

Featured Article

# Determining the impact of psychosis on rates of false-positive and false-negative diagnosis in Alzheimer's disease

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## Abstract

**Introduction:** The rate of clinical misdiagnosis of Alzheimer's disease (AD) and how psychosis impacts that clinical judgment is unclear.

**Methods:** Using data from National Alzheimer's Coordinating Center, we compared the clinical and neuropathologic diagnosis in patients with a diagnosis of AD with autopsy and in neuropathology-confirmed AD cases ( $n = 961$ ). We determined the rate of true positives, false positives, and false negatives in patients with and without psychosis.

**Results:** A total of 76% received a correct AD diagnosis, 11.9% had a false-negative diagnosis, and 12.1% had a false-positive diagnosis of AD. Psychotic patients had a higher rate of false-negative diagnosis and a lower rate of false-positive diagnosis of AD compared with nonpsychotic patients.

**Discussion:** Patients with psychosis were five times more likely to be misdiagnosed as dementia with Lewy bodies, whereas patients without psychosis were more likely to be falsely diagnosed with AD when vascular pathology is the underlying neuropathologic cause of dementia.

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## Keywords:

Psychosis; Alzheimer's disease; Misdiagnosis; Neuropathology; Delusions; Hallucinations; Diagnosis

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## 1. Introduction

Rates of misdiagnosis of Alzheimer's disease (AD) in general are uncertain. Patients may be erroneously diagnosed with AD during life (false positive) in the presence of high loads of other pathology such as cerebrovascular disease, Lewy bodies (LBs), and so forth. Conversely, AD may be missed if the

clinical features resemble other forms of dementia such as frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and so forth (false negatives). Many factors may contribute to high rates of misdiagnosis, both in terms of false-positive and false-negative rates. It has been estimated based on prior studies that only 20% to 50% of patients with dementia ever receive an actual specific diagnosis [1]. Moreover, several studies indicate that patients may be inaccurately given a diagnosis of AD when in fact based on postmortem analyses of brain tissue the actual diagnosis is that of vascular dementia (VaD) [2,3] or dementia with LBs [3–5]. On the basis of the analyses of data from the National Alzheimer's Coordinating Center (NACC) database, it has been estimated that sensitivity rates for an AD diagnosis are in the range of 71% to 87% whereas specificity rates range from 44% to 71%, leaving much to be desired [6]. How psychosis impacts rates of misdiagnosis is not clear. One could speculate the association of psychosis with alternative pathologies, mainly DLB, but also cerebrovascular disease might contribute to high rates of misdiagnosis. Alternatively, it is possible that psychosis is more strongly associated with other forms of pathology, such as tau. There is an emerging literature suggesting this may be the case [7,8].

Although psychotic symptoms occur in AD, they are observed more frequently in other forms of dementia, such as Parkinson's disease-related dementia, DLB, and VaD [9,10]. Conversely, the prevalence of psychosis in other forms of dementia, such as FTD, tends to be quite low [11]. One of the challenges related to identifying the prevalence of psychosis in various forms of dementia is that most studies to date have relied on clinical diagnosis when making such assertions, as opposed to cohorts that are neuropathologically verified. This may lead to erroneous assumptions. A second challenge is that many patients have overlapping pathologies at autopsy, thus making it more challenging to identify prevalence rates for different etiologies of dementia.

In our previous article [12] we established that psychosis in neuropathologically confirmed AD was not statistically significantly associated with increase in Alzheimer pathology load (i.e., plaques and tangles), but this finding was not replicated in patients with clinically attributed AD. One potential reason for the discrepancy may relate to high rates of misdiagnosis among patients with clinically attributed AD, specifically in patients without psychosis.

Misdiagnosis of AD has significant implications for clinical care as patients may not receive appropriate treatment and this may impact clinical outcomes. For example, treatment with existing cholinesterase inhibitors has shown some effectiveness in AD [13] but limited effectiveness in other forms of dementia such as VaD [14] or FTD [15]. With the advent of new disease-modifying therapies that may be specific to the etiology of dementia, this issue is likely to become more important in the years to come. There are increasing studies showing that correct conclusions are only reached when using autopsy-based neuropathologic diagnoses in research and not when clinical AD criteria are used

[16,17]. The purpose of our article is to examine rates of misdiagnosis in AD patients with and without psychotic features using data from the NACC database. We predict based on the association of psychosis with overlapping pathologies such as LBs and cerebrovascular disease that psychosis will be associated with lower rates of false-positive diagnosis and higher rate of false-negative diagnosis.

## 2. Methods

### 2.1. Data source

We used data from the NACC Uniform Data Set and Neuropathology Data Set, collected between the September 2005 and May 2012 data freeze [18]. The data were pooled from 29 National Institute of Aging (NIA) Alzheimer's disease Centers in the United States that collect standardized clinical and pathologic data on participants with normal cognition, mild cognitive impairment, AD, and other dementias. Subjects were recruited from clinical referrals, self-referrals, community organizations, and volunteers. All subjects from NACC were followed approximately annually by the Alzheimer's disease Centers for as long as they are able to participate.

### 2.2. Participants

We included subjects who received a clinical diagnosis of probable AD [19] before death and who have neuropathologic data collected at autopsy, as well as subjects who met neuropathologic criteria for AD at autopsy, according to the NIA-Reagan Institute neuropathologic criteria [20] ( $n = 961$ ). The clinical diagnosis stratified subjects as having "probable AD," "possible AD," or "not AD" (either another type of dementia or no dementia diagnosis). The neuropathologically diagnosis stratified subjects as having a "high likelihood of AD," "intermediate likelihood of AD," "low likelihood of AD," or "criteria not met". The demographic data are summarized in Table 1.

### 2.3. Misdiagnosis definitions

Subjects with both a clinical probable AD diagnosis and high likelihood of dementia due to AD on the NIA-Reagan Institute neuropathologic criteria were considered as having received a correct diagnosis, even if there are other coexisting pathologies (e.g., AD-VaD). Subjects with a clinical probable AD diagnosis but who did not meet the neuropathologic criteria for AD (i.e., low likelihood of AD or criteria not met) were considered false positives. All cases with a neuropathologic intermediate likelihood of AD were not included in the analyses. Subjects with a neuropathologic high likelihood of AD but who were not clinically diagnosed with probable AD were considered false negatives. A clinical diagnosis of possible AD has a much lower index of suspicion than probable AD in the eyes of clinicians. Therefore, it is debatable if possible AD with "high probability of AD" on neuropathology should be considered a correct diagnosis (specifically, a

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