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Oliver Riedel, Jens Klotsche, Federica Pisa

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Corresponding author
Oliver Riedel

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Psychiatric symptoms in patients with dementia – do caregivers and doctors see the same thing?

Oliver Riedel[1], PhD; Jens Klotsche[2], PhD; Federica E. Pisa[1], MD

[1] Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany
[2] Deutsches Rheumaforschungszentrum – ein Leibniz Institut, Berlin

Corresponding author:
Oliver Riedel, PhD
Leibniz Institute for Prevention Research and Epidemiology – BIPS
Achterstrasse 30, 28359 Bremen, GERMANY
Phone: ++ 49 421/21856883
E-Mail: riedel@leibniz-bips.de

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Summary

Purpose: Neuropsychiatric symptoms (NPS) are common in Alzheimer's Disease (AD). By supplementing the clinician's impression of a patient with information from the caregiver (CG) treatment could be optimized. Yet the agreement between CGs and physicians on the presence of NPS in patients with AD is understudied.

Methods: Data were obtained from a two-staged survey in neurology outpatient offices. At stage one, patients (n=403) were documented by their physicians, including an assessment on the presence of NPS. At stage two, patients' CGs (n=171) were asked about the presence of NPS in the patients, based on questions from the Neuropsychiatric Inventory. CGs were screened for depression with the Depression Screening Questionnaire.

Patients: The study sample comprised patients with mild or moderate AD.

Results: Frequencies NPS varied between 52.6% (95%-confidence interval (CI): 44.9%-60.3%) and 67.2% (95%-CI: 59.7%-74.2%, reported by CGs) and 34.2% (95%CI: 26.8%-42.1%) and 50.9% (95%CI: 42.9%-58.9%, reported by physicians). Apathy, depression, aggression and irritability occurred most frequently according to both sources. Kappa-values were lowest for euphoria (κ-value .03, 95%-CI: -.08-.25), and highest for depression (κ=.26, 95%-CI: .11-.43). CG depression was associated with an increased probability (OR=2.9, 95%-CI: 1.2-6.7) of disagreement between CGs and physicians on the patient's mental status.

Conclusion: NPS, though very prevalent in dementia patients, are perceived differently by CGs and physicians. This divergence increases depending on the psychological health of CGs.

Keywords: Dementia; depression; BPSD; neuropsychiatric symptoms; caregiver burden

Introduction

Alzheimer's Disease (AD) represents the most common form of dementia, affecting approximately 70% of all dementia cases.[1] Due to its progressive nature, AD leads to a rapid decline of patients' abilities to master everyday life, which makes early assistance of caregivers (CGs) necessary. Hence, in addition to the suffering associated with the disease, dementia is also very costly with estimated monetary costs of up to $215 billion in the United States in 2010 alone. At least 31% of the total costs are allotted to informal care.[2]

One of the most debilitating aspects of giving care to dementia patients is that the patients frequently also develop neuropsychiatric symptoms (NPS), including delusions, hallucinations, irritability or disinhibition.[3, 4] Management of these symptoms is essential for the reduction of both the patients' and caregivers' burden as well as treatment costs. This, however, requires an adequate assessment of these complications. For this estimation, the physician's clinical impression could be supplemented by an appraisal from the CG who usually is in close and daily contact with the patient. This is especially important since patients with dementia frequently also have anosognosia and therefore do not report symptoms themselves.[5] While it has been reported recently that patients' CGs and physicians might substantially differ in their perception of the CG's burden[6], little is known on whether CGs and physicians also appraise patients' NPS differently. In a recently published study[7], Stella and colleagues applied the Neuropsychiatric Inventory (NPI) to investigate the agreement between CGs and physicians on the neuropsychiatric symptom profile of AD patients.[8] The agreement varied widely across several domains and discrepancies between CGs and physicians were more pronounced for milder than advanced stage patients.

However, while Stella et al. have provided important insights into differing appraisals of NPS by the CGs and physicians, a number of factors were not considered that might have been influential, including, for instance, the CG's own depression status. Previous studies have repeatedly shown that affective disorders occur frequently in CGs of dementia patients, potentially influencing their judgement of NPS in terms of under- or overrating.[9, 10] This, however, has not been investigated satisfactorily. Therefore, the present paper aims to complement these findings by assessing the agreement between CGs and physicians on rating NPS in dementia patients who are cared for at home, factoring in the depression status of the CG.

Methods

Study design and study population

The design of the IDEA (*Improving Alzheimer Dementia Treatment: Epidemiological Assessment of Doctors, Patients' and Caregivers' Unmet Needs*) study has been previously presented in detail.[11] Briefly, the study was set up in two stages. At the first stage, office-based neurologists randomly enrolled patients with mild or moderate AD who attended the practices with their CGs.[12] Each patient was clinically characterized by the physician on a patient documentation sheet. Additionally, each CG was to fill in a questionnaire in the waiting room containing items regarding basic information on the CG and the patient and crude questions about the current home care situation. Both documents were then sent to the study center. Between 2 and 5 weeks later, at stage two clinical psychologists of the study center approached participating CGs and conducted a comprehensive telephone interview, which polled more details about the CG's health status and further aspects of the caregiving situation (please see next section).

In stage one, 403 patients and their CGs were enrolled and followed the above procedure. Of these pairs, 232 CGs agreed to participate in the interview during stage two. The reasons most frequently given by CGs for not participating at stage two (n=171) were lack of time (23%), concerns about privacy (9.8%) or other reasons (26.3%; e.g., emotional strain, logistic problems); 40.9% did not state a reason. As previously reported, CGs who participated in stage one did not differ from CGs who completed both stages regarding potentially relevant parameters, including sex, age or duration of caregiving.[6] Also, the associated patients did not differ regarding sex, age, duration and severity of dementia or the number of neuropsychiatric symptoms as estimated by the treating physicians (p=.541).

Of those CGs who were interviewed at stage two, 26.3% (N=61) did not provide a complete characterization of the patients' NPS according to the Neuropsychiatric Inventory (NPI, see section "Study material") and were excluded. Thus, the present analyses were based on N=171 patient-CG-pairs with complete information. Differences between excluded and included CGs and the relating patients are provided in Table 1 and will be discussed in the results section.

Study material

In both stages of the study, information about the patient as well as the CG was obtained. At stage one, the physician filled out the patient documentation sheet to record the clinical status of the patient, including sociodemographic information (e.g., sex, age, educational level), the current score on the Mini-Mental State Exam (MMSE) and the severity of AD.[13] With the CG questionnaire, the CG documented the patient's functional status and autonomy by using two measures. The Barthel-Index[14] was chosen to describe the patient's capabilities to perform basal activities, such as food intake, grooming, getting (un-)dressed, or climbing stairs. The I-ADL[15] was used to assess the patient's capabilities of performing daily activitities with higher cognitive demands, such as going grocery shopping, cooking, doing laundry, or the use of medication. The CG furthermore provided more detailed information on the caring situation, e.g., further patient morbidities.

At stage two, a comprehensive CG interview addressed the current care situation and complicating factors (including NPS, see next section) as well as the depression status of the CG based on the Depression Screening Questionnaire (DSQ). According to the DSQ-score, CGs were either classified as showing no depressive symptoms (≤7), suffering from a subthreshold depressive disorder (8-9) or suffering from a major depression episode (≥10).[16]

Assessment of NPS

The presence of NPS was assessed in two ways. At stage one, the patient's physician recorded on the documentation sheet, whether the patient currently featured paranoid symptoms or delusions, confusion, hallucinations, aberrant motor behavior, verbal assaults, aggression, night-time behavior disturbances, symptoms of depression and/or anxiety, apathy, euphoria, disinhibition or irritability. For those symptoms present, the physician rated the severity on a three point scale ("mild", "moderate", "severe").

At stage two, the CG interview comprised questions based on the Neuropsychiatric Inventory (NPI)[8] and covered the domains delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, apathy, irritability, disinhibition, aberrant motor behavior, night-time behavior disturbances and appetite changes. For each domain, the CG was asked to state how frequent corresponding symptoms were on a five-point scale (0="Not prevalent", 1="Occasionally, less than once per week", 2="Often, about once a week", 3="Frequently, several times per week, but less than every day" or 4="Very frequently, once or more per day").

Statistical Analysis

Standard descriptive statistics were used to report the distribution of parameters of interest. The agreement between CGs and physicians on the prevalence of NPS in patients was assessed by the weighted kappa statistics (with higher values indicating higher agreement) and the rate of absolute agreement for the entire sample and separately for male and female CGs, for the depression status of caregivers and patients. Bootstrapping was applied to estimate the 95% confidence intervals for kappa by the percentile method based on 500 bootstrap replications. The bootstrap samples were drawn on patient level rather than using the physician sites for stratification by the limited mean number of patients (4.0, 95%CI: 3.3-4.7) within a cluster. The confidence interval by the percentile method is taken on the 2.5th and 97.5th percentiles of the distribution that resulted from the bootstrapping. Logistic regression analyses were applied to investigate whether the disagreement on the prevalence of NPS between the GCs and physicians depends on the sex or depression status of the caregiver. Statistical inference was based on a significance level of 5%. All statistical analyses were conducted with SAS 9.3 (SAS Institute Inc., Cary, NC).

Ethical approval

The study was conducted in compliance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (Vote No. EK 75032009). Written informed consent was obtained from all participants.

Results

Study population

Table 1 compares patient-CG-pairs with complete and incomplete NPI data. Caregivers with completed NPI were significantly older, more likely to be the patients' spouses and more often living with the patients than CGs with incomplete data. No difference was found in CGs' depression status or in the mean DSQ-score (3.9 vs. 4.8, p=.112, data not shown). Most common missings on the NPI occurred on the item "Night-time behavior disturbances", which was omitted by n=49 CGs, of which n=44 (93.6%) did not live with the patient (data not shown).

Patients associated with CGs with complete NPI were significantly younger, more often male and had a shorter disease duration than patients associated with CGs with incomplete data. They were also less functionally impaired in terms of Barthel/I-ADL scores, but differed neither regarding severity of AD nor the need of daily assistance by the CG.

Prevalence of NPS

The prevalence of patients experiencing NPS at least “often” as reported by CGs and physicians, respectively, is displayed in Figure 1. Even though there were some discrepancies in the assessment of symptoms, both caregivers and physicians agreed on the two most frequent symptoms, apathy and depression. However, while caregivers reported apathy most frequently (67.2 %) followed by depression (60.2%), it was the other way around for physicians (apathy: 41.0 % and depression: 50.9%). Aggression was the third most commonly reported symptom according to the caregivers (53.8%) whereas it was only the fifth most reported symptom (34.2%) by physicians. The fourth most reported symptom according to the physician was night-time behavior disturbances (37.6%). Both sources reported a high proportion of patients being affected by at least one NPS (CGs: 95.3%; physicians: 89.5%). The median number of NPS was four according to CGs and three according to physicians. With the exception of night-time behavior disturbances, all NPS were more often reported by CGs than by physicians.

Agreement on NPS

Figure 2 displays the agreement between CGs and physicians on NPS. Overall, the kappa coefficients ranged between κ=.03 and κ=.26 and were lowest for euphoria, apathy and aggression (κ-values .03, .04 and .11) and highest for irritability (κ=.24), night-time behavior disturbances (κ=.24) and depression (κ=.26).

Table 2 stratifies the agreement according to CGs’ characteristics (depression status, sex) and to the patients’ sex. As compared to non-depressed CGs, the presence of depressive symptoms in CGs reduced the agreement on most NPS except hallucinations, aberrant motor behavior and night-time behavior disturbances. Comparing the CG-physician agreement between male and female CGs, the agreement was higher in male than in female CGs about the symptoms aggression, hallucinations and disinhibition while it was higher in female than in male CGs for the symptoms irritability and aberrant motor behavior.

Table 3 depicts the association between the rates of disagreement between CGs and physicians, as obtained from logistical regression analyses. Caregivers, who were depressed themselves were more likely (OR= 2.07) to disagree with the physician on the appraisal of the patient’s depression status. This effect was stronger (OR=2.90) for CGs who suffered from major depression. In both cases, the physician was more likely to assume a case of depression in the patient than the CG (for depressed CGs: OR=2.39, 95% CI: 1.11-5.17; for CGs with major depression: OR=3.25, 95% CI: 1.23-8.57, data not shown). Regarding the evaluation of disinhibition, female CGs were more likely to disagree with the physician than male CGs (OR=2.83). Here, female CGs more often stated the presence of disinhibition as opposed to the physician (OR=3.20, 95% CI: 1.41-7.26). The severity of AD was not associated at all with the rate of disagreement between CGs and physicians on any NPS.

Discussion

We presented data on the agreement between CGs and treating physicians regarding the frequency of NPS in patients with AD, obtained from an observational study in daily routine practice of office-based neurologists. So far, only few studies have directly compared the appraisals of CGs and physicians of patients with AD using standardized instruments for the assessment of NPS.[6, 7] To our best knowledge, this was the first study to also consider information on the CG, e.g. depression status. This is essential since it is well known that CGs have a high burden and suffer from psychological consequences that may strongly influence their judgement about NPS in patients with AD.[17, 18]

First and foremost, our results confirmed a high prevalence of NPS with apathy, depression, aggression and irritability as the symptoms most commonly reported by CGs as well as by their treating physicians. Two recently published reviews have identified just these symptoms as strongest contributors to CGs' burden.[19, 20] Thus, our findings underscore the substantial demands placed on CGs which have also been reported to be substantially higher than the burden caused by functional impairments or memory deficits.[21] With two exceptions, all symptoms were reported more often by the patients' CGs than by their physicians, and the differences between both sources ranged in the magnitude between 20% and 60%. Higher differences, however, were observed for disinhibition (265%), and delusions (135%). Several aspects could have accounted for CGs reporting these symptoms substantially more frequently. First of all, unlike rather persistent symptoms such as depression and anxiety, both delusions and disinhibitions are more often fluctuating. As they are also more likely situation-dependent, chances might simply be higher for CGs to notice these symptoms during their everyday life than for physicians whose contact with the patient is less intense. Moreover, delusional as well as disinhibited behavior (which often manifests as sexually inappropriate) might be regarded as stigmatizing, leading a patient to respond socially desirable during a physician-patient consultation. On the other hand, as these symptoms have been reported to substantially contribute to the CG burden[20], they are more likely to be mentioned by CGs during a confidential telephone interview. Interestingly, night-time behavior disturbances was the only symptom to be more often reported by physicians. This was surprising, since one would expect persons who do not live with the patient rather to underestimate night-time behavior disturbances. So far, however, we have no explanation for this particular result.

Concerning the CGs' sex, we found only few differences between male and female CGs regarding the agreement with the patients' physicians on the presence of NPS. Male CGs were more likely to agree with the physician on the presence of disinhibition and aggression (though the latter was not significant) than did female CGs. At first glance, the reason for this result is not obvious. Yet keeping the sociodemographic structure of our study sample in mind (the majority of female CGs cared for male patients and vice versa), this finding can also imply that CGs and physicians were more likely to agree on the presence of these symptoms in female patients than in male patients. In this view, it could be possible that aggressive and disinhibited behavior is more likely to be appraised as a new (disease-related) symptom in female patients, whereas these symptoms are more likely to be appraised as a potentiation of previously present personality traits. This is, however, highly speculative, and the sample size in this study was too small to investigate the interaction between the sex of the CG and the sex of the patient. Considering the rather large confidence intervals of the kappa values, these particular findings must be interpreted very cautiously anyway.

Second, the rates of agreement between CGs and physicians on the prevalence of NPS did not exceed .26, and for more than half (55%) of all NPS the rates were below .19. It was highest for depression, night-time behavior disturbances and hallucinations and lowest for aggression, euphoria and apathy. Between one quarter and one third of all patients were rated by their physician to suffer from delusions or depression, while the CGs disagreed on the presence of these symptoms. Almost 40% of all patients suffered from anxiety according to the CG but not according to the physician. At first glance it seems counterintuitive that the agreement in terms of kappa values sometimes contrasted the agreement in terms of higher percentages. The kappa coefficient calculates the random corrected match of two observers in the rating of a number of subjects by a predefined category system. It is known that low values of kappa can be calculated in presence of a high absolute agreement, which is well known as the "kappa paradoxon" in literature.[22] We observed this paradoxon for example for euphoria, for which the absolute agreement between CGs and physicians was 88%. This agreement was concentrated on the cell referring to the rating "no" of both raters in the respective 2x2 crosstable. In contrast, the cell referring to the "yes-yes" rating showed only a small number of ratings. This imbalance results in a low kappa in presence of a high absolute agreement.

For most of the NPS considered, the depression status or the sex of the CG had no effect on the agreement between CG and physician on the presence of these symptoms, with two exceptions only: 1.) The likelihood of disagreement on the depression status of the patients was higher when the CGs were depressed themselves, with physicians more often stating the presence of depression and CGs reporting its absence. This effect was even stronger for those CGs who met criteria for major depression; 2.) As compared to male CGs, female CGs were more likely to disagree with the physician on the appraisal of disinhibition. The severity of AD had no impact at all on the agreement between CGs and physicians on any NPS.

As we did not assess the depression status of patients directly, we ultimately do not know whether either the CGs' or the physicians' appraisals were correct. Nonetheless, our findings bear some important implications. Caregivers serve a key role in the implementation of treatment plans of patients already at early stages of dementia. Previous studies have consistently reported an impairment of judgement and decision-making in individuals with depressive disorders.[23, 24] Thus, our results might suggest that depressed patients with dementia are less likely to be treated against depression, if the CGs are depressed themselves and therefore do not consent since they might not recognize the necessity for the treatment of the patient.

Our study has some limitations that warrant a cautious interpretation of the presented data. First, to avoid bias related to the fact that CGs who did not provide complete NPI data may systematically differ from those who provided complete data, we restricted the analysis to CG-patient-pairs with complete NPI data. This led to a sample size smaller than that originally included. Nevertheless, this number is higher than in the prior study by Stella et al.[7] and is also above the median number of persons as reported by a recent review.[20] A larger sample would have probably enabled us to conduct more comprehensive analyses with sufficient power to consider more finely graded stratifications. However, CGs and patients who participated only in stage one of the study did not differ from the included sample in the parameters relevant for the present analyses. This reduces the possibility that agreement estimates were influenced by selection bias. Nonetheless, it should be noted that patients who were excluded from the final analyses due to incomplete NPI data were significantly older and more functionally impaired than included patients. Despite a lack of differences in the broad categories of “mild” and “moderate AD” between included and excluded patients, this might hint at a more advanced disease in the latter group and therefore an underestimation of the prevalence of NPS in our data because higher degrees of functional impairment may potentially mask milder NPS.[25] Age and gender distribution of the CGs under study fit well with previously published data on CGs of demented patients.[19] It is also important to keep in mind, that - while having a good characterization of patients and their CGs - we lack more information on the treating physicians, which could have helped us to further eliminate potential selection bias. For instance, physicians with less experience in rating of neuropsychiatric complications in dementia patients might have underestimated the number or severity of such symptoms, while CGs of more severely impaired patients could have been reluctant to participate in stage two of the study. This could have led to an underestimation of neuropsychiatric symptoms potentially further decreasing the extent of agreement between caregivers and physicians. Second, due to the cross-sectional design of the study, data on symptom fluctuations are not available and no longitudinal inference, e.g., regarding causality, can be drawn from the data. Third, while we had detailed information on the CGs, some characteristics of the physician were not available, e.g., experience, type of practice (e.g., specialization on AD treatment). Such additional information would have been useful in the identification of further variables that might influence the agreement between CGs and physicians on NPS. It should also be noted that the comparability of our data with results from other studies is partially limited due to the lack of an established caregiver burden scale (e. g. the Zarit Burden Inventory). As the IDEA study primarily aimed at the assessment of well-defined psychopathological conditions in the CGs, we refrained from additionally including such a scale to keep the interview feasible for the CGs. This also applies to anosognosia in the patients, which has been recently reported as contributing to the caregiver burden[26], but could not be assessed with an established scale in our study. Since the CGs were often at an advanced age themselves and/or lacked time due to care responsibilities, any further extension of the already comprehensive interview might have jeopardized the acquisition of data.

References

[1]. Berr C, Wancata J, Ritchie K. Prevalence of dementia in the elderly in Europe. *Eur Neuropsychopharmacol*. 2005; 15: 463-471.

[2]. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary Costs of Dementia in the United States. *N Engl J Med*. 2013; 368: 1326-1334.

[3]. Cipriani G, Vedovello M, Nuti A, Di Fiorino M. Aggressive behavior in patients with dementia: Correlates and management. *Geriatr Gerontol Int*. 2011; 11: 408-413.

[4]. Machnicki G, Allegri RF, Dillon C, Serrano CM, Taragano FE. Cognitive, functional and behavioral factors associated with the burden of caring for geriatric patients with cognitive impairment or depression: evidence from a South American sample. *Int J Geriatr Psychiatr*. 2009; 24: 382-389.

[5]. Migliorelli R, Teson A, Sabe L*, et al.* Anosognosia in Alzheimers Disease – a study of associated factors. *J Neuropsychiat Clin Neurosci*. 1995; 7: 338-344.

[6]. Riedel O, Klotsche J, Wittchen HU. Overlooking Informal Dementia Caregivers' Burden. *Res Gerontol Nurs*. 2016; 9: 167-174.

[7]. Stella F, Forlenza OV, Laks J*, et al.* Caregiver report versus clinician impression: disagreements in rating neuropsychiatric symptoms in Alzheimer's disease patients. *Int J Geriatr Psychiatr*. 2015; 30: 1230-1237.

[8]. Cummings JL. The neuropsychiatric inventory: Assessing psychopathology in dementia patients. *Neurology*. 1997; 48: S10-S16.

[9]. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS. Caregiver Burden A Clinical Review. *JAMA*. 2014; 311: 1052-1059.

[10]. Bin Sallim A, Sayampanathan AA, Cuttilan A, Ho RCM. Prevalence of mental health disorders among caregivers of patients with Alzheimer disease. *JAMA*. 2015; 16: 1034-1041.

[11]. Riedel O, Emmrich A, Klotsche J*, et al.* Alzheimer's Disease: Differences of transdermal versus oral treatment on caregiving time. *Dementia Geriatr Cog Disord Extra*. 2012; 2: 468-480.

[12]. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease - Report of the NINCDS-ARDRA work group under the auspices of department-of-health-and-human services task-force on Alzheimer's disease. *Neurology*. 1984; 34: 939-944.

[13]. Folstein M, Folstein S, McHugh P. Mini-Mental state: a practical method for grading the mental state of patients by the clinician. *J Psychiatr Res*. 1975; 12: 189-198.

[14]. Mahoney F, Barthel D. Functional evaluation - The Barthel Index. *MD State Med J*. 1965; 14: 61-65.

[15]. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969; 9: 179-186.

[16]. Wittchen H-U, Höfler M, Meister W. Prevalence and recognition of depressive syndromes in German primary care settings: poorly recognized and treated? *Int Clinical Psychopharmacol*. 2001; 16: 121-135.

[17]. Schulz R, Martire LM. Family caregiving of persons with dementia - Prevalence, health effects, and support strategies. *Am J Geriatr Psychiatr*. 2004; 12: 240-249.

[18]. Schulz R, McGinnis KA, Zhang S*, et al.* Dementia patient suffering and caregiver depression. *Alzheimer Dis Assoc Disord*. 2008; 22: 170-176.

[19]. Feast A, Moniz-Cook E, Stoner C, Charlesworth G, Orrell M. A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. *Int Psychogeriatr*. 2016; 28: 1761-1774.

[20]. Terum TM, Andersen JR, Rongve A, Aarsland D, Svendsboe EJ, Testad I. The relationship of specific items on the Neuropsychiatric Inventory to caregiver burden in dementia: a systematic review. *Int J Geriatr Psychiatr*. 2017; 32: 703-717.

[21]. Cheng ST. Dementia Caregiver Burden: a Research Update and Critical Analysis. *Curr Psychiatr Rep*. 2017; 19.

[22]. Feinstein A, Cicchetti D. High agreement but low kappa: I. The problems of two paradoxes. *J Clin Epidemiol*. 1990; 43: 543-549.

[23]. Fossati P. Is major depression a cognitive disorder? *Rev Neurol*. 2018; 174: 212-215.

[24]. Hindmarch T, Hotopf M, Owen GS. Depression and decision-making capacity for treatment or research: a systematic review. *BMC Med Ethics*. 2013; 14.

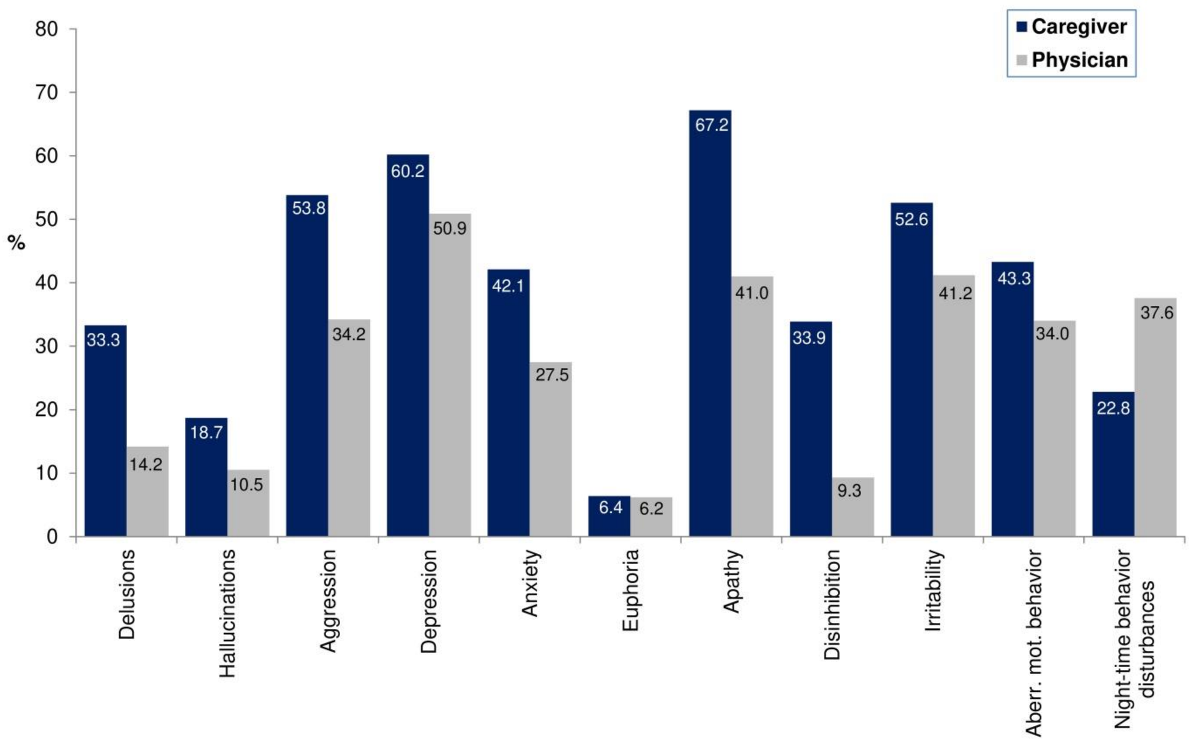
[25]. Garre-Olmo J, Vilalta-Franch J, Calvo-Perxas L*, et al.* A path analysis of patient dependence and caregiver burden in Alzheimer's disease. *Int Psychogeriatr*. 2016; 28: 1133-1141.

[26]. Perales J, Turro-Garriga O, Gascon-Bayarri J, Rene-Ramirez R, Conde-Sala JL. The Longitudinal Association Between a Discrepancy Measure of Anosognosia in Patients with Dementia, Caregiver Burden and Depression. *J Alzheimer Dis*. 2016; 53: 1133-1143.

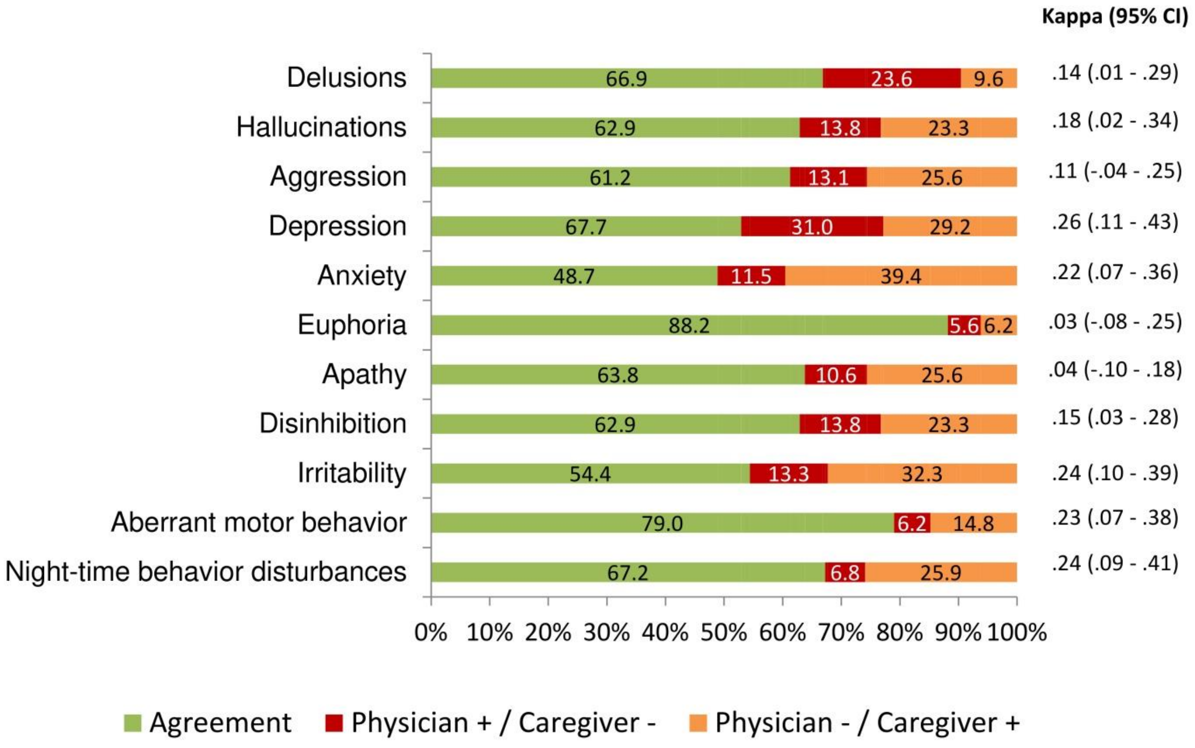
Figure Legends

Figure 1. Prevalence of NPS in patients according to their caregivers and physicians (at least rated to occur “often”).

Figure 2. Agreement between the patients’ caregivers and physicians on the presence of NPS in the patients.



Caregiver
Physician
%
80
70
60
50
40
30
20
10
0
33.3
14.2
18.7
10.5
53.8
34.2
60.2
50.9
42.1
27.5
6.4
6.2
67.2
41.0
33.9
9.3
52.6
41.2
43.3
34.0
22.8
37.6
Delusions
Hallucinations
Aggression
Depression
Anxiety
Euphoria
Apathy
Disinhibition
Irritability
Aberr. mot. behavior
Night-time behavior disturbances



Kappa (95% CI)
Delusions
66.9
23.6
9.6
.14 (.01 - .29)
Hallucinations
62.9
13.8
23.3
.18 (.02 - .34)
Aggression
61.2
13.1
25.6
.11 (-.04 - .25)
Depression
67.7
31.0
29.2
.26 (.11 - .43)
Anxiety
48.7
11.5
39.4
.22 (.07 - .36)
Euphoria
88.2
5.6
6.2
.03 (-.08 - .25)
Apathy
63.8
10.6
25.6
.04 (-.10 - .18)
Disinhibition
62.9
13.8
23.3
.15 (.03 - .28)
Irritability
54.4
13.3
32.3
.24 (.10 - .39)
Aberrant motor behavior
79.0
6.2
14.8
.23 (.07 - .38)
Night-time behavior disturbances
67.2
6.8
25.9
.24 (.09 - .41)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Agreement
Physician + / Caregiver -
Physician - / Caregiver +

Table 1. Study population.

	NPI incomplete	NPI complete	P Value
N (%)	61 (26.3)	171 (73.7)	---
Caregiver			
Age, years	57.4 ± 11.6	64.1 ± 12.6	<.001
Male : Female ratio (%)	27.9 : 72.1	36.8 : 63.2	.206
Duration of caregiving, months	47.6 ± 38.8	40.9 ± 32.0	.224
Relationship to patient (%)			
Spouse	14.7	61.4	<.0001
Son/daugther	65.6	26.3	
Son-in-law/daughter-in-law	4.9	4.7	
Other	14.8	7.0	
Living with patient (%)	18.6	80.0	<.0001
Depression (%)			
None	56.9	55.3	.440
Subthreshold	31.0	26.5	
Major depression	12.1	18.2	
Patient			
Age, years	80.9 ± 6.9	75.7 ± 7.9	<.0001
Male : Female ratio (%)	22.9 : 77.1	43.9 : 56.1	<.01
Duration of AD, years	3.8 ± 3.5	2.8 ± 2.4	<.05
Mild severity of AD (%)	31.3	34.6	.670
Moderate severity of AD (%)	68.8	65.4	
MMSE score	17.1 ± 5.9	18.8 ± 5.0	.05
Barthel Index score	59.7 ± 30.4	79.2 ± 20.6	<.0001
I-ADL score	1.7 ± 2.1	2.5 ± 2.3	<.05
Need of daily assistance by the caregiver, minutes	372.5 ± 428.0	449.5 ± 466.6	.265

AD = Alzheimer’s Disease; MMSE = Mini-Mental State Exam; I-ADL = Instrumental Activities of Daily Living

Table 2. Agreement (expressed as Kappa with 95% CI) between caregivers and physicians on the presence of NPS with a frequency of at least “often” in the the patients.

	Caregivers					Patients	
	No Depression[1]	Depressive Symptoms[2]	Major Depression[3]	Males	Females	Mild AD	Moderate AD
Delusions	.20 (.01 - .42)	.07 (-.10 - .29)	.12 (-.06 - .42)	.15 (-.10 - .42)	.14 (.00 - .35)	.02 (-.14 - .22)	.20 (.02 - .41)
Hallucinations	-.02 (-.14 - 0.21)	.35 (.08 - .61)	.09 (-.17 - .59)	.14 (-.09 - .48)	.20 (-.03 - .49)	.18 (-.06 - .63)	.17 (-.02 - .39)
Aggression	.16 (-.02 - .34)	.02 (-.19 - 0.23)	.07 (-.23 - .43)	.26 (-.03 - .49)	.02 (-.15 - .22)	.02 (-.20 - .23)	.16 (-.02 - .35)
Depression	.41 (.20 - .57)	.07 (-.16 - .27)	-.19 (-.45 - -.24)	- .37 (.14 - .64)	.19 (.03 - .36)	.32 (.05 - .58)	.25 (.05 - .43)
Anxiety	.27 (-.07 - .46)	.18 (-.03 - .38)	.18 (-.06 - .51)	.24 (-.02 - .47)	.20 (.01 - .39)	.27 (-.03 - .56)	.18 (.00 - .36)
Euphoria	.13 (-.07 - .49)	-.07(-.14 - .03)	-.05 (-.12 - .00)	.16 (-.08 - .65)	-.06 (-.16 - .03)	-.06 (-.17 - .03)	.08 (-.08 - .42)
Apathy	.11 (-.10 -.28)	-.05 (-.24 - .09)	-.16 (-.43 - -.05)	.16 (-.09 - .41)	-.02 (-.16 - -.12)	.04 (-.18 - .28)	.05 (-.11 - .21)
Disinhibition	.15 (.00 - .35)	.15 (-.01 - .34)	.19 (.00 - .54)	.26 (-.07 - .57)	.11 (-.02 - .25)	.17 (-.07 - .46)	.14 (.01 - .32)
Irritability	.24 (.03 - .43)	.22 (.01 - .43)	.05 (-.26 - .42)	.16 (-.08 - .40)	.28 (.12 - .47)	.19 (-.01 - .42)	.30 (.13 - .49)
Aberrant motor behavior	.14 (-.07 - 0.35)	.29 (.09 - .52)	.23 (-.13 - .50)	.10 (-.16 - .35)	.29 (.09 - .47)	.29 (.04 - .62)	.18 (.01 - .37)
Night-time behavior disturbances	.18 (-.06 - 0.38)	.24 (.03 - .45)	.30 (-.09 - 0.60)	.20 (-.05 - .46)	.25 (-.08 - .43)	.30 (.03 - .64)	.20 (.02 - .38)

[1]DSQ-Score ≤7; [2]DSQ-Score ≥8; [3]DSQ-Score ≥10

Table 3. Association between disagreement between caregivers and physicians on the presence of NPS, stratified to CG and patient characteristics (expressed as OR with 95% CI*).

	Caregiver characteristics				**Patient characteristics**
	Depression vs. no depression	**Major Depression vs. no depression**	**DSQ-Score**	**Female vs. male**	**Moderate AD vs. mild AD**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Delusions	1.93 (0.99-3.75)	2.30 (0.99-5.36)	1.06 (0.97-1.15)	1.04 (0.52-2.05)	0.74 (0.37-1.47)
Hallucinations	0.87 (0.41-1.88)	1.04 (0.39-2.75)	0.98 (0.88-1.08)	.66 (0.31-1.43)	2.35 (0.94-5.82)
Aggression	1.45 (0.77-2.72)	1.31 (0.57-3.04)	1.01 (0.93-1.10)	1.67 (0.86-3.24)	0.74 (0.38-1.43)
Depression	**2.07 (1.08-3.98)**	**2.90 (1.25-6.73)**	**1.11 (1.02-1.21)**	1.65 (0.83-3.29)	1.17 (0.58-2.35)
Anxiety	1.28 (0.67-2.45)	1.42 (0.61-3.28)	1.03 (0.95-1.13)	0.89 (0.46-1.74)	1.43 (0.71-2.87)
Euphoria	1.48 (0.56-3.85)	0.96 (0.24-3.82)	0.99 (0.87-1.13)	0.99 (0.37-2.67)	1.07 (0.38-3.02)
Apathy	1.62 (0.86-3.07)	1.92 (0.81-4.55)	1.08 (1.00- 1.18)	1.70 (0.88-3.28)	0.94 (0.48-1.85)
Disinhibition	1.32 (0.68-2.56)	1.19 (0.49-2.86)	1.06 (0.97-1.15)	**2.83 (1.31-6.08)**	1.48 (0.72-3.03)
Irritability	1.10 (0.58-2.08)	1.44 (0.63-3.32)	0.99 (0.91-1.08)	0.80 (0.42-1.56)	0.70 (0.35-1.36)
Aberrant motor behavior	0.90 (0.47-1.72)	1.08 (0.46-2.51)	1.02 (0.94-1.11)	0.81 (0.41-1.57)	1.81 (0.88-3.70)
Night-time behavior disturbances	1.44 (0.74-2.81)	1.26 (0.51-3.06)	1.02 (0.94-1.12)	1.17 (0.58- 2.36)	1.51 (0.73-3.11)

*Significant associations are printed in bol