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Utility of Amyloid PET Scans in the Evaluation of Patients Presenting with Diverse Cognitive Complaints

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Abstract

Background: The impact of amyloid positron emission tomography (A β -PET) in a “real-world” memory disorders clinic remains poorly studied.

Objective: we studied the impact of A β -PET in diagnosis and management in the memory clinic and factors making the most impact in diagnosis and management.

Methods: We studied 102 patients who had presented at a memory disorders clinic (the Wien Center for Alzheimer's Disease and Memory Disorders, Miami Beach, FL) and had a diagnostic work-up for cognitive complaints, including A β -PET scans.

Results: Following A β -PET, changes were made in diagnosis (37.3%), in specific treatments for Alzheimer's disease (26.5%) and in psychiatric treatments (25.5%). The agreement between diagnosis pre-A β -PET versus post-A β -PET diagnosis was only fair, with a Cohen's kappa of 0.23 (95% CI 0–0.42). Patients with MRI findings suggestive of AD (medial temporal and/or parietal atrophy) were more frequently amyloid positive than amyloid negative (66.2% versus 33.8%, $p = 0.04$). Among patients with atypical clinical features for AD, but with MRI findings suggestive of AD, an amyloid negative PET scan had a greater impact than an amyloid positive PET scan on diagnosis (84.2% versus 17.1%, $p < 0.001$), management (84.2% versus 40%, $p < 0.01$) and discussion of results and advice on lifestyles (73.7% versus 22.9%, $p < 0.001$).

Conclusions: We conclude that MRI features suggestive of AD predict a positive amyloid PET scan. However, among those with MRI features suggestive of AD but with atypical clinical features of AD, the clinical impact on diagnosis and management is greater for an amyloid negative than an amyloid positive A β -PET scans.

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Keywords

Alzheimer's disease; amyloid imaging; diagnosis; management; memory clinic; positron emission tomography

INTRODUCTION

Although Alzheimer's disease (AD) is the most common cause of major cognitive disorders, accounting for 60% or more of all of dementias [1], a clinical diagnosis of probable AD has a sensitivity and specificity of only 70.9% and 70.8%, respectively, when compared to the "gold standard" pathological findings [2]. The introduction of amyloid positron emission tomography (A β -PET) imaging, initially using ¹¹C-Pittsburgh Compound B (PiB), and subsequently using various ¹⁸F-amyloid-binding ligands with a longer half-life, has facilitated routine clinical application of amyloid PET. Importantly, the use of ¹⁸F-ligands for amyloid imaging has provided a clinical diagnostic tool with high sensitivity and specificity for predicting the presence of amyloid plaques in the brain, which is one of the requirements for a histopathological diagnosis of AD [3–7]. Nevertheless, the experience with A β -PET in the clinic has been limited because of the high cost of amyloid binding ligands and very restricted financial coverage by third party insurers.

Appropriate use criteria (AUC) have been published to guide clinicians to maximize the utility of A β -PET [8]. The three AUC criteria are: 1) Patients with persistent or progressive unexplained mild cognitive impairment (MCI); 2) Patients satisfying core clinical criteria for possible AD, because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation; 3) Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age) [8].

Various studies have been published on the impact of A β -PET, including changes in diagnosis (in 9% to 69% of cases) and change in management, including prescription or withdrawal of AD specific medications or psychiatric medications (in 25.4% to 81.3% of cases) [9–21]. Nevertheless, there is a very limited experience of the impact of A β -PET among patients presenting to a 'real-world' memory clinic [12, 13, 20, 21], where subsequent to a routine evaluation for cognitive complaints, including structural neuroimaging, they are provided a diagnosis and a management plan.

Clinicians in outpatient memory clinics often see patients who satisfy the second AUC criterion, namely, "core clinical criteria for possible AD, because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation". These cognitively impaired patients have multiple potential etiologies for cognitive impairment, and frequently have multiple medical or psychiatric co-morbidities and medications used to treat these conditions, all of which contribute to the difficulties in diagnosis. The purpose of this study was to determine the impact of A β -PET on diagnosis and management on patients with each of the three major indications outlined in the AUC for A β -PET. Another purpose of this study, which has not been addressed in previous studies, is the additional impact of A β -PET on diagnosis and management among patients in whom specific features on magnetic resonance imaging (MRI) scans have been taken into account in making an AD or

a non-AD diagnosis, i.e., whether the MRI scan shows features suggestive of a neurodegenerative dementia, such as AD, have been taken into consideration.

METHODS

Patient population

Patients were referred to the Wien Center for Alzheimer's disease and Memory disorder in Miami Beach, Florida by primary care physicians (PCP), specialists (e.g., psychiatrists, geriatricians, and neurologists), or were self-referred. Case records were reviewed of patients who were evaluated so as to determine the etiology and future management for an initial diagnosis of MCI or dementia. During the first clinic assessment, cognitive assessments in the clinic included the Mini-Mental State Examination scores (MMSE) [22], a multiple delayed recall test [23], naming and comprehension tests from the ADAS-Cog subscales [24], and the Clock Drawing Test [25], all administered by trained medical assistants. Laboratory studies (including liver and renal biochemistries, thyroid function test, and vitamin B12 level & folate level) and MRI of the brain, using a dementia protocol which included 3D coronally acquired series to enable detailed evaluation of medial temporal [26, 27] and neocortical atrophy [28] were obtained. At a second clinic visit, based on all the available results of their evaluation, patients were provided with an etiological diagnosis by a neurologist (RD), and the basis for the diagnosis, treatment, and prognosis were discussed. Recommendations were made for continuing management, including initiation of changes in medications for the cognitive and any associated behavioral disorders, as well as for any further testing, changes in lifestyle and participation in various research studies, including clinical trials.

Subsequently, when patients participated in various research protocols, they had additional tests, including more detailed neuropsychological evaluations (focusing on memory, language, executive function, visuospatial construction, and attention), the Clinical Dementia Rating (CDR) scale [29], the Neuropsychiatric Inventory (NPI) [30], Apolipoprotein E (ApoE) status, and A β -PET scans which were rated as amyloid positive or negative on visual rating. At a third clinic visit, results of the A β -PET were reviewed with the patient and any changes in diagnosis and management were discussed.

MRI-dementia protocol and visual rating

The MRI brain scans were obtained on a 1.5 or 3-tesla MRI machine, using the following sequences, including: coronally acquired Magnetization Prepared Rapid Gradient Echo (MPRAGE), axial T₂ or Fluid Attenuation Inversion Recovery (FLAIR), axial Susceptibility Weighted Imaging (SWI), and axial and sagittal T₁ sequences. The MRI scans were rated by an experienced neurologist (RD), using a visual rating system for medial temporal atrophy [26] and for neocortical atrophy [31]. Findings suggestive of a neurodegenerative disorder on the MRI scan were classified as being compatible with the limbic predominant, the hippocampal sparing, or a combination of the two subtypes [32] or compatible with another dementing disorder [33] such as frontotemporal or vascular dementia. Specifically, for patients with suspected AD, the MRI was further sub-classified into the following subtypes, as far as possible: 1) the limbic-predominant subtype was defined as having relatively

isolated medial temporal (hippocampus, entorhinal cortex and perirhinal cortex) atrophy; 2) the hippocampal sparing subtype was defined as having atrophy in the neocortex, especially the parietal cortical regions (including precuneus, posterior cingulate, superior and inferior parietal regions), but with relative sparing of the medial temporal lobe; 3) a mixed subtype was defined as having characteristics of both limbic predominant and hippocampal sparing subtypes [32].

Diagnosis of specific types of dementia and MCI

MCI was diagnosed according to the Peterson criteria [34]. AD was diagnosed according to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [35]. Dementia with Lewy bodies (DLB) was diagnosed by the McKeith criteria [36]. The behavioral variant (bv) of frontotemporal dementia (FTD) was diagnosed by the revised diagnostic criteria reported by the International bvFTD Criteria Consortium [37] and the language variant of FTD (lvFTD), including semantic dementia and progressive non-fluent aphasia, was diagnosed by the most recently published criteria [38]. If FTD patients could not be classified confidently into either bvFTD or lvFTD, a diagnosis of FTD not otherwise specified (NOS) was given. Vascular cognitive impairment (VCI) was diagnosed according to Vascular Impairment of Cognition Classification Consensus Study (VICCCS) diagnosis guidelines [39]. Behavioral changes were identified and rated for severity according to NPI.

A β -PET protocol

¹⁸F-florbetapir PET imaging: A 20-min dynamic list mode brain PET acquisition of the brain was obtained beginning 50 min after injection of an intravenous bolus of 370 mBq (10 mCi) ¹⁸F-florbetapir, on a Siemens Biograph 64 PET/CT scanner according to a standardized acquisition and image-processing protocol. For A β -PET using ¹⁸F-florbetaben: PET images were acquired 70–90 min after intravenous injection of 300 MBq ($\pm 20\%$) ¹⁸F-florbetaben, according to a standardized acquisition and image-processing protocol. All PET image interpretation was performed by a neuroradiologist and an experienced neurologist (RD) using greyscale images. The concordance between the two readers was 93.2% for positive scans and 100% for negative scans. Results were interpreted as being either amyloid positive (A+) or amyloid negative (A–), based on regional cortical tracer uptake assessment of the lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex. A previous study has reported on inter-reader agreement across five readers (kappa coefficient of 0.80; 95% CI = 0.77–0.83) [40].

Indications for A β -PET scans

Among the 102 participants who were selected for this study, the indications for A β -PET were those listed under the AUC, namely: 1) Patients with persistent or progressive unexplained MCI; 2) Patients satisfying core clinical criteria for possible AD, but with an atypical clinical course (including presentation with atypical features) or etiologically mixed presentation; 3) Patients with atypically young onset dementia (YOD) (onset prior to age 65 years) [8]. Atypical features are listed in Table 2 and include the following: possible cerebral amyloid angiopathy (CAA), frontal or behavioral symptoms, visual symptoms, parkinsonian features, progressive aphasia (language symptoms), previous non-conclusive investigation

results, or multiple medical or psychiatric co-morbidities that could cause cognitive impairment [12].

Assessment of the impact of A β -PET

The impact of A β -PET was assessed by a change in diagnosis or management. The change in diagnosis was defined as any change in etiological diagnosis in the third clinic visit as compared with the second clinic visit (e.g., AD dementia to non-AD dementia or MCI-AD to MCI- non-AD). Changes in management were categorized as: 1) initiation or discontinuation of medications, 2) adjustment of medications, 3) ordering of additional diagnostic tests, 4) providing additional explanation or discussion regarding tests results, diagnosis, prognosis, risk of dementia for family members, and 5) recommendations regarding changes in lifestyle (exercise, diet, social and cognitive activities, dental and general hygiene), and advice on safety measures. The pre-A β -PET time interval was defined as the time between the initial visit to the memory clinic and the date of the A β -PET. Post A β -PET time interval was defined as the difference between the date of A β -PET and the last follow-up date.

Statistical analysis

Pearson Chi-square test or Fisher exact tests were used to compare categorical variables. The agreement between pre-A β -PET or post-A β -PET etiological diagnoses of MCI or dementia was analyzed by the Cohen's kappa (κ) statistic. Logistic regression was performed with changes in diagnosis and changes in management as dependent variables. Statistical significance was inferred by a two-tailed *p*-value of less than 0.05. All statistical analyses were carried out using SPSS (Window version 24; SPSS Chicago, IL, USA).

RESULTS

Basic demographics and clinical profiles

One hundred and two patients, seen at the clinic underwent A β -PET between April 2014 and November 2017, were found to meet AUC for, and subsequently had the A β -PET scan. Most patients were referred by their PCP (41.2%) or were self-referred (41.2%) (Table 1). Mean age of the patients was 72.8 $\pm$ 8.6 years old (Table 1). The indications for A β -PET were persistent or progressive unexplained MCI in 45.1%, possible AD with atypical features in 41.2% and YOD in 13.7% (Table 1). The three most common types of atypical features were multiple medical or psychiatric co-morbidities (52.1%), frontal lobar symptoms (11.9%), and possible cerebral amyloid angiopathy on MRI (11.9%). Ninety patients had ApoE genotyping results of which 47.8% were ApoE ϵ 4 carriers (ϵ 2 ϵ 3 6.7%, ϵ 2 ϵ 4 2.2%, ϵ 3 ϵ 3 45.6%, ϵ 3 ϵ 4 38.9%, and ϵ 4 ϵ 4 6.7%).

Impact of A β -PET on diagnosis and management

NeuraCeq (¹⁸F-florbetaben) was used as the ligand for 90 patients and Amyvid (¹⁸F-florbetapir) for 12 patients. A β -PET was positive for amyloid plaque (A+) in 62 patients (60.8%) and negative (A-) in 40 patients (39.2%), resulting in changes in diagnosis among 38 patients (37.3%), including 7 out of 40 patients (18.9%) in whom diagnosis changed from AD dementia to non-AD dementia (all 7 patients presented with atypical clinical features)

and 9 out of 16 patients (56.3%) in whom diagnosis changed from non-AD dementia to AD dementia. Among patients diagnosed with MCI-AD, 13 out of 26 (50%) were diagnosed as MCI non-AD, and 7 out of 20 (35%) with MCI non-AD were re-diagnosed with MCI-AD (Table 3). The agreement between pre-A β -PET and post-A β -PET diagnoses was only fair with a Cohen's κ of 0.23 (95% CI 0–0.42).

Post-A β -PET changes in AD-specific treatments occurred in 26.5%. Significant changes in management (including adding new medications, withdrawing medications, providing additional diagnostic tests and advice on daily living and safety concerns, or combination of the above) occurred in 59.8% of patients (Table 4). There was no difference in the impact of the A β -PET scan results among patients representing the three AUC (Table 4). However, the impact of A β -PET was greater among patients carrying a non-AD than an AD diagnosis, prior to the A β -PET scan: 44.4% of non-AD patients changed diagnosis while 31.8% of AD patients changed diagnosis ($\chi^2 = 5.46$, $p = 0.02$). Moreover, there was also a greater impact of an A- scan than an A+ scan on diagnosis. Using logistic regression analysis for change in diagnosis, the odds ratio of an A- result as compared to an A+ was 3.18 (95% CI 1.37–7.37, $p < 0.01$) (Fig. 1). Significant changes in management also occurred more frequently ($\chi^2 = 8.57$, $p < 0.01$) in post A β -PET among non-AD patients (77.5%) than AD patients (48.4%) and explanation of results or advice on safety and lifestyle (also occurred more frequently ($\chi^2 = 17.94$, $p < 0.001$) in non-AD patients (62.5%) than AD patients (21%). Using logistic regression analysis for change in management, the odds ratio of an A- result, as compared to an A+ result was 3.67 (95% CI 1.50–8.98, $p < 0.01$) (Fig. 1). ApoE $\epsilon 4$ non-carriers received more explanation of results or advice on safety and lifestyles than ApoE $\epsilon 4$ carriers (46.8% versus 25.6%, $\chi^2 = 4.36$, $p = 0.04$).

A β -PET and MR imaging

All patients underwent MRI scans prior to A β -PET. Patients with MRI findings suggestive of AD were found to be A+ more frequently than those in whom MRI findings were not suggestive of AD (66.2% versus 33.8%; $\chi^2 = 4.50$, $p = 0.04$). In addition, there was a trend for suspected AD patients with limbic predominant or mixed limbic and hippocampal-sparing (i.e., neocortical) predominant patterns of atrophy than hippocampal sparing (neocortical predominant) subtypes to be A+ (73% versus 40%, $p = 0.06$). Among patients with a diagnosis of A- MCI or dementia, who presented with atypical features, but MRI findings suggestive of AD ($n = 19$) an A- result after A β -PET had a greater impact than an A+ result on change in diagnosis (84.2% versus 17.1%; $\chi^2 = 22.94$, $p < 0.001$), significant change in management (84.2% versus 40.0%; $\chi^2 = 9.75$, $p < 0.01$) and explanation of results and advice on safety and lifestyles (73.7% versus 22.9%; $\chi^2 = 13.18$, $p < 0.001$).

DISCUSSION

Our retrospective cohort was mainly an elderly population with mean age of 72.8 ± 8.6 years. Eighty-three percent of patients presented with atypical presentations and 46% suffered from multiple medical or psychiatric co-morbidities that may have contributed to cognitive impairment, representing the typical heterogeneity of elderly patients presenting to a memory disorders clinic. Such heterogeneity could be partially explained by the older

age of our patients. In this study, in which all patients fulfilled AUC [8], A β -PET was positive in 60.8% of patients, leading to change in diagnosis in 37% and significant change in management in 60%. Patients initially diagnosed with non-AD dementias were more likely to have their diagnoses changed, subsequent to A β -PET, to AD dementia, rather than from AD dementia to non-AD dementias. Among those patients diagnosed with AD dementia, all seven with atypical features were diagnosed to have non-AD dementia subsequent to A β -PET. The finding of an A β -PET scan was more likely to result in a change of the post A β -PET diagnosis than an A+ scan.

Our findings are in-line with previous studies [9–21] and also agree with those of our recent meta-analysis showing that for A β -PET, the pooled effect of change in diagnosis was 35.2% (95% CI 24.6–47.5) and change in management was 59.6% (95% CI 39.4–77%) [41]. The impact of A β -PET is also illustrated in the relatively poor agreement between pre-A β -PET and post-A β -PET diagnoses (Cohen's κ of 0.23), resulting from the changes in diagnosis. However, among the three criteria included in the AUC, there was no significant difference in the impact of A β -PET on diagnosis and management.

Features on brain MRI scans suggestive of a diagnosis of AD were predictive of amyloid positivity, although those with the hippocampal sparing subtype of AD tended to be amyloid negative. Patients with atypical clinical features, in the presence of MRI findings suggestive of an AD diagnosis ($n = 22$), also tended to be A- (19 out of 22, or 86%, were A-).

There were more patients with non-AD dementia than AD dementia (post A β -PET) who received changes in management and explanations on results or advice on safety and lifestyles than AD patients. ApoE $\epsilon 4$ negative patients received more explanation of results or advice on safety and lifestyles after A β -PET diagnosis. These non-AD etiological diagnoses are likely to be less familiar to the caregivers [42]. Our findings also are in line with previous reports showing that non-AD diagnoses subsequent to A β -PET diagnosis has a greater impact on management [17]. It has been found that around 20% of non-AD dementia patients are amyloid positive on A β -PET and such prevalence increases with age and among ApoE $\epsilon 4$ allele carriers [43, 44]. Using data from meta-analyses and previous studies comparing A β -PET with autopsy examination, it was found that a negative A β -PET has a greater impact on the diagnosis of AD, especially in elderly patients, while a positive A β -PET has a greater impact on the diagnosis of AD among young patients [45]. Our study, which mainly involved elderly patients, provides further evidence for the significance of negative A β -PET findings in older patients.

The limitations of our study include the small sample size and lack of validation of diagnosis by histopathology. The positivity of A β -PET depended on the visual readings, but there is a possibility of disagreement with the quantitative analysis, especially among the MCI A- patients, in whom the visual reading of the amyloid PET scan may be ambiguous, possibly converting to a positive scan on serial A β -PET. Replication of our findings in a larger sample, including diverse ethnic and cultural groups, would also help to validate our findings. The changes in diagnosis or management attributed to the results of A β -PET, may have over-predicted the impact of A β -PET, because other factors, such as the occurrence of new symptoms after the A β -PET scan was done, may have contributed to the change in

diagnosis and management. A single clinician was responsible for reading all MRIs and performing all neurological evaluations; this could impact the generalizability of these results. Nonetheless, this investigation is unique in that it assesses the impact of A β -PET in the context of the three criteria included in the AUC and includes the impact of structural MRI in the pre-A β -PET diagnosis. Our findings were obtained in a “real world” memory disorders clinic; as such the findings are more likely to be generalizable to typical patients presenting for evaluation of memory complaints.

In conclusion, we found that A β -PET has a significant impact on diagnosis and management, especially among those who were found to be A-. These findings were obtained among patients who were relatively unselected and presented with multiple potential causes of cognitive impairment to a typical memory disorders clinic. The presence of typical features of AD on MRI scans was associated with a higher likelihood of being A+. However, the impact on diagnosis and management was found to be greatest among those who were A- on A β -PET, those with atypical clinical features and those with non-AD diagnoses, especially if they had MRI features suggestive of AD.

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Fig. 1. Diagram showing the results of logistic regression with amyloid negative result as the independent variable.

Table 1

Patient characteristics, sources of referral and indications for amyloid PET imaging

Clinical characteristics	Results
Gender (female), n (%)	54 (52.9)
Age of presentation in years, mean $\pm$ SD	72.8 $\pm$ 8.6
MMSE, mean $\pm$ SD	22 $\pm$ 5.4
CDR, median (IQR)	1 (0.5–1.0)
CDR-SB, median (IQR)	3.5 (2–5)
Pre-A β -PET interval in months, median (IQR)	7.3 (4.2–20.1)
Post-A β -PET interval in months, median (IQR)	6.2(2.6–11.3)
Sources of referral, n (%):	
– Primary care physicians.	41(2)
– Specialists.	18 (17.6)
– Self-referral.	42(41.2)
Indications for A β -PET, n (%):	
– Persistent or progressive unexplained MCI.	(45.1)
– Possible AD with atypical clinical features.	42(41.2)
– Young-onset dementia.	14 (13.7)

A β -PET, amyloid PET imaging; AD, Alzheimer's disease; CDR, Clinical Dementia Rating; IQR, interquartile range; MMSE, Mini-Mental State Examination; SB, sum of boxes.

Table 2Atypical features ($n = 117$) among the patients

Atypical features	N(%)
Possible cerebral amyloid angiopathy	14 (11.9)
Parkinsonian features	4 (3.4)
Frontal lobar symptoms	14 (11.9)
Visual symptoms	6 (5.1)
Progressive aphasia	7 (6.0)
Inconclusive pre-A β -PET neuroimaging	11 (9.4)
Multiple medical co-morbidities	61 (52.1) ^a

A β -PET, amyloid PET imaging

^a47 with suspected depression, 5 with multiple cardiovascular co-morbidities, 1 with chronic kidney disease, 2 suspected depression and multiple cardiovascular co-morbidities, 1 depression and chronic kidney disease, 5 with other co-morbidities (including sleep apnea, significant history of head concussion, history of encephalitis, human immunodeficiency virus infection and history of transient ischemic attack).

Table 3Changes in diagnoses following A β -PET

	Post-A β -PET diagnosis			
	AD Dementia ^a	MCI+AD	Non-AD Dementia ^b	MCI non-AD ^c
Pre-A β -PET diagnosis				
AD Dementia ^a	32	0	7 [*]	1 [*]
MCI-AD	0	13	0	13 [*]
Non-AD Dementia ^b	9 [*]	0	7	0
MCI non-AD ^c	0	7 [*]	0	13
Total	41	20	14	27

A β -PET, amyloid PET imaging; AD Dementia, Alzheimer's disease dementia; MCI, mild cognitive impairment.^a Apart from AD patients, pre-A β -PET included 4 mixed AD & VaD and 2 mixed AD & DLB; post-A β -PET included 7 mixed AD & VaD and 2 mixed AD & DLB.^b Pre-A β -PET included 7 VaD, 4 DLB, 2 bvFTD, 2 FTD-NOS, and 1 NPH; post-A β -PET included 3 DLB, 4 FTD-NOS, 1 bvFTD, 1 VaD, 1 alcoholic dementia, and 4 suspected non-Alzheimer pathophysiology (SNAP).^c Pre-A β -PET also included 1 depression; post-A β -PET included 5 depression.^{*} 44.4% (16/36) of Pre-A β -PET non-AD patients (non-AD dementia and MCI non-AD) and 31.8% (21/66) of Pre-A β -PET AD patients (AD dementia and MCI AD) changed diagnosis (shaded areas; $\chi^2 = 5.46$, $p = 0.02$).

Table 4

Change in management according to three indications for Aβ-PET

Management	Persistent or progressive unexplained MCI (<i>n</i> = 46)	Possible AD with atypical Clinical features (<i>n</i> = 42)	Young-onset dementia (<i>n</i> = 14)	Overall (<i>n</i> = 102)	<i>p</i> -value (comparison among three indications)
Change in diagnosis, <i>n</i> (%)	20 (43.5)	13 (31.0)	4 (28.6)	38 (37.3)	0.39
Change in medications, <i>n</i> (%)	19 (41.3)	15 (35.7)	5 (35.7)	39 (38.2)	0.85
Change in AD-specific medications, ^a <i>n</i> (%)	13 (28.3)	10 (23.8)	4 (28.6)	27 (26.5)	0.88
Change in psychiatric treatments, ^b <i>n</i> (%)	12 (26.1)	10 (23.8)	4 (28.6)	26 (25.5)	0.93
Significant change in management, ^c <i>n</i> (%)	29 (63.0)	24 (57.1)	8 (57.1)	61 (59.8)	0.83
Explanation of results and advice on safety and lifestyles, <i>n</i> (%)	17 (37.0)	16 (38.1)	5 (35.7)	38 (37.3)	0.99

AD, Alzheimer's disease; ApoE, apolipoprotein E; MCI, mild cognitive impairment.

^aOverall changes in cholinesterase inhibitors or memantine; include 21 (increase dosage or newly started medications), 4 (decrease in dosage or stopping medications) and 2 (switching medications).

^bOverall changes including anti-depressants, antipsychotics, sleeping medications, and anti-epileptics; include 20 (increase dosage or newly started medications), 1 (decrease in dosage or stopping medications) and 5 (switching medications).

^cSignificant change in management includes added new medications, withdrawing medications, additional diagnostic tests, advice on daily living and safety concerns or combination of the above.