence as compared to the high cognitive function group. Some scales, such as ADL, included the evaluation of medication taking. Whether these scales had any association with medication adherence was still unknown. Nonadherence involved many factors, including subjective and objective categories,

that made the model complex and hard to research. Our previous studies identified some negative subjective factors affecting the medication adherence of patients with AD. After eliminating these factors, the medication adherences were improved distinctly and the medication patterns changed, which made the research model simpler. This study aimed to investigate whether the four widely used AD scales were related to improved medication adherence in patients with AD and tried to find out what part of scales' items might be valuable.

Material And Methods

Eligibility and enrollment of participants

Participants diagnosed with mild-to-moderate AD according to the 2011 the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria were enrolled in this prospective study from Guangzhou First People's Hospital from June 2014 to June 2018. The participants were evaluated and screened using the Mini-Mental State Examination (MMSE) score and Global Deterioration Scale (GDS). Patients with the MMSE score ranging from 11 to 26 points with the graduated primary school education level or above, patients with the MMSE score ranging from 11 to 22 points with primary school education level, and patients with GDS scales between mild and moderate degree were included in the study. Patients with severe and extremely severe dementia or with dementia caused by vascular diseases, depression, and other diseases were excluded. Patients under the primary school education level were excluded due to the need for the ADAS-Cog examination. All patients should have stable and well-communicated caregivers. Fifty-eight potentially eligible patients signed inform consent form. Twenty-seven patients were excluded because of lacking on collaboration in pre-experiment, such as caregivers did not have enough time to monitor medication intake for patients, or patients could not finish all scales in any reasons. Finally, thirty-one participants finished the procedures.

Follow-up visit procedures

Follow-up visits were conducted for 10 months after enrollment, and then scale evaluations were implemented in the 1st, 2nd, 4th, and 7th months and at the end of the follow-up period (10th month). After the second follow-up, two patients dropped out of the study due to the changes in their health conditions, and one patient quit before the last follow-up for personal reasons.

Improving the medication adherence

Physicians, clinical research nurses, and clinical pharmacists participated in the study as researchers. The principal investigator clarified the importance of medication adherence to participating physicians, patients, and caregivers before the study. The physicians encouraged patients and their caregivers to maintain adherence during every visit. The clinical research nurses handed out medication record cards to caregivers. The clinical pharmacists created and maintained medication files for each patient independently, calculated the remaining pills before taking, distributed the medications of next phase and recorded the medication adherence by counting the pills. The caregivers supervised the patients in taking

the drugs, recorded the card after taking medicine, and recorded the reasons for poor adherence, such as missing by mistake or barely forgetting to take medicine. White pills made from starch were used in the study.

Adherence calculations

Due to the frequent intake of medicine (two times per day) and pills (three pills per day), the medication adherence was directly measured by the pill counting method and rechecked using the medication record cards during the whole study period. The specific calculation method for the medication adherence rate was as follows: (Number of drugs dispensed minus the number of remaining drugs)/(Number of drugs prescribed per day× Number of days between two visits). For the treatment of overdose (i.e., the medication compliance rate exceeding 100%), the adherence rate started with 100%; the excess part was considered poor adherence, which was subtracted from 100% (if the actual measurement adherence was 125%, it was converted as follows: 100 – (125–100) % = 75%).

Implementation of scales and data collection

The data on name, age, sex, education level, relation between caregivers and patients, AD disease duration, and Apolipoprotein e 4 (APOE4) gene types of participants were collected after signing informed consent. Details on the MMSE score and GDS level of participants were collected after enrollment immediately. The same neurologist implemented the screening scales (MMSE and GDS) and all experimental scales (ADAS-Cog, ADL, and NPI) except the CIBIC-Plus. Another doctor independently completed the evaluation of the CIBIC-Plus scale. The scores of ADAS-Cog, ADL, NPI, and CIBIC-Plus scales were recorded at every visit. Because CIBIC-Plus is scoring on a 7-point Likert scale ranging from 1 (markedly improved) to 7 (markedly worse), we set no change as 0. The level of 3, 2, and 1 was set as markedly improved, moderately improved, and slightly improved, respectively. Also, the level of − 3, − 2, and − 1 was set as markedly deteriorated, moderately deteriorated, and slightly deteriorated, respectively. The NPI scale was divided into two parts: the total scores of the frequency and severity (frequency multiplied by severity) and the scores of caregivers' own distress, being tagged as NPI score and NPI boring.

Statistical analysis

Data were analyzed using SPSS 23.0 software (SPSS Inc., IL, USA), and OriginPro 8.0 SR2 (OriginLab Corp., MA, USA) was used for creating graphics. The scores and medication adherence data of all scales were consistent with the homogeneity of variance but not with normal distribution. According to clinical experience (population characteristics, disease incidence, and medication habits of Chinese patients), the distribution of patients' cognitive function, daily behavioral function, and overall function followed the normal distribution; medication adherence rate, the mental and behavioral abnormalities followed the skewed distribution. CIBIC-plus scores were orderly graded into seven levels and considered as multiple sets of non-qualitative variables. Because continuous variables also can be considered as interval variables, the relation between the medication adherence rate and CIBIC-Plus scores was evaluated using

the two-sample correlation analysis Kendall test, which was more efficient for ranked data. The correlation analyses for scales and adherence were performed using two-samples Spearman correlation analysis. The non-normal distribution data cannot undergo partial correlation analysis, and therefore scale scores and medication adherence rate were transformed before analysis being carrying out. An ascending order was found for ADL scores and medication adherence rate, while a descending order was observed for the remaining scales (the higher the scale score, the higher the functional deterioration). Our previous study showed that some objective factors (sex and disease course) related to patients significantly or nearly significantly correlated with medication adherence rate, so sex and disease course of patients were included as control factors in the partial correlation analysis after rank-sum transformation. Spearman correlation analysis was conducted between the 12 items of ADAS- cog scores and medication adherence separately. A significance level of $p < 0.05$ was assumed as statistically significant.

Results

Characteristics of study population, medication adherence and scales

The baseline cognition and demographic characteristics of participants are shown in Table_1. Overall improving medication adherence rate was 98.04% in median; 25 quartile was 91.22% and 75 quartile was 100%. The overall medication adherence changes and medication adherence of each participant during the follow-up period are shown in Figure_1, while the changes in each scale are shown in Figure_2.

Correlation between scales and medication adherence

The nonparametric correlation test was conducted between the neuropsychological assessment scales and the medication adherence rate of patients with AD, revealing no correlation (Table_2). The results also showed no correlation between the scale and medication adherence in partial correlation analysis (Table_2).

The correlation of scores of Commands and Constructional Praxis items from Alzheimer's Disease Assessment Scale-Cognitive with a medication adherence rate was statistically significant ($P < 0.05$, correlation coefficients 0.201 and 0.177, respectively) (Table_3).

Discussion

This study showed no relation in correlation and partial correlation analyses between the widely used AD-related assessment scales and the patients' medication adherence after negative subjective factors being eliminated. Meanwhile, items of Commands and Constructional Praxis of ADAS-Cog had a weak correlation with medication adherence with the involvement of caregivers.

The relation between cognition impairment and decline in adherence was established[6, 11, 13]. A rapid decline in cognitive function, increase in behavioral abnormalities [20], and heavy stress on caregivers

[21] could lead to a decline in medication adherence. Poor adherence existed long before dementia occurred, and might be a very sensitive marker of early functional decline [13]. Cognitive impairment, especially the deficits in the domains of memory or planning and executive function, has been found to increase the risk of unintentional nonadherence, such as simply forgetting doses [24], poor recall of drug names and dosing directions [25], and inability to organize complex dosing schedules [10]. However, whether scales assessing these cognitions would have effect on medication adherence was still in debate. Our results indicated that no relation between total points of each scale and the medication adherence. In the previous studies, correlations were found between MMSE, self-reported Instrumental Activities of Daily Living capacity with self-reported medication management capacity [12]. Hayes et al. (13) showed that correlation between MMSE and medication adherence was not found, while between ADAS-Cog and medication adherence did exist. The difference between results might be lie in three aspects. The patten of adherence of our study had been improved by eliminating the negative subjective factors. Secondly, these studies based on the different research populations. Hayes et al. [13] excluded the population with dementia, which meant that populations in their study received little help from caregivers. Edelberg et al. [12] chose the ambulatory community-dwelling old patients whose clinical level of functioning were unknown. And the involvement of caregivers should be taken considered. Our study design meant that the caregivers took the most part of responsibility in medicine taking.

ADAS-Cog consisted of 12 items. Item ‘Commands’ required performance and language; ‘Constructional Praxis’ reflected the visuospatial praxis ability [14]. Hayes et al. [13] revealed that both memory and nonmemory subtests of ADAS-Cog had relations with adherence, and the greatest difference between the different cognitive function groups was in the non-memory subtests. Although they did not check the relationship of each part of non-memory subtests with medication adherence, they excluded the planning and executive function combined with the results of Trails test. The result different from another study: executive function and working memory did have an effect on medication adherence [26]. The reason on these differences might be on the concept that medication taking requires multiple cognitive processes [13]. Previous finding suggesting that decreased adherence in patients with dementia was associated with decreased attention and memory [23]. Executive function (the ability to set priorities, plan, and organize) and memory (the ability to recall information) were thought to be critical for the tasks involved in medication self-management [26]. However, these studies were based on a mixture of patient self-medication and caregiver-assisted medication without any intervention. While the design of medicine taking in the present study was mainly based on the help from caregivers but not on participants’ self-management. The ability of patients with AD to take medication was significantly dependent on their caregivers [23]. Generally, patients with very mild dementia or no cognitive impairment would take medication mainly by themselves, while patients with very severe dementia completely relied on their caregivers to take medication [27]. The latter might have a higher adherent rate [11]. After intervention, the medication adherence was mainly related to poor executive ability, practical ability, language, or visuospatial ability but not with memory, orientation, and attention ability. The problem of memory and attention could be corrected by caregivers, but impairment involved with communication would undermine the adherence. The role of caregivers in medication management has not been paid enough

attention to [6]. The key points in improving medication adherence of patients with AD might be the help from caregivers and the communication with patients.

To deal with overdose medication, several methods were implemented in previous studies. One method was abandoning these data, and the other was resetting adherence to a fixed value, such as the adherence rate being more than 105% reset to 70%, and between 100% and 105% reset to 100% [28]. This qualitative method was based on the consideration that normal people might occasionally make mistakes. However, this method might lead to abnormally high adherence if overdose exceeded too much. We considered that 100% was different from 95% or 105%, but 95% had no discrimination with 105% on the medication adherence rate. This study was novel in adopting the method of deducting the part over 100% from 100% based on 100% to deal with the drug overdose taking status.

Previous studies indicated that some assessment scales exhibited the potential to evaluate medication adherence or management abilities of an old population with dementia, such as Medication Management Ability Assessment (MMAA), MedTake test, Drug Regimen Unassisted Grading Scale (DRUGS), and The Medication Discrepancy Tool (MDT) [11, 12, 29]. However, these scales have not been applied specially for the population of AD patients yet. Participants with the MMSE score < 16 were excluded in MMAA and DRUGS studies [29]. Further research on effective assessment was needed because of the lack of gold standard of assessment scales for this population [29].

This study had some limitations. Patients diagnosed with severe and very severe AD were excluded because some studies believed that such patients did not benefit much from continuing to take anti-dementia drugs [30]. This population had a totally different medication pattern because they lost the ability of taking medicine and needed the help from caregivers entirely. Secondly, some widely used scales, such as the Total Decline Scale and Clinical Dementia Rating or MMSE, were not included in the study. However, considering that the evaluated functions were similar to those of ADAS-Cog and CIBIC-Plus, we believed that the correlation with medication adherence would be similar to that in the present study. In addition, except for objective factors, whether these scales are related to subjective factors of adherence or whether some of them can better indicate the degree of adherence is not clear. Related studies should be carried out to finally establish a scale to predict the medication adherence of patients with AD.

Conclusions

Four widely used AD neuropsychological scales showed no relation with medication adherence rate which improved by multiple methods in AD patients. But performance, language, and visuospatial ability might be related to medication adherence in these population. Further research on medication adherence assessment scales for AD population was needed.

Declarations

Ethical considerations

All methods were carried out in this study were in accordance with the Declaration of Helsinki. Ethics approval and consent to participate. The study was approved by the ethics committee of Guangzhou First People's Hospital (approval No. K-2021-069-01) and SFDA (approval No. 2011L00942)). All consents from the patient’s legally authorized representative were received.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from Good Clinical Practice office of Guangzhou First People’s Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Good Clinical Practice office.

Conflict of interest

The authors declare that they have no competing interests

Funding information

This work was supported by Guangzhou Municipal Health Commission [grant number 20141A011001, 2014].

Author contributions

MH carried out the scales and data collection, was a major contributor in writing the manuscript. YW led on the statistical analysis, conception and design. All authors read and approved the final manuscript.

Acknowledgements

We gratefully acknowledge Xiaoping Pan, Yingjun Ouyang, Aihua Guo, Tao Zeng, Jianxi Hu, Rong Hu, and Lili Zheng for help on implementation of scales and enrollment of patients.

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Tables

Table 1 Baseline characteristics of the population

Variables	
Age, Year	74.71 ± 7.39
Sex, No. (%)	
Female	18 (58.06)
Male	13 (41.94)
Education, Year (%)	
Elementary school	21 (38.71)
Junior high school	5 (16.13)
Senior high school	11 (35.48)
University or above	3 (9.68)
Course of disease, year	2.06 ± 1.23
Caregivers, No. (%)	
Spouse	12 (38.71)
Son/Daughter	14 (45.16)
Grandson/Granddaughter	2 (6.45)
Sister/Brother	2 (6.45)
Others	1 (3.23)
APOE gene types, No. (%)	
ε2/ε2, ε2/ε3, ε3/ε3	17 (58.6)
ε3/ε4	9 (31.0)
ε4/ε4	3 (10.3)
GDS stage, No. (%)	
Mild cognition impairment	18 (58.06)
Moderate dementia	13 (41.94)
MMSE, Point	18.69 ± 4.78
ADAS-Cog, Point	20.24
ADL, Point	64.5
NPI score, Point	8.9
NPI boring, Point	4.32
CIBIC-Plus, Point	0

Adherence rate (%)	98.04 (91.22, 100)

Plus–minus values are means ± SD. APOE, apolipoprotein E; GDS Global Deterioration Scale; MMSE, Mini-Mental State Examination. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL, Activity of Daily Living Scale; NPI score Neuropsychiatric Inventory Point of patients' symptom score; NPI boring, Neuropsychiatric Inventory levels of caregivers' boring; and CIBIC-Plus, Clinician Interview-Based Impression of Change plus carer interview. CIBIC-plus scores were orderly reformatted from graded five levels: from 3 (markedly improved) to –3 (markedly worse), while no change was set as 0.

Table 2 Correlation and partial correlation between Alzheimer's disease assessment scales and medication adherence rate

	Medication adherence			
	Correlation coefficient*	P	Partial correlation coefficient	P
ADAS-Cog	0.121	0.147	–0.097	0.303
ADL	–0.090	0.281	–0.112	0.237
NPI score	0.047	0.570	–0.046	0.626
NPI boring	0.138	0.096	–0.119	0.206
CIBIC-plus	–0.015	0.839	0.025	0.794

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL, Activity of Daily Living Scale; NPI score Neuropsychiatric Inventory Point of patients' symptom score; NPI-boring Neuropsychiatric Inventory levels of caregivers' boring; and CIBIC-Plus, Clinician Interview-Based Impression of Change plus carer interview. *The correlation coefficient was Spearman rho coefficient or Kendall Tau_b coefficient. Sex and disease course of participants were included as control factors in the partial correlation analysis.

Table 3 Correlations between 12 items of Alzheimer's Disease Rating Scale-Cognitive and medication adherence rates

	Medication adherence rates	
ADAS-Cog	Correlation coefficients	P
Word recall	0.019	0.822
Naming objects and fingers	0.042	0.612
Commands	0.201	0.015*
Constructional praxis	0.177	0.033*
Ideational praxis	0.105	0.206
Orientation	0.060	0.472
Word recognition	0.131	0.114
Recall of test instructions	0.013	0.873
Spoken language ability	−0.088	0.289
Word-finding difficulty	−0.066	0.431
Comprehension of spoken language	0.005	0.948
Attention	0.017	0.843

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive. *P < 0.05 shows a statistically significance on correlation between the Alzheimer's disease rating scale-cognitive part and medication adherence rates.

Figures

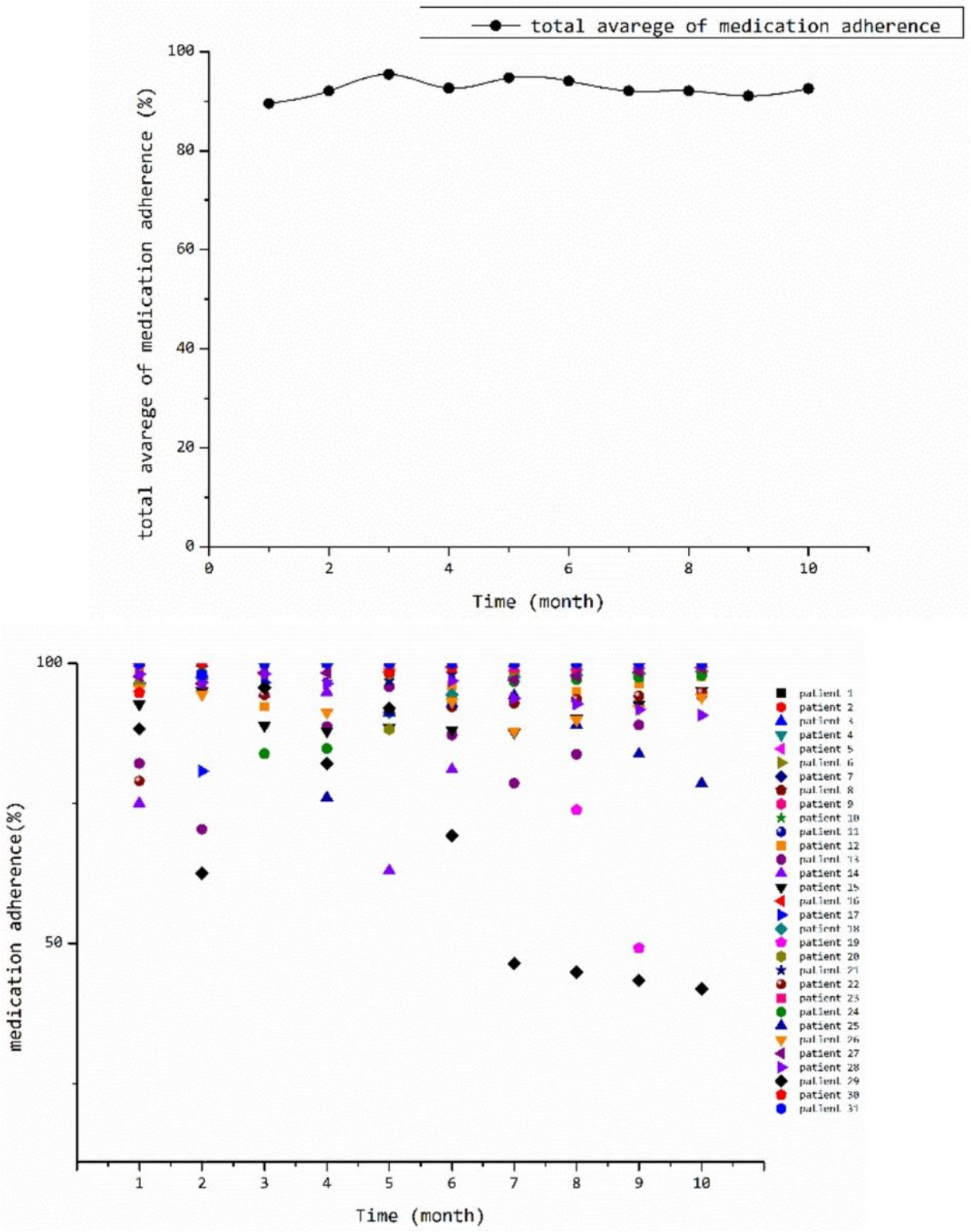

Figure 1

Medication adherence in participants with Alzheimer's disease

(Left) Overall average rate and changes in medication adherence in participants with Alzheimer's disease. (Right) Monthly medication adherence rate of each enrolled participant.

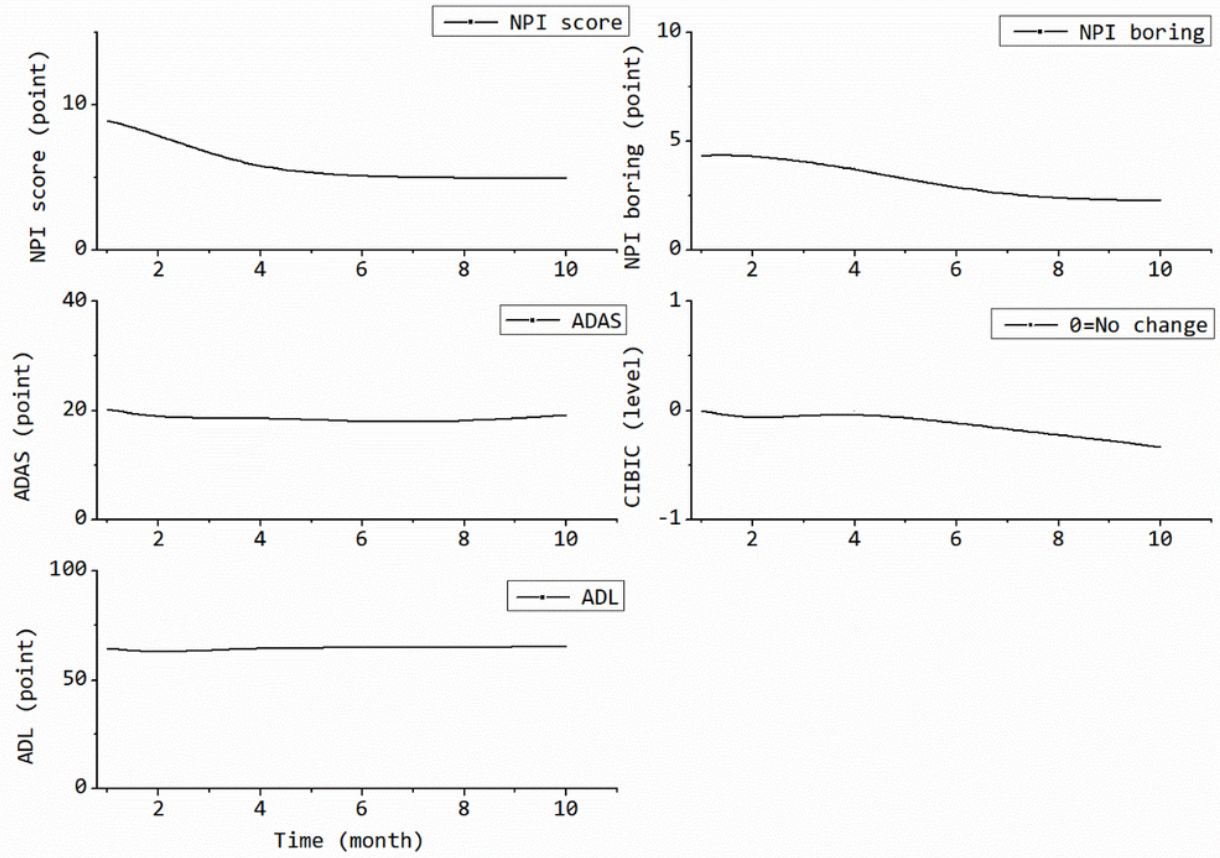

Figure 2

The changes of four scales in Alzheimer's disease patients over 10 months

ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL, Activity of Daily Living Scale; NPI score Neuropsychiatric Inventory Point of patients' symptom score; NPI-boring Neuropsychiatric Inventory levels of caregivers' boring; and CIBIC-Plus, Clinician Interview-Based Impression of Change plus carer interview.