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Efficacy of Acetylcholinesterase Inhibitors in the Logopenic Variant of Primary Progressive Aphasia

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Keywords
Acetylcholinesterase inhibitors · Alzheimer's disease · Primary progressive aphasia · Logopenic variant of primary progressive aphasia · Alzheimer therapy

Abstract
Introduction: For over 25 years, cholinesterase inhibitors (ChEIs) have been the main symptomatic treatment for Alzheimer's disease (AD). Several meta-analyses have supported their effectiveness in various neurocognitive, functional, and behavioral aspects of amnestic AD. Over 86% of cases of the logopenic variant of primary progressive aphasia (lvPPA), also named language variant AD, are caused by a similar pathologic process than AD, yet no study has examined the efficacy of ChEIs in this AD variant. We aimed to explore the efficacy of ChEIs in the treatment of lvPPA by comparing their evolution on the MMSE, and other functional and behavioral parameters, to that of treated amnestic AD patients. ***Methods:*** A retrospective chart review was performed in 45 patients with lvPPA and 52 patients with amnestic AD. Both groups were similar in terms of age, level of education, and onset of symptoms. Drug history and MMSE scores, as well as functional (activities of daily living [ADLs] and instrumental activities of daily living [IADLs]), neurocognitive and neuropsychiatric symptoms were collected on several time points before and after the introduction of ChEIs. Data were analyzed using ANOVA and a generalized linear mixed model. ***Results:*** Patients with lvPPA showed a similar trajectory of decline than amnestic AD patients on serial MMSEs up to 12–24 months after the introduction of ChEIs. There was a significant impact on ADLs but not IADLs and neuropsychiatric symptoms remained stable over time. ***Conclusion:*** This study provides preliminary evidence for efficacy of ChEIs in patients with lvPPA and suggests similar benefits to those seen in amnestic AD patients, hence reassuring patients and their physicians.

Introduction

Alzheimer's disease (AD) is a highly prevalent disorder that affects approximately 2–4% of the population [1] and represents 50–70% of cases of neurocognitive disorders [2]. It manifests in four distinct variants: amnestic (most prevalent) [3], language [4], visual [5] and behavioral [6]. The language variant AD is also classified under primary progressive aphasias (PPA) as the logopenic variant

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(lvPPA). Clinically, lvPPA presents with impaired word retrieval in spontaneous speech and naming as well as impaired repetition of long sentences, mostly the latter part, and phonological errors [7]. Language dysfunctions occur early into the disease and are often followed by executive, calculation, visuospatial, and memory deficits [8].

For many years, FDA-approved treatments for amnestic AD have included cholinesterase inhibitors (ChEIs) and N-methyl d-aspartate antagonists, or a combination of both [9]. These molecules do not address the underlying cause of the disease but rather aim to manage the symptoms [10]. Recently, two monoclonal antibodies (lecanemab and donanemab) which target the underlying causal process [9] have entered the therapeutic arsenal against AD. These drugs have successfully reduced amyloid burden and tau accumulation, and have led to moderately less decline on measures of cognition and function than placebo for patients in the early stages of the disease [9, 11–15]. Although promising, they are not widely accessible yet; thus, most patients continue to rely on ChEIs and N-methyl d-aspartate antagonists to manage their symptoms.

ChEIs are usually prescribed for mild to moderate stages of the disease. Multiple meta-analyses have shown their positive impact on cognition (increase on the Mini Mental State Examination [MMSE]), particularly during the first 6 months and sometimes up to 2 years after the introduction [16–20]. ChEIs are also known to improve general clinical impression as assessed by the clinician [16, 18, 19], symptoms [20] and functional capacities [20] as assessed by the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory or the Disability Assessment for Dementia (ADAS-Cog) [21], and to decrease mortality [20]. However, other meta-analyses have shown that ChEIs did not have a significant impact on the quality of life score [16, 22]. Regarding psychological and behavioral symptoms, results are mixed, showing little or no effect [16, 17, 19, 23, 24].

Clinical evidence of the benefits of ChEIs in lvPPA is scarce, as this variant AD is usually not included in AD clinical trials. Only one study suggested that a subpopulation of PPA patients could benefit from ChEIs, but they were not clearly identified as lvPPA patients [25]. Physiopathological studies strongly suggest that ChEIs would be justified among lvPPA patients to counteract acetylcholine decline. Mesulam and colleagues [26] determined that brains affected by PPA with an underlying Alzheimer pathology (PPA-AD) displayed greater damage in the cholinergic system than those with tau or TDP-43 pathology, and that this damage was more prominent in the language areas. Another study focusing on cholinergic deficits among the PPA variants suggested that only lvPPA showed a decrease in acetylcholine levels compared to controls [27].

The goal of this study was therefore to explore the efficacy of ChEIs in patients with lvPPA by comparing their cognitive performance on MMSE over time to that of patients with amnestic AD treated with ChEIs. We further explored the impact of treatment on various functional (activities of daily living [ADLs] and instrumental activities of daily living [IADLs]), neurocognitive and neuropsychiatric symptoms in lvPPA.

Methods

Participants

We conducted a monocentric retrospective study. We included patients with a diagnosis of lvPPA and amnestic AD. All patients had been followed at our tertiary memory clinic (La Clinique Interdisciplinaire de Mémoire – CIME du CHU de Québec, Quebec City, Canada). To be included in the study, participants needed to have received a diagnosis of lvPPA (based on Gorno-Tempini's criteria [7]) or amnestic AD (based on McKhann's criteria [3]) by an experienced neurologist. Patients who had a comorbid diagnosis of addiction (alcohol or drugs) according to DSM-V or a somatic comorbid diagnosis that could impact cognitive capacities or cerebral structures (brain tumor, MS, lupus, epilepsy, other neurodegenerative disease, normal pressure hydrocephalus, ischemic or hemorrhagic stroke) were excluded. Patients were included in treated groups if they had taken ChEIs for more than 3 months. Two lvPPA patients did not take ChEIs for personal reasons.

Ambiguous diagnoses were discussed with a team including a neurologist (R.L.) and a speech-language pathologist (M.L.), both with a strong clinical experience in PPA. Decision whether to include a participant or not was obtained by consensus. This study was approved by the Research Ethics Board at CHU de Québec, Quebec City, Canada. Participants gave their written informed consent to participate. Permission to used data from deceased participants was obtained through the closest living relative, whom was usually the person capable of consenting to care for the patient.

Data Collection

For lvPPA participants, data were collected from medical records including assessments by neurologists or geriatricians, speech-language pathologists, clinical neuropsychologists, occupational therapists, physiotherapists,

Table 1. Sociodemographic data

	Language variant AD (n = 45)	Amnestic variant AD (n = 52)
Sex (M/F)	21/24	20/32
Age (M, SD)	67.3 (17.1)	68.9 (9.6)
Number of years of education (M, SD)	13.3 (3.8)	13.96 (3.59)
Number of years since symptoms onset (M, SD)	3.0 (1.6)	2.19 (1.28)

AD, Alzheimer's disease.

and social workers. The following data were extracted: (1) sociodemographic data including gender, years of education, institutional placement, civil status; (2) clinical data, including cognitive tests scores on the MMSE (WORLD and 100-7)[1] as well as other cognitive skills (memory, executive, visuospatial, praxis, gnosis, calculation, language), functional independence (activities of daily living [ADL] and instrumental ADL), behavioral and psychological symptoms of dementia (BPSD); and (3) biomarkers including structural MRI – dementia protocol, molecular imaging (FDG-PET), and AD biomarkers in cerebrospinal fluid (aβ1-42, total-tau, phospho-tau).

For most variables, data were collected in an Excel file (binary scoring: 0 = not impaired; 1 = impaired). In order to minimize rater bias, we conducted an inter-rater reliability test on 10% of the data and the agreement was satisfactory (>80%). For the rest of the scoring, in case of doubt, the examiner discussed with the other team members who had strong clinical experience with PPA to ensure accuracy of scoring.

Data were adjusted so that the baseline corresponded to the introduction of the medication for each patient. The time point corresponding to the time at 6 months prior to introduction of ChEIs (−6 months) mainly consisted of visits with the family physician, speech therapist, or neuropsychologist. The baseline (also named "Introduction of medication") always corresponded to the establishment of the diagnosis at our memory clinic. The +6 months' time point after ChEIs introduction was gathered from follow-up visits at our memory clinic. Subsequent follow-up data were obtained from family physicians whenever possible. Medication-related data were collected through local pharmacists. For each patient, the pharmacist was asked to provide drug type (donepezil, rivastigmine, galantamine), intake period, dose, route of administration, frequency, and if possible, compliance with treatment and adverse reactions. For AD patients, cognitive performances were collected at similar time points than for lvPPA participants.

Statistical Analyses

A repeated measures analysis of variance (ANOVA) was performed to compare performance on the MMSE of treated lvPPA and AD patients. Since patients did not all have the same number of visits, they contributed to the analysis according to the number of available visits. The effect of time, group, and their interaction were considered with a type 3 fixed effects test. The effect was considered significant with a $p < 0.05$.

A generalized linear mixed model was performed to compare the percentage of lvPPA patients presenting with each symptom in all assessed domains (cognition, language, ADL, IADLs, BPSD) at each time point. Data were only analyzed for lvPPA treated with ChEIs. For all variables, only the time points at −6 months, baseline (medication introduction) and 6 months were considered in the analysis, as there was a lack of data at the other times. The model took into account the dependence between observations (the fact that we followed the same group of patients) and the fact that some data were missing (not all patients provided data at each time point). We tested for the effect of group, time, and the interaction between the two. When the interaction was significant, only this effect was interpreted. In case of significant differences over time, multiple comparisons adjustments were made using the Tukey method.

Results

Ninety-seven participants were included in this study. Since ChEIs are routinely prescribed at our tertiary memory clinic, only 2 lvPPA patients had not taken ChEIs (for personal reasons; not cardiac related).

[1]The MMSE is scored out of 30. Within this calculation, 5 points are attributed when participants either spell the word WORLD backwards correctly or count backwards by sevens starting from 100 down to 65.

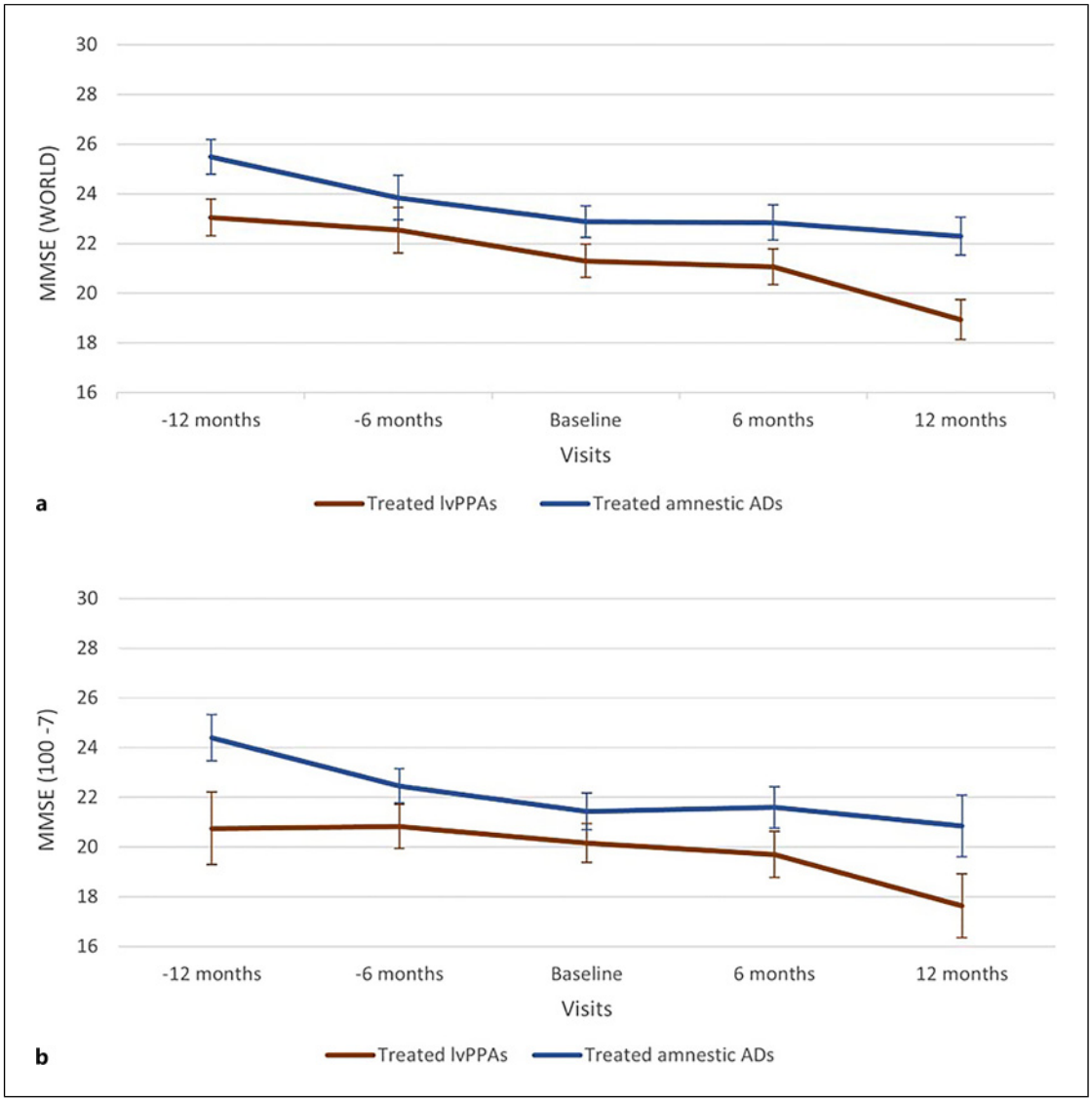

Fig. 1. a Cognitive trajectory of patients with lvPPA and amnestic variant AD on MMSE – WORLD over time. It should be noted that the data at −24 months and −12 months were obtained from a sample of fewer than 10 participants. **b** Cognitive trajectory of patients with lvPPA and amnestic variant AD on MMSE – 100-7 over time. It should be noted that the data at −24 months, −12 months, and 24 months were obtained from a sample of fewer than 10 participants. lvPPA, logopenic variant of primary progressive aphasia, also known as language variant AD.

Therefore, these 2 patients were not included in our analyses. Demographic and clinical data for both AD and lvPPA groups are presented in Table 1.

Cognitive Trajectories of lvPPA and Amnestic AD Patients on the MMSE over Time

Figures 1a, b and 2 show the cognitive trajectories of lvPPA and amnestic AD patients on the MMSE – WORLD and 100-7 in the year preceding and following introduction of ChEIs. Statistical analyses revealed a significant decline over time ($p < 0.0001$) in both amnestic AD and language AD groups for both MMSE versions. Analyses on the MMSE – WORLD showed that the AD group had a significantly higher score than lvPPA group at 12 ($p = 0.031$) and 24 months ($p = 0.001$) while analyses on the MMSE – 100-7 revealed the AD group had a significantly higher cognitive score than the lvPPA group at −12 months ($p = 0.037$) and 24 months ($p < 0.0001$). For the other time points, the treated lvPPA and AD groups followed a similar trajectory (see Table 2). The

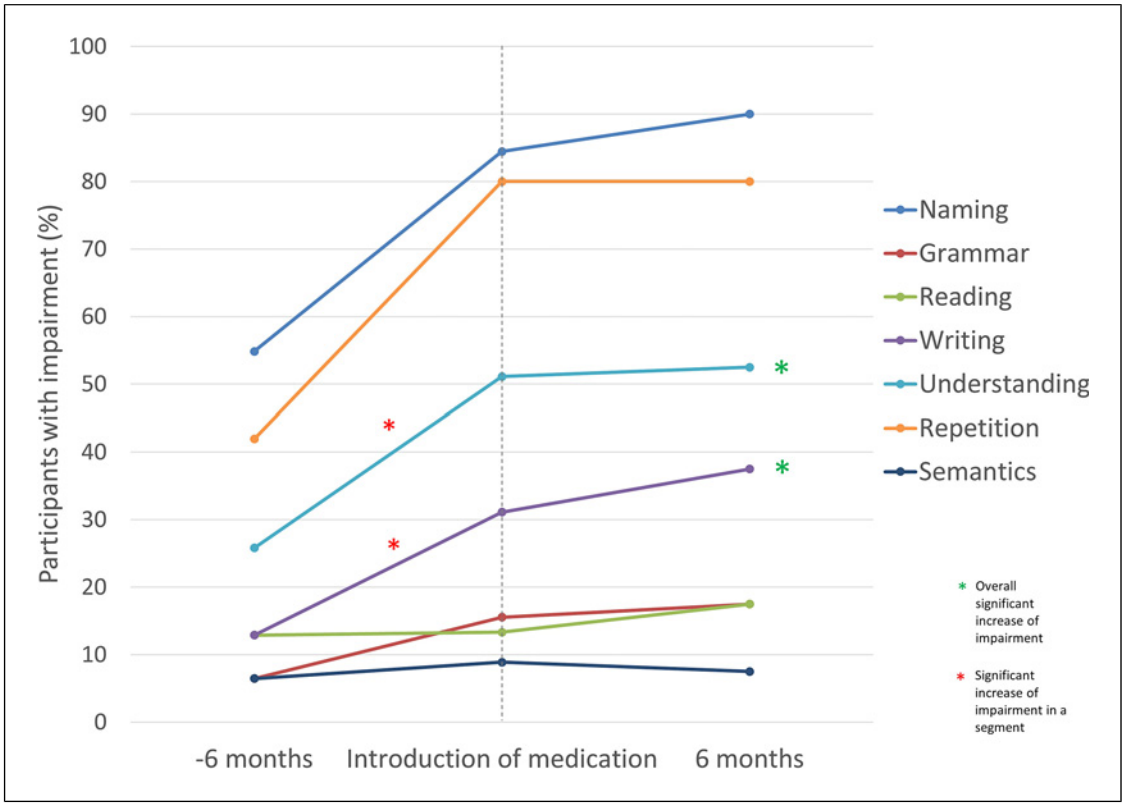

Fig. 2. Progression of various language impairments in participants with lvPPA before and after introduction of ChEIs.

Table 2. Mean scores on MMSE of treated amnestic and language variant AD at each time points

	MMSE – WORLD					MMSE – 100-7				
	language variant AD		amnestic variant AD		*p* value	language variant AD		amnestic variant AD		*p* value
	score	*n*	score	*n*		score	*n*	score	*n*	
–24 months	27.6	5	26.7	6	0.24	26.0	1	25.3	6	NA
–12 months	24.6	8	26.9	8	0.06	19.0	3	25.9	8	0.04
–6 months	23.5	22	25.0	24	0.16	23.3	10	23.8	24	0.15
Introduction	21.7	35	22.4	31	0.12	20.6	35	20.7	31	0.24
6 months	21.1	33	22.8	36	0.11	19.8	30	21.7	37	0.13
12 months	20.8	18	22.0	14	0.03	19.1	15	20.8	14	0.07
24 months	15.2	13	21.0	13	0.001	13.4	8	19.4	9	<0.0001

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination (max score on MMSE is 30).

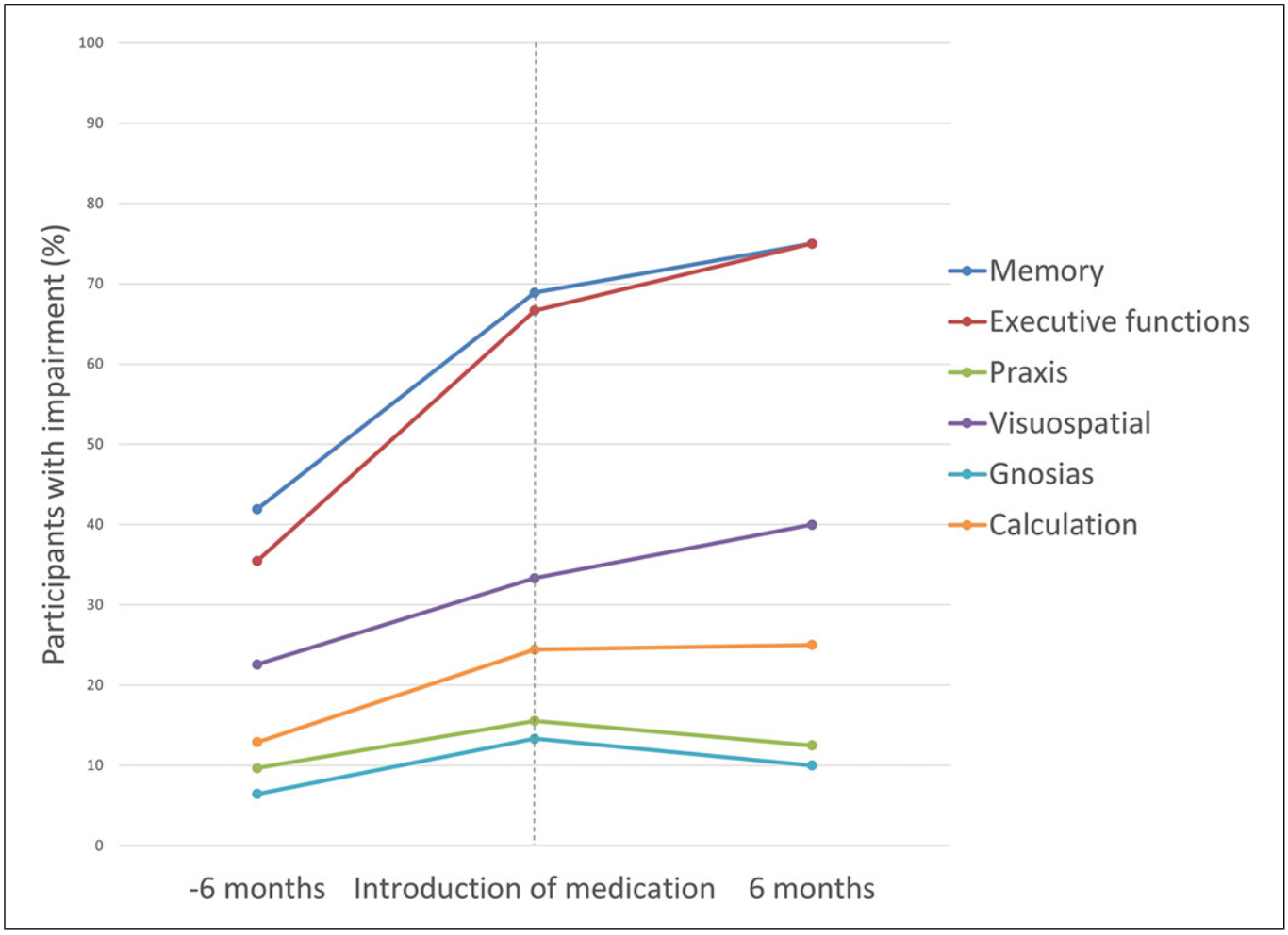

Fig. 3. Progression of various cognitive impairments in participants with lvPPA before and after introduction of ChEIs.

2 lvPPA patients who were not treated with ChEIs exhibited a severe decline in their MMSE (score of 7/30 at 12 months). It should also be noted that data at −24 months and −12 months for MMSE – WORLD and data at −24 months, −12 months, and 24 months for MMSE – 100-7 were obtained from a sample of fewer than 10 participants.

Progression of Impairment in the lvPPA Group

Figure 2 shows lvPPA participants' language impairments at each time point. No significant differences were observed between the different timepoints for naming, grammar, reading, repetition, and semantics. For writing and understanding, a significant increase in impairment was observed (for both $p = 0.009$). For both writing and understanding, post hoc analyses showed a significant difference between the −6 months and baseline time points (writing: $p = 0.031$; comprehension: $p = 0.015$), as well as between the −6 and 6 months' time points (writing: $p = 0.007$; comprehension: $p = 0.014$), but not between the baseline and 6 months' time points.

Progression of cognitive impairment is presented in Figure 3. No significant differences were found for executive functions, visuospatial abilities, gnosis, calculation, and praxis. However, a significant difference was found for memory ($p = 0.026$) for which a significant increase was found between the −6 and 6 months' time points only ($p = 0.037$).

In terms of functional independence (ADLs and IADLs), it should be noted that IADLs (cooking, housekeeping, grocery shopping, medication intake, driving, finances, gadgets) were significantly more impaired than ADLs (mobility, hygiene, dressing, eating, continence), as depicted in Figures 4 and 5. In fact,

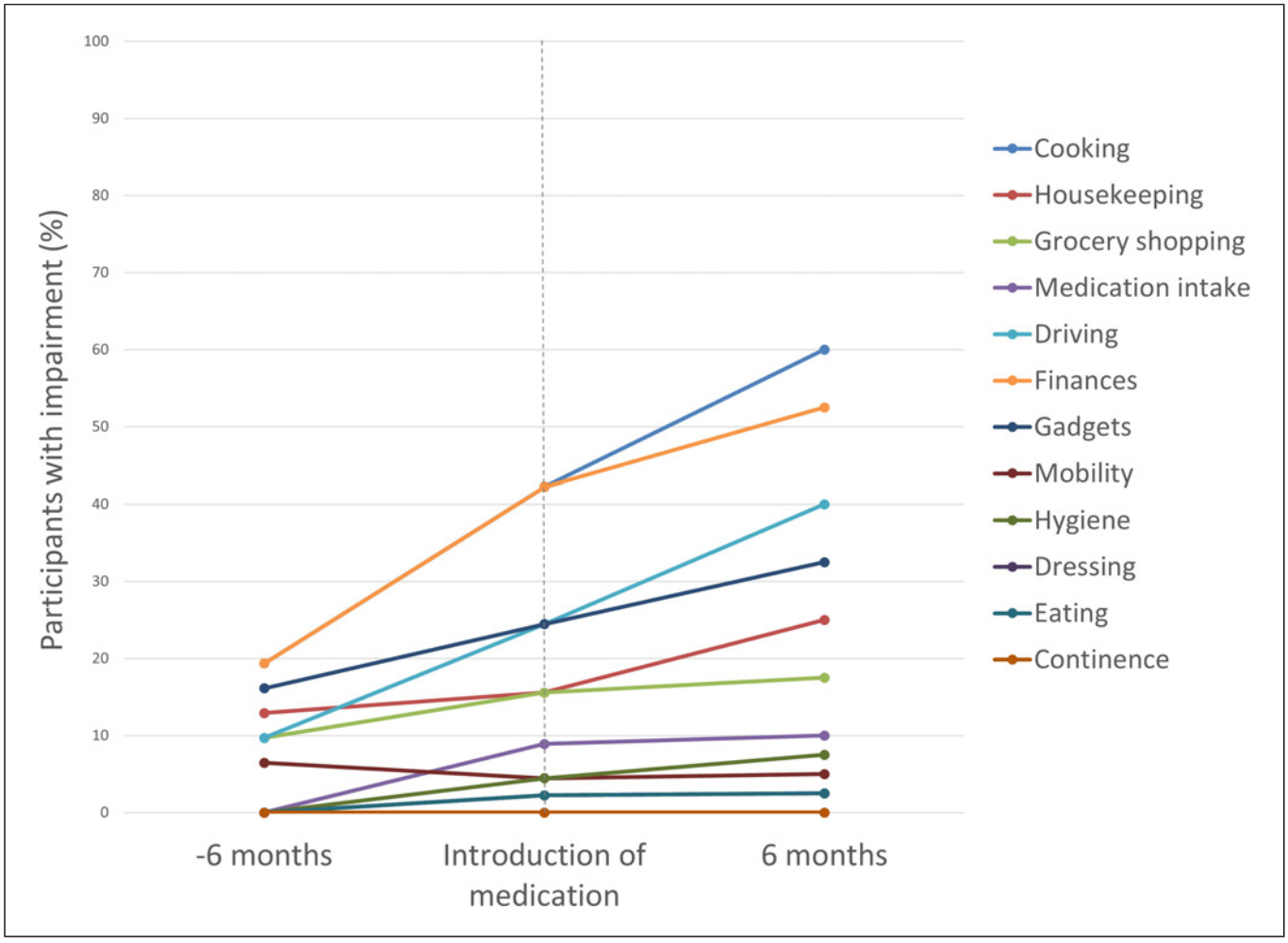

Fig. 4. Progression of various functional impairments in participants with lvPPA before and after introduction of ChEIs.

scarcity of ADLs' impairment prevented statistical analysis from being performed. Regarding IADLs, a significant increase in impairment was noted for cooking (p = 0.003), driving (p = 0.006), and finances (p = 0.010), but no differences were found for use of gadgets, housekeeping and grocery shopping. For cooking, post hoc analyses showed a significant difference between the −6 months and baseline time points (p = 0.038) as well as between the −6 and 6 months' time points (p = 0.001) and between the baseline and 6 months' time points (p = 0.042). Post hoc analyses on both finances and driving showed a significant increase in impairment between −6 months and baseline (finances: p = 0.011; driving: p = 0.038), −6 months and 6 months (finances: p = 0.003; driving: p = 0.001), but not between baseline and 6 months (finances: p = 0.419; driving: p = 0.058).

Results regarding BPSD are presented in Figure 6. No significant differences were found for anxiety, apathy, isolation, irritability, disinhibition, rituals, psychosis. However, a significant difference was found for depression (p = 0.045) and post hoc analyses showed a significant decrease between −6 months and baseline (p = 0.041). Figure 7 summarizes the results for all domains assessed in this study.

Discussion

This study suggests that ChEIs can slow cognitive decline in patients with the language variant AD [16–20] similarly to amnestic AD. We observed a similar longitudinal trajectory in their cognitive performance as assessed by MMSE up to 24 months after first medication intake.

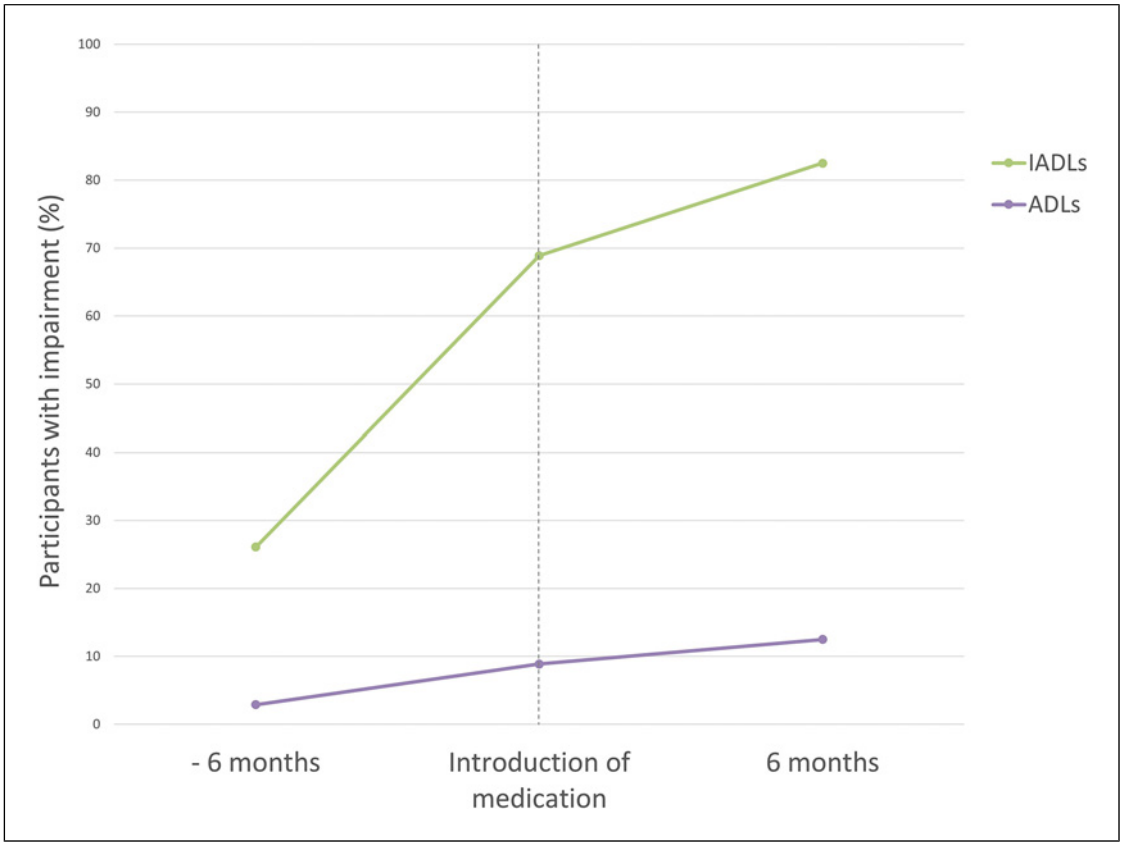

Fig. 5. Summary illustration of the progression of impairments in ADLs and IADLs in participants with lvPPA before and after introduction of ChEIs.

These results are in line with one study which found a positive impact of ChEIs in patients with a neurodegenerative language impairment and hypothesized that underlying amyloid pathology could be a therapeutic response predictor [26]. The cholinergic hypothesis of AD centers on the progressive loss of limbic and neocortical cholinergic innervation. Neurofibrillary degeneration in the basal forebrain is believed to be the primary cause for the dysfunction and death of forebrain cholinergic neurons, giving rise to a widespread presynaptic cholinergic denervation [28]. As lvPPA share the same pathophysiology as amnestic AD, it is likely that the use of anticholinergic medication help maintain cholinergic function for a certain period until the disease is more active and affects widespread areas of the brain. When this occurs, cognitive decline, as seen in amnestic AD and other AD variants becomes more severe. In this regard, upregulating the cholinergic system should be beneficial for all AD variants.

We observed a significant difference between the groups at the 12 months and 24 months' follow-ups on MMSE – WORLD, with amnestic AD participants performing better than logopenic patients. This could possibly be explained by progression of the language impairment in lvPPA and its growing impact on cognitive testing. Indeed, a study by Osher et al. [29] suggested that the MMSE score could overestimate the degree of cognitive impairment in PPA patients since it is highly dependent on language abilities. We must also consider several dropouts at follow-up, and less data at later time points, especially the 24 months' mark. Medication may also be less effective after that time point. Finally, the difference at –12 months for the MMSE 100-7 must be nuanced by the particularly low number of patients at this time point (n = 3) and the fact that one of them had a particularly low score.

Our descriptive data on the evolution of language impairments are consistent with the diagnosis, where naming and repetition are the most prevalent deficits [7]. For all language variables studied, there were no significant increases in the percentage of patients impaired between medication introduction and follow-up at 6 months. However, it is not possible to determine whether this is because medication delayed the onset of certain

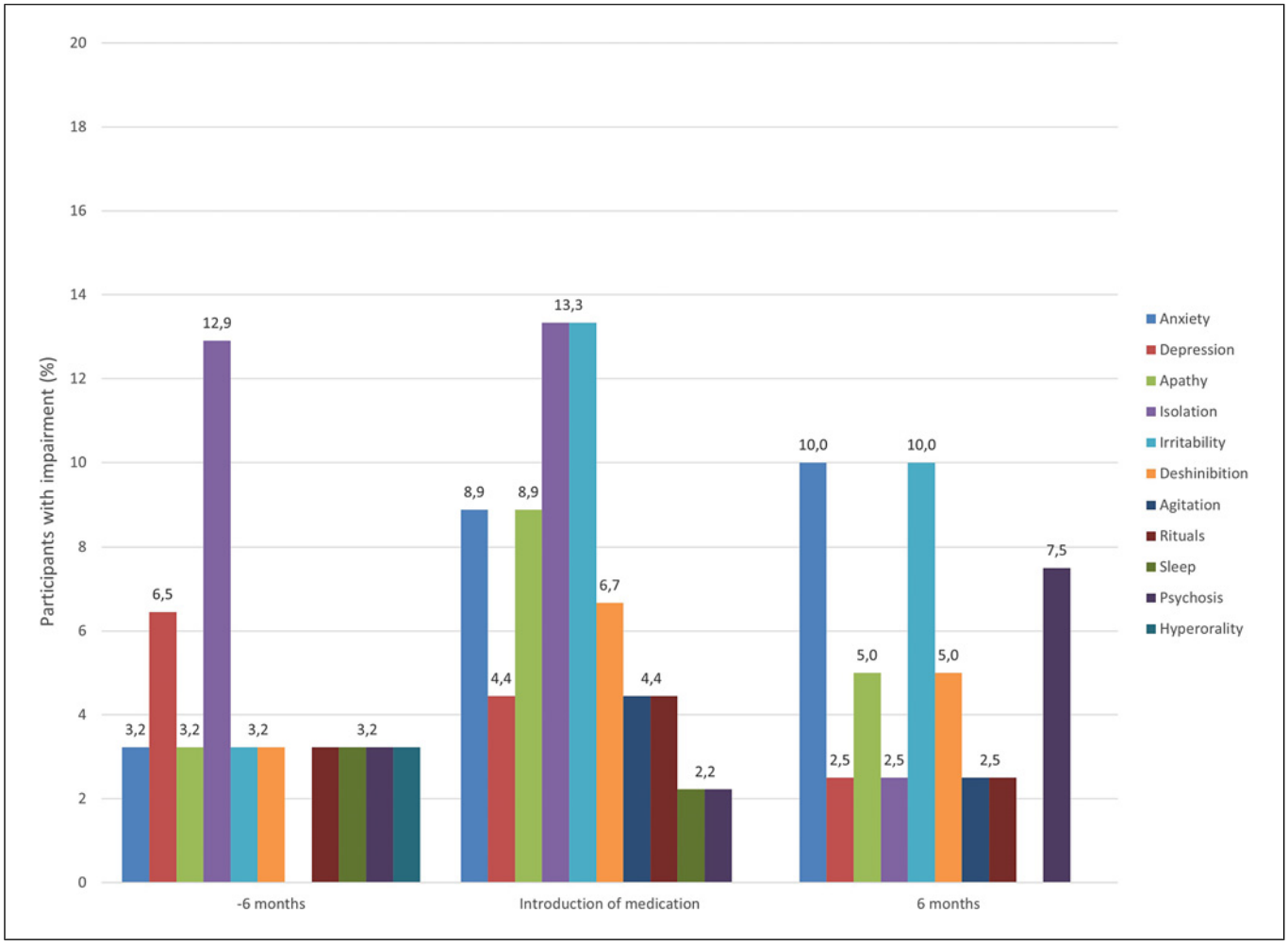

Fig. 6. Progression of various BPSD in participants with lvPPA before and after introduction of ChEIs.

deficits in participants that were not impaired at baseline or if the deficits were already present at medication introduction. Results for the various cognitive functions are in line with other studies showing memory, executive functions, and visuospatial abilities as being frequently impaired in this clinical population [8, 30, 31]. Previous studies suggested that ChEIs are effective in reducing cognitive symptoms [16–20] but that could not be entirely confirmed in this study. We observed marked impairments in functional independence, mostly for complex IADLs, which are expected in the context of a neurodegenerative disorder which affects cognition [32]. Although the introduction of the medication did not allow lvPPA participants to regain independence in their daily living, they remained stable regarding use of gadgets, housekeeping and grocery shopping. However, the binary scoring may not have been sensitive enough to capture mild changes in functioning after medication intake. Regarding BPSDs, the prevalence was relatively low for all symptoms and no significant changes were found between medication introduction and follow-up, consistent with previous studies [16, 17, 19, 23, 24].

This study is the first to include such a large number of patients, with 45 treated language variant AD and 52 treated amnestic AD. Its first and most important limitation is its retrospective nature. Most visits were not conducted at the same intervals due to time constraints. Data were not necessarily collected by the same professionals and such variability may have led to inconsistent assessments. A systematic comparison between functional and BPSD impairments in lvPPA and the amnestic variant AD would have also been very interesting. Transferring qualitative data from written report to a binary rating also proved to be complex. The variability in the terminology used by

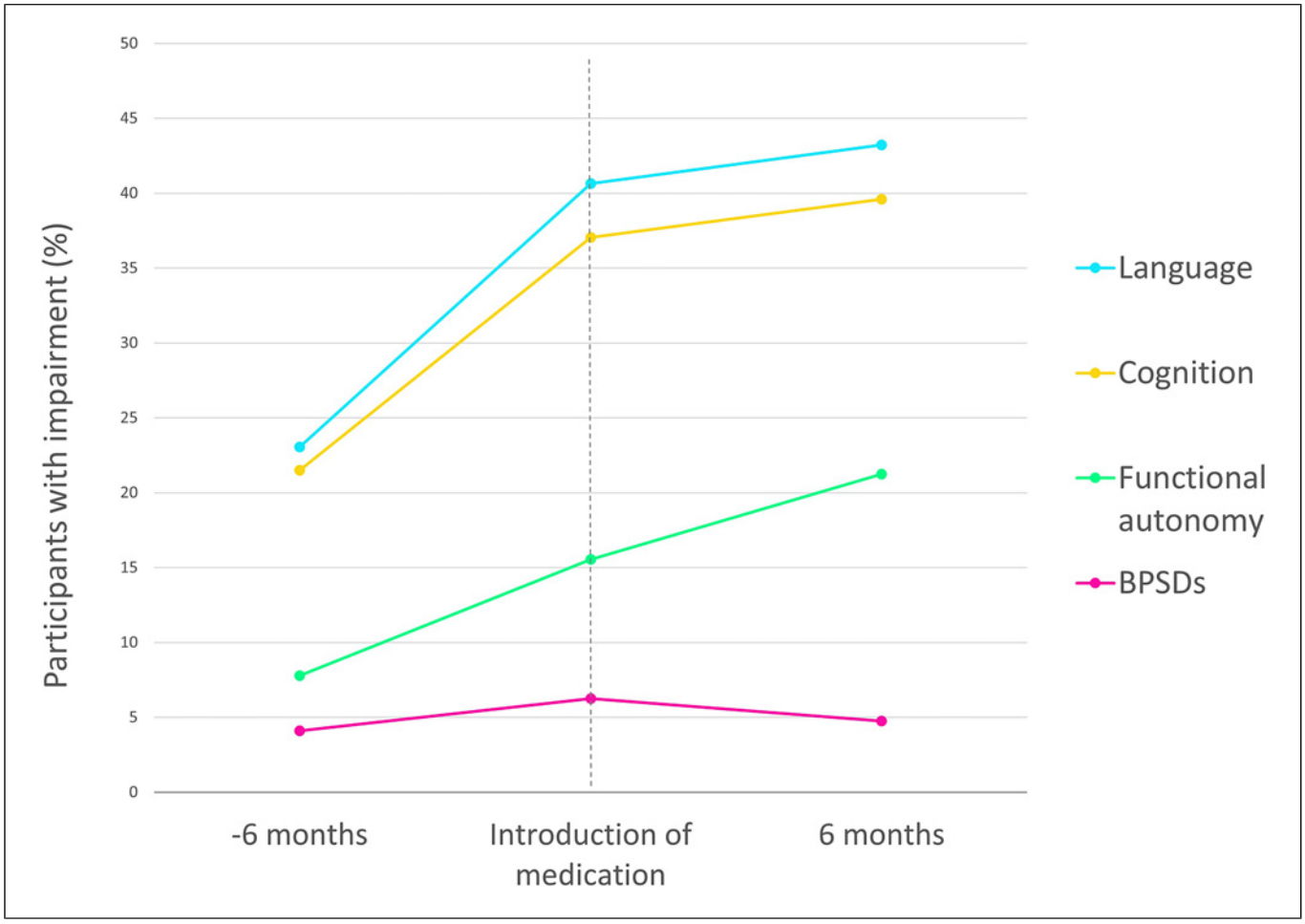

Fig. 7. Summary illustration of the progression in language, cognitive, and functional impairments as well as BPSD in participants with lvPPA before and after introduction of ChEIs.

different professionals when reporting observations made it challenging to consistently rate impairments. A second limitation is the absence of a control group. Indeed, the prescription of ChEIs is common practice in our part of the world where inhibitors are reimbursed by the government. Nonetheless, our data suggest that ChEIs are generally well accepted and tolerated by patients. The 2 patients in our cohort who did not take ChEIs seemed to have a significantly worse outcome than treated participants. Although there were losses to follow-up, it was primarily due to the difficulty in accessing primary care physicians' files (long-term follow-up beyond 6 months was performed by general practitioners). The number of patients who dropped out was not different between the two groups. Adverse effects typically occurred at the beginning of the follow-up period, so they cannot explain the dropouts at 1 or 2 years into the medication intake. The long follow-up period (24 months) is a strength of our study compared to previous work conducted in amnestic AD, where follow-up period is typically no longer than 36 weeks [20]. In future studies, a longer follow-up period would better assess the drug's window of effectiveness. Finally, another limitation is the use of MMSE [8]. While this screening tool allows quick and frequent evaluation of multiple cognitive domains, it is likely that subtle changes in cognition are not captured by the MMSE [33]. Moreover, it may not be well adapted for patients with language deficits [34]. Future work should focus on developing adequate language tools for follow-up of progressive degenerative aphasias.

In conclusion, results from this study suggest that ChEIs can slow cognitive decline in lvPPA patients to a similar degree than in amnestic AD. This is consistent with the fact that they share similar pathology. In turn, our results suggest that ChEIs are appropriate to treat

lvPPA patients and could stabilize their cognitive and language abilities, at least for 1 year after the beginning of medication intake. Despite the exploratory nature of this study and the need to replicate results in larger cohorts of participants, our results will help physicians be more confident when prescribing ChEIs to this clinical population. Patients and their families will also benefit from scientific data, which support its use and inform them about expected benefits.

Acknowledgments

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Statement of Ethics

This study protocol was reviewed and approved by the *Comité d'éthique de la recherche (CER) du CHU de Québec-Université Laval*, SIRUL 125822. Participants gave their written informed consent to participate. Permission to used data from deceased participants was obtained through the closest living relative, whom was usually the person capable of consenting to care for the patient.

Conflict of Interest Statement

All authors do not have any financial nor personal conflicts to disclose.

Funding Sources

The funder had no role in the design, data collection, data analysis, and reporting of this study.

Author Contributions

Julie Carrier-Auclair: study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript. Monica Lavoie and Robert Laforce Jr: study concept and design, analysis and interpretation of data, and preparation of manuscript. Maud Tastevin: study concept and design.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available the corresponding author (R.L.).

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