Management of patients with Alzheimer's disease: pharmacological treatment and quality of life

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Ther Adv Chronic Dis

[2012] 3(4) 183–193

DOI: 10.1177/
2040622312452387

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Abstract: A methodological approach to quality of life (QoL) assessment in Alzheimer's disease (AD) is challenging and few clinical trials have included it among outcomes, with conflicting results. In this review an indirect appraisal of evidence has been performed, searching the literature for the effect of drug treatments on determinants of QoL in AD. Among clinical factors associated with QoL, possible targets of drugs include cognition, which seems to be associated with QoL in early disease and can be positively affected by cholinesterase inhibitors (CIs) in this stage; functional decline, the risk of which can be decreased by CIs and memantine (MEM); behavioral and psychological symptoms, which can be reduced by MEM and atypical antipsychotics. Long-term observational studies have associated CIs and MEM treatment with a reduced institutionalization risk. According to the evidence, drug treatment of depression associated with AD should not be first choice from a QoL perspective, while treatment of pain can have beneficial effects on wellbeing indicators also in the late stages of the disease. Possible drug-related adverse events can affect QoL and should always be weighed against expected benefits from the patient's perspective. For this reason antipsychotic treatment is often problematic in AD and should be limited to severe psychosis and aggression, using the lowest effective doses for the shortest possible period. Conversely titration of CIs is necessary to reach the most effective dosages, although dose-related risk of adverse events has to be taken into account. Finally, CIs and MEM have been shown to reduce caregiver burden in randomized trials, possibly affecting caregivers' QoL.

Keywords: Alzheimer's disease, analgesics, antidepressive agents, antipsychotic agents, cholinesterase inhibitors, drug therapy, memantine, quality of life

Introduction

In recent years, the study of diseases has been increasingly spreading out from objective assessment of clinical, radiological and biological features to patients' individual experience of their own health status. Therefore, contemporary assessment of social and health interventions places an increasing emphasis on quality of life (QoL), which is considered today as one of the main outcomes of any pharmacological and non-pharmacological treatment.

Due to methodological difficulties of QoL assessment in Alzheimer's diseases (AD), inherent to the characteristics of the illness and discussed below, only few studies have directly assessed

the effects of pharmacological treatment on this outcome. Therefore the present paper, after discussing preliminary issues related to QoL assessment and determinants in AD, will be focused on available evidence regarding the effects of specific drug treatment on QoL and on its clinical correlates in AD.

Quality of life: how the concept applies to patients with Alzheimer's disease

QoL has been defined in a broad sense as an individuals' perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [WHOQOL Group,

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Table 1. Dementia-specific instruments validated for quality of life (QoL) assessment in Alzheimer's disease (modified from Schölzel-Dorenbos *et al.* [2007a]).

	DQoL [Brod <i>et al.</i> 1999]	QoL-AD [Logsdon <i>et al.</i> 2002]	DEMQOL [Smith <i>et al.</i> 2005]	CBS [Ready <i>et al.</i> 2002]	ADRQL [Rabins <i>et al.</i> 1999]	DS-DAT [Hurley <i>et al.</i> 1992]	Vienna List [Porzsolt <i>et al.</i> 2004]	Qualidem [Ettema <i>et al.</i> 2007]
Stage	Mild to moderate	Mild to moderate	Mild to moderate	Mild to moderate	All stages	Severe	Severe	All stages
Collection	Interview	Interview	Interview	Interview	Interview	Observation	Observation	Observation
Rater	Patient	Patient and proxy	Patient and proxy (severe: proxy only)	Clinician (patient and proxy rating)	Proxy (only objective behavior)	Professional	Professional	Professional

ADRQL, Alzheimer's Disease Health-Related Quality of Life; CBS, Cornell-Brown Scale for QoL in dementia; DQoL, Dementia Quality of Life scale; DS-DAT, Discomfort Scale – Dementia of Alzheimer Type; QoL-AD, Quality of Life Alzheimer's Disease scale.

1995]. Specifically, the concept of health-related QoL embraces aspects of QoL which pertain specifically to a person's health, and can be defined as perceived health status, including physical symptoms, level of functioning, psychological status, social interactions and general health perception [Wilson and Cleary, 1995].

Self-rating of health status has obvious potential limitations in dementia, due to cognitive deficit that induces amnesia, reduced insight of disease and awareness of impairments, and decreased critical judgment. Therefore, the use of specific instruments, rather than generic measure of health-related QoL, has been advocated for patients with AD [Ettema *et al.* 2005]. Different approaches to assess QoL in dementia have been adopted: self-rating, which is generally preferred if deemed possible according to disease severity; caregiver rating, which can be related to carer judgment *per se* or to the rating the carer believes the patient would give of his own status (substitute judgment) [Bosboom *et al.* 2012; Karlawish *et al.* 2001]; direct observation of behavior [Lawton *et al.* 1991].

Moreover, QoL assessment includes both objective indicators – describing the physical and environmental condition of the subject- and subjective factors – which include the personal experience of the individual. For example, in the model proposed by Lawton and colleagues, regarding older subjects in general [Lawton *et al.* 1991] and specifically adapted to dementia [Lawton, 1997], behavioral competence and living environment are assessed among objective factors, while psychological wellbeing and perceived competence are assessed in the subjective sector. When QoL has to be measured in

the dementia setting, several life domains should be assessed, including affect, self esteem, general health perception, appraisal of physical functioning, social interaction and environment (enjoyment of activities, privacy etc.) [Ettema *et al.* 2005]. The concurrent assessment of such domains is intended to provide a global picture, which is necessary to evaluate the outcome of different interventions in dementia care.

In this conceptual framework, several scales have been proposed and validated by different authors which adopt different perspectives [Schölzel-Dorenbos *et al.* 2007a]. One of the main determinants of the choice among different instruments is patient cognitive level, which may obviously interfere with the ability of the patient to understand the items of the scale and to be able to rate own life condition according to them. Beyond stage of the disease the instrument may be applied in, available scales differ for the way of collection (interview or observation) and the subject who is intended to complete the rating (patient, proxy, clinician or professional carer) (Table 1). A brief summary of the peculiarities of each instrument is provided below.

- (1) The Dementia Quality of Life scale (DQoL) is an interview including 29 items, each one rated on a 1–5 Likert scale, to be completed by patients with mild to moderate dementia [Brod *et al.* 1999].
- (2) The Quality of Life Alzheimer's Disease scale (QoL-AD) is a self-report questionnaire including 13 items, each one rated on a 1–4 Likert scale, which can be completed both by patients with mild to moderate dementia and by informal caregivers, and yields a single score which weights patient's score twice as much as

the caregiver's one. It also includes a caregiver's QoL subscale.

- (3) DEMQOL is a self-report questionnaire administered to both patients affected by mild-to-moderate dementia (28 items) and to carers independently of disease severity (DEMQOL-Proxy, 31 items) [Smith *et al.* 2005].
- (4) The Cornell–Brown Scale (CBS) includes the clinical rating of 19 bipolar items on a five-point scale, after a brief interview with both patient and caregiver [Ready *et al.* 2002].
- (5) Alzheimer's Disease Health-Related Quality of Life (ADRQL) is an interview including 47 items rated by proxy according only to observable behaviors, which is applicable irrespectively of disease severity [Rabins *et al.* 1999].
- (6) The Discomfort Scale – Dementia of Alzheimer Type (DS-DAT) encompasses nine behavioral indicators of discomfort in patients with severe dementia and language disorders, rated by professional caregivers [Hurley *et al.* 1992].
- (7) The Vienna list includes the rating of five factors describing the behavior of patients with severe dementia, performed by professional carers [Porzsolt *et al.* 2004].
- (8) Qualidem is a 49-item observation scale of patients with severe dementia in institutions, rated by professional carers, able to provide a profile of patients' behavior on nine subscales [Ettema *et al.* 2007].

Different instruments allow comparison between different perspectives on QoL, as it is reported by patients and by caregivers, which show only a limited correlation. For example, in a study conducted in the Memory Clinic of Hamburg (Germany), which enrolled 100 patients affected by dementia [Alzheimer's disease 58%, Mini Mental State Examination (MMSE) ≥ 11] and their caregivers, both were asked two questions: 'How would you describe your quality of life/the quality of life of your relative?' and 'How satisfied are you with your current health status/with the current health status of your relative?'. In both cases, caregivers rated patients' QoL significantly lower than patients themselves [Arlt *et al.* 2008]. Similar results were obtained in a cross-sectional study of 236 patients using a specific instrument such as QoL-AD, which has confirmed that patients have a better perception of QoL compared with caregivers, especially children [Conde-Sala

et al. 2009]. A possible explanation of this difference is linked to loss of impairment awareness in patients, as it has been shown that lower awareness of memory function is associated with higher QoL ratings [Trigg *et al.* 2011]. Conversely, the discrepancy may be explained by a possible underestimate of patients' QoL in caregivers' rating, as the latter results appear to be significantly associated with assistance burden and carers' own health status [Beer *et al.* 2010; Fuh and Wang, 2006; Karlawish *et al.* 2001]. Finally, 'adaptation to disability' may improve patients' perception of own status, helping them to change standard of evaluation and relative importance of life goals, as it has been generally shown in older subjects with functional decline [Rothermund and Brandtstadter, 2003].

Clinical determinants of quality of life in dementia

The above cited multidimensional approach to QoL shows similarities with the comprehensive assessment which, especially in the geriatric setting, is typically adopted for the care of patients with dementia. Several studies have searched for potential predictors of QoL among multiple clinical parameters describing health status in dementia, including cognitive impairment, disability, behavioral and psychological symptoms (BPSDs), depression, care setting, presence of pain, physical illness.

Earlier data show that the correlation between QoL and cognitive impairment is weak, more frequent in caregivers' than in patients' reports, and more evident in the early stages of the disease in comparison with later stages [Banerjee *et al.* 2009]. Yet recent data confirm an independent association between cognitive function and proxy-rated QoL, both in institutionalized patients with moderate to severe AD [Barca *et al.* 2011] and in community-dwelling patients with a mild to moderate stage of the disease [Bosboom *et al.* 2012]. Moreover AD is a chronic disorder, and the relationship between QoL and cognitive symptoms may change as the disease progresses. This hypothesis was tested in a multicenter AD study, which assessed the relationship between Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), a widely used measure of cognitive function, and patients' reported QoL within mild and moderate dementia subgroups. While no correlation was found in the moderate stages, a direct correlation between cognitive function and QoL was observed in patients with

mild dementia, supporting the importance of maintaining cognitive performance also from the patient's perspective, at least in early phases of the disease [Hurt *et al.* 2010].

Moreover, a moderate correlation between QoL and disability has been observed, more significant in caregivers' than in patients' reports, and more evident in later stages of the disease compared with earlier stages [Banerjee *et al.* 2009; Barca *et al.* 2011; Hoe *et al.* 2006], although the association has also been recently reported in milder cases [Karttunen *et al.* 2011].

BPSDs are strongly correlated with caregivers' reports of patients' QoL, while this association is weak in patients' self reports. This possibly reflects decreased insight associated with dementia, or a differential appraisal of the impact of emerging BPSDs in patients compared with carers [Banerjee *et al.* 2009]. This association has been reported both for family caregivers of community-dwelling patients [Hoe *et al.* 2007], including those with mild forms [Karttunen *et al.* 2011], and for nursing home residents with QoL rating performed by staff [Beer *et al.* 2010; Hoe *et al.* 2006].

The severity of depressive symptoms has shown a strong reverse association both with self-assessed and for proxy-rated QoL in all stages of dementia [Barca *et al.* 2011; Bosboom *et al.* 2012; Hoe *et al.* 2006; Hoe *et al.* 2007; Karttunen *et al.* 2011], although the observation is less consistent in more severe cases [Banerjee *et al.* 2009].

Moreover, although the data are sparse, the setting of care is a plausible determinant of QoL in dementia. In particular living at home, rather than in nursing home, is an independent predictor of higher QoL rated both by the patient and by the caregiver [Hoe *et al.* 2007].

Finally, physical illness is a frequently overlooked factor potentially affecting QoL in AD patients. For example in institutionalized patients pain, assessed with a validated instrument, is significantly related to self-rating and not proxy-rating of patients QoL [Beer *et al.* 2010].

Specific drug treatments and quality of life in Alzheimer's disease

Randomized clinical trials of specific pharmacologic treatments for AD have proven the efficacy of cholinesterase inhibitors (CIs) and memantine

(MEM) in reducing cognitive impairment, delaying functional decline, and improving clinical global rating *versus* placebo. However, only few trials have included QoL as a specific outcome (see the next paragraph). Owing to the scarcity and inconsistency of such data, an indirect appraisal of drug effects in this regard has been performed. Therefore, the remaining part of this section is devoted to a reasoned analysis of the evidence regarding the effect of drug treatment on possible clinical correlates of QoL, including cognition, disability, care setting, adverse events and BPSDs. In the last paragraph an alternative, goal-oriented approach to outcome assessment is introduced, as it takes into account the subjective relevance of symptoms and personal expectations regarding treatments, which seem conceptually related to QoL.

Direct assessment

Only four randomized clinical trials comparing donepezil with placebo have included a measure of QoL among their outcomes [Burns *et al.* 2011; Rogers *et al.* 1998b, 1998a; Rogers and Friedhoff, 1996] – in all cases a secondary one. The results were inconsistent as donepezil's effect was found to be superior to placebo in one study [Rogers *et al.* 1998b], comparable to placebo in two other studies [Burns *et al.* 2011; Rogers and Friedhoff, 1996] and slightly worse than placebo in another [Rogers *et al.* 1998a]. Of note, none of the studies had adopted assessment instruments which are validated in patients with AD; therefore, no clear conclusion can be drawn from them [Takeda *et al.* 2006]. Conversely, some observational studies have reported an independent association between patient-rated QoL, measured with appropriate instruments, and treatment with antidementia agents [Bosboom *et al.* 2012], especially CIs [Hoe *et al.* 2007].

Cognition

As discussed above, cognitive impairment is a first potential determinant of QoL in AD, at least during the early phases. Meta-analyses of studies have shown a significant cognitive benefit of the CIs donepezil, rivastigmine and galantamine over placebo after 6 months in mild to moderate AD [Birks, 2006]. Similar data are available for MEM, although the effect is more evident in moderate to severe stages of the disease compared with earlier stages [McShane *et al.* 2006], in agreement with the approved indication of the drug.

Disability

Similarly disability – another important determinant of QoL, at least in caregivers' reports – has been shown to decline less in subjects treated with CIs and MEM in comparison with placebo [Hansen *et al.* 2007]. The extent of such benefit, although significant, is difficult to quantify due to the number of different scales used for assessment. To clarify the meaning of these data, some review articles have reanalyzed the results of clinical trials using the risk of global cognitive and functional decline as a composite outcome of obvious meaning for daily life. Such data are available for donepezil, which in a meta-analysis of three randomized trials showed a reduced risk of such transition, both in mild stages of the disease and in moderate stages, with less than half of treated patients reaching the endpoint in the active drug *versus* placebo group [Wilkinson *et al.* 2009]. Similar results have been obtained in meta-analyses of three clinical trials of rivastigmine in mild to moderate AD [Raskind *et al.* 2000] and of six clinical trials of MEM in moderate to severe AD [Wilkinson and Andersen, 2007].

Care setting

As stated before, care of setting, in particular living at home *versus* in an institution, is a potential determinant of QoL in AD. Therefore, the ability of long-term drug treatment to prevent institutionalization may be considered as an outcome relevant to patient's QoL. The only randomized clinical trial which had sufficient duration to include institutionalization risk among its outcomes was AD2000, which showed no significant difference between donepezil and placebo after 3 years in this respect [Schneider, 2004]. Yet, in a subsequent Cochrane review several study limitations were pointed out, including reduced statistical power due to low enrolment and high dropout rate, and the review concluded that the study failed to meet its objectives [Birks, 2006]. Therefore, only observational studies are available to assess the long-term effects of available drugs, with obvious methodological limitations. In these studies, use of CIs has been associated with a decreased risk of nursing home admission compared with no specific drug treatment after a mean follow-up period of 3 years [Lopez *et al.* 2002], data which were separately confirmed both with donepezil [Geldmacher *et al.* 2003] and with rivastigmine [Beusterien *et al.* 2004]. Moreover, in a subsequent study, with a mean follow up of 62 months, combination with CIs and

MEM was associated with a reduced institutionalization risk compared with treatment with CIs only, and the latter was associated in turn with a reduced risk compared with no specific treatment [Lopez *et al.* 2009].

Adverse events risk versus efficacy

From a QoL perspective, symptomatic efficacy has to be balanced against risk of drug-related adverse events, especially in a chronic condition such as AD. This approach seems relevant for CIs, which have shown a greater risk of adverse events compared with placebo, especially gastrointestinal symptoms (nausea, vomiting, diarrhea) and, less frequently, syncope, fatigue, insomnia, headache and tremor [Birks, 2006]. Of note, the risk of such events is clearly dose dependent (as seems to be the case for efficacy), and this was shown, at least for donepezil and rivastigmine, in a meta-analysis of randomized clinical trials [Ritchie *et al.* 2004]. The clinical benefit of reaching higher doses from a QoL perspective is supported by a large 3-year, prospective, observational study of 880 patients with AD treated with CIs, in which a higher dose of CIs (donepezil >6.9 mg/day, oral rivastigmine >6 mg/day, galantamine >16 mg/day) was independently associated with a lower institutionalization risk [Wattmo *et al.* 2011]. The risk of gastrointestinal side effects leading to treatment withdrawal is particularly high for the oral formulation of rivastigmine, both in clinical trials [Birks *et al.* 2009] and in clinical practice [Mossello *et al.* 2004]. In this regard, the introduction of a transdermal formulation of rivastigmine has represented a relevant advantage, allowing the administration of higher, more efficacious doses with a reduction of adverse events by two-thirds in comparison with capsules [Winblad *et al.* 2007].

The balance between efficacy and adverse events seems to be a minor issue for MEM, which has been associated with no increased risk of adverse events in placebo-controlled studies [McShane *et al.* 2006].

Behavioral and psychological symptoms

Another important determinant of QoL, although limited to caregivers report, is the presence of BPSDs. In agreement with data supporting a delay of disease progression, treatment with CIs has been associated with a decreased risk of developing BPSDs requiring antipsychotic treatment, as has

been shown for rivastigmine in a pharmacoepidemiological study [Suh *et al.* 2004] and subsequently confirmed in the subset of nursing home residents [Narayanan *et al.* 2006]. With regard to BPSD treatment, a meta-analysis of six randomized clinical trials of CIs, including the Neuropsychiatric Inventory (NPI) as a secondary outcome, has found a small but significant benefit compared with placebo [1.72 points, 95% confidence interval (CI) 0.87–2.57] [Trinh *et al.* 2003]. Yet, in the cited studies all patients had mild to moderate disease and mean baseline NPI score at baseline was 9.2–13.9, suggesting that patients with significant BPSDs were few, and therefore making clinical meaning of such results unclear. In a pooled analysis of patients with moderate to severe AD enrolled in clinical trials, showing a greater prevalence of BPSDs, aggressiveness (present in 60% of the sample) was significantly reduced in the rivastigmine arm compared with those receiving placebo [Burns *et al.* 2004]. In a similar subanalysis of patients with moderate to severe AD enrolled in clinical trials of donepezil, a significant effect of the drug in comparison with placebo was observed on apathy, depression and anxiety, but not on agitation/aggression items of NPI. Only a few randomized clinical trials have targeted BPSDs as a primary outcome and the results have been inconsistent and generally negative. In the largest of those studies, which enrolled 272 patients with moderate to severe AD with clinically significant agitation, no significant benefit of donepezil was observed on the Cohen Mansfield Agitation Inventory after 12 weeks in comparison with placebo. More positive data are available regarding the effect of MEM on BPSDs. A Cochrane meta-analysis has reported a mean benefit of 2.76 NPI points (95% CI 0.88–4.63) in patients with moderate to severe AD (mean basal score 13.5–20.5) [McShane *et al.* 2006], thus suggesting a greater benefit in patients with a high prevalence of clinically relevant BPSDs in comparison with a CIs meta-analysis [Trinh *et al.* 2003]. Moreover, in a pooled analysis of 593 patients with moderate to severe AD with delusions, hallucinations or agitation at the NPI, the cumulative score of the three symptoms decreased significantly in the MEM group *versus* the placebo group after 6 weeks and 26 weeks [Wilcock *et al.* 2008].

From problem-oriented to goal-oriented approaches

Although available literature has clearly demonstrated the statistical efficacy of available drug

treatments on rating scales in AD, there is much debate on the clinical meaning of the observed effects [Raina *et al.* 2008], including the extent to which they affect patients' QoL [Schölzel-Dorenbos *et al.* 2007b]. Moreover, often the clinical impression is not fully consistent with the results of rating scales.

For this reason, in addition to the traditional problem-oriented assessment of clinical response, it has been proposed to combine a goal-oriented approach, which focuses on outcomes relevant to individuals and not on standardized impairment rating scales. One of the instruments used for this purpose is the Goal Attainment Scaling (GAS), in which the clinician identifies personalized goals with the patient and caregiver before the start of therapy, with the aim of assessing the extent to which the goals are reached after treatment [Bouwens *et al.* 2008]. This kind of assessment has been adopted in a pilot clinical trial of galantamine for AD, in which the clinician-rated GAS, completed together with patients and caregivers, has shown an increased goal attainment in patients receiving galantamine *versus* placebo after 4 months of treatment, thus paralleling the results of cognitive and global assessment [Rockwood *et al.* 2006]. A more widespread use of this promising approach seems to be advisable to understand how much treatments adopted in patients with AD can help reaching goals which are relevant for patients' and caregivers' daily life.

Other drug treatments and quality of life in Alzheimer's disease

Psychotropic medications

In the pharmacological treatment of BPSDs, atypical antipsychotics have been studied extensively. Reviews of several randomized controlled trials have concluded that risperidone, olanzapine and aripiprazole have a limited but definite efficacy in reducing aggression and psychotic symptoms [Ballard and Howard, 2006]. Yet their use is associated with a significant increase in severe adverse events, including extrapyramidal symptoms, drowsiness and falls. Moreover, in clinical trials which have included patients with dementia a small but significant increased risk of cerebrovascular events and total mortality *versus* placebo has been observed [Schneider *et al.* 2005]. For these reasons, atypical antipsychotics should only be used when symptoms are severe and distressing or when they pose a risk to the patient or others [Ballard and Howard,

2006]. Also, these drugs have to be used at the lowest effective dose for the shortest possible period, attempting to taper down and withdraw the treatment early after the control of symptoms.

In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared risperidone, olanzapine and quetiapine with placebo with a pragmatic design resembling clinical practice, olanzapine and risperidone resulted in an amelioration of clinical symptoms (including hostility and psychosis) at the expense of a significant increase of adverse events, with a net effect of no change in proxy-rated QoL [Schneider *et al.* 2006; Sultzer *et al.* 2008]. These data can be explained by the fact that the therapeutic effects are offset by drug-related adverse events, which make the effect of these drugs on QoL uncertain, possibly depending on individual response.

Depressive symptoms have consistently been identified as predictors of QoL in AD. However, data demonstrating the effect of antidepressants on mood in AD are still limited and inconsistent. In fact, while a previous meta-analysis of small-scale clinical trials concluded that antidepressants in AD were efficacious and safe [Thompson *et al.* 2007], a recent randomized clinical trial comparing sertraline, mirtazapine and placebo showed no significant difference between active comparators and placebo after 13 and 39 weeks, both in the change of depressive symptoms, which decreased in all groups over time, and in the change in health-related QoL rated with DEMQOL and DEMQOL-Proxy [Banerjee *et al.* 2011]. The evidence for cognitive effect of antidepressant drugs is even weaker. Observational data support a reduced cognitive decline associated with antidepressants in patients with AD treated with CIs [Mossello *et al.* 2008] and a pilot clinical trial has shown a beneficial effect of the association between selective serotonin reuptake inhibitors and CIs on functional status and clinical global impression [Mowla *et al.* 2007]. However, taking into account the increased risk of adverse events linked to antidepressant treatment and the high response rate observed with placebo, the use of antidepressants in patients with AD has little support from a QoL perspective, except in the case of severe symptoms.

Analgesics

The treatment of pain in older patients is often neglected, and this is particularly frequent in

patients with dementia. In a sample of Italian older home-care patients, reporting chronic daily pain, 34% received any analgesic drug, while only 26% of subjects with dementia received the treatment, with an adjusted odds ratio of 0.80 (95% CI 0.69–0.93) [Landi *et al.* 2001]. However, analgesia is associated with better proxy-rated QoL, measured with ADRQL, in nursing home patients with advanced dementia [Cordner *et al.* 2010]. This is in agreement with the results of a randomized, double-blind, placebo-controlled, crossover trial, which has shown that the administration of paracetamol 3 g/day to patients with moderate to severe AD in nursing homes results in increased social interaction and engagement with environment *versus* patients who received placebo [Chibnall *et al.* 2005].

Caregivers' quality of life and drug treatments

AD involves not only patients but also has a high impact on their families; thus, the issue of caregivers' QoL should not be neglected in assessing the efficacy of treatments. Determinants of caregiver QoL include both personal factors, such as female sex, depressive symptoms, physical health, care burden, and patient factors, including disease duration, BPSDs and QoL of patients themselves [Thomas *et al.* 2006]. Therefore, addressing patients' QoL is *per se* a way to ameliorate the impact of the disease on their caregivers.

Treatment with CIs has possible positive effects on caregivers' QoL: in a randomized clinical trial, donepezil was shown to reduce caregiver burden in moderate to severe AD, decreasing by 52 min per day the time of care in basal and instrumental activities of daily living compared with placebo [Feldman *et al.* 2003]. Similar data were obtained in a randomized clinical trial of MEM, which, after adjustment for baseline between-group difference, showed a decrease of time of care of 92 min per day [Wimo *et al.* 2003].

Finally, in regard to BPSDs, the recent results of the CATIE study have shown that treatment with atypical antipsychotics, although not associated with an increase in patient's QoL, might be associated with a small but significant benefit on caregivers' burden [Mohamed *et al.* 2012]. These data pose a possible ethical problem in daily clinical practice, suggesting a case-by-case approach, which weighs carefully the possible

harms and benefits for the patient and takes into account caregivers' wellbeing too.

Conclusion

The definition of QoL in AD has several shortcomings due to cognitive deficits and lack of insight typically associated with the disease, which can limit assessment reliability. However, caregivers' rating of patients' QoL is systematically worse than patients' self rating, and is influenced by different factors. For example, patient-rated QoL seems to correlate with cognitive performance only in milder cases, while the association of proxy-rated QoL with cognitive and functional performance seems stronger in more advanced stages. Moreover, a strong inverse association exists between BPSDs and proxy-rated, but not patient-rated QoL, while both ratings are inversely correlated with depressive symptoms.

Only a few clinical trials have directly assessed the effect of drug treatment on QoL in AD, and the results are inconsistent. Therefore, an indirect appraisal has been performed, searching the literature for the effects of drugs on clinical determinants of QoL in AD.

Randomized trials have shown a beneficial effect of CIs on cognition, which seems to be relevant for QoL in the early phases of the disease, and on risk of functional decline, while MEM has shown a decreased risk of functional decline and a positive effect on BPSDs, which have been associated with proxy-rated QoL in moderate to severe disease. Conversely atypical antipsychotics, which have been proven to be beneficial for psychosis and aggression, can negatively affect QoL due to the risk of severe adverse events. The risk of adverse events does not seem to be an issue for MEM, while for CIs the risks and benefits, which both increase with dosage, have to be assessed during drug titration. Observational studies suggest that CIs and MEM can decrease the risk of care setting. There is no strong evidence of a beneficial effect of antidepressants on QoL in AD, as recent data have shown a high response to placebo and a possible risk of drug-related adverse events for these patients. Treatment of physical illness should never be neglected from a QoL perspective, with a special focus on pain, the treatment of which seems to be associated with increased indicators of wellbeing also in the late stages of the disease. CIs and MEM have been shown to decrease caregiver stress.

A careful choice of drug treatment seems to be relevant for QoL in AD. The patient perspective should be adopted to balance expected efficacy of symptomatic treatment against the possible risk of adverse events. However, non-pharmacological treatments, including psychosocial approaches, environment modification and caregivers' education, can greatly affect QoL as well [Olazaran *et al.* 2010] and have a key role in the care management of these patients.

Funding

The present paper is based on a lecture sponsored by Novartis, held by EM at the VII European International Congress of the International Association of Gerontology and Geriatrics.

Conflict of interest statement

EM has received lecture honoraria from Novartis, Lundbeck and Pfizer.

References

- Arlt, S., Hornung, J., Eichenlaub, M., Jahn, H., Bullinger, M. and Petersen, C. (2008) The patient with dementia, the caregiver and the doctor: cognition, depression and quality of life from three perspectives. *Int J Geriatr Psychiatry* 23: 604–610.
- Ballard, C. and Howard, R. (2006) Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci* 7: 492–500.
- Banerjee, S., Hellier, J., Dewey, M., Romeo, R., Ballard, C., Baldwin, R. *et al.* (2011) Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet* 378: 403–411.
- Banerjee, S., Samsi, K., Petrie, C., Alvir, J., Treglia, M., Schwam, E. *et al.* (2009) What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry* 24: 15–24.
- Barca, M., Engedal, K., Laks, J. and Selbaek, G. (2011) Quality of life among elderly patients with dementia in institutions. *Dement Geriatr Cogn Disord* 31: 435–442.
- Beer, C., Flicker, L., Horner, B., Bretland, N., Scherer, S., Lautenschlager, N. *et al.* (2010) Factors associated with self and informant ratings of the quality of life of people with dementia living in care facilities: a cross sectional study. *PLoS One* 5: e15621.
- Beusterien, K., Thomas, S., Gause, D., Kimel, M., Arcona, S. and Mirski, D. (2004) Impact of

- rivastigmine use on the risk of nursing home placement in a US sample. *CNS Drugs* 18: 1143–1148.
- Birks, J. (2006) Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 1: CD005593.
- Birks, J., Grimley, E., Iakovidou, V., Tsolaki, M. and Holt, F. (2009) Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev* 4: CD001191.
- Bosboom, P., Alfonso, H., Eaton, J. and Almeida, O. (2012) Quality of life in Alzheimer's disease: different factors associated with complementary ratings by patients and family carers. *Int Psychogeriatr* 24: 708–721.
- Bouwens, S., van Heugten, C. and Verhey, F. (2008) Review of goal attainment scaling as a useful outcome measure in psychogeriatric patients with cognitive disorders. *Dement Geriatr Cogn Disord* 26: 528–540.
- Brod, M., Stewart, A., Sands, L. and Walton, P. (1999) Conceptualization and measurement of quality of life in dementia: the Dementia Quality of Life instrument (DQoL). *Gerontologist* 39: 25–35.
- Burns, A., Perry, E., Holmes, C., Francis, P., Morris, J., Howes, M. *et al.* (2011) A double-blind placebo-controlled randomized trial of Melissa officinalis oil and donepezil for the treatment of agitation in Alzheimer's disease. *Dement Geriatr Cogn Disord* 31: 158–164.
- Burns, A., Spiegel, R. and Quarg, P. (2004) Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *Int J Geriatr Psychiatry* 19: 243–249.
- Chibnall, J., Tait, R., Harman, B. and Luebbert, R. (2005) Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. *J Am Geriatr Soc* 53: 1921–1929.
- Conde-Sala, J., Garre-Olmo, J., Turro-Garriga, O., Lopez-Pousa, S. and Vilalta-Franch, J. (2009) Factors related to perceived quality of life in patients with Alzheimer's disease: the patient's perception compared with that of caregivers. *Int J Geriatr Psychiatry* 24: 585–594.
- Cordner, Z., Blass, D., Rabins, P. and Black, B. (2010) Quality of life in nursing home residents with advanced dementia. *J Am Geriatr Soc* 58: 2394–2400.
- Ettema, T., Droes, R., de Lange, J., Mellenbergh, G. and Ribbe, M. (2007) QUALIDEM: development and evaluation of a dementia specific quality of life instrument – validation. *Int J Geriatr Psychiatry* 22: 424–430.
- Ettema, T., Droes, R., de Lange, J., Ooms, M., Mellenbergh, G. and Ribbe, M. (2005) The concept of quality of life in dementia in the different stages of the disease. *Int Psychogeriatr* 17: 353–370.
- Feldman, H., Gauthier, S., Hecker, J., Vellas, B., Emir, B., Mastey, V. *et al.* (2003) Efficacy of donepezil on maintenance of activities of daily living in patients with moderate to severe Alzheimer's disease and the effect on caregiver burden. *J Am Geriatr Soc* 51: 737–744.
- Fuh, J. and Wang, S. (2006) Assessing quality of life in Taiwanese patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 21: 103–107.
- Geldmacher, D., Provenzano, G., McRae, T., Mastey, V. and Ieni, J. (2003) Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc* 51: 937–944.
- Hansen, R., Gartlehner, G., Lohr, K. and Kaufer, D. (2007) Functional outcomes of drug treatment in Alzheimer's disease: A systematic review and meta-analysis. *Drugs Aging* 24: 155–167.
- Hoe, J., Hancock, G., Livingston, G. and Orrell, M. (2006) Quality of life of people with dementia in residential care homes. *Br J Psychiatry* 188: 460–464.
- Hoe, J., Katona, C., Orrell, M. and Livingston, G. (2007) Quality of life in dementia: care recipient and caregiver perceptions of quality of life in dementia: the LASER-AD study. *Int J Geriatr Psychiatry* 22: 1031–1036.
- Hurley, A., Volicer, B., Hanrahan, P., Houde, S. and Volicer, L. (1992) Assessment of discomfort in advanced Alzheimer patients. *Res Nurs Health* 15: 369–377.
- Hurt, C., Banerjee, S., Tunnard, C., Whitehead, D., Tsolaki, M., Mecocci, P. *et al.* (2010) Insight, cognition and quality of life in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 81: 331–336.
- Karlawish, J., Casarett, D., Klocinski, J. and Clark, C. (2001) The relationship between caregivers' global ratings of Alzheimer's disease patients' quality of life, disease severity, and the caregiving experience. *J Am Geriatr Soc* 49: 1066–1070.
- Karttunen, K., Karppi, P., Hiltunen, A., Vanhanen, M., Valimäki, T., Martikainen, J. *et al.* (2011) Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. *Int J Geriatr Psychiatry* 26: 473–482.
- Landi, F., Onder, G., Cesari, M., Gambassi, G., Steel, K., Russo, A. *et al.* (2001) Pain management in frail, community-living elderly patients. *Arch Intern Med* 161: 2721–2724.
- Lawton, M. (1991) A multidimensional view of quality of life in frail elders. In: Birren, J.E., Lubben, J.E., Rowe, J.C. and Deutchman, D.E. (Eds.), *The Concept and Measurement of Quality of Life in the Frail Elderly*, 3–11. San Diego, CA: Academic Press.
- Lawton, M. (1997) Assessing quality of life in Alzheimer disease research. *Alzheimer Dis Assoc Disord* 11(Suppl. 6): 91–99.

- Lawton, M., Moss, M., Kleban, M., Glicksman, A. and Rovine, M. (1991) A two-factor model of caregiving appraisal and psychological well-being. *J Gerontol* 46: 181–189.
- Logsdon, R., Gibbons, L., McCurry, S. and Teri, L. (2002) Assessing quality of life in older adults with cognitive impairment. *Psychosom Med* 64: 510–519.
- Lopez, O., Becker, J., Wahed, A., Saxton, J., Sweet, R., and Wolk, D. *et al.* (2009) Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry* 80: 600–607.
- Lopez, O., Becker, J., Wisniewski, S., Saxton, J., Kaufer, D. and DeKosky, S. (2002) Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 72: 310–314.
- McShane, R., Areosa, S. and Minakaran, N. (2006) Memantine for dementia. *Cochrane Database Syst Rev* 2: CD003154.
- Mohamed, S., Rosenheck, R., Lyketsos, C., Kaczynski, R., Sultzer, D. and Schneider, L. (2012) Effect of second-generation antipsychotics on caregiver burden in Alzheimer's disease. *J Clin Psychiatry* 73: 121–128.
- Mossello, E., Boncinelli, M., Caleri, V., Cavallini, M., Palermo, E., Di Bari, M. *et al.* (2008) Is antidepressant treatment associated with reduced cognitive decline in Alzheimer's disease? *Dement Geriatr Cogn Disord* 25: 372–379.
- Mossello, E., Tonon, E., Caleri, V., Tilli, S., Cantini, C., Cavallini, M. *et al.* (2004) Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a 'real world' study. *Arch Gerontol Geriatr Suppl* 9: 297–307.
- Mowla, A., Mosavinasab, M., Haghshenas, H. and Borhani, H. (2007) Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. *J Clin Psychopharmacol* 27: 484–487.
- Narayanan, S., Beusterien, K., Thomas, S., Musher, J. and Strunk, B. (2006) Antipsychotic drug use among nursing home residents taking rivastigmine. *J Am Med Dir Assoc* 7: 12–16.
- Olazaran, J., Reisberg, B., Clare, L., Cruz, I., Pena-Casanova, J., Del Ser, T. *et al.* (2010) Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. *Dement Geriatr Cogn Disord* 30: 161–178.
- Porzolt, F., Kojer, M., Schmidl, M., Greimel, E., Sigle, J., Richter, J. *et al.* (2004) A new instrument to describe indicators of well-being in old-old patients with severe dementia – the Vienna List. *Health Qual Life Outcomes* 2: 10.
- Rabins, P., Kasper, J., Kleinman, L., Black, B. and Patrick, D. (1999) Concepts and methods in the development of the ADRQL: an instrument for assessing health-related quality of life in persons with Alzheimer's disease. *J Ment Health Aging* 5: 33–48.
- Raina, P., Santaguida, P., Ismaila, A., Patterson, C., Cowan, D., Levine, M. *et al.* (2008) Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. *Ann Intern Med* 148: 379–397.
- Raskind, M., Kumar, V., Malaty, L., Messina, J., Hartman, R. and Anand, R. (2000) Rivastigmine for Alzheimer's disease: improvement versus reduced worsening. *Prim Care Companion J Clin Psychiatry* 2: 134–138.
- Ready, R., Ott, B., Grace, J. and Fernandez, I. (2002) The Cornell–Brown Scale for Quality of Life in dementia. *Alzheimer Dis Assoc Disord* 16: 109–115.
- Ritchie, C., Ames, D., Clayton, T. and Lai, R. (2004) Metaanalysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer disease. *Am J Geriatr Psychiatry* 12: 358–369.
- Rockwood, K., Fay, S., Song, X., MacKnight, C. and Gorman, M. (2006) Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. *CMAJ* 174: 1099–1105.
- Rogers, S., Doody, R., Mohs, R. and Friedhoff, L. (1998a) Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. *Arch Intern Med* 158: 1021–1031.
- Rogers, S., Farlow, M., Doody, R., Mohs, R. and Friedhoff, L. (1998b) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 50: 136–145.
- Rogers, S. and Friedhoff, L. (1996) The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicentre, randomized, double-blind, placebo-controlled trial. The Donepezil Study Group. *Dementia* 7: 293–303.
- Rothermund, K. and Brandtstadter, J. (2003) Coping with deficits and losses in later life: from compensatory action to accommodation. *Psychol Aging* 18: 896–905.
- Schneider, L. (2004) AD2000: donepezil in Alzheimer's disease. *Lancet* 363: 2100–2101.
- Schneider, L., Dagerman, K. and Insel, P. (2005) Risk of death with atypical antipsychotic drug

- treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 294: 1934–1943.
- Schneider, L., Tariot, P., Dagerman, K., Davis, S., Hsiao, J., Ismail, M. *et al.* (2006) Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 355: 1525–1538.
- Schölzel-Dorenbos, C., Ettema, T., Bos, J., Boelens-van der Knoop, E., Gerritsen, D., Hoogeveen, F. *et al.* (2007a) Evaluating the outcome of interventions on quality of life in dementia: selection of the appropriate scale. *Int J Geriatr Psychiatry* 22: 511–519.
- Schölzel-Dorenbos, C., van der Steen, M., Engels, L. and Olde Rikkert, M. (2007b) Assessment of quality of life as outcome in dementia and MCI intervention trials: a systematic review. *Alzheimer Dis Assoc Disord* 21: 172–178.
- Smith, S., Lamping, D., Banerjee, S., Harwood, R., Foley, B., Smith, P. *et al.* (2005) Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 9: 1–iv.
- Suh, D., Arcona, S., Thomas, S., Powers, C., Rabinowicz, A., Shin, H. *et al.* (2004) Risk of antipsychotic drug use in patients with Alzheimer's disease treated with rivastigmine. *Drugs Aging* 21: 395–403.
- Sultzer, D., Davis, S., Tariot, P., Dagerman, K., Lebowitz, B., Lyketsos, C. *et al.* (2008) Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry* 165: 844–854.
- Takeda, A., Loveman, E., Clegg, A., Kirby, J., Picot, J., Payne, E. *et al.* (2006) A systematic review of the clinical effectiveness of donepezil, rivastigmine and galantamine on cognition, quality of life and adverse events in Alzheimer's disease. *Int J Geriatr Psychiatry* 21: 17–28.
- Thomas, P., Lalloue, F., Preux, P., Hazif-Thomas, C., Pariel, S., Inscale, R. *et al.* (2006) Dementia patients caregivers quality of life: the PIXEL study. *Int J Geriatr Psychiatry* 21: 50–56.
- Thompson, S., Herrmann, N., Rapoport, M. and Lanctot, K. (2007) Efficacy and safety of antidepressants for treatment of depression in Alzheimer's disease: a metaanalysis. *Can J Psychiatry* 52: 248–255.
- Trigg, R., Watts, S., Jones, R. and Tod, A. (2011) Predictors of quality of life ratings from persons with dementia: the role of insight. *Int J Geriatr Psychiatry* 26: 83–91.
- Trinh, N., Hoblyn, J., Mohanty, S. and Yaffe, K. (2003) Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA* 289: 210–216.
- Wattmo, C., Wallin, A., Londos, E. and Minthon, L. (2011) Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. *Gerontologist* 51: 17–27.
- WHOQOL Group (1995) The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med* 41: 1403–1409.
- Wilcock, G., Ballard, C., Cooper, J. and Loft, H. (2008) Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J Clin Psychiatry* 69: 341–348.
- Wilkinson, D. and Andersen, H. (2007) Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* 24: 138–145.
- Wilkinson, D., Schindler, R., Schwam, E., Waldemar, G., Jones, R., Gauthier, S. *et al.* (2009) Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 28: 244–251.
- Wilson, I. and Cleary, P. (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 273: 59–65.
- Wimo, A., Winblad, B., Stoffler, A., Wirth, Y. and Mobius, H. (2003) Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics* 21: 327–340.
- Winblad, B., Grossberg, G., Frolich, L., Farlow, M., Zechner, S., Nagel, J. *et al.* (2007) IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology* 69: S14–S22.