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ORIGINAL RESEARCH

Understanding treatment goals and their application in clinical trial design for patients with Alzheimer disease and caregivers

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Abstract

Background: As research continues towards improved treatments for Alzheimer disease (AD), there is growing interest in the views and needs from patients and caregivers on AD treatments.

Methods: In this study, we surveyed patients with AD and caregivers to determine the treatment goals that are most important to them. Patients with AD and caregivers were independently recruited in Europe and North America to complete a web-based survey. Eligible participants were ≥18 years old and diagnosed with mild cognitive impairment or mild-to-moderate AD (patient-reported group) or persons involved in the care of patients with AD (caregiver-reported group). A total of 322 patients and 614 caregivers completed the survey.

Results: The demographic characteristics of patients in the patient-reported and the caregiver-reported groups were similar. Disease severity of patients was greater in the caregiver-reported group compared with the patient-reported group (72.1% *versus* 46.9% moderate AD). The most important goal of AD treatment in both groups was maintenance of quality of life (QoL) (patient-reported group 31.1% and caregiver-reported group 38.8%; p=0.01). This was consistent across disease stages or symptom severity except for patients with mild cognitive impairment in the caregiver-reported group where slowing the progression of memory loss was the most important treatment goal.

Conclusions: Patient QoL was consistently the most relevant treatment goal for patients with AD and caregivers. In AD clinical trials, patient-relevant outcomes, for example, QoL, should be given high priority to reflect the needs and demands of patients with AD and their caregivers.

A preliminary report of this work was presented at the 14th Clinical Trials on Alzheimer's Disease meeting (November 9–12, 2021).

Keywords: Alzheimer disease, clinical trial, cognitive dysfunction, dementia, quality of life.

Citation

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Introduction

As elderly populations grow worldwide, dementia is increasing in prevalence and presents a significant public health challenge both medically and economically. In 2019, it was estimated that over 50 million people were living with dementia globally; this number has been projected to dramatically expand to 152 million people by 2050.[1] Of the people currently living with dementia,

60–80% have been classified as having Alzheimer disease (AD).[2] The economic impact of dementia was estimated at US$818 billion in 2015 and has been projected to climb to US$2 trillion by 2050.[3]

The symptoms of AD include memory impairment, cognitive and functional decline, depression, and loss of communication and spatial skills.[4] At the cellular level, AD has been associated with microscopic changes in the brain of patients with AD (observed post-mortem), including amyloid plaques and neurofibrillary tangles that have been linked to declines in cellular function and neuronal cell death. Amyloid plaques are formed by amyloid-β peptides, and the neurofibrillary tangles are made up of phosphorylated tau proteins.[5,6] Until recently, treatments for AD were purely symptomatic, consisting of acetylcholinesterase inhibitors (AChIs) and NMDA receptor antagonists.[7]

Aducanumab, the first therapy with a proposed disease-modifying mechanism of action, received accelerated approval by the FDA in June 2021 based on reduction of amyloid plaques in the brain as a surrogate clinical endpoint.[8] Approval applications for aducanumab were withdrawn in Europe and Canada in 2022,[9] and development was discontinued in the USA in January 2024 for reasons not related to safety or efficacy.[10]

Lecanemab is the second approved agent in this category; it received accelerated approval in January 2023 utilizing the same surrogate endpoint as aducanumab and receiving traditional approval in July 2023.[11,12]

Because only two treatments have been approved that may affect the underlying mechanisms of AD, the quest for new treatments remains an active area of research. Clinical research into new treatments for AD is controlled by guidelines issued by regulatory agencies such as the FDA and the EMA. Some regulators, for example, the FDA, recommend global scores that include functional and cognitive components as the primary endpoints in AD clinical trials whilst surrogate pathophysiological measures can be applied in patients with early-stage disease without significant functional impairment.[13]

Patients and caregivers, on the other hand, take a broader view that incorporates other relevant outcome measures.[14] In order to quantify the importance of these different outcome measures to patients with AD and caregivers, the *What Matters Most* initiative was formed by a consortium of academic institutions, pharmaceutical companies and patient advocacy groups. The results of *What Matters Most* have shown a multidimensional pattern of items that are meaningful to patients and caregivers. These items cover not only attributes included in outcomes measures currently assessed in clinical trials but also incorporate other categories such as changes in behaviour or personality and dependence, for example, not feeling down or depressed, not feeling anxious, worried or stressed, being able to stay safe or not feeling like a burden to others.[15,16]

In the present study, patients with AD and caregivers were surveyed regarding the treatment objectives that were meaningful to them. The goal of the present study was to survey patients with AD and caregivers to establish what they considered to be the most important treatment goals, thereby providing data for the systematic incorporation of these goals into AD clinical trials.

Methods

Survey participants

Web-based surveys (one completed by patients with AD and one completed by caregivers (see Supplemental Material for survey text; available at: https://www.drugsincontext.com/wp-content/uploads/2024/04/dic.2023-11-6-Suppl.pdf) were conducted in five countries in Europe (Germany, Italy, Spain, Sweden and UK) and two in North America (Canada and USA). Patients and caregivers were independently recruited from existing respondent panels in each country. Panels consisted of adult members who previously opted into the panels and agreed to participate in survey research. Panel members were invited to participate in the survey via email or telephone, and those interested were directed to the survey website and screened for eligibility. Eligible study participants were ≥18 years of age and had been diagnosed with either mild cognitive impairment (MCI) or mild-to-moderate AD (patient-reported group) or were involved in the care of a patient with MCI or mild-to-moderate AD (caregiver-reported group). Participants were requested to provide socio-demographic and disease-related details (time since diagnosis, medications, staging and symptoms) on the patients and their preferences for AD treatment goals.

Survey questionnaire design

A single questionnaire was developed for both caregivers and patients and adjusted for each population. The survey was comprised of 48 questions regarding severity stage, symptoms experienced, treatment history, treatment goals and perceptions on AD therapies and included 11 screener and 7 demographic questions. Programming was used to make question wording specific to respondent type (caregiver or patient) and to present response options in random order on the survey site.

Survey questions and response options were designed by the authors utilizing their research experiences and

the AD literature. For example, a literature review of the signs and symptoms most commonly present in patients with AD at different stages of the disease and on the disease milestones that have the greatest impact from patient perspectives was performed to identify key inputs for treatment goals. These goals were subsequently grouped into categories and used to draft response options. Examples were included for response options that required further detail (e.g. list of activities of daily living and psychological symptoms in questions related to their goals for the treatment of AD). Questions and response options were presented in lay language, and the final wording of the questionnaire was validated by a clinical expert on AD. Please refer to the survey questionnaire for further details (Supplemental Information).

Prior to data collection, the survey was pilot tested with three caregivers in the USA. The survey was first administered to caregivers, those data were reviewed and the survey was then administered to patients. This sequential approach was used as a quality check to identify additional questions that might be asked to patients and to validate the understanding of the questions and response options included in the questionnaire. Completing the online survey took respondents an average of 14 minutes.

Regulatory compliance

As a non-interventional study, this study was exempt from registration at ClinicalTrials.gov and the EU Clinical Trials Register. The study protocol was reviewed by the Copernicus Group Institutional Review Board and issued an Institutional Review Board exemption under 45 CFR § 46.104(d)(2).

Survey translations

The final survey was translated into the language of each study country by qualified and experienced native-speaking linguists with healthcare research experience. In Canada, the survey was offered in English and French-Canadian.

Data analysis and statistics

Descriptive statistics were performed using χ^2 and *t* tests to evaluate differences across ratio variables. Logistic regression models were applied to compare results between relevant sub-groups, including the reported patient severity stage and a weighted symptom severity score classification.

Weighted symptom severity scores were generated based on the sum of symptoms reported: clinically mild symptoms = 1; clinically moderate symptoms = 2. Symptoms were classified as 'mild' if they were deemed more characteristic of mild disease and 'moderate' if considered more representative of moderate disease.[17,18] The following symptoms were classified as mild: getting lost or misplacing things, changes in behaviour and mood, challenges in planning or solving problems, compromised judgement that could lead to poor decisions, difficulty with language or problems with reading, writing or working with numbers, and memory loss that does not disrupt daily life. Symptoms that were considered moderate were: memory loss that disrupts daily life, difficulty completing familiar tasks (e.g. eating, getting dressed and maintaining personal hygiene), problems recognizing friends and family members, inability to learn or to cope with new or unexpected situations, and trouble understanding visual images and spatial relationships (e.g. trouble getting out of a chair or setting a table).

After assigning scores to patients based on the presence of mild or moderate symptoms, total scores were calculated for each patient. Total scores ranged from 1–10 with a mode of seven for both patient and caregiver-reported groups. Patients in both groups were divided into two approximately equal groups: the group with fewer severe symptoms (FSS; total score, 1–6) and the group with more severe symptoms (MSS; total score, 7–10).

Statistical significance was assessed at the alpha level of $p<0.05$. Descriptive analyses were performed using SPSS Statistics 26.0 (IBM; Armonk, NY, USA), and data analysis was performed by study author PN.

Results

A total of 322 patients and 614 caregivers completed the survey. The mean age of patients (± SD) was 62.3±9.9 years in the patient-reported group and 76.0±16.9 years in the caregiver-reported group. Female patients comprised 40.4% of the patient-reported group and 51.1% of patients in the caregiver-reported group (Table 1). The country of residence with the largest number of patients in both groups was Spain (23.6% and 16.6% of the patient-reported and caregiver-reported groups, respectively). The patient-reported group described a higher level of patient education (59.0% with 13 or more years of education) than the caregiver-reported group (20.2% with 13 or more years of education).

In the patient-reported group, most patients (196; 60.8%) had been diagnosed in the previous 2 years. Current AD staging in the patient-reported group was 24.2% MCI, 28.9% mild AD and 46.9% moderate AD, according to the latest healthcare provider-patient/caregiver communication (Table 1).

In the caregiver-reported group, 265 (43.2%) patients had been diagnosed in the previous 2 years, a smaller

Table 1. Demographic and clinical characteristics of patients with Alzheimer disease in the patient and caregiver-reported groups.

	Patient-reported group (*n*=322)		Caregiver-reported group (*n*=614)	
	n	**%**	***n***	**%**
Country				
Canada	41	12.7%	100	16.3%
Germany	24	7.5%	82	13.4%
Italy	57	17.7%	101	16.4%
Spain	76	23.6%	102	16.6%
Sweden	5	1.6%	27	4.4%
UK	44	13.7%	102	16.6%
USA	75	23.3%	100	16.3%
Patient age, mean (SD)	62.3	9.9	76.0	16.9
Patient sex, women	130	40.4%	314	51.1%
Years of schooling				
0–3 years	6	1.9%	32	5.2%
4–5 years	7	2.2%	57	9.3%
6–8 years	13	4.0%	135	22.0%
9–13 years	97	30.1%	212	34.5%
13 or more years	190	59.0%	124	20.2%
I do not know	7	2.2%	54	8.8%
Prefer not to answer	2	0.6%	–	–
Time since diagnosis				
Less than 6 months	59	18.3%	20	3.3%
At least 6 months ago but less than 1 year	69	21.4%	77	12.5%
At least 1 year ago but less than 2 years	68	21.1%	168	27.4%
At least 2 years ago but less than 3 years	49	15.2%	170	27.7%
3 or more years	74	23.0%	171	27.9%
Not sure	3	0.9%	8	1.3%
Current medication				
Donepezil	94	29.2%	204	33.2%
Rivastigmine	83	25.8%	98	16.0%
Galantamine	119	37.0%	88	14.3%
Memantine	108	33.5%	131	21.3%
Memantine + Donepezil	14	4.3%	24	3.9%
Not sure	5	1.6%	8	1.3%
None of the above	1	0.3%	13	2.1%
Current reported staging				
Mild cognitive impairment	78	24.2%	37	6.0%
Mild (early stage)	93	28.9%	134	21.8%
Moderate (middle stage)	151	46.9%	443	72.1%

Totals for each parameter in the table may not equal 100% due to rounding. Current medications reflect that patients may have been taking more than one Alzheimer disease medication at the time of the survey. Not all the caregivers responded to the current medication question (*n*=566).

percentage than in the patient-reported group. Staging in the caregiver-reported group was 6.0%, 21.8% and 72.1% reported as MCI, mild AD and moderate AD, respectively (Table 1). Patients in this group were somewhat older and more advanced in their disease course, which may relate to their participation in the study through a caregiver rather than directly.

In terms of current treatment, galantamine, an AChI, was the most frequently reported current AD medication in the patient-reported group (37.0%), followed by memantine, an NMDA receptor antagonist (33.5%). Conversely, in the caregiver-reported group, the most common current medications were donepezil (another AChI; 33.2%) and memantine (21.3%) (Table 1).

When surveyed about symptoms, the patient-reported group indicated these symptoms most frequently (Figure 1): memory loss not disrupting daily life (50.6%), getting lost and misplacing things (46.6%), and memory loss disrupting daily life (46.0%). For the caregiver-reported group, memory loss that disrupts daily life, getting lost and misplacing things, and changes in behaviour or mood were the most frequently reported symptoms (59.3%, 55.4% and 49.7%, respectively). Memory loss that does not disrupt daily life was stated for a smaller percentage of patients in the caregiver-reported group (30.6%).

Symptoms in the patient-reported group were also analysed by disease stage. Some symptoms were communicated by patients with similar frequency in all disease groups, whilst others showed distinct differences (Figure 2). Memory loss not disrupting daily life was reported more frequently in the MCI group (65.4%) than in the mild (47.3%) or moderate AD groups (45.0%). Conversely, memory loss that disrupts daily life was reported more frequently in the mild (49.5%) and moderate AD groups (53.6%) than in the MCI group (26.9%). Predictably, several symptoms were described more commonly in patients with more severe disease (i.e. patients with moderate AD). These included challenges in planning or solving problems (41.7%), difficulty completing familiar tasks (41.7%), trouble understanding visual images (41.1%), difficulty with language or problems with reading (35.1%) and problems recognizing friends and family members (33.1%).

Symptoms in the caregiver-reported group were somewhat different than in the patient-reported group (Figure 3). In the caregiver-reported group, changes in behaviour/mood (59.5%), inability to learn or cope with new situations (56.8%) and challenges in planning or solving problems (56.8%) were communicated more commonly than memory loss that does not disrupt daily life (37.8%) in patients with MCI. For patients with more advanced disease (moderate AD), the symptoms reported in a greater

Figure 1. Most frequent symptoms of patients with Alzheimer disease (AD) in patient-reported and caregiver-reported groups. Patients and caregivers were surveyed regarding the symptoms experienced by the patient with AD, and the results are presented as the percentage of patients reporting each symptom.

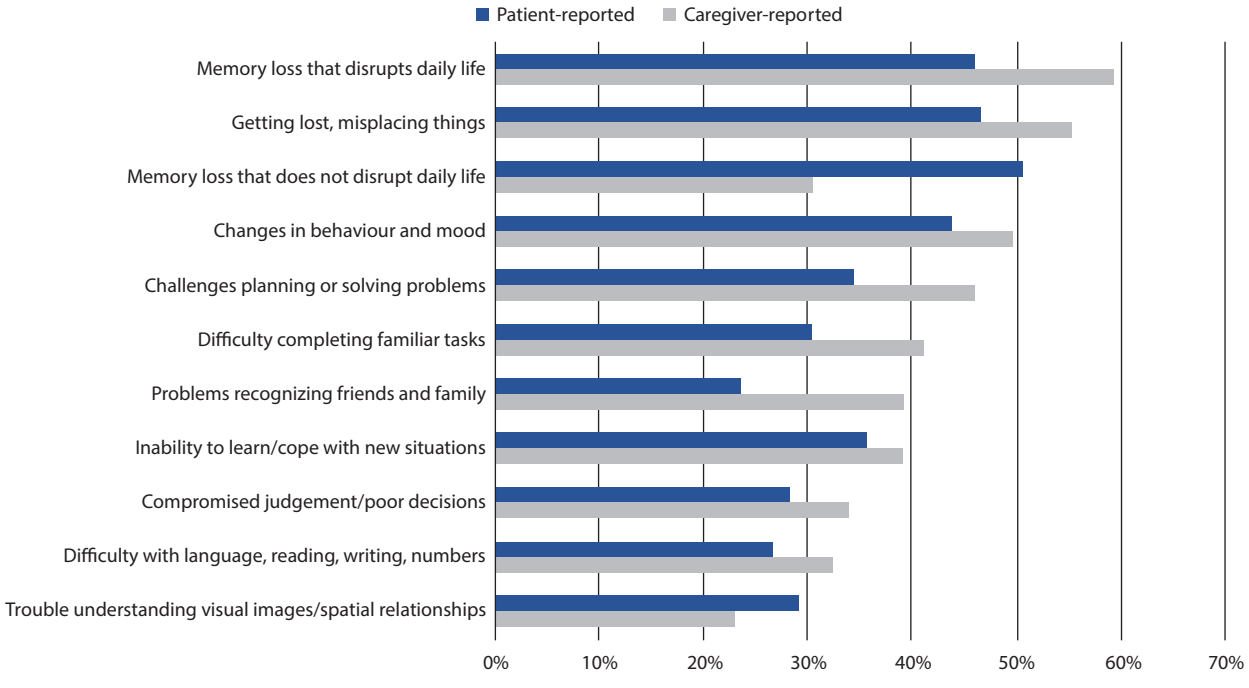


Figure 2. Most frequent symptoms of patients with Alzheimer disease (AD) in the patient-reported group separated by disease stage. The percentage of patients reporting each symptom is shown in the graph with patients separated by disease stage: mild cognitive impairment (MCI), mild AD and moderate AD.

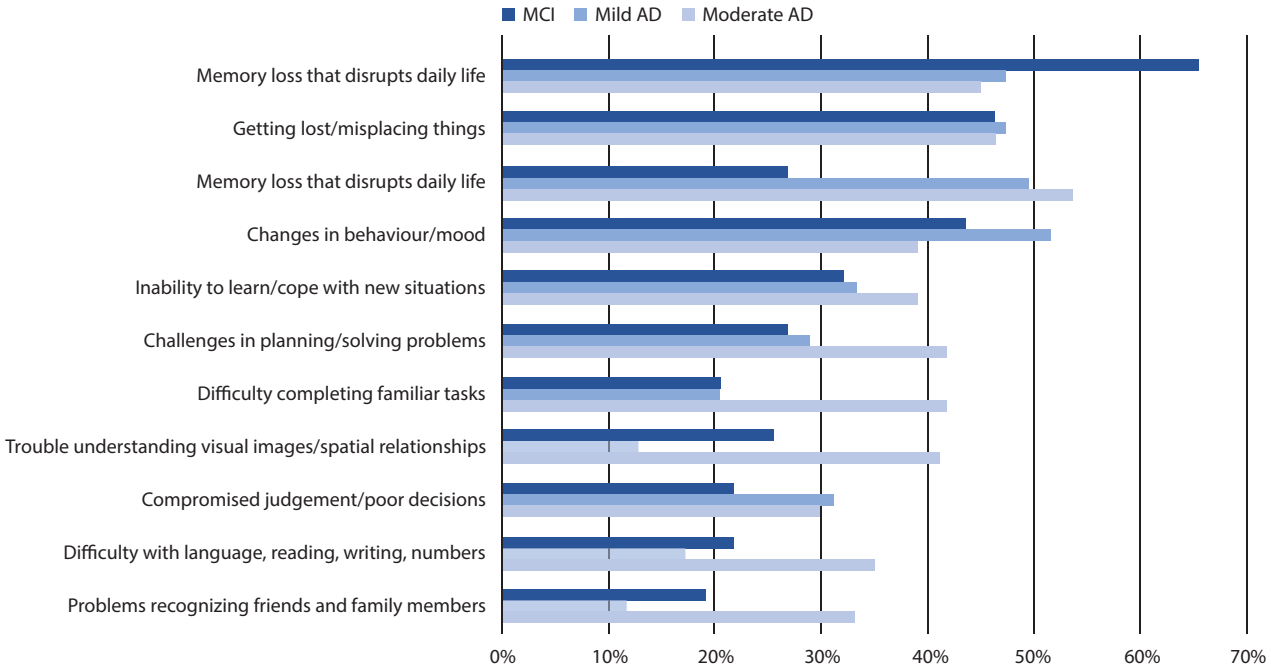
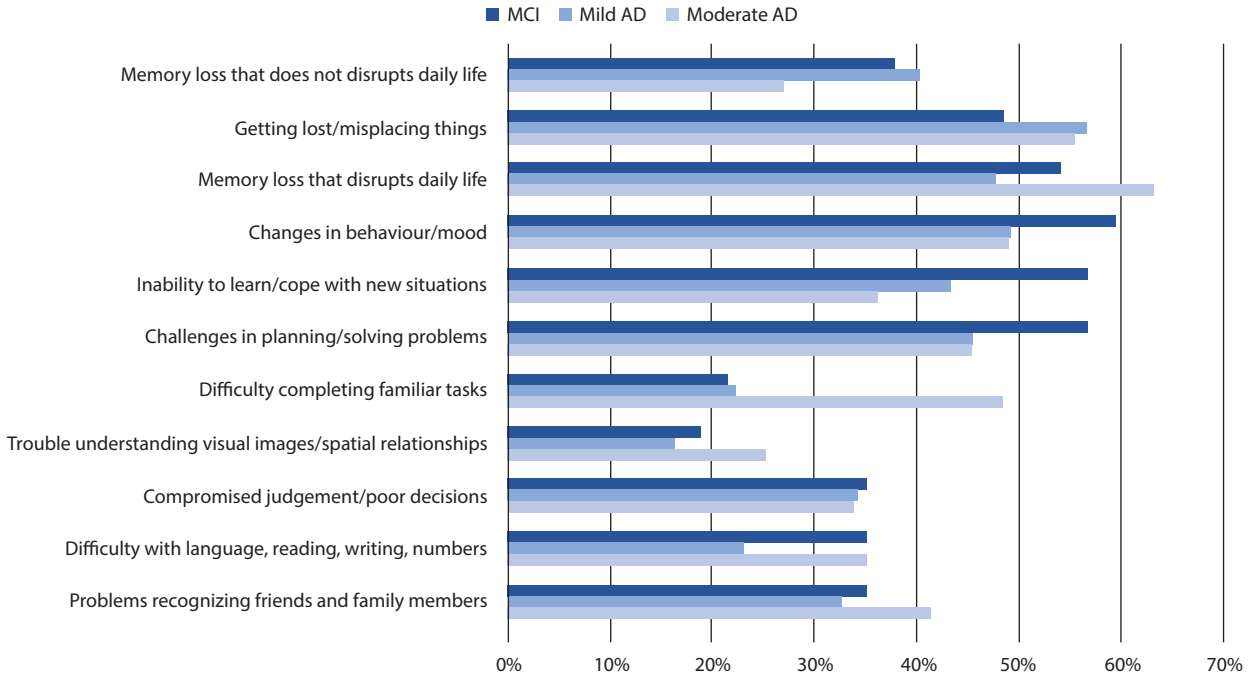


Figure 3. Most frequent symptoms of patients with Alzheimer disease (AD) in the caregiver-reported group separated by disease stage. The percentage of patients reporting each symptom is shown in the graph with patients separated by disease stage: mild cognitive impairment (MCI), mild AD and moderate AD.



percentage of patients than in MCI were memory loss that disrupts daily life (63.2%), difficulty completing familiar tasks (48.5%), trouble understanding visual images (25.3%) and problems recognizing friends and family (41.5%).

When asked to pick the primary goal for the treatment of AD, maintenance of quality of life (QoL) was selected as the single most important treatment goal for both the patient-reported (31.1%) and the caregiver-reported (38.8%) groups (p=0.01 for the comparison), followed by slowing the progression of memory loss (15.4% and 20.1% in the patient-reported and the caregiver-reported groups, respectively; p=0.055) (Figure 4).

The preference for maintenance of QoL as the main AD treatment goal was consistent across disease stages, both in the patient-reported group (MCI: 34.7%, mild AD: 27.8% and moderate AD: 31.3%; Figure 5) and the caregiver-reported group (MCI: 24.3%, mild AD: 35.1% and moderate AD: 41.1%; Figure 6). An exception was the caregiver-reported MCI sub-group, in which slowing the progression of memory loss was identified as the main treatment goal by 27.0% of participants (Figure 6).

When the participants were divided by symptom severity score rather than by disease stage, maintenance of QoL was the most commonly selected top treatment goal in both groups (Table 2). Similar percentages were seen in patients with FSS (32.7%) versus patients with MSS (29.2%) in the patient-reported group. Although numerically higher values were seen in the caregiver-reported group, symptom severity score had little effect on the percentage of patients selecting maintenance of QoL as a top treatment goal (FSS 34.9% *versus* MSS 41.1%). The next most commonly selected treatment goal was slowing the progression of memory loss. In both the patient-reported (FSS 17.3% *versus* MSS 13.2%) and the caregiver-reported groups (FSS 23.6% *versus* MSS 18.1%), sub-dividing patients by symptom severity had no significant effect on selection of this goal. In both patient-reported and caregiver-reported groups, there were no differences between the groups partitioned by symptom severity (FSS *versus* MSS).

Discussion

The survey described in this paper was comprised of 936 responses: 322 in the patient-reported group and 614 in the caregiver-reported group. The results of this survey revealed that maintenance of QoL was the single most important treatment goal for patients with MCI, mild AD and moderate AD. However, current guidelines

Figure 4. The most important goal of Alzheimer disease (AD) treatment for patient-reported and caregiver-reported groups. Patients and caregivers were surveyed regarding their most important goal for AD treatment. The results are expressed as a percentage of each group indicating a goal as most important. The difference between the caregiver-reported and patient-reported importance of the goal of maintaining quality of life was statistically significant (p=0.01).

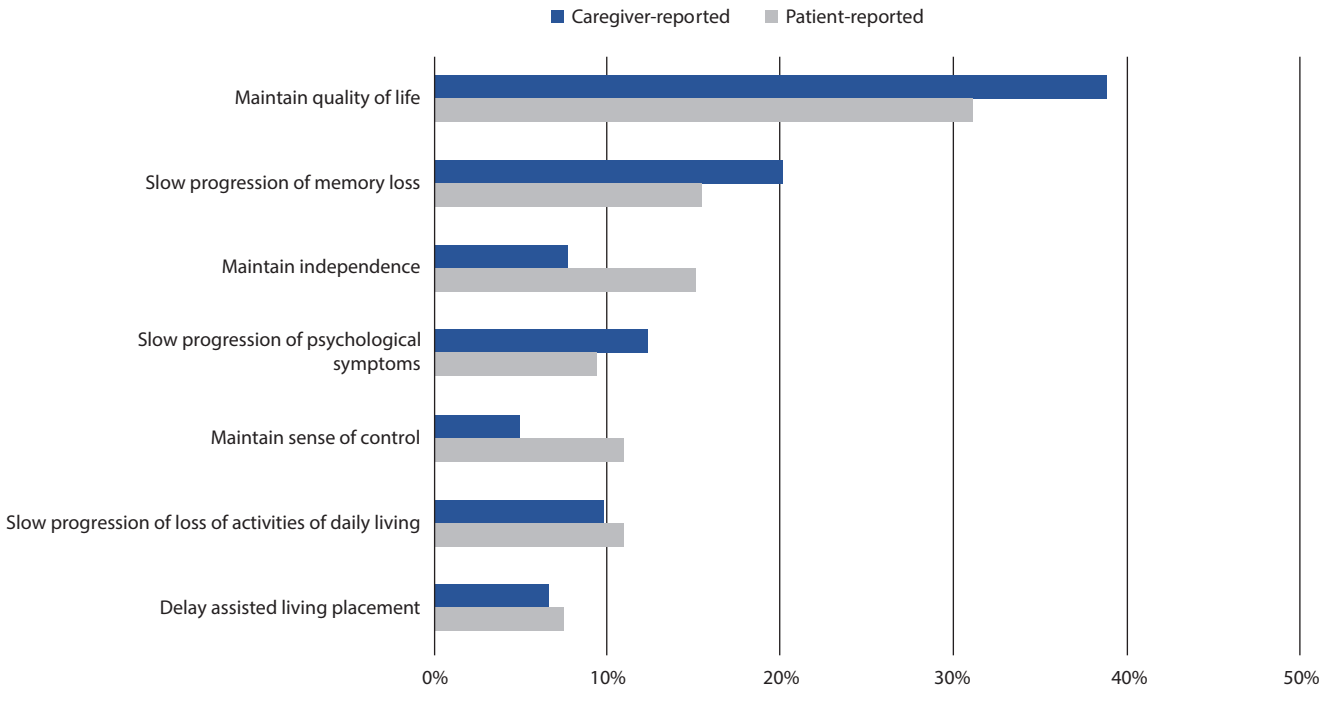


Figure 5. The most important goal of Alzheimer disease (AD) treatment for the patient-reported group separated by AD stage. This graph shows the percentage of patients in the patient-reported group rating each goal as most important for their AD treatment. Patients were subdivided by disease stage: mild cognitive impairment (MCI), mild AD or moderate AD.

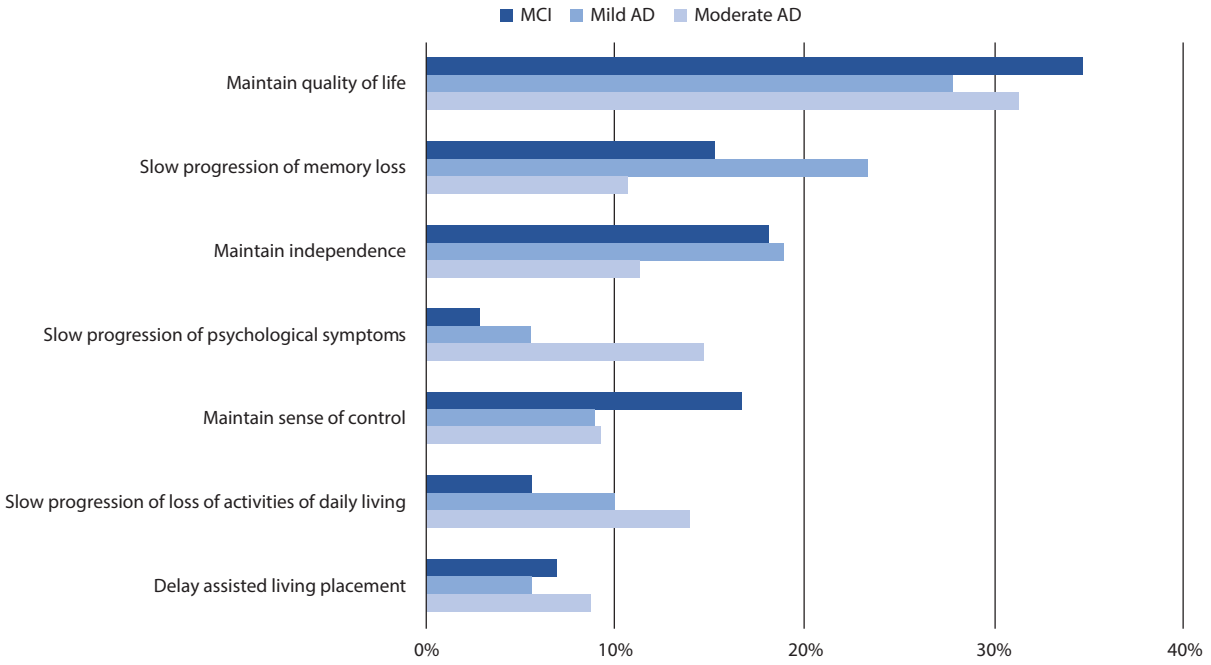


Figure 6. The most important goal of Alzheimer disease (AD) treatment for the caregiver-reported group separated by AD stage. This graph shows the percentage of patients in the patient-reported group rating each goal as most important for their AD treatment. Patients were subdivided by disease stage: mild cognitive impairment (MCI), mild AD or moderate AD.

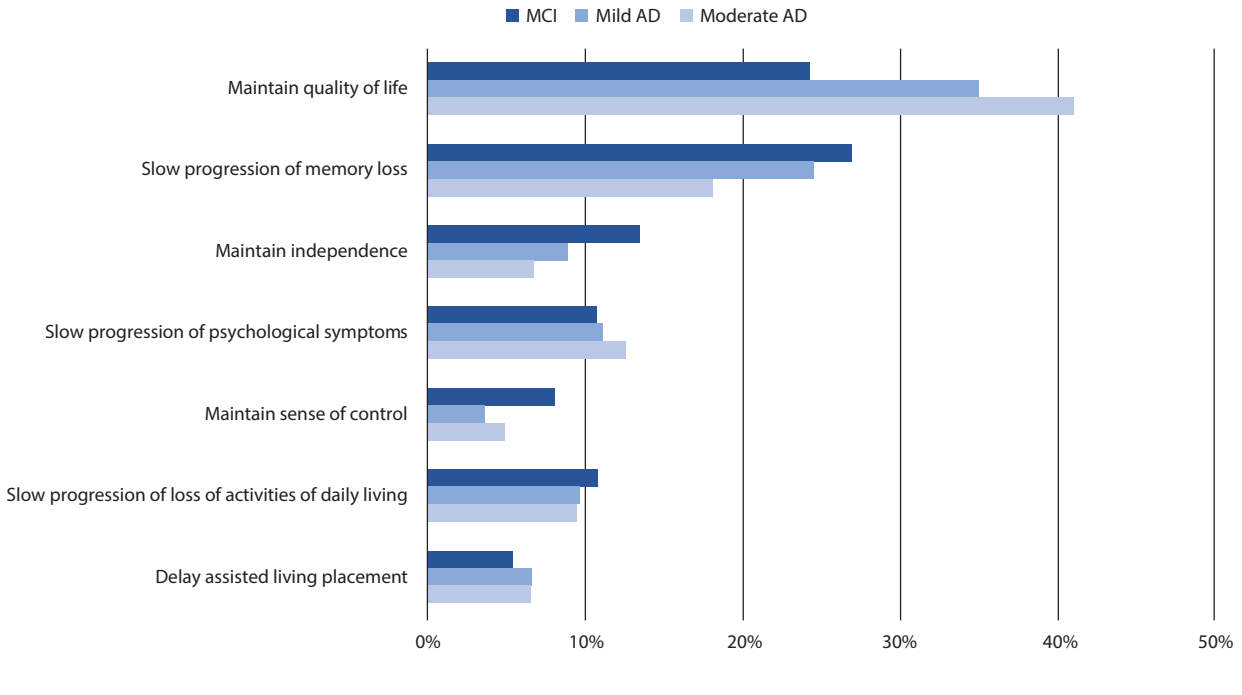


Table 2. Survey results reported with patients grouped based on symptom severity.

A. Patient-reported group

Most important treatment goal (%)	Symptom severity score		
	Total (*n*=312)	FSS (*n*=168)	MSS (*n*=144)
Maintain QoL	31.1	32.7	29.2
Slow progression of memory loss	15.4	17.3	13.2
Maintain independence	15.1	16.1	13.9
Maintain sense of control	10.9	10.1	11.8
Slow progression of loss of ADL[a]	10.9	8.9	13.2
Slow progression of psychological symptoms[b]	9.3	9.5	9.0
Delay assisted living placement	7.4	5.4	9.7

B. Caregiver-reported group

Most important treatment goal (%)	Symptom severity score		
	Total (*n*=611)	FSS (*n*=229)	MSS (*n*=382)
Maintain QoL	38.8	34.9	41.1
Slow progression of memory loss	20.1	23.6	18.1
Slow progression of psychological symptoms[b]	12.3	12.2	12.3
Slow progression of loss of ADL[a]	9.7	7.4	11.0
Maintain independence	7.7	9.2	6.8
Delay assisted living placement	6.5	7.4	6.0
Maintain sense of control	4.9	5.2	4.7

Goals for each group were ordered by the number of patients selecting a goal as most important. Totals for each parameter in the table may not equal 100% due to rounding.
[a]ADL include, for example, paying bills, using tools, driving, doing laundry, eating, and toileting.
[b]Psychological/psychiatric symptoms include delusions, hallucinations, apathy, depression and agitation.
ADL, activities of daily living; FSS, fewer severe symptoms: symptom severity score = 1–6; MSS, more severe symptoms: symptom severity score = 7–10; QoL, quality of life.

for AD clinical trials place the emphasis on primary outcome measures that evaluate clinical endpoints, such as the assessment of daily function and cognition, and little emphasis on other relevant outcomes for patients and caregivers, such as QoL.[13] The findings of the current study are in line with previous results revealing that the outcome measures in clinical trials are not evaluating all conceptually relevant elements for patients and caregivers.[19–21] The *What Matters Most* study and ROADMAP (Real-World Outcomes Across the AD Spectrum for Better Care) meta-analysis have also assessed the importance of various measures to patients with AD and their caregivers. Whilst the maintenance/improvement of memory and stopping or slowing progression of the disease are rated as the most important goals in the *What Matters Most* study, both sets of authors also concluded that the neuropsychological assessments commonly used in clinical trials do not assess many of the concepts that are important to patients and caregivers.[16] A recent update of the *What Matters Most* study found that the QoL items important to patients with AD (asymptomatic-to-severe AD) and caregivers (for those with moderate-to-severe AD) went beyond daily function and cognitive capacity to include overall physical, mental and emotional health, maintenance of independence and safety.[22]

In another recent study, a team from the United Kingdom developed an electronic person-specific outcome measure to capture person-specific outcomes and preferences in AD clinical trials. Whilst conducting focus groups as part of the development process, they found that the outcomes that matter most to patients in daily life lie in the five key domains of everyday functioning,

relationships and social connections, enjoying life, sense of identity and alleviating symptoms.[23]

The results of the current survey are also comparable to those of an international survey that was designed to identify gaps in AD-related information and communication and barriers to treatment compliance. That survey included both patients with AD and their families or other caregivers.[24] Across all the countries surveyed, the majority of patients with AD indicated that QoL issues were important to them. Of the 11 issues rated in the study, those found to be of greatest importance (>90% of the respondents rated the issue as important) were QoL-related issues: achieving the best possible QoL, keeping up a social life with family and friends, medical treatment that helps control symptoms, feeling safe and supported at home, and the ability to enjoy life.

The results of the current survey showing the importance of QoL issues are also in agreement with a study conducted in the USA that evaluated the preferences of patients with MCI and their caregivers after a behavioural intervention programme. Their results indicated that, for the MCI stage, QoL and self-efficacy (an individual's belief in their own ability to perform tasks or achieve goals) were most important to both patients with MCI and their caregivers.[25]

A systematic literature review published in 2018 as part of the ROADMAP initiative identified important outcomes for patients with AD, their caregivers and their healthcare providers.[20] This review found that clinical aspects of the disease were important (e.g. memory and mental health) as were QoL issues such as the social aspects of the disease and the devastating burden and impact of caregiving. Other important outcomes reflected the practical challenges of the disease, including accessing information about AD and completion of the activities of daily living. Additional outcomes reflected more personal aspects of the disease, including maintenance of person autonomy, identity and general QoL.

Despite evidence of their importance to patients with AD, their caregivers and their healthcare providers, regulatory guidelines have been slow to incorporate QoL outcomes. However, the most recent EMA guidelines for AD clinical trials state that "*cognition, function and global assessments cover key domains in the evaluation of patients with AD. Health-related QoL tools, both generic and disease specific, should also be included.*"[26] More concretely, the new guidelines state that, in addition to measurements of cognition, function, and the ability to carry out essential activities and executive functions, health-related QoL measures and behavioural and psychiatric symptoms should be included as secondary measures in an overall assessment of efficacy. These recent guidelines are an indicator that regulators may be viewing QoL measures as increasingly relevant in AD clinical trial design.[26]

It is also important to note that the appropriate outcome measures may be dependent on the clinical staging of the patients involved.[27] QoL self-assessments by patients have been found to be reliable in patients with early-stage AD, whilst the limited decline of patient self-reported QoL commonly observed in more severe stages has been attributed to patient lack of self-awareness.[28] Because most therapies in development are targeted towards early and preclinical AD, the inclusion of QoL endpoints and the selection of the appropriate measures of QoL in AD trials are potentially even more important. Conversely, as AD progresses, caregiver assessments of QoL for the patients and themselves could have more relevance, though they may also be subject to bias depending on caregiver burden and well-being.[27–29]

However, despite the apparent change in the regulatory view of QoL measures, several recently conducted or ongoing phase III studies of potential AD treatments did not include QoL measures as primary or secondary outcomes. These studies included trials with aducanumab,[30,31] donanemab[32] and gantenerumab.[33–36] However, some recent studies of potential AD treatments have included QoL measures (AMBAR[37,38] and solanezumab[39]). The results of the current survey and similar surveys indicate that QoL outcomes are of great importance to patients with AD, their caregivers and their healthcare providers. Inclusion of QoL measures in AD clinical trials would help to give a broader overall measure of the effects of potential AD treatments on the health and general well-being of the trial participants.

Strengths of this survey include the large sample size (936 responses: 322 in the patient-reported group and 614 in the caregiver-reported group) and that it encompassed several countries in Europe and North America.

Limitations

The current study has limitations that should be considered when interpreting the results. (1) AD severity was reported by the patients and caregivers based on their latest communication with their treating physician and not directly by a healthcare provider. (2) The recruitment of patients and caregivers was performed independently. In consequence, the responses of patients and their corresponding caregivers could not be correlated. (3) Recruitment for this study was through existing patient and caregiver panels and was conducted through a web-based survey. These facts may

have biased the study towards patients with AD with less severe disease and skewed the AD patient population towards those with higher levels of education (Table 1). In addition, self-reporting of AD severity may have inadvertently produced a misclassification of AD severity in some patients. Some patients with more advanced disease (moderate AD) might have difficulty completing a survey like the one used in this study. Because patients self-reported to have moderate AD were able to successfully complete the survey, it is possible that some of these patients may have inadvertently misclassified their disease state. (4) QoL was not specifically defined in the survey and, consequently, may have been interpreted differently by different survey participants, especially given the different cultures. Whilst QoL was not a rigidly defined concept for this study, it was not the objective of this study to quantify QoL but to assess the importance of the concept of perceived well-being to the survey participants.

Conclusion

The results from this survey suggest that maintenance of patient QoL is consistently considered as the most relevant treatment goal for both patients with AD and caregivers across the different stages of AD. Currently, there is a discrepancy between the primary clinical trial outcomes recommended by regulators and relevant outcomes for patients with AD and caregivers. In other words, whilst clinical trial investigators are most interested in biomarkers and clinical outcomes, patients and caregivers are most interested in how the treatment will affect the general well-being of the patients and their caregivers. When considering the design of an AD clinical trial, patient-relevant outcomes, specifically QoL, should be given more emphasis to reflect the needs and demands of patients with AD and their caregivers.

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