

## CAREGIVER OUTCOMES IN DISEASE MODIFYING TRIALS

F.R.J. VERHEY<sup>1,2</sup>, M.E. DE VUGT<sup>2</sup>, P. AALTEN<sup>1,2</sup>, M.J. VERNOOIJ-DASSEN<sup>3</sup>,  
E.J. BYRNE<sup>1,4</sup>, P. ROBERT<sup>1,5</sup>

1. European Alzheimer's Disease Consortium – BPSD subgroup; 2. Department of Psychiatry and Neuropsychology, Alzheimer Centre Limburg, Maastricht University Hospital, Netherlands; 3. Centre for Quality of Care Research (WOK)/ Alzheimer Centre Nijmegen, Radboud University Nijmegen, The Netherlands; 4. Division of Psychiatry, University of Manchester, Education and Research Centre, Wythenshawe Hospital, Manchester, UK; 5. Centre Mémoire de Ressources & de Recherche, CHU, Hôpital Pasteur, Université de Nice-Sophia Antipolis, Nice, France; Correspondence: Prof Frans Verhey, University Hospital of Maastricht / Alzheimer Centre Limburg, PO Box 5800, 6202 AZ Maastricht, the Netherlands, Tel +31-43-3874175/ FAX +31-43-3875444/ e-mail: f.verhey@np.unimaas.nl

### Introduction

Alzheimer's disease is a disorder with huge impact upon patients and their caregivers. The majority of dementia patients are living at home and are usually cared for by family

or friends. Caring for a demented person who has dementia, and especially in the case of problematic behaviour, poses great demands and has detrimental consequences for many caregivers. Although some caregivers may also experience positive aspects in the process of caring for their loved ones, day-to-day care for a relative with dementia is mostly extremely demanding and has detrimental consequences for the caregiver (1-3). Caregivers have high risks for depression and other mental health problems, an increased physical morbidity, higher health-care related costs, and feel more isolated than non-caregivers (4). Therefore, lessening of caregiver's burden is a relevant and important outcome in therapeutic interventions for people with dementia.

### Conceptual issues

The concept of caregiver's burden is complex and to date only partially understood, although this topic is receiving increasing attention. Different concepts have been applied in this context to capture the negative aspects of caregiving.

In the first place, caregivers burden is a multi-component construct, influenced by the characteristics of both the person with dementia (e.g., behavioural problems) and his/her caregiver (e.g., perceived stress, psychological wellbeing, lack of knowledge, immature coping), the social context (e.g., finances, social support, family help). When measuring caregivers burden, the specific component of interest should be specified. Secondly, a distinction should be made between objective and subjective burden. Caregivers differ in their competence and skills to successfully manage problem behaviours and may even trigger or exacerbate difficult behaviours in the patient. Those who feel that the demands of caring exceed their capacities will feel stressed, whereas those who do feel equipped will not (5). Objective burden refers to the practical problems associated with caregiving such as the patient functional dependence and problem behaviours. Subjective burden refers to the emotional reaction of the caregiver to the demands of the situation, such as feelings of incompetence or exhaustion. Furthermore, the concept of

subjective burden can be distinguished from psychiatric symptoms in the caregiver, such as anxiety and depression. The distinction between objective and subjective burden is important because the association between the severity of impairment in the dementia patient and caregiver well-being is not straightforward. Thirdly, the multi-dimensional changes in the dementia patient have differential effects on the caregiver (6). It has been shown that the presence of behavioural problems in the dementia patient rather than the cognitive problems or functional dependence appears to be the major contributor to caregiver subjective burden (3). Interventions directed to support caregivers coping skills are also of influence on perceived burden. Fourthly, the relationship between burden and dementia is not bidirectional, as there exists a mutual negative interaction in the vulnerable couples, with both patient and caregiver reacting with irritation and anger towards each other, resulting in an exacerbation of patient hyperactivity (7). These negative emotions may change the caregiver's feelings towards the patient and adversely affect the patient-caregiver relationship. In addition, caregivers themselves are also, vice versa, likely to play a role in the emergence of patient behavioural problems. Fifthly, researchers and caregivers may differ what outcome measures are relevant. For instance, contrary to the expectations of researchers, reduction of the psychological effects of caregiving such as depression or subjective burden was not mentioned by caregivers as important, but instead they highly appreciated practical information and financial outcomes (8). Interestingly, delay of nursing home placement was not regarded as a positive outcome, reflecting that keeping people at home as long as possible is not necessarily a desirable goal (8). In the sixth place, in many intervention studies, caregivers burden has been shown to be remarkably insensitive to change. This may be due to the fact that caregivers who start to take over tasks of caring (for instance cooking or driving), generally do not try handling these task back to the patient, even in case of clinical improvement. Seventh, whether benefits of antidementia drugs extend to caregivers may also be depending of the relationship between carer and patient (spouse or children) and the circumstances. Finally, even in case changes in burden cannot be detected there may be positive effects that are highly appreciated by caregivers. Qualitative studies have shown that patients may report that 'a fog had cleared', or are 'cognitive more alert', or that family members noticed that the patient

'looked more alive' (9, 10). The recognition of patients being more like their old selves may be highly motivational even under continuous burden. Possibly, these subtle but highly valued changes may better be detected by a global approach such as used in the Goal Attainment Scale (GAS) (11, 12). So far, this method has unsufficiently been adapted in clinical drug trials.

### Methodological issues in drug trials

Lack of theoretical frameworks to generate hypotheses and operational definitions have hampered research so far. Given the complex relationship between the pathology of Alzheimer's disease and its consequences for caregivers, there is no consensus to date how to operationalize caregivers' outcomes. Various caregiver specific outcome measures have been adopted as endpoints within recent Alzheimer clinical trials. These include, but are not restricted to, scales for psychological morbidity (e.g. depression, anxiety), physical health, quality of life, social support, burden (objective and subjective), knowledge of Alzheimer's disease (AD), health care utilisation and expenditure, coping styles, relationship strain (between caregiver and patient) and activity restriction (8).

Available drugs, notably the cholinesterase inhibitors, may have a small but significant effect on burden and active time use among caregivers of persons with AD. Lingler and colleagues have recently evaluated these outcomes in a recent systematic review and meta-analysis (13). They concluded that, despite their embedment in high-quality studies of drug efficacy, there were several methodological problems. For example, none of the studies specified caregiver eligibility criteria, but, at best, only required the need for a reliable informant to accompany the person with dementia to study visits. Description of baseline caregiver characteristics was often incomplete or lacking. Operational definitions for caregiver outcomes were found to be largely unspecified, which was especially problematic for complex constructs such as burden and psychological morbidity (13). As a result, outcome measures used in intervention studies are far from uniform, making comparison among studies impossible. Heterogeneity in caregivers' characteristics (gender, relation to the patient, style of caring) leads to an undesirably large variability in treatment response, and therefore, analysis of treatment responses in subgroups of caregivers may be of interest.

### Description of caregiver specific outcome measures

Instruments that have been used in trials vary among themselves with regard to underlying concepts, goals and procedures. Grossly, caregiver specific outcome measures that were used in clinical trials for drugs and other interventions can be divided in those aimed to measure caregiver burden, time use by the informal caregiver, and other measures (13, 14). The most frequently used measures are briefly discussed here.

### Caregiver burden instruments

The 22-item version of the Zarit Burden Interview is the most widely used scale to assess feelings of burden in informal caregivers (15). It was adapted from an original 29-items scale. Several shorter versions were proposed (18-items, 14-items, 12-items, 8-items, and 4-items) for use in dementia care and research. The 12-item scale is probably best used in clinical practice. The 22-item scale has often been used in studies to assess baseline data on feelings of burden or in cross-sectional studies to find factors related to caregiver burden and in longitudinal and prospective studies. No major intervention studies found any significant change of burden using the Zarit Burden Interview. These findings confirm findings of recent meta-analyses that the pooled effect of interventions evaluated by the Zarit Burden Interview was near to zero (16). In a recent meta-analysis of psychosocial interventions (14), Brodaty et al found that in the only study that showed a statistically significant effect on burden the Zarit Burden Interview was not used.

The Sense of Competence Questionnaire (SOC) is a 27-item scale adapted from the Zarit Burden Interview. Three domains are distinguished: (1) satisfaction with the demented person as a care recipient; (2) satisfaction with one's own performance as a caregiver; and (3) consequences of involvement in care for the personal life of the caregiver. The SOC consists of 7 items rated on a 5-point scale from 1 (agree very strongly) to 5 (disagree very strongly). The validity and reliability of the SOC were assessed in a study of 141 caregivers of community-living dementia patients (17). The advantage of the SOC is that it refers to the specific situation of caregiving and does not measure a general characteristic of the caregiver. In addition, the concept of competence is preferred because it refers to caregiver capabilities, while caregiver burden is more related to the patient. A 7-item version is proposed for use in clinical practice. The sense of competence questionnaire is recommended in a recent overview of the international study group INTERDEM on psychosocial interventions, but has not been used so far in clinical drug studies.

The Relatives Stress Scale is a 15-item scale originally developed for measuring stress in dementia caregivers (18). A 3-item version and an abridged version was mentioned in literature but no publications about validity, reliability, or use in studies have been published so far. Its psychometric properties were at least studied in England and Norway. Like the other scales its sensitivity to change is not clear. The RSS has also been used in several drug studies and showed some significant changes (19, 20).

The NeuroPsychiatric Inventory (NPI) was used to assess patient's behavioural and psychological problems (21). The scale is widely used and assesses a wide range of behaviours. The NPI is based on a structured interview with a caregiver who is familiar with the patient's daily functioning. After explaining the purpose of the interview, questions are asked for twelve different neuropsychiatric domains. For each domain, the caregiver is asked to rate the frequency on a scale from 1

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(occasionally) to 4 (very frequently), and the severity on a scale from 1 (mild) to 3 (severe). In addition, the NPI-D (Distress) measures distress appraisals in response to up to the behavioral domains mentioned above. Several trials have used the NPI-D as burden outcome.

### Psychological morbidity

The general health Questionnaire (GHQ) is a self-administered screening instrument for the detection of non-psychotic psychiatric illness. The scale is widely used in the rating of psychological distress. Construct validity has been demonstrated in several settings (GP practice, hospital).

### Time use

Several trials have used the amount of active time spent by the informal caregiver as a measure of burden. Some studies also reported estimations of passive caregiver time, i.e., time providing supervision but not engaging in a task per se. The most frequent instrument measuring time use is the Caregiver Activity Survey (CAS) (22).

The CAS exists of six items, including communication, using transportation, dressing, eating, looking after self-appearance and necessary supervision. The outcome is the amount of time caregivers were spending looking after patients with AD on these six aspects. The CAS has been successful in showing significant effects in drug trials (13).

Although the approach measuring time use, such as in the CAS, is attractively simple and easily measurable, the underlying idea that time spend by the caregiver is similar to burden is problematic from a conceptual point of view.

## Recommendations

As underlying concepts of caregivers burden are complex and influenced partly by factors that are not related to the intervention studied, caregiver specific outcomes are less appropriate as primary outcome measures. However, they are clinically relevant and important, and should therefore be included as secondary outcome measures in clinical drug trials. Compared to trials of symptomatic drug interventions, in disease modifying trials caregiver-specific outcomes pertain more to long-term consequences of the disease process, such as institutionalisation, need for home help or long-term satisfaction of the caregiver.

The quality and interpretability of Alzheimer clinical research with caregiver-specific outcomes may be improved by a better specification of the entry criteria for caregiver study participants, a more detailed documentation of basic caregiver demographic data (13).

The choice for a particular scale is largely dependent of the exact goal, which should be specified beforehand. A complete overview of available scales has been published recently (8).

We recommend the RSS as a measure for global burden, and the GHQ for caregiver's psychological comorbidity. The SOC

may be a new interesting alternative, but should be studied in more depth. Time use, as measured for instance in the CAS, is usable, but should be specified in more detail. The often-used Burden Inventory may be a good measure of caregivers' strain, but it is not sensitive to change, making it not very apt for clinical drug trials of long duration. Personalized approaches such as a GAS may detect subtle but highly valued and motivating changes in functioning of the person with dementia.

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