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Psychosis in Alzheimer's Disease: a Review of Recent Research Findings

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Abstract
Purpose of Review The purpose of this review paper is to examine the latest research findings in psychosis in Alzheimer's disease (AD) and to reconcile conflicting perspectives regarding whether psychotic symptoms should be considered individually (as delusions/hallucinations) or as a whole.
Recent Findings AD patients with psychosis demonstrate accelerated onset of cognitive decline prior to the onset of psychosis and are at increased risk of conversion to AD, emphasizing the importance of early detection. Data from neurobiological studies, including imaging and neuropathological studies, suggest there may be merit in breaking down symptoms into delusions and hallucinations while epidemiologic and genetic studies suggest the opposite conclusion.
Summary It is conceivable based on the research to date that genetic factors interact with neurodegeneration to create a vulnerability to the development of psychosis in AD. Future studies are required to clarify the specific mechanisms that lead to individual symptoms (delusions/hallucinations).

Keywords Psychosis · Delusions · Hallucinations · Dementia · Alzheimer's disease

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Introduction

Psychotic symptoms are estimated to occur in approximately 50 % of patients with Alzheimer's disease (AD) over the disease course [1] and are even more common in related dementias such as dementia with Lewy bodies (DLB) where they are a defining feature [2]. Moreover, recent research suggests their presence may be associated with dramatically worse outcomes relative to patients without psychosis, in terms of rates of conversion to AD, mortality, caregiver burden, and accelerated cognitive decline [3••]. In addition, existing psychoactive treatments have shown limited benefit [4] and moreover may be associated with increased mortality [5]. Thus, it is imperative that we increase our understanding of the underlying disease mechanisms that are associated with these symptoms.

One of the barriers to understanding psychosis relates to its phenomenology, specifically its clinical presentation. Confusion around phenomenology has resulted in researchers pursuing different paths, with some arguing that delusions and hallucinations should be studied separately and others arguing they should be considered together. This has resulted in a similar split in research findings, with some studies, mainly imaging studies, focusing on delusions or hallucinations

exclusively and other studies, genetic and epidemiological, focusing on psychosis as a single construct.

Whether symptoms are considered together or individually, there may be arguments for both approaches. In AD, research to date has suggested that delusions occur much earlier in the disease trajectory compared to hallucinations [6]. In addition, clinical outcomes differ with hallucinations largely being associated with worse outcomes relative to delusions [7••, 8]. Moreover, imaging studies, both cross-sectional and longitudinal, have identified patterns of gray matter loss among patients with delusions relative to controls [9••, 10••]. On the other hand, the majority of genetic and neuropathologic studies have looked at patients with combined symptoms. Proponents of this approach point to the common overlap between psychotic symptoms (delusions and hallucinations) and the impact of isolating symptoms on sample size. Using combined symptoms to define psychosis, family studies have established that psychosis in AD is familial, with an estimated heritability of 61 % [11–14, 15••]. Similarly, neuropathologic and biomarker studies have found consistent associations of psychosis with quantitative increases in tau pathology [16••, 17, 18••, 19, 20••]. Nevertheless, it is possible that these approaches fail to detect more specific associations of genes or pathologies with subsets of psychotic symptoms.

Complicating matters further, psychosis occurs in a broad spectrum of other psychiatric disorders, including schizophrenia, delusional disorder, and bipolar disorder. The question that then arises is whether or not there is a common pathophysiology that may explain psychosis in multiple disease states. Advances in neuropsychiatry in the last decade suggest that perhaps there may be a unifying explanation for psychosis. The discovery of functional networks in the brain, which have been found to mediate a number of psychiatric symptoms [21] including psychosis, has revolutionized our understanding of these symptoms. The purpose of this review paper is to examine the phenomenology, clinical correlates, and epidemiology of psychosis in AD. The authors reconcile conflicting perspectives regarding whether psychotic symptoms should be considered individually or as whole and the implications this has for our field and discuss these symptoms in the broader context of recent discoveries.

Phenomenology

The clinical presentation of psychotic symptoms has bolstered the argument that delusions and hallucinations should be considered separately, given differences in terms of both their clinical presentation and where they present in terms of the disease trajectory. However, the overlap between symptoms conversely leads to the opposite conclusion. In terms of phenomenology, psychotic symptoms in dementia tend to be more concrete and predictable [22] when compared to psychotic symptoms in other disorders such as schizophrenia or bipolar disorder. There are two main categories of delusions: persecutory (such as the delusion of theft) or misidentification (such as a persistent belief that someone well known to the patient is someone else) [23], although misidentification delusions may be confused with confabulation and are seldom observed in primary psychiatric disorders. Other common delusions include phantom boarders (the belief that the house is occupied by strangers), the mirror delusion (belief that someone in the mirror is a different person), and capgras syndrome (the belief that a person is not who they appear to be but rather an imitation) [22]. Persecutory delusions of abandonment and infidelity may also be observed [22]. Relative to patients with schizophrenia, delusions in AD are less likely to be bizarre in quality [24], meaning they are more likely to be in the realm of everyday possibility (e.g., theft of property by a neighbor). Studies comparing patients with persecutory versus misidentification delusions have consistently shown greater impairment in the misidentification subgroup, suggesting potentially a separate neuropathology [25, 26].

Psychotic symptoms in some cases may be hard to differentiate from more cognitively based symptoms such as disorientation or confabulation. Fluctuation may help to discriminate these symptoms as cognitive symptoms may be more likely to fluctuate while psychotic symptoms, and specifically delusions, are more likely to be fixed. Where symptoms occur in the disease trajectory differs considerably. Delusions in AD usually occur before the onset of hallucinations, which are usually visual in nature and are associated with more advanced disease [24, 27]. One potential explanation for this observation could relate to the interaction of cognitive impairment with psychosis. It is possible that delusions and hallucinations are in fact the same symptom but are expressed differently depending on the degree of cognitive impairment. Patients with more advanced cognitive decline may be more likely to be diagnosed with hallucinations as they may no longer have the cognitive ability to express delusions. Conversely, in certain forms of dementia, hallucinations may occur earlier and be a presenting feature. One example are the hallucinations observed in patients with DLB, which occur early in the course of the disease, usually within the first 2 to 3 years of illness, are often very vivid, and are associated with sleep disturbance and vivid nightmares [28].

Clinical Correlates

Recent findings suggest on balance that the presence of psychosis in dementia is universally associated with adverse outcomes and a more malignant disease course, adding support to the argument that psychosis in AD represents a distinct

subgroup of patients [3••]. When compared to patients without psychosis, patients with AD and psychosis have worse outcomes in terms of functional impairment, disease progression, increased cognitive impairment, increased behavioral symptoms, premature placement, mortality, and caregiver burden [3••]. The vast majority of studies looking at clinical correlates have combined delusions and hallucinations together, though recent studies suggest they may have slightly different associations.

Multiple studies suggest psychosis is associated with accelerated cognitive decline [14, 29–33, 34••, 35••]. Ropacki and Jeste [1] examined cognitive decline in 55 studies, observing a relationship between psychosis and increased cognitive impairment in 20 of 30 studies. Moreover, they determined that the observed increased cognitive decline was not attributable to other confounding factors such as age or level of education. Emanuel et al. [30] examined rates of cognitive decline in early AD among patients destined to develop psychosis and found more rapid cognitive decline, even in the earliest stages of the disease process. As well, the emergence of psychosis in patients with preclinical disease or MCI may be associated with increased risk of conversion to AD, similar to other NPS such as depression [36••]. According to Peters et al. [36••] who examined the progression of Alzheimer's disease in 335 participants in Cache County, the presence of psychosis was associated with not only more rapid progression of dementia but also increased mortality. Moreover, non-demented patients presenting with late-onset psychosis, including transient psychosis, may be at significantly increased risk for conversion to dementia based on a recent study [37]. Studies combined suggest older patients presenting with psychotic symptoms with or without associated cognitive decline should be monitored carefully for conversion to dementia. The association between psychosis and specific cognitive deficits has been less clear, though the majority of studies suggest a link with frontal-executive impairment which manifests itself as deficits in working memory [38••]. This may be mediated by damage to frontal circuits which has been shown extensively in psychotic patients, even in the absence of dementia [39].

It is also conceivable that patients with different psychotic symptoms may have different clinical outcomes, providing rational for considering symptoms separately. For example, Christie et al. [8] established that AD patients with delusions and hallucinations relative to patients just with delusions had worse clinical outcomes in terms of longer duration of illness, lower Mini-Mental State Exam (MMSE) scores, and higher Clinical Dementia Rating (CDR) scores. Fischer et al. [7••] established similar findings, noting that AD patients with delusions had much better outcomes relative to patients with hallucinations, even when compared to patients without psychosis. D'Onofrio et al. [40] looked at AD patients with delusions versus those without and found on the contrary increased cognitive decline, increased depressive symptoms, and excess NPS. Thus, more research is required to clarify the clinical outcomes associated with individual psychotic symptoms.

Epidemiology

Psychotic symptoms are frequently a presenting symptom of AD and are estimated to occur in approximately one third to one half of patients [1]. The vast majority of epidemiologic studies to date neglected to separate delusions from hallucinations when examining these symptoms, due perhaps to the overlap in their presentation and confusion around their phenomenology. More recently, we estimated the incidence in a large research clinic cohort as ~10 % annually [41••]. The point prevalence has been estimated to be somewhat lower, approximately 25 % [42]. The Cache County study, which looked at a large cohort of patients in a US county and followed them prospectively over time, established that 50.9 % of the sample had at least one NPS, with 18.1 % showing symptoms of psychosis [36••]. In some subtypes of dementia, such as dementia with Lewy bodies or Parkinson's disease dementia (PDD), psychosis may even be more common, occurring in over 50 % of patients [2, 43, 44]. In other neurodegenerative conditions, such as frontal-temporal dementia (FTD), psychosis is surprisingly rare [45], with a recent study demonstrating psychosis in only 2.3 % of patients, suggesting that lack of involvement of temporal limbic regions may explain this. However, a more recent study has suggested that the rates can be as high as 32 % in patients with FTD [46••]. Psychotic symptoms have been shown to be particularly common among patients with *C9orf72* expansions, who clinically may present with a combination of FTD and/or motor neuron disease [47••, 48].

A compelling argument for considering delusions and hallucinations in combination relates to the outcome of factor analysis studies, which have demonstrated psychosis to be a valid and reliable neuropsychiatric symptom (NPS) cluster, both within AD [49, 50] and more recently in mild cognitive impairment (MCI) [51••], along with other NPS such as depression and agitation. Moreover, psychosis has been identified as a valid and reliable symptom cluster, across multiple dementia subtypes, ages, and genders [52], emphasizing its importance and reinforcing its consistency. Recent studies suggest that psychosis may even be present in patients with preclinical disease. Van der Mussele et al. [51••] examined the rates of various NPS in patients with MCI and found depression, psychosis, and agitation explained most of the variance while in AD, the same factors occurred in a slightly different order (agitation, depression, psychosis). As well, he found that psychosis in MCI was associated with more severe frontal lobe dysfunction while in AD, there was a strong association with other NPS [53••]. One potential explanation for the

existence of psychosis as a stable factor in MCI may result from focal neurodegeneration in brain regions implicated in psychosis at the MCI stage, such as the frontal and limbic regions [54]. These findings are consistent with the notion that behavioral symptoms, in the absence of significant cognitive decline, may be the presenting feature of neurodegenerative conditions such as AD, providing support for the concept of "mild behavioral impairment" [55••].

Neurobiology

How psychotic symptoms arise in patients with dementia remains unclear. Numerous imaging studies to date using computed tomography (CT) and magnetic resonance imaging (MRI) and techniques such as voxel-based morphometry (VBM) have suggested that psychotic symptoms in AD tend to be associated with gray matter volume loss, most prominently in the frontal lobes [56–58] (see Table 1). This fits with existing theories regarding the development of psychosis as well as the bulk of clinical studies. Recent studies have suggested that gender differences may play a role [59] as well as anatomical areas known to be associated with the development of psychosis in other disorders, including the cingulate gyrus [60], the cerebellum, and the precuneus [10••]. Functional imaging studies using SPECT have produced variable results, though on balance tend to implicate reduced perfusion to the frontal lobes, while some studies have shown involvement of the temporal and parietal lobes [3••]. Gender differences were also detected in one study [61]. Studies conducted to date using fludeoxyglucose positron emission tomography (FDG PET) in AD patients with psychosis have for the most part demonstrated hypoperfusion to the frontal cortices and prefrontal regions, though a minority of studies have demonstrated increased metabolism to sensory regions [3••].

There is an emerging preponderance of evidence that psychosis in AD may be heritable [62, 63••], thus bolstering the argument that AD patients with psychosis represent a distinct genetic subtype. Moreover, heritability increases from 30 to 60 % when considering multiple psychotic symptoms versus a single psychotic symptom [12]. The estimated odds ratio for AD with psychosis among siblings is estimated to be 3.2, thus providing a compelling argument for heritability [11]. This initial finding has been reproduced in two additional cohort studies [13, 14]. As well, there are various genetic theories regarding the role of *APOEε4* and other genes that may be involved in the development of psychosis in AD. In spite of a minority of studies showing an association [8, 64], to date, no consistent link between psychosis in AD and *APOEε4* [65–68] and, moreover, no link with genes corresponding to neurodegeneration have been established [69]. However, linkage to specific chromosomes has been postulated [12, 13, 70]. Specifically, AD with psychosis has been linked to loci on chromosomes 2, 7, 8, and 15 [12, 71, 72]. The first genomewide comparison of AD patients with psychosis versus AD patients without psychosis produced mixed results [73] with serine/threonine kinase 11 (*SKT 11*) and visinin-like 1(*VSNL1*) both showing as prominent single nuclear polymorphisms. Interestingly, both genes have been implicated in schizophrenia [74, 75]. Conversely, Middle et al. [76] examined the relationship between psychosis and the gene

Table 1 Voxel-based morphometry studies of psychosis in AD

Study	Number of subjects	Psychotic symptom	Study design	Finding
Bruen et al. 2008 [56]	$n = 31$ patients with mild AD	Delusions	Cross-sectional	Decreased gray matter density in right fronto-parietal, left frontal, and left claustrum
Ting et al. 2015 [9••]	$n = 58$ patients with AD/MCI from ADNI (29 with and without delusions)	Delusions	Cross-sectional	Reduced gray matter in the right precentral gyrus, right inferior frontal gyrus, right insula, and left middle occipital gyrus
Fischer et al. 2016 [10••]	$n = 24$ patients with AD from ADNI	Delusions	Longitudinal	Right and left insular, left precuneus, right and left cerebellar culmen, left superior temporal gyrus, right posterior cingulate, right thalamus, left parahippocampal gyrus
Serra et al. 2010 [57]	$n = 27$ with AD/MCI	Misidentifications	Cross-sectional	Decreased gray matter in the right hippocampus
Whitehead et al. 2010 [59]	$n = 113$ with AD	Persecutory delusions	Cross-sectional	Female participants displayed left mediaorbital and superior temporal atrophy
Rafii et al. 2014 [60]	$n = 389$ patients with AD/MCI from ADNI database	Patients with psychosis or requiring medication	Longitudinal	Atrophy in lateral frontal, lateral parietal, and anterior cingulate gyrus

neuregulin 1 (*NRG1*), which is often implicated in patients with psychotic disorders such as schizophrenia, and found no difference. There is also evidence suggesting a link between psychosis in AD and the serotonin transporter gene (*SLC6A4*) according to research [77–80]. Recently, there has been significant interest in *C9orf72* expansions and their role in FTD and amyotrophic lateral sclerosis (ALS) [81••, 82••]. More recently, the presence of an intermediate number of repeats in the *C9orf72* gene has been implicated in psychotic disorders, including schizophrenia [83]. The potential relevance of this finding to AD with psychosis has yet to be explored, though FTD patients with this expansion appear to commonly have symptoms of psychosis according to recent studies [47••, 48, 82••].

In terms of neuropathologic findings, results are mixed with regard to the association of psychosis with β-amyloid pathology, with some studies showing a strong correlation between psychosis and β-amyloid load and other studies showing no such association [3••] (see Table 2). Discrepancy in the results may have been driven by failure to take into account confounding Lewy body pathology, design issues, and the failure to separate patients with delusions from those with hallucinations. Sweet et al. [86] in a well-designed comparison study examined rates of neuritic plaques between AD patients with and without psychosis and found no difference, which was consistent with the findings by Forstl et al. [85]. In another study [87], rates of soluble β-amyloid 40 and 42 were compared across multiple brain regions of AD patients with and without psychosis and an increased rate of soluble β-amyloid 42 to 40 was demonstrated in the dorsolateral prefrontal cortex of psychotic patients, suggesting regional specificity. Conversely, studies looking at quantitative measures of tau pathology have shown to be consistently increased in AD patients with psychosis [16••, 17, 18••, 19, 84], specifically in prefrontal brain regions, although other studies using semi-quantitative ratings of tau pathology have been negative [7••, 86] exceptions. Recently, studies have shown a gender separation between men and women based on the work of Koppel et al. [16••], who showed higher levels of phosphorylated tau in the frontal lobe of women showing AD and psychosis compared to men. Fischer et al. [7••] in a recent study examined the neuropathologic correlates of psychosis and associated symptoms and found a strong association between AD patients with psychosis, Lewy body, and vascular pathology, suggesting these may be important risk modifiers of psychosis in AD. As well, there

Table 2 Postmortem studies of the association of β-amyloid and tau pathology with psychosis in Alzheimer's disease

Study	Participants	Design	Findings
Zubenko et al. 1991 [84]	13 AD patients with psychosis, 14 AD patients without psychosis	Senile plaque and neurofibrillary tangle area density	Increased senile plaques and neurofibrillary tangles in the prosubiculum and middle frontal cortex
Förstl et al. 1993 [85]	3 AD patients with psychosis, 5 AD patients without psychosis	Senile plaque density	No associations with psychosis
Mukaetova-Ladinska et al. 1995 [19]	18 patients with AD	Senile plaque density, ELISA of phosphorylated tau	Higher area densities of neuritic plaques and higher phosphorylated tau concentrations in psychosis
Farber et al. 2000 [17]	109 subjects with AD	Neurofibrillary tangle area density	Patients with psychosis had a 2.3-fold increase in neurofibrillary tangles
Sweet et al. 2000 [86]	24 AD patients with psychosis, 25 AD patients without psychosis	Semi-quantitative ratings of senile plaque and neurofibrillary tangle frequency	No correlation with neurofibrillary plaques or tangles in multiple brain regions, controlling for Lewy bodies and multiple comparisons
Murray et al. 2012 [87]	30 AD patients with psychosis, 22 AD patients without psychosis	ELISA for soluble β-amyloid 1–42 and β-amyloid 1–40	Increased β-amyloid 1–42/β-amyloid 1–40 ratio in prefrontal cortex in psychosis
Murray et al. 2014 [18••]	26 AD patients with psychosis, 19 AD patients without psychosis	Quantitative fluorescent microscopy of phosphorylated tau	Higher phosphorylated tau concentrations in prefrontal cortex in psychosis
Koppel et al. 2013 [20••]	26 patients without psychosis, 45 with psychosis	ELISA for phosphorylated tau	Female patients had high levels of phosphorylated tau in the frontal cortex, males displayed increased alpha-synuclein
Fischer et al. 2016 [7••]	1073 subjects with AD (890 with clinical AD, 728 with confirmed AD) from the NACC database	Semi-quantitative ratings of senile plaque and neurofibrillary tangle frequency	Increased senile plaques and neurofibrillary tangles only in the clinical group; increased correlation with Lewy bodies and subcortical ischemic vasculopathy in all groups

was an association with vascular risk factors, in contrast to prior studies [67].

There have also been numerous studies that have examined the role of chemical neurotransmitters in various brain regions and how they correlate with the presence of psychotic symptoms in AD. The density of dopamine 3 (D3) receptors has been found to be elevated in AD patients with psychosis in the nucleus accumbens, for example [88]. In addition, low levels of serotonin (5HT) have been found in the ventral temporal cortex and prosibiculum of AD patients with psychosis [89]. As well, Vermeiren et al. [90] found an inverse correlation between the presence of hallucinations and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in the thalamus when examining neurotransmitter levels in various brain regions of patients with AD. Herrmann et al. [91] reviewing the literature in this area postulated that reductions in brain norepinephrine (NE) levels and elevations in MHPG suggest enhanced NE metabolism, perhaps in response to reductions in NE levels in the locus coeruleus (LC), providing a putative mechanism for the onset of psychosis in AD. Modulation in brain catecholamine levels has been recently postulated as a strategy for treatment of AD and related dementias [92]. Another potential theory relating to the genesis of psychosis in AD relates to the cholinergic hypothesis [93]. DLB is associated with prominent psychosis and also a much more profound cholinergic deficit when compared to AD [94]. In addition, studies conducted using donepezil (a cholinesterase inhibitor) have shown a 27 % reduction in the prevalence of psychotic symptoms among treated patients [95]. The recent discovery by Dalmau et al. [96] that antibodies binding to the *N*-methyl-D-aspartate receptor (NMDAR) may be associated with psychotic symptoms has led to an increased interest in whether this may provide a unifying explanation for the onset of these symptoms in other brain disorders such as dementia. Although studies to date are limited, Busse et al. [97••] did look for NMDAR serum antibodies in a small cohort of patients with AD ($n = 24$) and subcortical ischemic vasculopathy (SIVD, $n = 20$) and found positive results in four AD patients and three SIVD patients. All but one of these patients exhibited psychosis and furthermore none of them had positive CSF antibodies, thus suggesting more work is required to clarify the relationship between these autoantibodies and the presence of psychosis, particularly in light of false-positive results in some studies [98].

Conclusion and Future Directions

Discoveries to date in the area of psychosis and dementia have the potential to improve treatment of these symptoms. A summary of the existing literature suggests there is incontrovertible evidence that the presence of psychosis exerts a malignant effect on the course of AD, with patients undergoing significantly greater cognitive decline and suffering increased mortality. Realizing this to be the case, the question arises as to whether the excess mortality associated with the use of antipsychotic medications [5] is related to the underlying disease process or the medications themselves. In either case, given that the effectiveness of antipsychotics are questionable at best [5], the question arises as to whether they should be used at all or alternative agents, such as antidepressants, should be used instead. Intervening early with existing treatments such as cholinesterase inhibitors [99] and monitoring patients carefully may make sense in view of recent research findings. As well, there are emerging trends in the study of AD in general suggesting that modification of vascular risk factors, such as cholesterol and hypertension, may significantly delay the onset of Alzheimer's disease or prevent it from manifesting [100••]. Perhaps, the same could be said of psychotic symptoms, where vascular risk factors may play a role according to a recent study [7••].

The broader question of there being a unifying theory for psychosis across multiple disease pathologies remains unanswered. However, significant progress has been made with the discovery of the heritability of psychosis in AD, which lends promise to possible genetic discovery of disease mechanisms underlying the neurobiology of psychosis and may ultimately lead to the establishment of effective treatments [63••]. Recent studies exploring brain networks and their relevance to brain diseases such as psychosis raise the specter of treatment with alternative modalities such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS). Future studies are needed to further establish relevance to psychosis in dementia. Where studies fit in with the broader question of NPS in dementia remains to be seen. An important focus will be identifying at-risk patients in the preclinical phase, to allow interventions before the manifestation of overt psychotic symptoms and the associated poor outcomes. Moreover, the separation of lines of research is becoming clearer, given the recent findings that delusions and hallucinations may have distinct clinical and neurobiological correlates. It is conceivable based on the research to date that genetic and other inflammatory factors may create a vulnerability to the development of psychosis, the expression of which may be affected by subtle differences in brain network disruption.

A number of opportunities hold the promise of enhanced scientific discovery in the future. The first relates to the establishment of large databases with thousands of patients and the potential this provides for examining the clinical and neurobiological underpinnings of individual symptoms. The second relates to advances in medical imaging, specifically in functional brain imaging, which will ultimately allow us to understand how seemingly minor disruption in network connectivity may give rise to distinct psychotic symptoms. Finally, the discovery of genetic risk factors for psychosis in AD will provide a putative mechanism through which this disruption may occur. It is anticipated with these advances that further

study of psychosis will yield important answers not only to the field of NPS but rather to the broader fields of dementia and psychosis.

Compliance with Ethical Standards

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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