AGITATION AND AGGRESSION IN ALZHEIMER'S DISEASE AS A DIAGNOSTIC ENTITY FOR DRUG DEVELOPMENT

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Introduction: Neuropsychiatric symptoms (NPS) are highly prevalent in Alzheimer 's disease (AD) and their profile and severity evolves with disease progression (Lyketsos et al. 2002; Steinberg et al. 2008). Agitation and aggression are among the most disruptive NPS since they are frequently associated with patient distress and increased morbidity (Gonzalez-Salvador, 1999). Agitation and aggression are therefore a leading cause of institutionalization, increased caregiver burden and health care costs in AD (Ballard et al. 2009; Soto et al. 2012). To date, effective and safe treatments for agitation and aggression remain elusive (Schneider et al. 2006), and are thus important targets for drug development. The definition of agitation and aggression as a distinct clinical entity is justified by the clinical evidence, and is critical to the identification of a homogeneous patient population for therapeutic trials.

Objective: To review recent clinical and nonclinical studies that suggest a common neurobiological basis for agitation/ aggression in AD, and to propose provisional clinical criteria to define this patient population for therapeutic trials.

Methods: Published epidemiological and imaging studies that evaluated AD patients with NPS, including agitation and aggression, were reviewed. Studies in transgenic animal models of AD that explored the pathophysiology of NPS, by correlating Amyloid pathology to aberrant behavior were also considered.

Results: Across most clinical studies, NPS frequency and severity were assessed using the Neuropsychiatric Inventory, which includes agitation/aggression as single domain (NPI, Cummings et al. 1994). Using the NPI, consistent clusters of NPS in AD have been reported in large epidemiological studies across various geographies and included patients with a wide range of AD severity (Aalten et al. 2008; Spalletta et al. 2010; Johnson et al. 2011). These studies consistently identified an affective, (depression) and a psychotic (delusions, hallucinations) cluster of symptoms, while apathy was usually a distinct cluster. A recent study which compared these clusters between Mild and Moderate AD subgroups (Lyketsos et al. Abstract, 2012), showed that agitation/aggression is associated with delusions in Mild AD and with depression in Moderate AD. In Amyloid transgenic PDAPP mice, spreading amyloid cortical pathology correlated with increasing degeneration of monoaminergic afferent terminals in frontal areas, and with increasing hyperactivity (Liu et al. 2011). This is consistent with clinical findings of metabolite abnormality in the anterior cingulate (elevated myo-inositol measured by MR spectroscopy), which correlated with NPS severity (Shinno et al. 2007). A recent FDG-PET imaging study in AD patients showed hypometabolism in frontal and anterior cingulate cortex which also correlated with the presence of agitation, but not with disinhibition symptoms (Sultzer et al. Abstract, 2011). In a diffusion tensor imaging study, AD patients showed abnormal white mater signal in anterior cingulate which correlated with severity of agitation (Tighe et al., Abstract, 2011).

Conclusion: NPS consistently occur in specific clusters suggesting that syndromes, such as agitation/aggression, may have distinct underlying neurobiology. The above described imaging studies suggest that agitation/aggression is usually associated with metabolic abnormalities and synaptic dysfunction in frontal cortical networks, which increases with disease progression. The elucidation of the common neurobiological basis of agitation/aggression in AD argues for its consideration as a distinct clinical entity. These patients can be clinically defined as those who fulfill the updated NIA-AA criteria for AD dementia (McKhann II critieria), with agitation symptoms present over several weeks, and who have no other reversible cause for agitation, such as inappropriate medication use or intercurrent infection. The severity of agitation/aggression can be assessed by the NPI

scale. The apparent association of agitation/aggression with depression in Moderate AD, and with delusions in Mild AD, raises the possibility that drugs may have differential effects in these 2 groups of patients. It may therefore be optimal to conduct separate studies in Mild and Moderate AD to enhance the homogeneity of the study population. There are currently several ongoing treatment trials (clinicaltrials.gov) that utilize these diagnostic criteria to define agitation/aggression in AD. Results from these studies may further validate the utility of these provisional criteria in drug development.

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