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Hanževački, Miroslav; Lucijanić, Jelena; Librenjak, Dina; Lucijanić, Marko; Jureša, Vesna

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Title: Unique contributions of specific neuropsychiatric symptoms to caregiver burden in informal caregivers family members of patients with dementia

Authors: Miroslav Hanzevacki* [1,2], Jelena Lucijanic* [2], Dina Librenjak [3], Marko Lucijanic [1,4], Vesna Juresa [1]

*both authors contributed equally and share first author place

Affiliations:

[1] School medicine University of Zagreb, Zagreb, Croatia

[2] Health Care Center Zagreb-West, Zagreb, Croatia

[3] Sveti Ivan Psychiatric Hospital, Zagreb, Croatia

[4] Hematology department, University hospital Dubrava, Zagreb, Croatia

Corresponding author: Jelena Lucijanic, Health Care Center Zagreb-West, Prilaz Baruna Filipovica 11, 10000 Zagreb, Croatia. Email: jemileti@yahoo.com

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Abstract:

Introduction: We aimed to evaluate how the presence of individual neuropsychiatric symptoms in non-institutionalized patients with dementia is associated with caregiver burden of their informal caregivers, family members.

Methods: We performed a cross-sectional study on a total of 131 pairs of one informal caregiver family member and non-institutionalized patient with dementia in a family medicine practices in a city of Zagreb, Croatia. Caregiver measures included Zarit Burden Interview (ZBI) whereas patient measures included Mini mental state examination (MMSE), Barthel index and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Results: Total NPI-Q score explained 21% of overall burden. In order of strength of the association, after adjustments for age, sex, MMSE and Barthel index, overall burden was significantly associated with higher NPI-Q scores for agitation/aggression, apathy/indifference, irritability/lability, disinhibition, motor disturbance, appetite/eating, depression/dysphoria, anxiety, elation/euphoria, and nightime behaviors. When evaluating mutually independent contribution of unique NPI-Q symptoms to caregiver burden, agitation/aggression and apathy/indifference remained only two mutually independently associated symptoms, each explaining 5% of overall burden in this context.

Conclusions: Informal caregivers who provide for family members with dementia suffering from agitation/aggression or apathy/indifference should be recognized as under special risk for development of caregiver burden and considered as candidates for early targeted interventions.

Keywords: caregiver burden, dementia, neuropsychiatric symptoms, family medicine

Introduction:

Informal caregiver family members of patients with dementia are highly burdened with caregiving and prone to a number of physical, psychical and economic stressors. Neuropsychiatric symptoms that are prevalent in patients with dementia substantially affect quality of life (Lucijanić et al., 2021) and caregiver burden of informal caregivers (Tsai et al., 2022). Caregiver burden estimated by Zarit Burden Interview (ZBI) is a multifactorial construct and several domains of caregiver burden have been recognized by multiple author groups in different demographic contexts (Lu, Wang, Yang, & Feng, 2009; Springate & Tremont, 2014). Presence and intensity of neuropsychiatric symptoms are the most notable and strongest determinants of caregiver burden, as shown in multiple studies from different cultural contexts (Baharudin, Din, Subramaniam, & Razali, 2019; Basu & Mukhopadhyay, 2022; Clyburn, Stones, Hadjistavropoulos, & Tuokko, 2000; Pinquart & Sorensen, 2007). Data are scarce in what extent specific neuropsychiatric symptoms may affect the burden. Thus, we aimed to evaluate how individual neuropsychiatric symptoms in non-institutionalized patients with dementia are associated with overall burden in our cohort of informal caregivers.

Materials and methods:

The study was performed in 60 family medicine practices in the Health Care Center Zagreb-West, Zagreb, Croatia, in period from 10/2017 to 9/2018. We have cross-sectionally evaluated a total of 131 dyads of non-institutionalized patients with dementia and their informal caregivers who were family members. Diagnosis of dementia was established by neurologist or psychiatrist. Dyads including institutionalized patients, those who did not have established diagnosis as above and those whose informal caregivers were not family members were excluded from the study. Caregiver burden was evaluated using the ZBI (Zarit, Reever, & Bach-Peterson, 1980). Four domains of caregiver burden in our cohort of patients were recognized: personal strain, frustration, embarrassment and guilt which we described previously (Lucijanić et al., 2020). Level of patient cognitive impairment was evaluated using the Mini mental state examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Level of patient functional impairment was evaluated using the Barthel index (Mahoney & Barthel, 1965). Presence of neuropsychiatric symptoms was evaluated using the Neuropsychiatric inventory questionnaire (NPI-Q) (Cummings et al., 1994) assessing presence and frequency of delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, appetite/eating. More details on study protocol, caregiver and patient characteristics have been published previously (Lucijanić et al., 2020). All caregivers provided written informed consent for personal and patient participation in the study. The study was approved by the Health Care Center Zagreb-West and University of Zagreb School of medicine review boards.

Normality of distribution of numerical variables was tested using the Kolmogorov Smirnov test. Due to non-normal distribution of majority of evaluated numerical variables, they were presented as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Linear regression analysis was used to provide association of unique neuropsychiatric symptoms to overall burden, both in univariate and multivariate context (adjusted for age, sex, MMSE and Barthel index). Multivariate linear regression was also used to assess independent contribution of unique neuropsychiatric symptoms (using backwards model building process starting with all NPI-Q domains, age, sex, MMSE and Barthel index). Burden and NPI-Q domain scores were treated as continuous variables. *p* values less than .05 were considered to be statistically significant. MedCalc ver. 19.0.4. (MedCalc Software bvba, Ostend, Belgium) was used for all analyses.

Results:

A total of 131 dyads of patients with dementia and their informal caregivers were analyzed. Median age was 60 years, IQR (53-73) for caregivers and 80 years, IQR (76-83) for patients. There were 89 (68%) female caregivers and 92 (70%) female patients. A total of 67 (51%) caregivers were children of patients and 51 (39%) were spouses. Majority of patients had Alzheimer dementia (58%), followed by vascular dementia (36%). Median MMSE was 15 points, IQR (9-20). Median Barthel index was 85 points, IQR (65 - 100). Median NPI-Q score was 26 points, IQR (12-39).

Neuropsychiatric symptoms were present in 130 (99%) patients. Frequencies of specific neuropsychiatric symptoms assessed by NPI-Q are presented in Table 1. Median overall ZBI was 27 points, IQR (21 - 39).

Table 2 presents unadjusted and adjusted relationship of NPI-Q and specific NPI-Q domains with overall ZBI score. Total NPI-Q score uniquely contributed to 21% of variation in **overall burden** ($r_{semipartial}^2$ = .21). In order of strength of the association, after adjustment of analyses for age, sex, MMSE and Barthel index, overall burden was significantly associated with higher NPI-Q scores for agitation/aggression ($r_{semipartial}$ = .35), apathy/indifference ($r_{semipartial}$ = .34), irritability/lability ($r_{semipartial}$ = .29), disinhibition ($r_{semipartial}$ = .27), motor disturbance ($r_{semipartial}$ = .25), appetite/eating ($r_{semipartial}$ = .24), depression/dysphoria ($r_{semipartial}$ = .23), anxiety ($r_{semipartial}$ = .22), elation/euphoria ($r_{semipartial}$ = .20) and nightime behaviors ($r_{semipartial}$ = .17), $p < 0.05$ for all analyses.

When evaluating mutually independent contribution of unique NPI-Q symptoms to caregiver burden, agitation/aggression ($r_{semipartial}$ = .23, p = .004) and apathy/indifference ($r_{semipartial}$ = .23, p = .004) remained only two mutually independently associated symptoms.

Discussion:

There are several important points emerging from our study that we would like to emphasize. Neuropsychiatric symptoms are among best predictors of caregiver burden (Naglie et al., 2011), explaining 21% of overall burden in our cohort of patients. This association remained consistent and of similar magnitude after adjustments for age and sex of caregivers, MMSE score and Barthel index, further stressing its importance.

The most prevalent symptoms in our cohort were apathy/indifference in 84% of patients, followed by motor disturbance, agitation/aggression, depression/dysphoria and anxiety in about two thirds of patients and appetite/eating disorders in half of all patients. High number of specific symptoms were associated with overall burden. However, despite their high and in some cases similar prevalence, intensity of specific neuropsychiatric symptoms is differently associated with caregiver burden. Hallucinations shown no significant associations in neither univariate nor multivariate analyses, whereas associations of delusions with an overall burden diminished after adjustments for age, sex, MMSE and Barthel index. Thus, delusions and hallucinations seem to be the neuropsychiatric symptoms with the weakest impact on caregiver burden. Agitation/aggression and apathy/indifference were two symptoms that were most profoundly associated with overall burden, as well as remained only two mutually independent predictors of overall burden as well. These two types of symptoms each explained 15% and 14% of the overall burden in unadjusted context, respectively. When considered as mutually independent predictors these two types of symptoms independently explained 5% of overall burden each. Thus, both types of symptoms seem to be among most prevalent ones, a degree of overlap in their relationship with caregiver burden seems to exist, but they also seem to substantially independently contribute to its prediction. Informal caregivers who provide for family members with dementia suffering from agitation/aggression or apathy/indifference should be recognized as under special risk for development of caregiver burden and considered as candidates for early targeted interventions.

Limitations of our work are cross-sectional study design disabling conclusions on causal relationship between associated variables. Due to sample size, some of the analyses might be underpowered to detect statistical significance for some of existing relationships. ZBI was created within a particular cultural context, and even within this context some have questioned its cultural relevance, such as its application to specific ethnic and racial subgroups. We have previously performed a psychometric validation of ZBI in our population and we showed that ZBI is a reliable and valid tool (Lucijanić et al., 2020). All included participants were of white race and Croatians, thus no adjustments regarding race and ethnicity were possible. We consider our findings to be representative of an urban cohort of patients and caregivers from a capital city of Croatia, and they might not translate to rural or other geographical contexts.

Despite presented and other potential limitations, our findings might help in understanding the contribution of specific neuropsychiatric symptoms to the caregiver burden. Therefore, they might help in early recognition and timely targeted interventions to prevent burden and consequent morbidity.

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Table 1: Frequency of overall and specific neuropsychiatric symptoms assessed by Neuropsychiatric inventory questionnaire (NPI-Q).

NPI-Q domains	NPI-Q score	Presence of symptoms
Total NPI-Q score	26 IQR (12 - 39)	130/131 (99%)
Delusions	0 IQR (0 - 2)	50/131 (38%)
Hallucinations	0 IQR (0 - 2)	47/131 (35%)
Agitation/aggression	2 IQR (0 - 4)	84/131 (64%)
Depression/dysphoria	2 IQR (0 - 4)	80/131 (61%)
Anxiety	2 IQR (0 - 4)	80/131 (61%)
Elation/euphoria	0 IQR (0 – 0)	24/131 (18%)
Apathy/indifference	4 IQR (2 - 8)	110/131 (84%)
Disinhibition	0 IQR (0 - 2)	43/131 (33%)
Irritability/lability	0 IQR (0 - 4)	63/131 (48%)
Motor disturbance	3 IQR (0 - 6)	87/131 (66%)
Nighttime behaviors	0 IQR (0 - 3)	50/131 (38%)
Appetite/eating	2 IQR (0 - 4)	73/131 (56%)

Table 2: Relationship between specific Neuropsychiatric inventory questionnaire (NPI-Q) domains and Zarit burden interview (ZBI) overall burden.

NPI-Q domains	**ZBI overall burden, unadjusted analyses**	**ZBI overall burden, adjusted analyses +**
Total NPI-Q score	**$p < .001$** *, $\beta = .37$ $r_{semipartial} = .46$	**$p < .001$** *, $\beta = .36$ $r_{semipartial} = .43$
Delusions	**$p = .038$** *, $\beta = 1.34$ $r_{semipartial} = .18$	$p = .087$, $\beta = 1.13$ $r_{semipartial} = .15$
Hallucinations	$p = .207$, $\beta = .70$ $r_{semipartial} = .11$	$p = .477$, $\beta = .41$ $r_{semipartial} = .06$
Agitation/aggression	**$p <.001$** *, $\beta = 2.03$ $r_{semipartial} = .39$	**$p < .001$** *, $\beta = 1.93$ $r_{semipartial} = .35$
Depression/dysphoria	**$p = .017$** *, $\beta = 1.27$ $r_{semipartial} = .21$	**$p = .008$** *, $\beta = 1.42$ $r_{semipartial} = .23$
Anxiety	**$p = .010$** *, $\beta = 1.25$ $r_{semipartial} = .22$	**$p <.001$** *, $\beta = 1.27$ $r_{semipartial} = .22$
Elation/euphoria	**$p = .017$** *, $\beta = 1.73$ $r_{semipartial} = .21$	**$p = .023$** *, $\beta = 1.66$ $r_{semipartial} = .20$
Apathy/indifference	**$p < .001$** *, $\beta = 1.35$ $r_{semipartial} = .38$	**$p <.001$** *, $\beta = 1.42$ $r_{semipartial} = .34$
Disinhibition	**$p = .002$** *, $\beta = 1.56$ $r_{semipartial} = .27$	**$p = .001$** *, $\beta = 1.64$ $r_{semipartial} = .27$
Irritability/lability	**$p = .004$** *, $\beta = 1.50$ $r_{semipartial} = .25$	**$p <.001$** *, $\beta = 1.75$ $r_{semipartial} = .29$
Motor disturbance	**$p = .001$** *, $\beta = 1.23$ $r_{semipartial} = .28$	**$p = .004$** *, $\beta = 1.15$ $r_{semipartial} = .25$
Nighttime behaviors	**$p = .021$** *, $\beta = 1.08$ $r_{semipartial} = .20$	**$p = .047$** *, $\beta = .96$ $r_{semipartial} = .17$
Appetite/eating	**$p = .005$** *, $\beta = 1.26$ $r_{semipartial} = .25$	**$p = .006$** *, $\beta = 1.26$ $r_{semipartial} = .24$

*statistically significant at level $p < .05$

+ analyses adjusted for age and sex of caregivers and MMSE score and Barthel index of patients with dementia.