Improving Quality of Life in Caregivers of Alzheimer Dementia Patients- A Stepwise Approach

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https://doi.org/10.18662/lumproc.rsacvp2017.86

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Abstract

Caregivers’ burden could have serious impact over social and professional functioning in adult and active population. Quality of life in caregivers of Alzheimer Disease (AD) patients should be monitored as an important indicator of their well-being and functional resources. The main objective of this research is to formulate a plan for the evaluation of the quality of life in caregivers of the AD patients as a first step in the recommendation of an adequate, stratified therapeutic intervention. Regarding the research methodology, the first step consisted in a review of the most validated instruments for caregiver status evaluation - SF-36, EuroQoL, Zarit Burden Interview (BI), Global Assessment of Functioning Scale (GAF), and Neuropsychiatric Inventory (NPI). A composite score (cs) could be calculated based on these scales, and 3 classes of quality of life impairment severity could be defined. The second step consists in recommendations regarding the monitoring of the caregivers’ status using the same instruments, and the formulation of therapeutic interventions according to the severity of quality of life impairments. It is expected that applying this algorithm would decrease the AD burden’s functional impact over caregivers, while increasing their quality of life. Learning new ways to cope with stress, a better management of their own time and engaging in changing coping methods during group therapy sessions are expected to have a significant impact over caregivers overall psychological status. In conclusion, a better care should be provided for AD patients’ caregivers, in order to increase their functionality and quality of life.

Keywords: quality of life, caregivers’ burden, Alzheimer Dementia, resources management, therapeutic interventions.

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https://doi.org/10.18662/lumproc.rsacvp2017.86

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Selection and peer-review under responsibility of the Organizing Committee of the conference
1. Introduction

In chronic and progressive disorders like Alzheimer Disease (AD), patients rely on caregivers to help them in daily activities, and in the late stage patients need continuous supervision for even the basic actions. Caregivers’ burden could have serious impact over social and professional functioning in the adult and active population (patients’ children and grandchildren, d.e.).

Poor quality of life in family members of AD patients predicts nursing-home placement for these patients. [1] Healthcare costs and economic consequences of AD are important in the context of the increasing incidence of this disease. Indirect costs of AD are derived from decreasing professional performances and absenteeism in family members, discomfort in carers relationship, and even onset of psychiatric or psychosomatic disorders in caregivers. According to a meta-analysis that included 17 trials, the aggregate prevalence of depression among caregivers was 34% (odds of having depression is 1.53 times higher in female caregivers, 1.86 times higher in caregivers to male care-recipients, and 2.51 times higher in spousal caregivers), anxiety 43.6%, and the use of psychotropic drugs 27.2%. [2].

Quality of life in patients’ caregivers should be monitored as an important indicator of their well-being and functional resources. Methods for improving quality of life in AD caregivers have been explored and variables that correlated with better values of this parameter have been defined. In a cross-sectional study, informal social support acted as a mediator between depression and life satisfaction in caregivers of AD patients. [3] A community-based occupational therapy intervention for people with mild to moderate dementia and their family carers proved itself clinical and cost effective in the Netherlands but not in Germany. [4]

2. Objective

Available data in the literature suggest there is a need for more detailed methods and algorithms regarding the evaluation of the quality of life in caregivers of AD patients. [2-4] If the caregivers’ quality of life is not satisfactory, this could reflect in their ability to care for the AD patients, and this may further fuel a possible accelerated deterioration in patients’ general status. Breaking this vicious circle is considered in our opinion very important as it associates significant healthcare costs and worsen the patient prognosis.
Therefore, finding a structured way to evaluate quality of life in AD patients’ caregivers could be the first step in planning a therapeutic intervention focused on increasing quality in life both in AD patients and their caregivers. The main objective of this paper is to construct a new instrument for the determination of AD patients’ caregivers, based upon already validated clinical questionnaires and scales. The novelty of this research is derived from the integration of a large set of information about caregivers’ perceived burden, quality of life and overall functioning in a single algorithm. Also, according to the score derived from the algorithm, specific recommendations with therapeutic value could be formulated for AD patients’ caregivers.

3. Research Methods

In order to formulate a plan for caregivers’ evaluation, this paper started from the detection of available data regarding the most frequently used instruments for the evaluation of AD patient caregivers’ quality of life, global functioning and disease burden.

A systematic literature review was conducted in the main electronic databases - PubMed, Cochrane, EMBASE, CINAHL - using as keywords and paradigm “quality of life”, “neuropsychiatric symptoms”, “global functioning”, and “Alzheimer Disease”, and “caregivers”. The time interval selected for published papers was 1980-2017, and the patients must have been diagnosed with AD according to structured criteria. Dyad-based trials (patients and their caregivers) were preferred as this design could offer a more detailed perspective over the familial interactions and quality of life.

All studies containing psychometric evaluations for quality of life in caregivers of AD patients were included in the review, regardless of the trials design.

4. Results of the review

SF-36 or the “Short Form Survey” was created to survey the overall health status in the Medical Outcomes Study, a large-scale, cross-sectional research focused upon the relation between differences in the systems of care, clinician specialty, and clinicians’ technical and interpersonal styles, on one side, and variations in patients’ outcomes, on the other. [5,6]

SF-36 is a multi-item scale with 8 factors: limitations in physical roles due to health problems; limitations in social activities because of physical or
emotional problems; limitations in usual roles secondary to physical health problems; bodily pain; general mental health; limitations in usual role activities because emotional problems; vitality; general health perceptions. [6] Each factor is scored from 0 to 100, the lower the score, the greater the perceived dysfunction.

The questionnaire has been validated, it is used almost in every medical specialty, and it could be self-administered by the individual for various reasons, from screening of the psychological and behavioural variables that can improve quality of life in chronic dialysis patients [7], to analysing the musculoskeletal disorders impact over patient’s health related quality of life. [8]

SF-36 is also used for the determination of the cost-effectiveness ratio in pharmaco-economic analyses and for the calculation of the disease’s “negative impact” over life expectancy through QALY variable (“quality-adjusted life year”). Many health systems use currently cost-effectiveness analysis to decide the funding of interventions and programmes. [9]

Informal caregivers of patients diagnosed with AD have been evaluated using SF-36 and obtained lower scores on all the 8 factors at 12 months, with significant variations except for “physical function” and “social function”. [10] A descriptive study that included 63 caregivers of AD patients reported lower levels of the quality of life, lowest score being observed on the role-emotional, role-physical, social functioning and vitality scales of the SF-36. [11]

The correlations between SF-36 scales and Zarit Burden Interview (ZBI) were moderate to strong (p<0.001), and correlations between SF-36, Mini Mental State Examination (MMSE) and Neuropsychiatric Inventory (NPI) were significant, being strongest in mental health-related scales of the SF-36, in a study that involved 48 caregivers of AD patients. [12]

Caregivers of patients who had not been placed in nursing home had better quality of life scores on SF-36, even after controlling for potential confounding variables, and the adjusted odds ratio of being admitted to a nursing home was 6.4 for patients being cared-for by relatives who rated their health as being much worse compared with the previous year. [1] Caregiver time increased for caregivers of AD-affected persons with more severe cognitive impairment. [13]

**EuroQoL (EQ-5D)** is a standardized instrument used for quantifying health related quality of life based on visual analogic scale. This instrument has been developed since 1987 by the EuroQoL Group, and it is based on a descriptive model with 5 dimensions- mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. [14] Each dimension has 3 degrees, ranging from no problems to severe problems. Also, a visual
analogic scale (VAS) scored from 0 to 100 (worst imaginable health to best imaginable health) is included in this instrument.

According to a systematic review of studies which used EQ-5D in patients with AD as self-rated scores and reported by and their caregivers, there are problems with the validity of self-rated data because of a lack of association between patient and proxy ratings. [15] A ceiling effect was detected for patient rating, and the visual analogue scale has poor reliability, even in patients with mild to moderate dementia. [15]

A prospective, non-interventional cohort study in community-dwelling patients with AD and their informal caregivers (GERAS) reflected worsening in EQ-5D domains was associated with increases in ZBI scores. [16] Authors of this analysis mentioned that EuroQoL may not be the best instrument for AD patients’ caregiver due to its focus on physical health. [16]

Patients with AD obtained a significantly higher health-related quality of life determined by EQ-5D and EQ-VAS (p<0.001) compared to their caregivers. [17] Also, different AD group according to the severity of the disease presented significantly worse results on the quality of life scales for patients with lower MMSE scores, and institutionalized patients had considerably lower quality of life versus participants in outpatient settings (p<0.001). [17]

A cross-sectional study of 488 dyads (AD patient-caregiver) using EQ-5D showed a satisfactory rate of the scale, but the agreement between self- and family caregiver ratings was poor. [18] The most important predictors for health-related quality of life in patients with mild to moderate AD living in the community and in their caregivers were family caregiver’ ratings of activities of daily living and mood. [18] The type of the caregiving relationship influenced caregiver ratings of health-related quality of life, with the sons and daughters rated the lower scores on EQ-5D for AD patients, compared to spousal caregivers. [18]

EQ-5D was applied for the determination of the predictors for lower quality of life in institutionalized AD patients, and the results were significant for the number of chronic problems and baseline scores of the quality of life measures. [19] There is a relationship between quality of life, functional scales and cognitive scale, with the functional aspects being correlated with quality of life better than cognitive ones in patients with AD. [20]

EQ-5D and the Health Utilities Index Mark 2 (HUI2) were compared by caregivers of AD patients as measurements for the quality of life. [21] Both instruments correlated with caregivers’ assessments of patients’ function, AD-specific quality of life, physical and mental health and
selected subscales of the measures of AD-specific quality of life and overall health. [21] Caregiver scores presented relationships with patient self-rated function, mood, and physical health but not AD-specific quality of life, and caregiver burden was associated with caregivers’ scores. [21]

EQ-5D was used as an indicator for the economic burden in AD and to reflect the disease’ impact on health-related quality of life for patients and caregivers. [22] This analysis included 237 patients and the average annual cost per patient with AD was 36,144 USD; the most important categories of costs were for informal care and drugs, and costs increased with cognitive impairment with an average annual cost 19,171 USD for mild, 32,765 USD for moderate, and 53,411 USD for severe patients. [22] The EQ-5D VAS score was 42 for patients and 62 for caregivers, and the severity of the clinical status of AD patients influenced the quality of life in patients, but not in caregivers. [22]

A study that investigated if patient and informant reported quality of life differed in early AD revealed that on most measures patients rated their quality of life higher than their informants. [23] Self-reported quality of life was significantly correlated to depression, but not to age, dementia severity, behavioral symptoms or memory impairment; informant ratings of quality of life were significantly correlated to behavioral symptoms and informant ratings on the EQ-5D VAS were significantly correlated to patient reported depression. [23] Anosognosia correlated with the presence of disagreement between patient and caregiver ratings of the quality of life. [23]

Caregivers of AD patients suffer a negative impact on their health state and health-related quality of life, as the caregivers scored lower EQ-5D than the general population, except for the self-care dimension. [24] Data collected from the caregivers showed that 84% of them presented physical problems related to care given to the AD patients, and 94.4% had psychological problems. [24]

Zarit Burden Interview (ZBI) has a history of more than 20 years, and it is considered the most commonly used instrument for the measurement of caregiver burden. [25] Responses to ZBI appear reliable across populations of caregivers and patients, but non-standard versions with more or less than 22 items have a degree of reliability difference both statistically and meaningfully. [25] Therefore, the standard, 22-item version of ZBI is the most commonly used. Three dimensions of burden were found on ZBI factorial analysis: effect on the social and personal life of caregivers, psychological burden and feelings of guilt. [26]

In an 18-month study in Germany (GERAS) (N=550) caregiver burden evaluated through ZBI increased most acute in moderate (MMSE scores between 15 and 20) AD patients with 7.2 (CI 4.2–9.7), 90.7% of the
patients received antidementia drugs and 26.6% received psychotropic medication. [27] In the same study caregivers total time increased by 70% and 33% in AD patients showing functional or cognitive decline compared with those not showing decline, and ZBI scores increased with 5.3 and 3.4 points, respectively. [28]

ZBI scores reflected a level of burden between severe and moderated in 46.5% of caregivers, while in 34.7% it was severe. [24] The burden of caregivers had a negative relationship with physical, psychological, social, and environmental domains of quality of life, but neither caregiver burden nor quality of life predicted anxiety and depression in the caregivers, as reflected a 60-subject trial that used ZBI and the brief version of World Health Organization Quality of Life Scale. [29]

Caregiver burden in AD is predicted by the Behavioral Pathology in Alzheimer’s Disease Scale score, income, diabetes, and in-laws as caregivers (p<0.001) in a multivariate stepwise regression analysis. [30] Being the son of the AD patient and high-income status negatively correlated with caregiver burden. [30]

Cross-cultural studies reflected different factors associated with caregiver burden, according to societal peculiarities. A trial which involved ZBI compared 343 outpatients with AD and their caregivers from Japan and Taiwan. [31] The score on “Impact on caregiver’s life” in Taiwanese caregivers was significantly higher than that in Japanese (P=0.001), and “Dependency” in Taiwanese caregivers was lower than that in Japanese (p<0.001). [31] Another ZBI-using trial detected higher burden level in Brazil than in Spain, where female caregivers and patients not attending Day Care Center. [32] In Spain, high levels of caregiver burden were associated with living with the patient, younger caregivers, and participation of patients at Day Care Center; also, in Spain apathy/indifference, agitation/aggression, and irritability/lability were associated with high level of burden for caregivers, while in Brazil depression and anxiety correlated with this parameter. [32] In Greece, lower caregiver’s age, high behavioral symptoms of dementia patients and caregivers’ depression were found to be independently associated with caregiver’s burden evaluated on ZBI. [33] The European ICTUS study showed that progression of caregiver burden (evaluated on ZBI) was most rapid in Northern Europe, while functional decline tended to be faster in Southern Europe. [34]

No significant difference was found in quality of life (determined by ZBI) between male and female spouse-caregivers (p=0.71), and no correlation between spouse-caregivers’ quality of life and sexual satisfaction reached the level of significance. [35] Impaired awareness and lower quality
of life of patients with AD were significantly related to spouse-caregivers’ quality of life in a linear regression analysis. [35]

ZBI scores correlated with Instrumental Activities of Daily Living (IADL) scores, Neuropsychiatric Inventory (NPI) scores, antidepressant drugs prescriptions, and MMSE scores, while the etiology of the dementia and disease stage were not significantly correlated with the caregivers’ burden: ZBI decreased by 0.34 point for every unit of IADL, and by 0.03 point for every unit of MMSE; ZBI increased by 0.03 point for every unit of NPI. [36] A number of 5 area of the NPI increased the ZBI scores: apathy, agitation, aberrant motor behavior, appetite disorders, and irritability, and 5 domains of the IADL increased the ZBI values- the ability to handle finances, food preparation, responsibility to take medications, mode of transportation, and ability to use the telephone. [36]

A 3-year analysis of AD caregiver burden trajectories showed that spouse and adult children who lived with their parent were more likely to belong to the group with initial moderate ZBI scores that increased gradually, while being the sole caregiver, and poor mental health are also relevant for the caregiver perceived burden. [37]

ZBI scores were higher in patients with lower MMSE scores, and Dementia Behavior Disturbance Scale (DBD) score was associated with caregiver burden in all patients. [38] Symptoms related to memory deficit were correlated to caregiver burden in amnestic mild cognitive impairment, and differential IADL, such as inability to use a telephone, use transportation, manage finances, shop, cook and take responsibility for own medication, were related to caregiver burden in patients with MMSE scores between 29 and 12. [38] Geriatric syndrome with falls and motor disturbance, sleep problems, urinary incontinence, and fatigue was related to caregiver burden in patients with MMSE score between 23 and 12. [38]

ZBI scores indicated in bivariate regression analyses that caregiver burden was related to age, diagnosis, memory, impulse control and emotion recognition, while in stepwise multivariate regression independent significant contributions were patient age, memory and emotion recognition, explaining 23% of the variance. [39]

ZBI is used in detecting differences in caregiver burden during pharmacological treatment of AD patients. For example, ZBI scores changed significantly from baseline to week 12 in a 416-subject AD trial with donepezil in patients with behavioral and psychological symptoms of dementia, but not in those without these symptoms. [40]

Neuropsychiatric Inventory (NPI) is frequently used in neurocognitive disorders trials for the purpose of quantifying and monitoring the changes in the associated psychiatric symptoms. This
instrument uses a structured format, with caregiver-based interview, and it assesses 10 behavioural domains - Delusions, Hallucinations, Agitation, Dysphoria, Anxiety, Apathy, Irritability, Euphoria, Disinhibition, and Aberrant motor behaviour, but other two domains - Night-time behavioural disturbance, and Appetite/weight changes - are often added. [41,42] Each domain is scored based on its severity from 1 (mild) to 3 (severe), and the domain total score is obtained by multiplying the frequency score by the severity score. Also, a measure for the level of caregiver distress is also calculated, distinct from the total NPI score. [42]

A one-point NPI increase was associated with an increase of the odds of using any psychotropic medication class by 4% (OR=1.04, 95% CI=1.01-1.07) in a 3-year prospective trial of home-dwelling persons with AD and their caregivers (N=236 dyads). [43]

High NPI scores predicted subsequent hypo-metabolism in the posterior cingulate cortex over 2 years in individuals with preclinical AD (both amyloid and tau pathologies present), but not in asymptomatic at risk for AD. [44] Sleep/nighttime behavior disorders and irritability-lability were the domains of the NPI that correlated most with the metabolic dysfunction in preclinical AD. [44]

Variations in the NPI are used as the primary outcome measure in many randomized controlled trials, and a PubMed search detected substantial variation in placebo effect when NPI was used in recent studies, but not in older ones (2009-2015 versus 2000-2008). [45] This increase in the NPI effect size in placebo groups is important for the calculation of the power of future trials with AD and behavioral-psychological symptoms, therefore effect size for NPI need to be based on more recent studies. [45]

ALSOVA study 5-year follow-up detected no significant changes in very mild or mild AD patient self-reported quality of life, despite their increase in the neuropsychiatric symptoms. [46] Nevertheless, caregiver-rated patient quality of life declined significantly, as total NPI scores increased during follow-up, and apathy at follow-up correlated significantly with patient self-rated quality of life score. [46]

Baseline high NPI scores are important predictors for a loss of quality of life in AD patients according to a multiple logistic regression analysis in a 4-year follow-up. [47] Also, higher NPI total scores were associated with a more negative rating of Quality of life - Alzheimer’s Disease (QoL-AD) among caregivers, and also with a smaller negative effect on patients’ self-rating. [48] NPI dimension “depression” was associated with a more negative view of the quality of life on patients’ self-ratings, and “apathy” and “agitation” were associated with caregiver rating. [48]
Global Assessment of Functioning Scale (GAF) is the Axis V of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised. [49] GAF is an independently-of-diagnosis scale used for initial evaluation, but also for monitorization of patients with practically any kind of psychiatric disorder. This instrument attributes an overall score from 1 to 100 based on the severity of symptoms and global functioning of the patient. The higher the score, the better the overall functionality of the individual.

Also, this scale may be considered too simplistic, GAF could be easy to apply and interpret in both AD patients and in their caregivers with psychiatric disorders. In veterans with AD, this scale had a high level of internal consistency and was highly consistent across facilities over time. [50]

5. Algorithm for the evaluation of quality of life in caregivers of AD patients

The first stage of the evaluation of the quality of life in AD patients’ caregivers includes the application of SF-36, EuroQoL (EQ-5D), ZBI, GAF, and NPI. The rationale for selection of this set of instruments is based on the need to encompass the severity of the patients’ neuropsychiatric symptoms impact over caregivers (NPI), the caregivers burden (ZBI), and the global functioning (GAF) that could detect decreases of the caregivers’ functionality and could signal the possibility of a psychiatric or psychosomatic pathology in family members (depressive disorders, anxiety disorders etc). SF-36 and EuroQoL are measures for the quality of life which can offer both global values, but also more differentiated values in the factorial analysis.

We formulate the possibility of calculating a composite score (cs) based on the results of the previously mentioned scales (table 1). For GAF, SF-36 and EQ-5D the scores obtained after the scales application is subtracted from 100 and then divided by 10, since all these scales have the highest score for the better function/quality of life. As an example, if the caregiver scores 70 on GAF, the value used for calculating the “composite score” is 100-70=30/10=3. This formula is conceived in order to maintain the proportion between ZBI and NPI which have low composite scores, and all the other scales.

After this calculation 3 classes of risk could be defined: low (cs=0-9), medium (cs=10-19), and high (cs≥20) (table 2). The interval of values for the composite score is 0-35.
Table 1. Calculation of the composite score for the caregivers’ quality of life

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Obtained score/interval</th>
<th>Composite score equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZBI (22-item)</td>
<td>0-21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21-40</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>41-60</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>61-88</td>
<td>3</td>
</tr>
<tr>
<td>NPI- Caregiver disruption assessment</td>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>21-50</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>2</td>
</tr>
<tr>
<td>GAF</td>
<td>100-0</td>
<td>0-10</td>
</tr>
<tr>
<td>SF-36</td>
<td>100-0</td>
<td>0-10</td>
</tr>
<tr>
<td>EuroQoL(EQ-5D)-VAS</td>
<td>100-0</td>
<td>0-10</td>
</tr>
</tbody>
</table>

Table 2. Severity of the caregivers’ quality of life disruption

<table>
<thead>
<tr>
<th>Composite score</th>
<th>Severity of disruption</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>Low</td>
<td>Caregiver overall status, functionality and quality of life are considered good</td>
</tr>
<tr>
<td>10-19</td>
<td>Moderate</td>
<td>Caregiver presents several problems in his/her clinical status, functionality and quality of life</td>
</tr>
<tr>
<td>≥20</td>
<td>Severe</td>
<td>Caregiver could have serious problems related to his/her status, and his/her quality of life is severely impaired</td>
</tr>
</tbody>
</table>

Table 3. Calculation of the composite score for the caregivers’ quality of life

<table>
<thead>
<tr>
<th>Composite score</th>
<th>Therapeutic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>No therapeutic intervention is needed. Monitoring at 3 months is still recommended.</td>
</tr>
<tr>
<td>10-19</td>
<td>Specific training for coping to stress, measures for increasing social support, self-help group for caregivers, addressing dispositional disorders. Monitoring according to the severity of the problems and detected pathologies, but no less than every 3</td>
</tr>
</tbody>
</table>
months.

≥20 Coping to stress training, social support, self-help group for caregivers, addressing dispositional disorders. Monitoring according to the severity of the problems and detected pathologies, but no less then every 3 months

This evaluation is the first step of a more comprehensive, therapeutic-oriented approach. After the inclusion in one of the three classes of risk, caregivers could receive appropriate therapeutic interventions (table 3).

The following step consists in monitoring every three months caregivers’ status using the same instruments, and to quantify the impact of specific medical or psychological measures that were applied.

It is expected that applying this algorithm would decrease the functional impact of the AD burden over caregivers, while increasing their quality of life.

6. Discussions

The clinical interest of our research derives from the construction of an algorithm which includes validated psychometric instruments for the determination of quality of life, global functionality and AD’ burden. Based on the score resulted from the application of this algorithm a therapeutic approach could be initiated.

Further research is needed in order to establish the clinical effectiveness and impact over healthcare costs of our suggested algorithm. Quality of life monitoring and applying the therapeutic intervention at the appropriate time could have a beneficial impact over caregivers, but also, indirectly, over patients’ clinical status. It would be important to prove if a caregiver’ better quality of life could delay the institutionalization of an AD patient. Early detection of dispositional pathology in caregivers could also be a beneficial effect of our proposed algorithm.

Learning new ways to cope with stress, a better management of their own time and engaging in changing coping methods with peers during group therapy sessions are expected to have a significant impact over caregivers overall psychological status.

7. Ethical considerations

No Ethical Committee approval was required.
8. Conclusions

This research objective to find a way for a better evaluation of quality of life in caregivers of AD patients could be accomplished by implementing this suggested plan of monitoring and intervention into clinical practice.

Better care should be provided for AD patients’ caregivers, in order to increase their functionality and quality of life, and to prevent the appearance of dispositional disorders, burn-out syndrome, anxiety reactions etc.

An integrated and structured approach for evaluation and intervention is considered the key for attaining these objectives.

References


