Published in final edited form as:
Am J Geriatr Psychiatry. 2015 February ; 23(2): 115–118. doi:10.1016/j.jagp.2014.11.002.

Beyond Memory: A Focus on the Other Neuropsychiatric Symptoms of Dementia

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The number of people living with dementia worldwide is estimated at 44 million, with projections indicating this number will double by 2030 and more than triple by 2050 (1). Neuropsychiatric symptoms (NPS) accompany cognitive decline almost universally, with 98% of patients experiencing NPS at some point in their illness (2). NPS are especially concerning as they are associated with more rapid disease progression, worse patient outcomes, excess morbidity and mortality, greater healthcare utilization, earlier nursing home placement, and increased caregiver burden (3, 4). Treatment of NPS may alter disease course, improve patient outcomes, decrease healthcare costs, and improve patient and caregiver quality of life.

Although the cognitive impairment associated with dementia is by itself concerning, the other NPS (e.g., agitation, apathy, depression, sleep disturbances) are part of the reason why caregivers seek help from clinicians. In addition, caregivers can often tolerate increasing forgetfulness and worse functional dependence if associated NPS are managed. Management of NPS, their prognostic impact, and their cause is a major area of interest. This issue of the American Journal of Geriatric Psychiatry (AJGP) contains several papers that advance our understanding in this important area.

Before discussion of the individual papers, a review of the current hypotheses linking NPS to dementia is warranted. Under what has become known as the *symptom hypothesis*, NPS are thought to result from AD-related neurodegenerative changes in the brain and are therefore considered a dementia symptom (5). The same pathological, neurodegenerative process causes both the displayed NPS and the cognitive impairment. Under this hypothesis, treatment should focus on the neurodegenerative process itself. A second hypothesis, the *risk factor hypothesis*, states that NPS are caused by concurrent non-AD pathology that also lowers brain reserve reducing the brain's ability to cope with AD pathology. Different pathological processes are therefore responsible for the cognitive impairment or the NPS. Treatment of a particular NPS under this hypothesis should focus on this second pathological pathway. Another hypothesis, most relevant to individuals with more severe dementia where communication is limited, is the *unmet needs model* (6). This states that behavioral symptoms arise because an individual is unable to meet their own needs and

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caregivers have insufficient knowledge/ability to do so. It is probable that all of these hypotheses are in play with the importance of each varying across individual patients and NPS.

In this AJGP issue, Gracia-Gracia et al. (7) focus specifically on depression in a 5-year longitudinal study of community dwelling adults in Zaragoza, Spain aged 55 or more. Following initially cognitively intact individuals over time, they estimated the incidence of AD to be almost double in those with clinically significant depression, almost four times higher in those with severe depression. Both first-ever depression and untreated depression were associated with AD, while persistent depression (present at study onset and persistent five years later) was not. The association with first-ever depression lends support to the *symptom hypothesis*. Of note, the authors use a competing risk model in studying depression as a risk factor for AD since death may prevent (i.e. compete with) the occurrence AD in the aged population. This is a novel analytic method that future studies on this topic should consider.

In an international study of memory clinics in the United States and France, Zahodne et al. (8) characterize cross-sectional and longitudinal relationships between three NPS (psychosis, depressed mood, agitation/aggression) and dementia progression (as measured by cognition and dependence) to better understand their interplay over time. Impact of individual NPS on patient care needs are indexed by patient dependence, as opposed to nursing home placement used in some other studies. Both psychosis and depressed mood at entry were associated with worse subsequent cognitive decline. Independent of cognitive decline, initial psychosis was associated with worse subsequent increase in dependence. Rates of increase in agitation/aggression separately correlated with rates of decline in both outcomes. This is consistent with recent work from our group in the Cache County Dementia Progression Study (9), where psychosis, agitation/aggression, and any one clinically significant NPS were associated with more rapid progression from dementia onset to severe dementia. Psychosis, affective symptoms, agitation/aggression, and mildly symptomatic / clinically significant NPS were associated with earlier death. It is increasingly clear that NPS are *risk factors* for dementia progression, as they are for dementia onset. However, it could be that these NPS signify worse or more widely distributed AD pathology.

Beyond epidemiology, Whitfield et al. (10) examine the molecular basis of depression in dementia. Current antidepressants, effective in treating depression in people *without* dementia, have limited effectiveness for depression *in* dementia patients (11), suggesting a different pathology. Using post-mortem examination of the brains of individuals with AD, Parkinson's disease dementia, and dementia with Lewy bodies, the researchers investigated the relationship between synaptic zinc regulation (specifically zinc transporter 3 levels, ZnT3) and depression. This follows research in rodents, where zinc deficiency results in the display of depressive-like symptoms. In all three conditions, lower ZnT3 levels were associated with greater depression severity. This association was evident in brain tissue from the dorsolateral prefrontal cortex, but not from the cingulate gyrus or parietal cortex. Tissue staining for cell volume (beta-III-tubulin level) demonstrated that lower zinc levels were not related to neuronal loss. Both age and central/peripheral inflammation have been linked to

dementia and can lead to reduced serum zinc levels. The authors concluded that a loss of regulation of synaptic zinc may have a role in depression in these dementias. If we consider this loss of regulation to be a dementia-related process, this lends support to the *symptom hypothesis*. If we consider loss of zinc regulation to be a separate process that lowers the brain's ability to cope with subsequent AD pathology, this lends support to the *risk factor hypothesis*. Either way, this paper puts forth zinc modulation as a candidate treatment approach for depression in dementia and, if the *risk factor hypothesis* is correct, for altering dementia progression.

Aguera-Ortiz et al. (12) change our focus to a novel rating for apathy: the Apathy in Institutionalized Persons with Dementia (APADEM-NH) scale. Using task force-proposed diagnostic criteria (13), this 26-item scale focuses on three apathy dimensions: deficit of thinking and self-generated behaviors, emotional blunting, and cognitive inertia. The scale is designed to assess a patient's state of apathy through interview with a professional caregiver who has good level of knowledge of the patient's cognitive and functional status. Unlike other rating scales, which have a ceiling effect when applied to institutionalized individuals, the APADEM-NH was designed specifically to measure apathy in these individuals, considering special characteristics of the most severe stages of neurodegenerative dementia and the distinctiveness of the instructional environment. The scale was administered to all patients institutionalized at the Alzheimer Center Reina Sofia Foundation (Madrid, Spain). Subscales lacked appreciable floor or ceiling effects (<15%), and internal consistency was high (Cronbach's alpha ≥0.83). The scale showed good test-retest reliability, inter-rater reliability, and correlation with dementia severity, but lacked correlation with measures of depression. The authors concluded that APADEM-NH is a feasible, reliable, and valid way of identifying apathy in institutionalized patients suffering from mild to severe dementia, discerning well between apathy and depression. Further study will be needed to identify clinically meaningful cut-off points and to see if the scale can measure change after therapeutic interventions.

Lastly, Cohen-Mansfield et al. (14) take a structured, research-oriented approach towards the evaluation of tailored non-pharmacological interventions for the behavioral symptoms in dementia. The authors work off the *Unmet Needs Model* (6), which states that behaviors are based on difficulty communicating/fulfilling needs, implying that if the needs are met the behaviors will improve. In an effort to test this model, which requires a relatively high severity of dementia, the researchers applied their novel approach to nursing home residents. Nine different categories of non-pharmacological interventions were studied: care, theme, manipulative, sensory stimulation, movement activities, artistic activities, work-like activities, simulated social, and social. Interventions were individualized and started with a trial phase to assess which approach would be best suited to each person. The most utilized interventions were the social intervention of "one-on-one interaction," simulated social interventions (e.g., "lifelike doll," "respite video"), the theme intervention of "magazine," and the sensory stimulation intervention of "music." Interventions with the highest impact on behavioral symptoms included the care interventions of "care" and "food or drink," the manipulative intervention of "ball toss," the movement interventions of "going outside" and "walking," the artistic interventions of "color or painting" and "sewing," the work-like

intervention of “folding towels,” and the simulated social intervention of “family video.” The authors noted the importance of tailoring the activity to the cognitive abilities and gender of each participant. The authors concluded that this study provides initial directions for choosing specific interventions for persons with dementia, while demonstrating a methodology for increasing knowledge through ongoing monitoring of practice.

In summary, this is an exciting time for the study of NPS in dementia. The *symptom hypothesis* and *risk factor hypothesis*, although offering different complementary explanations, both show the likely importance of NPS. The *Unmet Needs Model* gives us a way of understanding NPS in more severe dementia where communication is limited. These hypotheses provide a framework for understanding NPS and directing future research. As the field learns more about the associations between various NPS and morbidity/mortality in dementia, the importance of monitoring, treating, and understanding the causal mechanism of these symptoms is taking light. Future research should focus on identification of affected brain pathways/regions in individuals with dementia and these other NPS. Identification of these pathway associations may assist with identification of treatment targets and teach us about brain vulnerability to neurodegeneration.

Acknowledgments

Grant Support: This editorial was supported in part by grant 5PO1-AGO5146 to the Johns Hopkins Alzheimer’s Disease Research Center where Dr. Lyketsos serves as Clinical Core Leader.

Authors have no conflicts of interest unless listed: Dr. Lyketsos receives grant support (research or CME) from NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, Elan, Functional Neuromodulation; is a consultant/advisor to Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, Abvie, Janssen, Orion, Otsuka; and has received honorarium or travel support from Pfizer, Forest, Glaxo-Smith Kline, Health Monitor

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