

Perspectives

# Addressing the Alzheimer's disease crisis through better understanding, treatment, and eventual prevention of associated neuropsychiatric syndromes

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## 1. Introduction

This *Perspectives* article offers a series of recommendations to the implementers of the National Alzheimer's Project Act (NAPA) under the premise that better treatment and preventive strategies targeting neuropsychiatric syndromes (NPS) will improve patient outcomes, lessen caregiver burden, and potentially lead to prevention of Alzheimer's disease (AD) and related primary dementias. These recommendations arise from the activities of the Neuropsychiatric Syndromes Professional Interest Area (NPS-PIA) of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment. The NPS-PIA was constituted after an Alzheimer's Association Research Roundtable meeting devoted to this topic in April 2010. The Roundtable concluded that, despite several decades of efforts, few effective treatments are currently available for NPS and that redoubled efforts are needed in this area because of their great public health impact. We seek to ensure that the NAPA-created Advisory Council on Alzheimer's Research, Care, and Services gives serious and careful consideration to the challenges created by NPS. We further seek inclusion of NPS-focused recommendations in the National Alzheimer's Strategic Plan. As the AD crisis is a worldwide challenge, and the NPS-PIA is an international group, we anticipate that these recommendations will serve as an example for other nations facing the challenge of AD + NPS.

In the interest of time and space, these recommendations are high level and abbreviated. They will be followed by more specific recommendations as well as detailed supporting

documentation in the next few months. Although we primarily discuss NPS in the context of AD, these recommendations also apply to related dementias, such as those associated with frontotemporal degeneration, Lewy body disease, dementia due to brain vascular disease, and others.

Although AD is considered by many people as simply a memory or cognitive disorder, almost all individuals with AD develop one or more NPS at some point in their disease [1]. It is now well accepted that, in the vast majority of cases, NPS are fundamental expressions of the underlying brain disease and do not simply reflect the "secondary reactions" of ill patients [2]. Most common are affective syndromes (depression, anxiety, and irritability), apathy, psychosis (delusions and hallucinations), agitation, aggression, and sleep disorders. Although these are often identifiable as unique syndromes, they often co-occur across patients or occur in the same patient at different points in their illness [3]. NPS lead to disability, dangerous behaviors, reduced life quality, accelerated dementia progression, earlier institutionalization, higher cost, and mortality [4–8]. For caregivers, NPS are major sources of anguish and depression and one of the *major* day-to-day burdens they face [7]. In the prodromal stages of AD/dementia, such as mild cognitive impairment (MCI), NPS are one of the strongest known risk factors for progression to dementia, associated with double the risk of developing dementia [6]. Indeed, mild behavioral impairment is a risk factor for dementia *even in the absence of cognitive symptoms* [9].

Despite near universal occurrence and serious adverse impact, few effective treatments for NPS are available. Although it is known that NPS are a high risk factor for transition from MCI to dementia, why this is the case is not well established. Better understanding of this connection may lead to important strategies to prevent NPS-associated

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transition from MCI to dementia [6,10]. A summary of several of these issues can be found in the 2011 report of the Research Roundtable [6]. Rather than repeating that information, we focus the remainder of this *Perspective* on specific recommendations in the three NAPA areas—research, care, and services.

## 2. Recommendations for Research

A major barrier to improved treatment and prevention of NPS in AD is the poor understanding of their neurobiology and interactions with genetic and environmental risk factors. For example, the syndrome of psychosis, one of the better understood NPS, is not associated with the genetic risk factors for AD itself [11]. Rather, it appears to have its own unique genetic underpinnings in AD, emerging from an interplay with neurodegeneration in specific areas of the brain [12]. Similar theoretical models have been proposed for other syndromes, such as affective disorder, agitation, sleep disorder, or apathy. Now that well-validated tools for quantifying brain amyloid load in life are available, it is particularly important to understand interactions between regional and temporal associations of brain amyloid with receptors implicated in psychiatric disorders, including serotonin, norepinephrine, dopamine,  $\gamma$ -aminobutyric acid, and glutamate, in the development of NPS.

Treatment development has been further hampered by the long presumption, in retrospect perhaps naïve, that treatments for similar symptoms in other disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder) would also be effective in patients with AD. This assumption has not been supported by empirical evidence, especially randomized controlled trials. In situations where some efficacy has been demonstrated, such as with antipsychotic medications, benefits are limited and the treatments carry significant risks.

Another barrier has been limited interaction between researchers developing pharmacologic therapies and those evaluating nonpharmacologic therapies for NPS. This has led to parallel tracks of treatment development, even though the most common clinical recommendation is that nonpharmacologic approaches should be tried first, followed by pharmacologic approaches [13]. NPS-specific nonpharmacologic treatments have been or are being developed, and they show great promise. How they should be targeted, and whether, and how they should be used with pharmacologic therapies (i.e., alone, in combination, or in sequence) have received surprisingly little attention. Furthermore, research is needed to understand the effect of nonpharmacologic interventions on biomarkers of AD, such as amyloid load, neuronal loss, and disease progression (e.g., transition from MCI to dementia).

Finally, major barriers to treatment development have been the lack of an NPS-dedicated research community and lack of direction from funding agencies regarding a “home” for this field. Before the NPS-PIA, there were

very few international, interdisciplinary scientific efforts focused on treatment development for NPS. Although professional associations (e.g., International Psychogeriatric Association, American Association for Geriatric Psychiatry) have at times shown interest, this has not been sufficiently focused or sustained. One of the major objectives of the NPS-PIA is to develop a forum where sustained attention is paid to this important area.

On the funding front, both the National Institutes of Health (NIH) and the Alzheimer’s Association have over the years provided funding for NPS research; however, their commitment has, until recently, been limited. This area has been a low priority for major research collaboratives, such as the National Institute of Mental Health (NIMH)-funded Conte Centers for the Neuroscience of Mental Disorders, National Institute on Aging (NIA)-funded AD Research Centers (ADRCs), National Alzheimer’s Coordinating Center (NACC), Alzheimer’s Disease Collaborative Study (ADCS), and Alzheimer’s Disease Neuroimaging Initiative (ADNI), as reflected in the data they collect and the kinds of research or publications they foster or promote.

Considering the aforementioned data, we make the following recommendations regarding core processes needed to make advances in this field:

- The NIH should *designate as primary*, for promulgating research on NPS in AD, one of the three institutes that typically funds dementia/AD research (NIA, NIMH, National Institute of Neurological Disorders and Stroke), and the NIH should include a mandate to work with other institutes to foster holistic NPS treatment development. The latter can be accomplished through a commitment to fund research centers (perhaps existing or new ADRCs) focused on treatment development for NPS. This would be facilitated by funding supplements to existing grants (e.g., R01, program projects, centers); setting aside funds designated for NPS research; regularly holding conferences on aspects of NPS, including their biological underpinnings; and developing study sections with focused experts in this field.
- The NIH should require all AD clinical research grants to include a standardized measure of NPS (e.g., using the Neuropsychiatric Inventory [14] in one of its several versions [15]).
- The NIA should require major AD research collaboratives (ADRCs, ADNI, and ADCS) to collect *refined* data on NPS, in at least a subset of participants. This could be accomplished, for example, by wider use of the Neuropsychiatric Inventory–Clinician rating scale [16] in conjunction with research using neuroimaging, neuropathology, or disease progression indices.
- The NIMH should incentivize major collaboratives studying the neurobiology of psychiatric syndromes to focus attention on NPS pathogenesis in neurodegenerative disease, preferably as part of translational research.

- Working together with the research community, the NIH should foster the development of scientists working in this field through training grants, career development awards, and Summer Institute training activities, so that during the next 5 years a strong cadre of investigators with expertise, interest, and resources can supply the necessary human power to research this field.
- The Alzheimer's Association and other nonprofits funding AD research should designate NPS as a clear priority by inviting specific research applications, setting aside funds, and convening grant review committees with special expertise.
- Incentives for collaborative university, biotech, and pharmaceutical research around novel targets for NPS (e.g., new approaches to the monoamine systems, therapies targeting glutamate and other systems) should be created. These incentives might include clearer direction from the Food and Drug Administration, perhaps through the creation of a unit that bridges oversight of the development of treatments for NPS in the dementias [17,18].
- Develop new medications for NPS based on a better understanding of their biology. Further study the new medications in combination with nonpharmacologic approaches, either in a parallel or in sequential fashion, and use clinical trial methodologies suited to the use of the medications in the real world (e.g., adaptive, sequential).
- Refine nonpharmacologic approaches that can easily be scaled up for broad use, so that at least three such approaches targeting NPS are available for wide use in the next 5 years [20].
- Through analyses of existing data sets (e.g., NIH-funded epidemiologic studies, ADRCs, NACC, ADCS, ADNI, Minimal Data Set, Veterans Affairs Medical Centers, Medicare/Medicaid, and private efforts, such as Kaiser, Group Health, or other health maintenance organizations), further quantify the economic burden of NPS and estimate cost savings associated with better detection and treatment using current approaches.

Regarding specific research content to be fostered, we make the following recommendations:

- Develop animal models for NPS from the transgenic AD mouse models that have already been developed. It is already known that some of these models exhibit aggressive, inappropriate social, or sleep–wake cycle disorders that could serve as phenotypic equivalents of NPS [19]. Additionally, the behavioral phenotypes of AD animal models with monoamine degeneration should be better studied.
- Validate phenotypes and refine measures for treatment development targets through sustained effort in the next 3 to 4 years for the apathy, psychosis, agitation, sleep, and affective syndromes associated with AD and other dementias (frontotemporal degeneration, Lewy body disease, dementia due to brain vascular disease), as well as for delirium in the context of dementia. Consensus on how to handle overlap among these syndromes, perhaps by further subtyping the heterogeneity of NPS, should be part of the validation process.
- Clarify brain mechanisms underlying NPS through neuropathology and brain imaging, especially in MCI and early dementia where brain damage is less extensive. For example, understand critical factors in the expression of distinct symptoms and identify biomarkers and intermediate phenotypes that define risk for development of individual NPS.
- Elucidate why NPS increase the risk of progressing from MCI to dementia, even in the absence of cognitive symptoms (e.g., preclinical AD, mild behavioral impairment). Understanding the underlying neurobiology may lead to effective dementia prevention approaches not heretofore considered.

### 3. Recommendations for Care

Despite the relative dearth of highly effective therapies for NPS in AD, randomized controlled trials have suggested that specific interventions, if delivered in the context of systematic dementia care [21], are effective in reducing symptoms, improving quality of life (of both the patient and caregiver), and, in some cases, delaying institutionalization [20,22–26]. Effective approaches involve improving adherence to treatment guidelines, bringing special expertise to the care environment (e.g., care management, expert consultation), and/or improving the sophistication of caregivers.

Existing know-how should be widely translated into the settings where NPS are most common and have their greatest adverse effects. This know-how is not widely used, partly because NPS are poorly recognized and managed in primary care, assisted-living, and nursing home settings. Recognition may be lagging because of the false perception that little can be done at present for NPS or that the solutions are simple (e.g., antipsychotic prescription), thereby creating a vicious cycle. Therefore, the major care priority is to clearly articulate effective interventions in ways that make them most likely to be used to treat or prevent NPS, despite constraints of individual settings (e.g., time limits in primary care, lack of access to specialists in chronic care). This should be combined with incentives that encourage the creation of a workforce to deliver these effective therapies.

In line with that mentioned previously, we make the following specific recommendations:

- Improve “packaging” and facilitate dissemination of current know-how regarding nonpharmacologic therapies for NPS for use in primary care, area agencies on aging, assisted-living facilities, and nursing homes.

- Create Medicare incentives to facilitate payment for effective nonpharmacologic therapies, including payment for allied professionals who typically administer these therapies.
- Create incentives for providers and healthcare organizations (e.g., better reimbursement) to encourage detection and management of NPS in emergency departments or acute care hospitals. These incentives will be offset by reductions in length of stay, hospital readmissions, adverse clinical outcomes (e.g., falls), and use of costly resources (e.g., restraints, sitters, sedatives).
- Prioritize efforts to detect, differentiate, and manage sleep disturbances through easier access to home-based assessment (e.g., using actigraphy) and dissemination of currently available sleep hygiene interventions implemented by caregivers.
- Create and implement curricula (such as certification programs for specific competencies that relate to NPS), along with reimbursement incentives, for the development of a workforce of health professionals (e.g., nurses, occupational therapists, physical therapists, speech language pathologists, and possibly a new cadre of *dementia care therapists*) who could be deployed in key areas to better manage NPS in primary care, hospitals, and institutional settings.
- Refine for use in the United States successful models of community care to provide for extra challenges and service demands of NPS, such as those used in Australia.

#### 4. Recommendations for Services

Expertise in NPS treatment is not geographically aligned with the location of those who suffer from NPS. Rural and inner city areas, as well as institutional settings (hospitals, assisted-living facilities, and nursing homes), are particularly underserved. Acute hospitals and emergency departments are poorly designed and poorly equipped to manage NPS (or dementia for that matter), resulting in high rates of restraint use, excessive use of sedating medications, adverse outcomes (falls, delirium), prolonged hospitalization, readmission, decreased ability to function, and mortality [6]. These situations arise from lack of preparation in NPS detection, unavailability of trained workers, and use of policies and procedures that create barriers for the detection and management of NPS.

Based on the aforementioned, we make the following specific recommendations:

- By applying established epidemiologic estimates for dementia and NPS, use 2010 census data to estimate the specific number of individuals with dementia and NPS residing in individual zip codes (by 5-year increments, beginning in 2010). Similar maps have been used in Australia and are effective in targeting services locally to areas where the burden of these disturbances is highest.
- Survey governmental and regional health care providers regarding their know-how and preparedness to detect, evaluate, and manage NPS, thereby identifying and filling gaps in service delivery in the context of the aforementioned map.
- Convene experts to develop model protocols for different types of health care organizations regarding state-of-the-art detection and management of NPS and make these widely available (perhaps required by the Joint Commission) along with necessary training and program evaluation methods.

#### 5. Conclusions

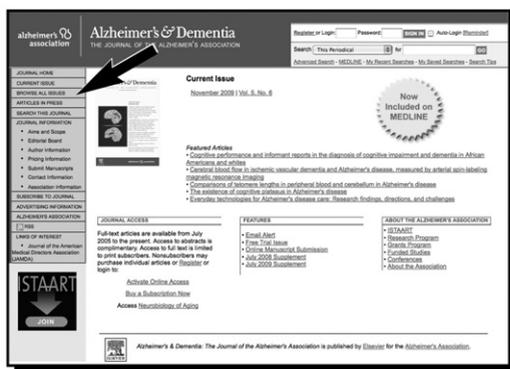
The NPS associated with AD and the other dementias are a major public health concern and a central component of the AD crisis. Effective strategies to better understand their etiology, presentation, diagnosis, and successful treatment (both pharmacologic and nonpharmacologic) need to be addressed at the local, state, and national levels. The field interested in advancing treatment for NPS has developed a strong voice and is stepping forward to make recommendations to ensure that these important conditions are addressed, with adequate resources, in the National Alzheimer's Strategic Plan. We make specific recommendations for advances in research, dissemination of care practices known to be effective, and improvements in service delivery. The short-term objective is to improve NPS detection and management with available therapies. The long-term objective is to develop more effective therapies, followed by their dissemination. Of special interest is better understanding of how NPS contribute to risk of dementia, as this could lead to improved dementia prevention strategies incorporating approaches that have not been considered.

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