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Neuropsychiatric symptoms in Alzheimer's disease: Past progress and anticipation of the future

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Abstract Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) are widespread and disabling. This has been known since Dr. Alois Alzheimer's first case, Frau Auguste D., presented with emotional distress and delusions of infidelity/excessive jealousy, followed by cognitive symptoms. Being cognizant of this, in 2010 the Alzheimer's Association convened a research roundtable on the topic of NPS in AD. A major outcome of the roundtable was the founding of a Professional Interest Area (PIA) within the International Society to Advance Alzheimer's Research and Treatment (ISTAART). The NPS-PIA has prepared a series of documents that are intended to summarize the literature and provide more detailed specific recommendations for NPS research. This overview paper is the first of these living documents that will be updated periodically as the science advances. The overview is followed by syndrome-specific synthetic reviews and recommendations prepared by NPS-PIA workgroups on depression, apathy, sleep, agitation, and psychosis.

Keywords: Neuropsychiatric symptoms; Behavioral and psychological symptoms of dementia; Agitation/aggression; Sleep disorders; Depression; Apathy; Psychosis; Delusions; Hallucinations; Dementia; Alzheimer's disease; Mild cognitive impairment; Mild behavioral impairment

1. Introduction

At the advent of the 21st century, *Neurology* and *American Journal of Psychiatry*, the official journals of the American Academy of Neurology and the American Psychiatric Association, respectively, reviewed the past and anticipated the future of neurology and psychiatry [1,2]. Both journals eloquently indicated that the history of Alzheimer's disease (AD) is a history of neuropsychiatry. Alois Alzheimer, Emil Kraepelin, and other prominent neuropsychiatrists were keen to understand brain changes underlying mental illness [2].

It was at that historical moment that Alzheimer described the clinical manifestations and subsequent classic neuropathological features of what was later known as AD. Alzheimer's first case, Frau Auguste D., presented with emotional distress and delusions of infidelity/excessive jealousy. She developed subsequently developed memory, visuospatial, and language problems [3]. Autopsy revealed what later became known as "the classic AD pathology" (neuritic plaques, neurofibrillary tangles, and neuronal loss). Thus, the search for the physical basis of mental illness led to the discovery of AD pathology, and the other byproduct of this effort was the genesis of the field of neuropathology [1,2].

Over the last 100 years, mankind has acquired substantial scientific knowledge about AD. Part of this success is attributable to having reliable criteria to define dementia, including dementia of Alzheimer's type (DAT). The American Psychiatric Association's *Diagnostic and Statistical Manual IV* (DSM-IV) diagnostic criteria for dementia [4] and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD [5] are widely used in research and clinical settings. Although these criteria have excellent correlation with neuropathological changes on postmortem examination [6], investigators, particularly clinical trialists in the field of AD, later advocated for biomarker-based diagnostic criteria for AD and related disorders [7]. A recent initiative of the National Institute on Aging along with the Alzheimer's Association (NIA-AA) developed new diagnostic criteria. The NIA-AA task force classified AD into three phases: preclinical phase (research category) [8], mild cognitive impairment (MCI) due to AD [9], and dementia due to AD [10]. The preclinical criteria are based on brain imaging and biomarkers [8], although the validity of AD biomarkers has yet to be established [6]. The clinical phases (i.e., MCI due to AD [9] and dementia due to AD [10]) are primarily defined by using cognitive signs and symptoms in combination with biomarkers.

Although AD is well known to cause cognitive symptoms, advances in neuroscience have established that there are extensive and reciprocal neuronal connections between the epicenters of emotions and cognitions [11]. Thus, it should be no surprise that the manifestations of AD are not limited to cognitive symptoms; rather, they include a range of neuropsychiatric symptoms (NPS) of AD. The near universal prevalence of NPS in AD, combined with the serious and disabling effects they have on patients and caregivers [12], has focused significant recent attention on the fact that few effective and safe treatments exist [12].

In an effort to address this major gap, the Alzheimer's Association convened a 2010 research roundtable on the topic of NPS in AD [12]. A major outcome of the roundtable was the founding of the Neuropsychiatric Syndromes of AD Professional Interest Area (NPS-PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART), composed of a large international group of scientists, clinicians, and educators. NPS-PIA has as its mission to educate the broader AD field on this area and to stimulate