Revisiting criteria for psychosis in Alzheimer's disease and related dementias- towards better phenotypic classification and biomarker research

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_ABSTRACT_:

Psychotic symptoms are common in Alzheimer's disease (AD) and related neurodegenerative disorders and are associated with more rapid disease progression and increased mortality. It is unclear to what degree existing criteria are utilized in clinical research and practice. The International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuropsychiatric Symptoms (NPS) Professional Interest Area (PIA) psychosis subgroup reviewed existing criteria for psychosis in AD and related dementias. Through a series of in person and on-line meetings, a priority checklist was devised to capture features necessary for current research and clinical needs. PubMed, Medline and other relevant databases were searched for relevant criteria. Consensus identified 3 sets of criteria suitable for review including those of Jeste and Finkel, Lyketsos, and the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5). It was concluded that existing criteria could be augmented by including a more specific differentiation between delusions and hallucinations, address overlap with related conditions (agitation in particular), adding the possibility of symptoms emerging in the preclinical and prodromal phases, and building on developing research in disease biomarkers. We propose criteria, developed to improve phenotypic classification of psychosis in AD, and advance the research agenda in the field to improve epidemiological, biomarker and genetics research in the field. These criteria serve as a complement to the IPA criteria for psychosis in neurocognitive disorders.

INTRODUCTION:

Psychotic symptoms occur across a broad range of dementias including Alzheimer's disease (AD), Frontotemporal dementia (FTD), and Dementia with Lewy Bodies (DLB) [1], though they have been most extensively studied in AD. Studies suggest that one third to one half of patients with AD may experience psychotic symptoms during their dementia.[2] In spite of the frequency of these symptoms, it is unclear to what extent the existence of psychotic symptoms impacts clinical decision making.. Criteria have been established for the diagnosis of the syndrome of psychosis in AD, and include the Jeste and Finkel[3], Lyketsos [4], and DSM - 5 criteria [5] but these have not been validated extensively and their relative utility remains uncertain. Criteria are important given the impact of psychosis on clinical outcomes. For example, there is compelling literature to suggest that the presence of psychotic symptoms is associated with accelerated cognitive and functional decline through mechanisms that have yet to be delineated.[6] Further, psychotic symptoms are associated with greater distress for the patient and caregiver [7], poor general health [8], increased likelihood of institutionalization [7, 9], and increased mortality [9, 10]. Management of psychotic symptoms could mitigate cognitive and functional decline thereby reducing burden in caregivers [11]. Therefore, identifying and classifying psychotic symptoms has important implications for prognosis, disease management and the testing of new interventions.

Current criteria may benefit from addressing unresolved areas of controversy such as lack of clarity regarding sub categorization of psychotic symptoms (e.g. delusions, hallucinations), their differentiation from related neuropsychiatric symptoms (NPS) such as agitation, and issues with

exclusion of psychosis in the prodromal phase of cognitive disorders.  The first major question is whether psychotic symptoms  should be considered as one entity or should be broken down into delusions and hallucinations[12].  There is evidence for both approaches; epidemiological and genetic studies support pooling delusions and hallucinations, whereas neuroimaging studies and neuropathology support treating them as distinct categories [12]. Variability in clinical outcomes, symptom onset and divergent associations with different neurodegenerative pathologies also support separating delusions and hallucinations into separate categories.  Moreover, psychotic symptoms also frequently overlap with other NPS such as agitation and depression[13], making it difficult to discern which symptom is driving the observed adverse outcomes.

Another potential concern relates to how to differentiate psychotic symptoms as part of a dementia prodrome from psychotic symptoms in established or late onset psychotic disorders. The relationship between psychotic phenomena that appear in the context of neurodegenerative disease and those occurring in the context of idiopathic psychotic disorders has been the subject of recent research [14]. Although intuitively it may seem that psychotic phenomena occurring earlier or later in life may have a similar etiology given that they respond to similar pharmacological agents, this relationship is controversial and far from established. For example, in the CitAD study of citalopram for agitation in AD, the serotonergic antidepressant improved psychotic symptoms, an effect we would not expect in schizophrenia in early life, suggesting different mechanisms for the psychosis in AD in the presence of agitation [15], though further studies are required to confirm this finding. Population studies describe a two to five-fold risk of developing dementia in patients with early onset schizophrenia, after adjusting for medical comorbidities and general dementia risk factors [16, 17] although there is evidence that this

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dementia is not AD[18] and findings are far from consistent on this point[19, 20]. Late life

schizophrenia has an overlapping but distinct cognitive profile from AD and Late Life

Depression [21]. Bipolar disorder (BD) is the other major psychiatric illness that can be

associated with psychotic phenomena and cognitive deficits, and polygenic overlap with AD has

recently been shown [22]. Large population studies have demonstrated between a two and four-

fold increase in the odds of dementia in bipolar disorder patients [23]. The risk seems especially

high in patients with onset of BD after the age of 70. A number of them may be suffering a

prodromal dementia state [24, 25], similar to the profile of those with late onset depression [26].

All of the above data support the association of psychotic phenomena and some form of

cognitive impairment in two major psychiatric disorders, schizophrenia and bipolar disorder.

However, the absence of clear etiopathological links between these psychiatric disorders and

neurodegenerative disorders such as AD, advise against directly transposing traditional psychosis

diagnostic criteria designed for a neurodevelopmental disorder such as schizophrenia, onto later

life emergent disease.


These challenges are further complicated by the fact that late onset psychotic symptoms may be

early indicators of an emerging neurodegenerative disorder [14]. With the recent development

and validation of constructs such as Mild Behavioral Impairment (MBI) [27], in which psychotic

symptomatology is an independent domain, behavioral symptoms can be seen as an early

manifestation of a neurodegenerative disorder. Psychosis prior to the onset of cognitive decline

and functional impairment (i.e. diagnosis of dementia) is often considered as an exclusion under

the current criteria [14]. Further, data suggest that psychosis, when present in AD, may be

associated with lower rates of clinical misdiagnosis in pathologically confirmed AD, suggesting

psychosis may be a core feature of the disease process [28]. This finding is consistent with the historical accounts of AD, in that Alois Alzheimer's first published case presented with psychotic symptoms in advance of gross cognitive impairment [29].

Finally, the availability of disease biomarkers opens up new possibilities. Biomarkers may enable prediction of who will and will not develop a neurodegenerative disorder, thus allowing for the deployment of disease modifying treatments. The National Institute of Aging has recently developed a new research framework for diagnosing biological AD that takes into account the presence or absence of disease biomarkers [30]. To what extent the presence of psychosis may be associated with specific disease biomarkers is not yet clear, but the association of psychosis with accelerated cognitive decline [6] suggests that a search for disease biomarkers in patients with minimal cognitive decline expressing psychosis may be worthwhile as an avenue for early detection. Diagnostic criteria should have the ability to incorporate newly available biomarkers and should accommodate periodic revisions as new data emerge.

There have been several attempts to establish formalized criteria for psychosis in AD. Moreover, recent developments in the field, including constructs like Mild Behavioral Impairment [31] using neuropsychiatric symptoms to quantify dementia risk, and advances in imaging and biomarkers supporting earlier diagnosis in advance of overt dementia and functional decline, necessitate a review of the criteria. This paper presents a critical review of the existing criteria on psychosis in AD, to determine if these criteria reflect recent advances in the field. These AD-specific criteria are a complement to the provisional clinical criteria for dementia related

psychosis developed by the International Psychogeriatric Association which are pan-diagnostic from a neurocognitive disorder perspective, and have been developed to assist in detection and clinical trials, both pharmacologic and nonpharmacologic.  Specifically, we will review each set of criteria, highlighting their strengths and weaknesses, to inform the discussion on what is required for new criteria, to foster future research and discovery, and address knowledge gaps in the field.

*METHODS:*

The International Society to Advance Alzheimer's Research and Treatment (ISTAART) NPS Professional Interest Area (PIA) psychosis subgroup, a professional organization within the Alzheimer's Association, is a body of experts dedicated to advancing the study of psychosis in AD and related dementias. The NPS PIA held several meetings both on-line and in-person from October 2017 to the present, for the purpose of reviewing existing criteria for psychosis in AD. The group established by consensus an approach to reviewing published criteria for psychosis in AD.  Specifically, criteria had to: 1) pertain to AD or Mild Cognitive Impairment (MCI); 2) refer to specific symptoms such as delusions and hallucinations; and 3) have some description of frequency and/or severity. This approach was combined with an exhaustive Medline search including the following key words:  psychosis, dementia, criteria, Alzheimer's disease, delusions, and hallucinations, and supplemented by expert consensus.  All criteria were reviewed using a predetermined framework (see attached—figure 1) which asked questions such as "are delusions distinguished from hallucinations?", "are the criteria limited to AD?", "is there

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reference to prodromal conditions such as MCI?", "is there a link to biomarkers or cognitive decline?", and "are exclusionary pathologies considered?"

## RESULTS:

Three sets of criteria were identified using this method including those described by Jeste and Finkel [3], Lyketsos [4], and the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) [5] (see below).

## JESTE AND FINKEL CRITERIA

Estimates on the prevalence of psychosis in dementia have been hampered by lack of consensus on definition and limited availability of appropriate assessment methods [32]. Early efforts to address this case ascertainment dilemma included the Jeste and Finkel diagnostic criteria for Psychosis of AD and Related Dementias [33]. Those criteria were developed in DSM-IV[34] style, in order to address the gap between the diagnostic criteria for schizophrenia, as applied to older adults, and those for dementia, which at best offered additional coding if delusions were a prominent part of the illness[33]. Published in 2000, the Jeste and Finkel criteria [3] represented an important advance in the field, as operationalized criteria were essential for appropriately classifying psychosis in dementia, in order to improve prevalence estimates, and for case selection for treatment trials, as several new atypical antipsychotics were being tested in FDA-approved randomized controlled trials for examining efficacy for controlling psychosis and agitation in older people with dementia. Importantly hallucinations and delusions were both included, the presence of either being adequate to trigger the diagnosis, supported by literature

indicating that both hallucinations and delusions are important in understanding psychosis in dementia[35]. Those criteria excluded psychotic symptoms that predated dementia, in order to clearly demarcate psychosis in dementia from schizophrenia, delusional disorders, and psychotic mood disorders in older adults. As is standard with DSM criteria, other exclusions were general medical conditions, or psychotic symptoms in the context of delirium. Clinical trial data were used to validate the Jeste and Finkel criteria [3]. Schneider reanalyzed data from a risperidone clinical trial for agitation in dementia, demonstrating that 75% of participants met the psychosis in dementia criteria [36]. This validation supported psychosis in dementia as a distinct clinical syndrome, with demographic features distinct from dementia without psychosis.

The Jeste and Finkel criteria [3] were immediately helpful, influential in Food and Drug Administration (FDA) deliberations[37] and remain in use today, especially for clinical trial inclusion/exclusion. However, over time, issues have arisen suggesting a need for modification. This is similar to the diagnostic criteria for most psychiatric and medical disorders. As science advances and more research is conducted resulting in new data and insights, it is inevitable that the criteria change with time. Indeed, new versions of the DSM as well as ICD is published every few years. In terms of the Jeste-Finkel criteria, these are somewhat vague with respect to severity and duration. While the criteria are explicit for duration of symptoms, (at least intermittently, for 1 month or longer), the severity requirement is simply that of "some disruption in patients' and/or others' functioning." In the context of a clinical diagnosis of dementia, which necessitates functional impairment, attributing a proportion of this to psychosis can be challenging. Even more importantly, however, is the exclusion of pre-existing psychotic symptoms in advance of a formal dementia diagnosis. While intended to separate psychosis in

dementia from other psychotic conditions, there are unintended consequences of this demarcation. Clinicians are well aware that there is some imprecision in the cutoff for functional impairment between MCI and dementia, and this imprecision contributes to case ascertainment error in the psychosis of dementia criteria as described by Jeste and Finkel [3]. Evidence suggests that psychosis can precede a formal dementia diagnosis and be manifest during the MCI phase [38-41]. For example, one new study demonstrates that in those with MCI and delusions, the hazard ratio for progression to AD is 13.99 over a 4-year follow up, emphasizing the significance of psychosis in pre-dementia conditions [42]. To exclude those with hallucinations or delusions in the MCI phase restricts the sample, and undermines the ability to link psychosis of the early phases of AD. This dilemma underscores some challenges in the DSM approach, which is mostly silent on natural history and age of onset of illness, features which in this case are salient in distinguishing primary psychotic disorders from psychotic symptoms as part of a neurodegenerative illness[31]. Finally, these criteria were developed before biomarkers became readily available, and were not part of clinical care at the time. Technological advances have raised issues relevant to development of criteria. For example, amyloid positive individuals with MCI and new delusions of theft may have been diagnosed with a delusional disorder under older criteria, but under the new NIA-AA Research Framework criteria for dementia[30], these individuals would be diagnosed as having prodromal AD.., Thus, with the field moving towards earlier detection, prevention strategies, and including biomarkers, there is need for the criteria for psychosis in AD to be adjusted to these new circumstances.


*LYKETSOS CRITERIA*

Lyketsos, Breitner and Rabins (2001)[4] suggested that the Jeste criteria [3] were not empirically based and proposed an alternative approach. They did not begin by describing psychosis in dementia or initially establishing diagnostic criteria. Rather, based on their analysis of the participants in the Cache County study of memory and aging who had complete Neuropsychiatric Inventory (NPI) data, they explored the relationships among the various neuropsychiatric symptoms. These investigators observed that AD patients fall into three natural groupings of neuropsychiatric symptoms based on identification of patterns of symptoms that co-occurred in individual patients: 1) those who were unaffected or minimally affected, almost always having only one symptom; 2) those who have a complex polysymptomatic neuropsychiatric disturbance that is predominantly *affective*; and 3) those who have a complex polysymptomatic neuropsychiatric disturbance that is predominantly *psychotic* [43]. Notably, almost half the participants with delusions were assigned to the affective and not the psychotic group. Lyketsos et al proposed that the latter two clusters may be thought of as distinct syndromes and proposed criteria to identify patients in those syndromes by emphasizing what symptoms (i.e., affective vs. psychotic) were most prominent.

Like the Jeste and Finkel criteria, the criteria for 'Alzheimer-associated psychotic disorder' do not distinguish between delusions and hallucinations and require that the symptoms be associated with disruptions of the patient's life or lives of others. They differ by requiring another neuropsychiatric symptom to be present, such as aberrant motor behavior, although no level of severity for these is indicated. A major strength of these criteria is the distinction between affective and psychotic syndromes, an important feature for incorporation into future criteria, and the recognition that an affective, and _not_ psychotic, disturbance can be present even though there

are delusions if affective symptoms predominate. While the criteria may represent partial improvement in measurement over the Jeste and Finkel criteria [3], there is no reference to prodromal states or preclinical symptoms, beyond the  arbitrarily defined  maximum 2 year time frame between the onset of psychosis and the onset of cognitive symptoms. Further, the empirical criteria were informed by psychotic symptoms in patients from the Cache County study, captured via the NPI. However, evidence suggests that instruments such as the NPI, Neurobehavioral Rating Scale, and BEHAVE-AD can capture psychosis in AD differently, thus introducing measurement error into the empirical classification [44]. Furthermore, it is possible that someone could be "minimally symptomatic" but could have a single psychotic feature (9% of their minimally symptomatic subgroup had delusions), but the criteria would not classify that individual as having psychosis (because an additional neuropsychiatric symptom might not be present). Thus, while the criteria were a useful advance, further refinement is needed.

*DSM-5*

DSM-5 criteria for dementia and related behavioral symptoms were developed after extensive consultation with a task force composed of working groups made up of 160 clinicians and researchers around the world.  Final criteria were subsequently approved by a scientific committee appointed by the American Psychiatric Association board of trustees.  As such, it was not subject to clinical trial validation as per some of the other criteria.  DSM-5 [5] acknowledges that psychotic symptoms (including delusions and hallucinations) may occur in the context of a Major Neurocognitive Disorder such as AD, DLB, FTD.  The complete nomenclature is "Major Neurocognitive Disorder due to AD with behavioral disturbance (psychosis)".  DSM-5 does make a distinction between "mild" and "major" neurocognitive disorder so it is possible that psychosis may be present even in patients with mild neurocognitive disorder.  When considering

other aspects, there is no distinction between delusions and hallucinations—rather, they are

considered together as psychosis.  There is diagnostic specificity to the degree that the symptoms

are framed in the context of a specific neurocognitive disorder (i.e. Major Neurocognitive

disorder due to AD with behavioral disturbance (psychosis)).  There is no reference to *frequency,*

*severity or duration* of behavioral symptoms, so it is essentially left to the discretion of the

clinician to determine whether or not the observed symptoms meet the clinical threshold for

psychosis in AD. There may be reference to other NPS if they exist (ie. Major Neurocognitive

Disorder with behavioral disturbance (depression, psychosis)).  There is no reference to cognitive

symptoms but there is a reference to the standard DSM exclusionary criteria that symptoms are

not better explained by another disorder.  There is no reference to preclinical disease or disease

biomarkers, including cerebrospinal fluid (CSF) measures or positron emission tomography

(PET) imaging, though there is a clear reference to prodromal conditions (ie. Mild

Neurocognitive Disorder with behavioral disturbance).  In summary, the criteria include

reference to specific neurodegenerative diagnoses, account for co-existent NPS, and make

reference to prodromal conditions.  However, psychotic symptoms are not identified, there is no

reference to disease biomarkers, and measures of frequency, duration or severity are absent,

which were felt to be important factors for clinical and research applications


*DISCUSSION:*

*PREVALENCE AND PHENOMENOLOGY*

Discrepancies in prevalence estimates of psychosis in AD and related dementias provide further

impetus for establishing agreed upon criteria.  In patients with dementia due to AD the

prevalence of psychosis is estimated to range between 10% - 74%, with a median prevalence of 41% [2]. Delusions are known to be the most common presentation of psychosis in AD with prevalence estimates ranging from 15- 30% in most studies, though some studies report a higher prevalence [2, 45-47]. The reported prevalence rates of hallucinations range from 5-15%, again with some reports of higher prevalence [2, 45-48]. Importantly, delusions and hallucinations frequently co-occur with other disturbances such as depression and agitation which must be accounted for in future criteria.  This broad range of prevalence resulted from the use of a variety of case ascertainment methods in a variety of settings. However, the majority of studies used a combination of semi-structured interviews and formalized rating scales.  Nonetheless, the need for psychosis in dementia criteria was highlighted by the broad spectrum of prevalence estimates and frequencies.


Psychosis of AD may be differentiated in mainly two subtypes: the *paranoid subtype*, which includes persecutory delusions, and the *misidentification subtype*, which includes misidentification phenomena and hallucinations [49].  Misidentification delusions may reflect cognitive impairment according to some authorities rather than a delusion per se.  Cook and others [49] performed a cross-sectional factor and cluster analysis using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) behavior rating scale in 188 patients with probable and possible AD. The authors found that patients with a Clinical Dementia Rating Scale (CDR) sum of boxes with severity of dementia >2 had the greatest risk of developing psychosis and 42% of the population had only one psychotic symptom whereas 11% had > 6. Using exploratory factor and cluster analyses, these authors found that there were mainly two principal sub-types of psychosis in AD that were stable according to severity: 1) The *auditory*

*and visual hallucinations (though it is understood that occasionally patients can manifest olfactory and tactile hallucinations)*, combined with misidentification of people; and 2) those with *persecutory delusions*. These groups were independent of each other on both factor and cluster analyses. These analyses supported the need for separate categories of psychosis in AD.; There is a high degree of comorbidity between delusions and hallucinations in AD but evidence from longitudinal studies indicates that around 10-20% of people experience hallucinations without delusions and that the two symptoms are associated with different clinical outcomes [7, 50], suggesting the presence of two distinct clinical phenotypes.  Psychotic symptoms are less well characterized in patients with vascular dementia and other dementia etiologies as compared to AD with the possible exception of PD, possibly due to the absence of well-defined patient cohorts.


## TRANS-DIAGNOSTIC ISSUES

The appearance of psychotic symptoms with aging may result in a broad differential diagnosis. Establishing unified and agreed upon criteria may assist in distinguishing psychosis resulting from late onset primary psychotic disorders versus psychosis secondary to neurodegeneration. Based on clinical symptoms alone, it might be particularly difficult to distinguish between AD, DLB and very late onset schizophrenia-like psychoses (VLOSLP)[51], though some studies have demonstrated phenomenological differences between psychosis in dementia versus primary psychosis suggesting a unique neuropathogenesis[52].

*Differential Diagnosis in Dementia:*

The criteria currently applied for psychosis of AD as described above include a diagnosis of AD according to established criteria.  These criteria do not, however, with the possible exception of

DSM-5, consider the possibility that psychosis symptoms may manifest in the phase of MCI due to AD, and none consider symptoms that are in the pre-clinical phase preceding cognitive impairment as established for MBI [27]. The AD neuropathological process is known to start many years before the appearance of cognitive symptoms and it has recently been demonstrated that the presence of neuritic plaques is associated with a higher risk of psychosis in subjects without cognitive impairment [53]. Detecting specific phenomenological characteristics of psychosis of AD, even before the onset of cognitive decline, may help to define criteria specific to the AD psychotic phenotype.

Visual hallucinations have not specifically been described in the criteria yet have distinct phenomenological characteristics across different types of dementia. Visual hallucinations in AD usually consist of familiar or unfamiliar people and objects [54]. In PD dementia and DLB, psychotic symptoms are distinct and well characterized: illusions and pareidolia (misinterpreting a stimulus), passage hallucinations, sensation of presence and vivid stereotyped visual hallucinations [55, 56]. They appear in premorbid stages, even prior to cognitive impairment and are associated with neuroimaging and neuropathological changes in regions associated with the integration of visual stimuli[57]. In frontotemporal dementia, psychotic symptoms are less frequent (10%) except in some genetic variants like C9Orf72 where 21-56% of patients present with bizarre somatic delusions and multimodal hallucinations[58].In this disease, there is a psychosis phenotype since probands of C9ORF72 FTD are more at risk for schizophrenia or late-onset schizophrenia[59]. Late onset psychotic disorders have also been associated with other tauopathies like argyrophilic grain disease[60].

*Differential Diagnosis in Psychotic Disorders:*

Persecutory delusions importantly are also common in psychiatric disorders such as schizophrenia or delusional disorder, making the distinction from late onset psychotic disorders challenging. However, in such disorders delusions may be more bizarre and the cognitive decline, if present, is not progressive. In AD, persecutory delusions when present tend to have a less bizarre quality [61]. When present in MCI and early phase AD, misidentification delusions are associated with more rapid cognitive decline [62]. Misidentifications in AD, however, generally occur later in the disease course compared to persecutory ones[35], are more common in AD than primary psychiatric disorders, are associated with greater hippocampal pathology,[63] and might reflect abnormalities of memory or other cognitive functions. While these subtle distinctions are generally known to clinicians, in particular the distinction between misidentification delusions and delusions of theft with dementia, they have not to date been incorporated into any formalized criteria.

In other psychiatric disorders, although visual hallucinations are less frequent than auditory hallucinations, visual hallucinations are reported to bear the perceptual properties of externally-originating stimuli, to be vivid, and often to be associated with auditory hallucinations and delusions related to the content of the hallucinations. The content, which is frightening, can consist of visions of angels, the devil and saints [64]. In LOS, or VLOS, paranoid or partition

delusions with visual, olfactory and tactile hallucinations are more often present, and have not been associated with AD biomarkers[65, 66]. While the paranoid subtype of delusion in AD includes only delusions with persecutory contents, the misidentification subtype of delusion in AD includes delusions of misidentification and hallucinations[67]. It might be important to distinguish disorders of thought (delusion) from disorders of perception (hallucination), both of which are traditionally included under the rubric of the work "psychosis".

*Trajectory of psychotic symptoms in dementia:*

The natural history of psychotic symptoms in dementia is an important dimension of an emerging definition. Typically, symptoms of psychosis vary in people with AD. Psychotic symptoms once present commonly persist for at least a year in two thirds of people [68]. A follow-up study reported a 2-year persistence of delusions and hallucinations in 43% and 73% of people, respectively[69]. However, this apparent persistence may conceal an underlying pattern of remission and recurrence. For example, in 125 people with AD followed monthly for 12 months, 30 (54%) had resolution of symptoms over 3 months without specific treatment, but among these, eight (27%) had a subsequent relapse in the first year[70]. In a related study, Devanand and colleagues followed 235 patients with early AD using the Columbia University Scale for Psychopathology in AD for 5 years and discovered that psychotic symptoms were moderately persistent relative to agitation which was very persistent and mood symptoms which were mildly persistent [71]. By comparison, in DLB, visual hallucinations are more persistent, with 80% of individuals who have these symptoms continuing to experience them after 12 months [72]. Similarly, in late onset psychosis without dementia the delusional beliefs are very persistent, with periods of resolution unlikely without antipsychotic therapy; treatment response is more likely to reduce severity rather than to achieve resolution.

The temporal onset of psychosis during the disease course should be considered in a definition. Persecutory delusions may manifest themselves early in the disease course whereas misidentifications generally emerge later as a part of a continuum [73]. Psychotic symptoms have been found to be less well documented in the later stages of dementia, as patients may become unable to express their delusions or hallucinations [33]. At the other end of the spectrum, psychotic symptoms of lesser severity may also occur in the absence of cognitive deficits in elderly people and may represent a prodromal phase of AD or other neurodegenerative dementia. It would be at least theoretically relevant to include differences in temporal onset of psychotic symptoms related to disease phase in the criteria for psychosis in AD.

*NEUROBIOLOGICAL STUDIES:*

*Imaging Markers:*

None of the criteria discussed above make reference to disease-specific or psychosis-specific biomarkers. However, several studies have found abnormalities of neuroimaging biomarkers for dementia-related psychosis, including reduced gray matter volume on T1 weighted structural magnetic resonance imaging (MRI) [74-77], decreased cerebral blood flow on single photon emission computed tomography (SPECT) [78-80], and decreased metabolism on FDG-PET[81]. Several qualitative reviews have summarized these findings, noting significant heterogeneity, although in general findings have implicated the right frontal cortex [82-84]. A recent study has suggested that delusional AD patients may undergo more rapid grey matter volume loss in the temporal lobes prior to manifesting delusions and this may be preceded by an increase in grey matter in these same brain regions, raising the possibility of neuroplastic mechanisms [85]. The assumption that neuropsychiatric symptoms in dementia should reproducibly localize to a

specific brain location has been challenging, and it has been proposed that lesions associated with delusions are distributed in different parts of the same functionally connected brain network [86]. Neurodegeneration in several different parts of the same functionally connected brain network, including the right frontal cortex, can lead to psychosis. Network localization may offer a method for accounting for the heterogeneity in neuroimaging biomarkers of psychosis among different patients.

*Molecular Imaging Studies:*

Molecular imaging has been used to investigate changes to neurotransmitter systems in patients with dementia-related psychosis. A new medication targeting the serotonin 5HT-2A receptor, pimavanserin, has recently been approved for the treatment of psychosis in PD [87]. Parkinson's disease patients with hallucinations have increased serotonin 5HT-2A receptor binding in the ventral visual stream compared with PD patients without psychosis using the PET radioligand [$F^{18}$] setoperone [88]. Studies have shown decreased serotonin 5HT-2A receptors in AD but have not assessed the relationship of this to neuropsychiatric symptoms [89]. Parkinson's patients who go on to develop hallucinations have decreased dopamine transport (DAT) activity in the ventral striatum at baseline.[90]. One prior study found that dopamine D2/3 receptor binding relates to anti-psychotic efficacy in AD [91]. These preliminary studies suggest that neurotransmitter receptor imaging may be a useful approach to individualizing treatment approaches to psychosis in AD and to understanding the relationship of these symptoms with underlying dementia etiologies.

*Genetic Studies:*

Genetic studies suggest some overlap between AD with psychosis and schizophrenia [92, 93] and recent evidence has shown that the association between AD with psychosis and genetic liability for schizophrenia is strongest when analysis is restricted to individuals with delusions [94] suggesting common mechanisms of delusions as a central feature of psychosis across the lifespan. However, while potentially informative for refining clinical classifications, given the small amount of variance explained, this approach will not be useful for clinical prediction. Genetic studies suggest that psychosis in AD may be a partially heritable condition, with an estimated odds ratio of 3.2 among siblings presenting with dementia-related psychosis [95], a finding that has been replicated in multiple cohort studies [96]. It does not appear that APO-E4 mediates psychotic symptoms in AD patients[97], though more recent studies focused on analyses of post-mortem suggests a possible association[51].

*Biomarker Studies:*

There are limited studies investigating the relationship between in vivo neuropathological biomarkers and psychosis symptoms in dementia. Elevated total CSF tau levels have been reported in AD patients with psychosis vs. AD patients without psychosis, although there were no differences in amyloid beta protein levels or phosphorylated tau levels [98]. Neuropathological studies additionally seem to support a role for phosphorylated tau in AD patients with psychosis, thus suggesting it may serve as a useful biomarker in future studies.[99] CSF biomarkers of amyloid and tau may also be useful in differentiating psychosis related to AD versus  psychosis related to a psychiatric condition in older adults [100, 101]. No prior studies have used amyloid or tau PET tracers to investigate regionally specific neuropathological markers of psychosis in dementia, though evidence linking psychosis in AD to phosphorylated tau suggests this may be a useful approach[98, 99]. There is a suggested link of psychosis with

vascular and Lewy body pathology based on post-mortem data though replication with in vivo samples is required[102]. In summary, preliminary data suggest that biomarkers of psychosis in AD may exist, and that pTau is a promising target for study. Future studies examining psychosis in AD should incorporate measures of tau as well as other biomarkers. To date there is no definitive biomarker based on existing evidence, thus limiting the utility of a biomarker based approach. What may be more helpful would be an approach where biomarkers are evaluated in patients who present with psychotic symptoms in late life, to further ascertain whether symptoms are secondary to a neurodegenerative disorder versus a primary psychiatric illness.

*Future Directions:*

Neurobiological studies to date suggest that psychosis in AD and related dementias may be associated with distinct imaging, genetic, neuropathological and CSF biomarkers. Notably, most of the neurobiological studies to date have focused on patients with established dementia given psychotic symptoms are much more rare in prodromal states and may be confused with primary psychiatric pathology. Further study of psychosis associated biomarkers in patients with prodromal conditions is clearly required.

### SUMMARY AND NEXT STEPS:

We have reviewed the existing criteria for dementia related psychosis, including those published by Jeste and Finkel[3], Lyketsos [4], and the DSM-5 working group [5]. While all of these criteria have specific strengths and have substantially furthered our understanding of the relationship between psychosis and neurodegeneration, there are several issues that limit their utility. These limitations include: 1) the lack of symptom specificity, particularly in relation to psychotic symptoms observed in other primary psychiatric illnesses; 2) the inconsistent

separation of hallucinations and delusions and differentiation of persecutory from misidentification delusions; 3) not framing psychotic symptoms in a natural history timeline thus underappreciating age of illness onset/phase of life, dementia stage, or symptom persistence and fluctuations; 4) not accounting for co-occurrent depression or agitation which might be the primary symptoms of the disturbance (with psychotic symptoms being secondary); 5) not incorporating prodromal or preclinical states; 6) and the absence of disease biomarkers in the criteria themselves (i.e. for patients with AD/MCI, are they biomarker positive)). Moreover, with the exception of the Jeste and Finkel criteria [3], it is not clear to what extent these criteria have been employed in clinical drug trials. Future criteria should incorporate specific symptoms that are indicative of dementia related psychosis and allow for the possibility that psychosis may be an early symptom of an emerging neurocognitive disorder. These changes will result in more specific prevalence estimates for AD related psychosis, assist with research into the underlying disease mechanisms and provide a means of measuring the effectiveness of novel drug treatments where appropriate. We propose new research criteria that define a *psychotic phenotype of AD*, distinct from affective or agitation phenotypes of AD, which recognizes symptoms may precede the onset of clinical dementia and which address the gaps identified above. These criteria improve phenotypic classification of psychosis in AD, and advance the research agenda in the field to improve epidemiological, biomarker and genetics research in the field. These criteria serve as a complement to the provisional clinical criteria psychosis related to neurocognitive disorders recently developed by the International Psychogeriatric Association, which are pan-diagnostic from a neurocognitive disorder perspective, and have been developed with input from clinicians and caregivers to assist in detection, treatment and for use in clinical

trials of both nonpharmacological and pharmacological interventions to assist in the development

of drugs and other interventions to reduce symptoms and distress.

We propose our criteria in Table 1. The recommended framework incorporates the strengths of

current criteria, addresses the weaknesses identified in this review, and incorporates recent

advances in our understanding of psychosis in AD and related dementias. These criteria

complement the IPA criteria, in that they formally include preclinical and prodromal AD.  In

addition these criteria focus on biomarkers, and foster genetic research via clear exclusion

criteria for case definitions. This foundational work can inform future research and further

exploration of psychosis in AD and related dementias by capturing salient illness features that

can be missed in current nosological approaches.

## *TABLE 1. DEMENTIA-RELATED PSYCHOSIS FRAMEWORK:*

### *1.   NEUROCOGNITIVE DISORDER OR NEURODEGENERATIVE DISEASE*

Diagnosed by established criteria (eg. National Institute on Aging (NIA)-Alzheimer's

Association (AA) Research Diagnostic Framework for AD; NIA-AA diagnosis of Alzheimer's

Dementia or MCI due to AD, DSM, International Working Group criteria for prodromal AD,

etc.) Neurodegenerative disease may manifest with *either* clinical, neuroimaging, or biomarker

findings.

    a.   Clinical –progressive deterioration of behaviour or cognition by observation or

       history (as provided by a knowledgeable informant)

    b.   Neuroimaging findings suggesting neurodegeneration (eg. MRI, PET)

     c.    Fluid biomarker positivity for relevant markers (eg. Amyloid, Tau)

## 2. *STAGE OF NEURODEGENERATIVE DISEASE:*

     a.    Preclinical disease (eg. normal cognition, subjective cognitive decline, MBI-preclinical)

     b.    Prodromal disease (MCI, MBI-prodromal)

     c.    Dementia (i) mild; ii) moderate; or iii) severe

## 3. *PSYCHOTIC SYMPTOMS – PERSISTING, AT LEAST INTERMITTENTLY, FOR 4 WEEKS EITHER I) FLUCTUATING OR; II) PERSISTENT*

     a.    Delusions

          i.    persecutory or

          ii.    misidentification

          iii    other

     b.    Hallucinations

          i.    Code sensory modality (auditory, visual, etc.)

## 4. *EXCLUSION CRITERIA:*

     a.    Psychotic symptoms better accounted for by non-neurodegenerative nervous system disease or medical conditions or Delirium

     b.    Psychotic symptoms better accounted for by a present primary psychiatric disorder

c.   Psychotic symptoms better accounted for by an affective or agitation

neuropsychiatric syndrome

d.   Past history of psychotic symptoms

*FIGURE 1 PSYCHOSIS CRITERIA CHECKLIST*

1. How is psychosis defined (are delusions distinguished from hallucinations, are there subtypes of hallucinations/ illusions).
2. Are the symptoms specific to AD or do they extend to other dementia subtypes?
3. Is there a measure of frequency?
4. Is there a measure of severity?
5. Is there a measure of duration?
6. Is there reference to other neuropsychiatric symptoms?
7. Is there reference to other cognitive symptoms?
8. Does the definition encompass exclusionary criteria?
9. Is there a reference to disease biomarkers?
10. Is there a reference to prodromal states (MCI/MBI)?

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