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Baseline neuropsychiatric symptoms and psychotropic medication use midway through data collection of the Longitudinal Early- Onset Alzheimer's Disease Study (LEADS) Cohort

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Abstract

INTRODUCTION: We examined neuropsychiatric symptoms (NPS) and psychotropic medication use in a large sample of individuals with early-onset Alzheimer's disease (EOAD; onset 40–64 years) at the midway point of data collection for the Longitudinal Early-onset Alzheimer's Disease Study (LEADS).

METHODS: Baseline NPS (Neuropsychiatric Inventory – Questionnaire; Geriatric Depression Scale) and psychotropic medication use from 282 participants enrolled in LEADS were compared across diagnostic groups – amyloid-positive EOAD (n=212) and amyloid negative early-onset non-Alzheimer's disease (EOnonAD; n=70).

RESULTS: Affective behaviors were the most common NPS in EOAD at similar frequencies to EOnonAD. Tension and impulse control behaviors were more common in EOnonAD. A minority of participants were using psychotropic medications, and use was higher in EOnonAD.

DISCUSSION: Overall NPS burden and psychotropic medication use were higher in EOnonAD than EOAD participants. Future research will investigate moderators and etiological drivers of NPS, and NPS differences in EOAD vs. late-onset AD.

Keywords

Neuropsychiatric symptoms; neuropharmacology; psychotropic medications; early-onset Alzheimer's disease; mild cognitive impairment; early-onset dementia

INTRODUCTION

While early-onset Alzheimer's disease (EOAD; onset 40–64 years-old) is rare – comprising only 5% of AD cases in the U.S. – the aggressive course leads to substantial impact for patients and families.[1, 2] Similar to late-onset AD (LOAD; onset ≥65 years-old), neuropsychiatric symptoms (NPS) present throughout its course.[3] Affective symptoms are common, which may reflect disease progression and stress of receiving this diagnosis while still managing substantial societal responsibilities (e.g., occupational and caregiving responsibilities).[4–6] Additionally, relatively preserved insight of this early decline can

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contribute to depression.[5] While affective symptoms are relatively common, findings for non-affective NPS and treatment of NPS represent gaps in the literature. Prior work examining prevalence of non-depression NPS is mixed.[3, 7–10] Inconsistent results could be related to small sample sizes, inclusion of individuals with genetic mutations, and etiological heterogeneity without the use of AD biomarkers. Additionally, few examinations of psychotropic medication use exist in EOAD.

The Longitudinal Early-Onset Alzheimer's Disease Study[11] (LEADS, *NIA R56057195, NIA U016057195*) is the largest prospective observational study of EOAD in the U.S. LEADS is approximately midway through enrollment. The focus of the current manuscript was to characterize the baseline NPS and psychotropic medication use in this cohort to date. We compared amyloid-positive EOAD participants and amyloid-negative early-onset non-Alzheimer's disease [EOnonAD]) participants across NPS domains and psychotropic medication categories. Due to the heterogeneity of the literature on NPS and limited pre-existing studies of psychotropic medication use in EOAD, no *a-priori* hypotheses were made.

METHOD

Participants

LEADS has enrolled 212 EOAD and 70 EOnonAD participants. All participants were fluent in English, with a knowledgeable informant, without another significant neurological or psychiatric disorder, and without pathogenic variants in *APP, PSEN1, PSEN2, GRN*, or MAPT or repeat expansions in *C9ORF72*. All had a Clinical Dementia Rating (CDR®[12]) global score of ≤ 1 at the time of enrollment. Diagnosis was made through consensus. A central Internal Review Board overseen by Indiana University approved the study, and written informed consent was obtained.

Procedure

For a detailed description of LEADS enrollment procedures, please refer to Apostolova et al.[11] Briefly, baseline assessment included a standardized clinical evaluation, cognitive, functional, and neuropsychiatric assessments, genetic testing, fluid biomarkers, and brain imaging. Non-neuropsychiatric data are reported elsewhere in this Special Issue.

Measures

Neuropsychiatric symptoms.—The Neuropsychiatric Inventory– Questionnaire[13] (NPI-Q) and the Geriatric Depression Scale – Short Form[14] (GDS-SF) assessed NPS. The NPI-Q is an informant-based rating scale of 12 NPS common in dementia. Informants indicated presence/absence of the symptom (i.e., frequency). Previous factor analysis identified four behavioral categories for the NPI-Q in neurodegenerative samples: Affective (depression, apathy and anxiety); Distress-Tension (irritability and agitation); Impulse Control (disinhibition, elation and aberrant motor behavior), and Psychotic behaviors (delusions and hallucinations).[15] If participants had one individual NPS (e.g., apathy) in a particular category (e.g., Affective behaviors), they were included in the frequency count for that behavioral category. The GDS-SF is a self-report measure of 15 depressive symptoms.

Participants indicate presence or absence of each symptom. The total score represents the sum of all endorsed symptoms.

Psychotropic medications.—Medications reported by participants at baseline were reviewed by A.P.G. and S.W. (geriatric psychiatrist) and psychotropics categorized as anticonvulsants, antidepressants, antihistamines, antipsychotics, anxiolytics, benzodiazepines, cholinesterase inhibitors, hypnotics, mood stabilizers, NMDA-receptor antagonists, and stimulants. Presence/absence of a medication in each psychotropic category was recorded. Additionally, total number of medications across all categories and across a subset of categories more specific to treating NPS (i.e., antidepressants, antipsychotics, anxiolytics, benzodiazepines, hypnotics, mood stabilizers, and stimulants) were recorded.

Data Analysis

Demographics were compared using *t-tests* (continuous variables) and *Chi square* analysis (categorical variables). NPI-Q categories of behavior (e.g., Affective) and NPI-Q individual symptoms (e.g., depression) were analyzed using binary logistic regression with EOnonAD as the reference group. Odds ratios (OR) for the effect of group were estimated after adjusting for sex and disease severity (CDR-sum of boxes [CDR-SB]). Linear regression adjusting for sex and disease severity compared groups on the total GDS-SF and NPI-Q scores (effect sizes = partial eta squared). Psychotropic medication categories were compared across EOAD and EOnonAD groups using *Chi square* analysis (or *Fisher's exact test* if insufficient data). Effect sizes were expressed as *Cohen W*.

RESULTS

Demographics

There were no significant demographic differences between EOAD and EOnonAD for age, education, and race/ethnicity (ps > .05; Table 1). The EOnonAD group was less impaired (CDR® global & SB, p = .03 & .02) and had more males (p = .009) and these variables were included as covariates in our regression models.

Neuropsychiatric Profiles

Average total NPI-Q score was higher in EOnonAD than EOAD (p = .002, η_p^2 =.03). Regardless of group, informants endorsed Affective behaviors most frequently (76.2%), and Psychotic behaviors least frequently (13.4%), with no significant group differences (ps > .59). EOAD informants endorsed fewer Distress-Tension behaviors (p = .02, OR = .498) and Impulse Control behaviors (p = .01, OR = .438). At an individual variables level, the most frequently endorsed NPS in EOAD were depression (49%) followed by anxiety (44%), irritability (41%), and apathy (35%). In EOnonAD, the most frequently endorsed NPS were irritability (58%) followed by apathy (56%), depression (53%), and anxiety (46%). EOAD informants endorsed apathy (p < .001, OR = .316), irritability (p = .02, OR = .498), and disinhibition (p = .04, OR = .476) at lower frequency than EOnonAD. No other significant differences were seen between groups on the NPI-Q. Examining the GDS-SF showed that the EOnonAD participants self-reported more symptoms of depression than the EOAD group (p = .002, η_p^2 =.03). (Table 2A).

Psychotropic Medication Use

A minority of participants, regardless of diagnostic group, reported psychotropic medication use (35%). Comparing the subset of medications more specific to treating NPS showed higher use in EOnonAD (38%) than EOAD (24%) ($p = .03$, Cohen W = .14). Antidepressants were most prescribed regardless of diagnostic group (21%). Use of antihistamines ($p < .001$, $W = .238$) and mood stabilizers ($p = .042$, $W = .132$) were higher in EOnonAD (Table 2B).

DISCUSSION

These data represent the neuropsychiatric profiles of cognitively impaired LEADS participants.[11] Results are consistent with prior work demonstrating high frequency of affective symptoms in EOAD.[16] Given the early symptomatic stage of disease in this cohort, these findings may be explained by preserved insight into the condition,[16] along with the timing of decline occurring while participants have multiple personal and occupational responsibilities.[5] For example, our results suggest substantially higher frequency of affective symptoms in EOAD (35–49%) compared to LOAD of similar mild disease stage (18–27%).[15]

NPS symptoms were not unique to EOAD, as amyloid-negative EOnonAD participants displayed greater total NPS burden, higher frequency of tension-related behaviors (especially irritability) and impulse-control behaviors (especially disinhibition), and comparable frequency of affective behaviors (but greater apathy). Furthermore, the EOnonAD group endorsed greater depressive symptom severity. Greater NPS may reflect the etiologic diversity represented in our EOnonAD group, as previous research has suggested that TDP-43 is associated with aberrant motor activity and Lewy body disease is related to anxiety, irritability, sleep behavior, and appetite problems.[17] More frequent apathy, irritability, and disinhibition in EOnonAD could reflect more frontally-mediated neurodegenerative diseases (e.g., behavioral variant frontotemporal dementia).[18] Future studies will need to examine whether non-AD etiologies may be larger drivers of NPS than AD neuropathology, though amyloid is linked to the progression of many common NPS in AD.[6]

While delusions and hallucinations are relatively common in LOAD,[19] these symptoms were uncommon in this EOAD cohort. However, the literature suggests that the prevalence of psychotic behaviors increases with disease progression.[20] Longitudinal assessment of psychotic behaviors in EOAD will better inform these trajectories over the illness course.

Surprisingly, despite most participants presenting with at least one NPS, psychotropic medication use was low in both groups. Prior work in EOAD suggests rates of pharmacological treatment for NPS range from 3% (antipsychotics) to 60% (antidepressants).[3, 9, 10] Relatively low prevalence across our groups could reflect the early symptomatic stage of disease that LEADS requires for enrollment, whereas previous studies have included a wider range of disease severity. Additionally, most prior studies did not confirm amyloid-positivity in EOAD participants, leaving open the possibility that etiological heterogeneity lead to more variability in rates of NPS and medication use.

Regardless, in the current LEADS cohort, the EOnonAD group showed greater psychotropic medication use.

NPS are among the most robust predictors of care partners' quality of life in dementia.[21] Irritability in particular is strongly correlated with distress and burden.[22] Close to half of the EOAD study partners and more than half of EOnonAD study partners endorsed irritability, suggesting high risk of negative psychological outcomes for care partners in these groups. Given high prevalence of NPS in both EOAD and EOnonAD, especially irritability, health providers should routinely assess for presence and severity of these symptoms, burden and distress among care partners, and identify appropriate management strategies (pharmacological and nonpharmacological).

Limitations

First, these data represent approximately 50% data collection in LEADS; results may change as more participants are enrolled. Second, these data reflect only relatively early symptomatic stages of disease. Third, the sample is predominantly White, non-Hispanic, and highly educated. Race, ethnicity, and education are linked to the development of NPS in AD and other dementias, limiting the generalizability of these results. Current efforts are underway to increase ethnic, racial, and educational diversity within the LEADS samples (Alzheimer's Association*, LDRFP-21–818464*).

CONCLUSION

Overall NPS burden and psychotropic medication use were higher in EOnonAD than EOAD participants. LEADS continues to collect data. Future studies will examine etiologies that may be larger drivers of NPS than AD neuropathology, mediators (e.g., race, ethnicity) in the association between NPS and diagnostic group classification (EOAD vs. EOnonAD), compare NPS in EOAD vs. LOAD, and examine longitudinal changes in neuropsychiatric profiles over the course of EOAD, EOnonAD, and LOAD.

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DISCLOSURES AND CONFLICTS OF INTEREST

J.L.D is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents and / or compositions of matter related to measurement of P-tau217. J.L.D. has served as a consultant for Abbvie, Genotix Biotechnologies Inc, Gates Ventures, Karuna Therapeutics, AlzPath Inc, Cognito Therapeutics, Inc., and received research support from ADx Neurosciences, Fujirebio, AlzPath Inc, Roche Diagnostics and Eli Lilly and Company in the past two years. J.L.D. has received speaker fees from Eli Lilly and Company.

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Leonardo Iaccarino is currently a full-time employee of Eli Lilly and Company / Avid Radiopharmaceuticals and a minor shareholder of Eli Lilly and Company. His contribution to the work presented in this manuscript was performed while he was affiliated with the University of California San Francisco.

No other authors associated with this project have reported conflicts of interest that would impact these results.

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Table 1.

Participant demographic information

	EOAD	EOnonAD	*p* value	Effect size
N	212	70		
Age (*M, SD*)	58.78 (3.9)	57.99 (6.0)	.30	.175
Sex (% Female)	52.4%	34.3%	**.009**	**.156**
Minority * %	7.5%	14.3%	.09	.100
Education, years (*M, SD*)	15.42 (2.4)	15.37 (2.6)	.88	.022
CDR Global (0.5% / 1.0%)	66.5% / 33.5%	80.0% / 20.0%	**.03**	**.127**
CDR SB *(M, SD)*	3.63 (1.72)	3.01 (2.03)	**.02**	**.345**

Note: EOAD = Early-Onset Alzheimer's Disease, EOnonAD = Early-Onset non-Alzheimer's Disease, CDR Global = Clinical Dementia Rating scale – global score, CDR SB = Clinical Dementia Rating scale – sum of boxes. *P* values represent *t-tests* (continuous variables) *or Chi square* analysis (categorical variables) for group comparisons. Effect sizes were calculated using Cohen D for continuous and Cohen W for categorical variables.

* Minority includes participants whose ethnicity is Hispanic or race is Asian, Black or African American, and more than one race

Table 2.

Presence of neuropsychiatric symptoms and psychotropic medication use in EOAD and EOnonAD

	EOAD n (%)	**EOnonAD n (%)**	***p* value**	**OR**
A. Neuropsychiatric Symptoms				
NPI-Q				
Affective composite	n=205 154 (75.1%)	n=68 54 (79.4%)	.148	.595
Depression	n=206 102 (49.5%)	n=68 36 (52.9%)	.354	.764
Apathy	n=204 72 (35.3%)	n=68 38 (55.9%)	**<.001**	**.316**
Anxiety	n=205 91 (44.4%)	n=68 31 (45.6%)	.305	.734
Distress-tension composite	n=206 97 (47.1%)	n=68 43 (63.2%)	**.020**	**.498**
Irritability	n=206 85 (41.3%)	n=67 39 (58.2%)	**.018**	**.498**
Agitation	n=207 63 (30.4%)	n=67 23 (34.3%)	.506	.814
Impulse control composite	n=206 57 (27.7%)	n=67 27 (40.3%)	**.012**	**.438**
Disinhibition	n=206 34 (16.5%)	n=67 18 (26.9%)	**.041**	**.476**
Elation	n=205 9 (4.4%)	n=68 5 (7.4%)	.336	.565
Motor Behavior	n=206 36 (17.5%)	n=68 15 (22.1%)	.178	.600
Psychosis composite	n=207 28 (13.5%)	n=68 9 (13.2%)	.847	.914
Delusions	n=207 21 (10.1%)	n=68 8 (11.8%)	.585	.758
Hallucinations	n=207 13 (6.3%)	n=68 5 (7.4%)	.111	.726
Sleep changes	n=201 60 (29.9%)	n=68 27 (39.7%)	.133	.618
Total NPI-Q score (*M,SD*) *	n=212 2.76 (2.34)	n=70 3.50 (2.60)	**.002**	**.033**
GDS-SF				
Total Score, (*M, SD*) *	n=212 2.66 (2.57)	n=70 3.5 (2.62)	**.002**	**.034**
B. Psychotropic Medications				
	EOAD n (%) *n* = 210	**EOnonAD n (%) *n* = 68**	***p* value**	**Effect size (Cohen W)**
Anticonvulsants	2 (0.95%)	2 (2.94%)	.252	.072
Antidepressants **	41 (19.52%)	17 (25.00%)	.334	.058
Antihistamines	0 (0.00%)	5 (7.35%)	**<.001**	**.238**
Antipsychotics	4 (1.90%)	3 (4.41%)	.367	.069

Anxiolytics	1 (0.48%)	1 (1.47%)	.430	.051
Benzodiazepines	5 (2.38%)	5 (7.35%)	.068	.115
Cholinesterase Inhibitors **	20 (9.52%)	3 (4.41%)	.183	.08
Hypnotics	1 (0.48%)	0 (0.00%)	1.00	.034
Mood Stabilizers	4 (1.90%)	5 (7.35%)	**.042**	**.132**
NMDA-receptor antagonists **	19 (9.05%)	2 (2.94%)	.098	.099
Stimulants	5 (2.38%)	2 (2.94%)	.681	.015
Total medications	69 (32.86%)	30 (44.12%)	.110	.101
Subset of NPS medications	50 (23.81%)	26 (38.24%)	**.028**	**.139**

Note: EOAD = Early-Onset Alzheimer's Disease, EOnonAD = Early-Onset non-Alzheimer's Disease, NPI-Q = neuropsychiatric inventory questionnaire, GDS-SF = Geriatric Depression Scale – Short Form, OR = odds ratio, *M* = mean, *SD* = standard deviation. Subset of neuropsychiatric (NPS) medication = antidepressants, antipsychotics, anxiolytics, benzodiazepines, hypnotics, mood stabilizers, and stimulants. *P* values for NPI-Q categories of behavior and individual symptoms reflect binary logistic regression. Effect sizes are odds ratios (OR) with EOnonAD as the reference group adjusting for sex and disease severity (CDR-sum of boxes [SB]). *P* values for NPI-Q total and GDS-SF analyses reflect linear regression models. Effect sizes are calculated as partial eta squared adjusting for sex and disease severity (CDR-SB). *P* values for psychotropic medications reflect *Fisher Exact Test* between EOAD and EOnonAD except where otherwise specified. Effect sizes for psychotropic medications were calculated using *Cohen W*. Bolded values reflect statistical significance ($p < .05$).

** *Chi square* analyses conducted instead of *Fisher's Exact Test*