Incident Psychosis in Subjects With Mild Cognitive Impairment or Alzheimer's Disease

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ABSTRACT

Objective: To estimate the incidence of psychotic symptoms in Alzheimer's disease.

Methods: The study consists of 776 elderly subjects presenting to the Alzheimer Disease Research Center at the University of Pittsburgh (Pittsburgh, Pennsylvania) between May 9, 2000, and August 19, 2014. All participants were diagnosed with mild cognitive impairment (National Institute on Aging-Alzheimer's Association workgroup criteria) or possible or probable Alzheimer's disease (National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria) and were without psychosis at entry. Psychotic symptoms were evaluated using the Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale every 6 months. One-, 3- and 5-year cumulative incidences of psychosis were calculated.

Results: The 1-year psychosis incidence was 10% (95% CI, 8%–12%), and this annual rate remained remarkably consistent at 3 and 5 years. Psychosis incidence was related to cognitive status at all time points. However, the incidence rate reached a plateau during the disease course. Cumulative psychosis incidence at 5 years was 61% (95% CI, 52%–69%) in individuals with moderate to severe Alzheimer's disease, not statistically significantly different from the cumulative incidence at 3 years in this group, which was 48% (95% CI, 40%–55%) or from the 5-year incidence in individuals who entered the study with mild Alzheimer's disease, which was 48% (95% CI, 41%–56%).

Conclusions: Psychosis in Alzheimer's disease has been associated with a number of adverse clinical outcomes. We provide estimates of the risk of psychosis onset within clinically defined subgroups of individuals, a tool clinicians can use in treatment planning. Anticipating which subjects are at high risk for psychosis and the poor outcomes associated with it can help with family education and support decisions to implement nonpharmacologic strategies that may reduce or prevent symptoms.

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Psychotic symptoms such as hallucinations and delusions can occur in patients with Alzheimer's disease (AD), where their presence identifies a subgroup with poor outcomes.[1] In comparison to AD subjects without psychosis, subjects who have AD with psychosis (AD+P) have more rapid cognitive decline,[2–4] more rapid functional decline,[5] higher rates of aggression,[6] worse overall health,[7] and shorter time to placement in a nursing home.[5,8] As a result, psychotic symptoms in individuals with AD are associated with more distress for the caregiver.[9]

Ropacki and Jeste reviewed data from 55 studies of the prevalence of psychotic symptoms in patients with AD.[10] That review restricted itself to studies reported beginning in 1990, as earlier reports were limited by small sample sizes, the use of nonvalidated diagnostic criteria for dementia leading to the inclusion of other types of dementia, and the use of methods to assess and define psychosis without established reliability and validity. Ropacki and Jeste identified 55 studies comprising 9,749 subjects, predominantly drawn from outpatient clinical research settings. The reported median prevalence of AD+P in these studies was 41.1%, with a range from 12.2% to 74.1%.[10] The most consistent clinical correlates of psychosis presence were more rapid cognitive decline and greater cognitive impairment.

Given the frequent occurrence of AD+P and its associated poor outcomes, estimates of the incidence of AD+P within subgroups of at-risk subjects are needed. Only 7 studies were identified by Ropacki and Jeste as reporting on the incidence of AD+P,[11–17] and we have identified 3 additional studies published since the date of their review.[18–20] A summary of these studies is provided in Supplementary eTable 1. Annualized incidence rates of psychosis within at-risk populations with AD could be determined for 7 of 10 studies and ranged from 7.6% to 25%, with a median of 15.6%. Nevertheless, a number of methodological issues limit the utility of these estimates for the clinician. Three of these studies were very small (less than 100 subjects), and only 2 studies reported on more than 300 subjects. Only 2 reports included individuals with mild cognitive impairment (MCI), although this is now typically considered the earliest clinical stage of Alzheimer's disease.[21,22] None of the studies reported incidence rates stratified by severity of cognitive impairment, although AD+P risk is strongly associated with such measures. Finally, although AD+P occurs in an elderly population with a terminal neurodegenerative disease, prior studies have not accounted for the competing risk of death in estimating AD+P incidence or in evaluating any association of AD+P with potential risk factors. Analyses that fail to account for events (ie, competing risks) such as death—which preclude the future occurrence of the outcome of interest (ie, psychosis)—will overestimate the incidence of the outcome.[23]

To address these limitations, we describe the incidence of psychosis in a large cohort of subjects diagnosed with MCI or

Clinical Points

- Psychosis in Alzheimer's disease is a known marker for poor outcomes, yet prior estimates of the incidence of psychosis during Alzheimer's disease have had methodological limitations.
- We found an incidence of psychosis in Alzheimer's disease of ~10% per year, with rates varying according to diagnosis and cognitive impairment at baseline. Using these estimates to identify individuals at high risk for psychosis may allow clinicians to provide additional nonpharmacologic interventions in an effort to reduce the associated morbidity.

AD by an outpatient Alzheimer Disease Research Center (ADRC). All subjects were without psychosis at baseline and were reevaluated for psychotic symptoms every 6 months via telephone and in-person interviews with an informant knowledgeable about the subject's behavior. Using a competing risks analysis, 1-, 3-, and 5-year cumulative incidences of psychosis were generated for the overall group and within clinical strata.

METHODS

Subjects

All subjects were participants in the University of Pittsburgh ADRC, seen between May 9, 2000, and August 19, 2014. Subjects were included if they had an initial primary diagnosis of mild cognitive impairment (MCI)[24,25] or probable or possible AD,[26] had an age at onset of cognitive problems starting ≥ 60 years old, and did not have current or prior psychosis, including a personal history of a primary psychotic disorder (eg, schizophrenia). Subjects were recruited in 2 waves. Wave 1 ran from May 2000–May 2005, and Wave 2 ran from May 2007 to present. All procedures were conducted under the research protocol approved by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from subjects and/or their proxy.

Diagnostic Assessment

As described elsewhere, the clinical diagnostic evaluation consisted of a baseline neurologic, neuropsychological, and psychiatric evaluation; laboratory studies; and brain imaging with annual reevaluation of neurologic presentation, behavioral symptoms, cognitive tests, and functioning.[27–30] The neuropsychological assessment included the Mini-Mental State Examination (MMSE),[31] a test of global cognitive functioning. Additional tests evaluated domains of immediate, delayed, and working memory; attention; visuospatial function; language abilities; and executive function. At annual evaluations, the Clinical Dementia Rating Scale (CDR),[32] a measure of global impairment due to dementia, was also completed.

Psychosis Assessment

To assess psychosis, the Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale (BRS) was administered to an informant knowledgeable about the patients' symptoms. Interrater reliability for both the in-person and telephone administration of the BRS has been previously established.[33] A total of 4,128 BRS assessments were conducted for the 776 individuals included in this analysis. Information regarding the informant's relationship to the study subject was available for 97.8% of participants, for whom the vast majority of BRS assessments were completed by a spouse (55%) or child (38%). Information on informant contact with the participant was available for 90.9% of all ratings, for which 83% had frequent contact (5+ days/wk) with the participant, including 63% who were living with the informant. Patients were classified as psychotic if they had 1 or more of BRS items 33–45 rated as present at least 3 to 8 days in the past month: delusional misidentification of people, self, or objects; paranoia; beliefs of abandonment or infidelity; belief that someone is an imposter; belief that characters on television are real; belief that there are people in or around house that are not there; belief that a dead person is still alive; belief that their house is not their home; auditory hallucinations; and visual hallucinations. Symptoms were not rated if they occurred during an episode of delirium, were medication induced, or were hypnopompic or hypnogogic.

Alzheimer's disease subjects with multiple psychotic symptoms at any 1 point in time, or with psychotic symptoms that are recurrent over time, may represent a more biologically homogeneous subgroup.[1] We therefore also classified subjects as having recurrent/multiple psychosis if they were classified as psychotic on more than 1 BRS assessment or if they had more than 1 BRS psychosis item present at least 3 to 8 days in the past month at any single assessment.

Telephone Assessments

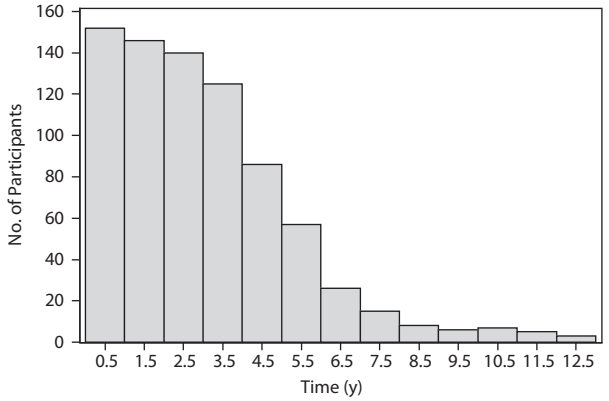
Telephone assessments were conducted at approximately 6-month intervals between annual in-person assessments and were also conducted at the time of annual assessment for individuals unable to return to clinic. Telephone assessments consisted of the BRS and a review of current medications.[34] Beginning in November 2007, annual telephone assessments also included the CDR. Telephone interviews were continued until the subject became too impaired (CDR ≥ 2 and/or MMSE ≤ 12), refused further participation, died, was lost to follow-up, or lost their informant. The availability of telephone interviews in addition to in-person assessments provided for high fidelity of follow-up in this elderly, cognitively impaired cohort. Missed visits averaged only 5.5% during this interval. Subjects were evaluated for a mean (SD) of 3.0 (2.2) years of follow-up, resulting in a corresponding 5.3 (3.9) BRS ratings completed (Figure 1).

Statistical Analysis

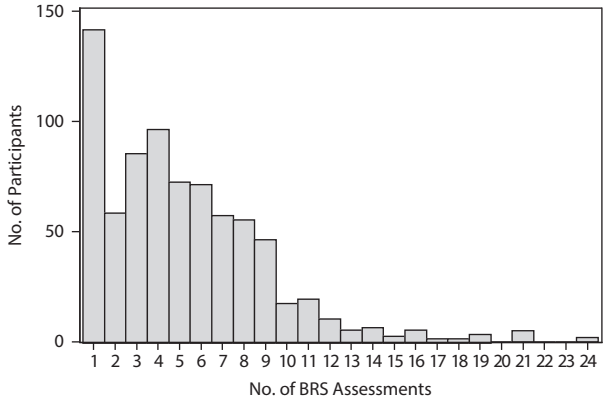
Subjects were excluded from analyses if they did not have at least 1 follow-up visit that included BRS ratings or if their primary diagnosis changed during follow-up such that they no longer had MCI or possible or probable AD. This resulted in a total of 776 subjects included for analysis.

Figure 1. Durations of Follow-Up and Number of Psychosis Assessments in 776 Elderly Outpatients With Mild Cognitive Impairment and Alzheimer's Disease

A. Time From Study Entry to Last Psychosis Assessment for All Participants



B. Number of Assessments for Psychosis per Participant



Abbreviation: BRS = Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale.

Table 1. Subject Characteristics at Baseline Evaluation

Characteristic	MCI	AD
Total	n = 191	n = 585
Sex, n (%)		
Female	97 (50.8)	366 (62.6)
Male	94 (49.2)	219 (37.4)
Age at entry, y	n = 191	n = 585
Mean (SD)	76.0 (7.1)	77.2 (6.4)
Median (IQR)	75 (70.3–81.2)	77.3 (72.6–81.7)
Education, y	n = 191	n = 585
Mean (SD)	15.4 (3.0)	13.6 (3.1)
Median (IQR)	16 (12–18)	12 (12–16)
Race, n (%)		
White	166 (86.9)	543 (92.8)
Black	23 (12.0)	41 (7.0)
Asian	2 (1.0)	1 (0.2)
Age at onset, y	n = 174	n = 585
Mean (SD)	73.2 (7.3)	73.4 (6.7)
Median (IQR)	72 (68–79)	73 (69–79)
MMSE category, n (%)		
0–9	0 (0.0)	0 (0.0)
10–19	1 (0.5)	215 (36.8)
20–24	28 (14.7)	258 (44.2)
> 24	162 (84.8)	111 (19.0)
CDR total score	n = 191	n = 583
Mean (SD)	0.5 (0.1)	0.9 (0.5)
Median (IQR)	0.5 (0.5–0.5)	1 (0.5–1)

Abbreviations: AD = Alzheimer's disease, CDR = Clinical Dementia Rating Scale, IQR = interquartile range, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

Participant demographic characteristics and neurocognitive functioning (MMSE, CDR) at baseline were summarized using frequencies and percentages for categorical variables and means (standard deviations) and medians (interquartile ranges) for continuous variables. Events of interest included (1) first reported psychotic symptom(s) and (2) recurrent/multiple psychosis. Analysis of recurrent/multiple psychosis was restricted to participants with at least 2 follow-up visits.

Person-time was calculated as the number of years from the baseline visit to the date of the first visit at which the event of interest (ie, psychosis or recurrent/multiple psychosis) was noted. Follow-up time was censored at the date of last BRS assessment plus 9 months, unless death occurred within 9 months of the last visit, in which case follow-up time was defined by the date of death.

One-, 3-, and 5-year cumulative incidence of psychosis (and recurrent/multiple psychosis) was calculated with 95% CIs using the SAS CIF macro.[35] Death was treated as a competing risk in these estimates. We then calculated cumulative incidence after stratifying by (1) diagnosis at baseline (MCI, AD), (2) sex, (3) MMSE score at baseline (0–19, 20–24, > 24), and (4) categories defined by diagnosis, sex, and MMSE (0–19, ≥ 20).

RESULTS

The demographic and clinical characteristics of the 776 subjects are presented in Table 1. The sample consisted predominantly of patients with an AD diagnosis (75.4%). The mean age at onset of cognitive impairment was the same for both AD and MCI subjects, consistent with a view of MCI as a prodromal stage of AD in many individuals. Most subjects were female (59.7%), and the vast majority were white (91.4%).

The 1-, 3- and 5-year cumulative incidences of psychosis and recurrent/multiple psychosis are shown in Table 2. A 1-year cumulative incidence of 10% for psychosis was observed, and this annual rate remained remarkably stable across the initial 5-year observation period. Rates of recurrent/multiple psychosis were significantly lower at all time points. At 3 and 5 years of follow-up, the annualized incidence rates for recurrent/multiple psychosis were 6.3% and 6.4%, respectively. Psychosis and recurrent/multiple psychosis rates were slightly, but not significantly, higher in women, as at each time point the 95% confidence intervals between men and women were overlapping.

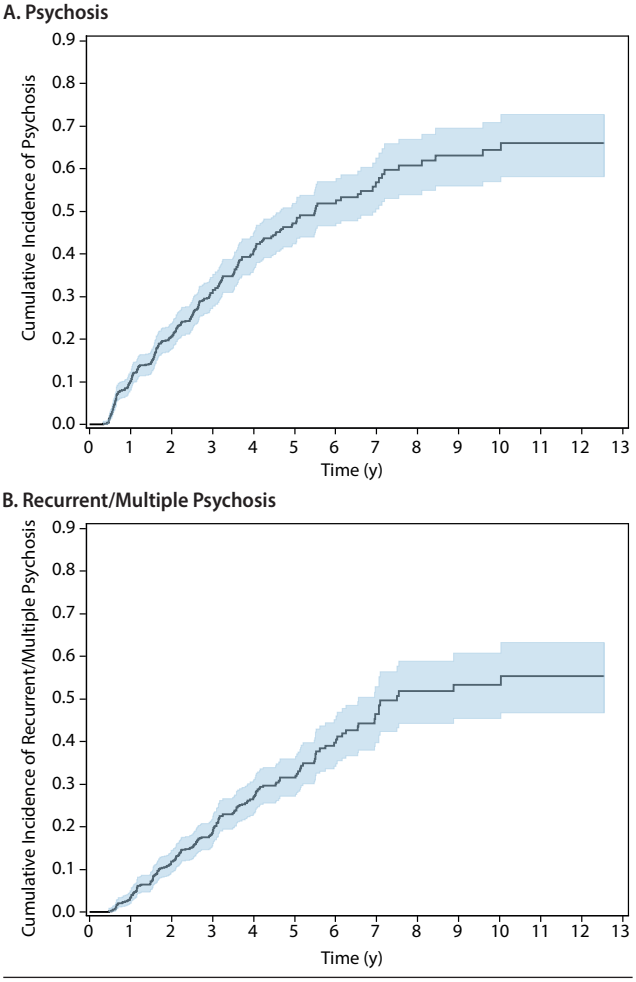
In contrast, there were substantial differences by diagnosis, as rates of psychosis and recurrent/multiple psychosis for MCI subjects were significantly lower than for AD subjects at each time point (Table 2). When AD subjects were considered separately, the average annual incidence rate for psychosis was 11.7% in the first 3 years of follow-up and

Table 2. One-Year, 3-Year, and 5-Year Cumulative Incidence (95% CI) of Psychosis and Recurrent/Multiple Psychosis: Overall and by Diagnosis, Sex, and Cognitive Impairment

Event	Group	1-Year	3-Year	5-Year
Overall				
Psychosis		0.10 (0.08–0.12)	0.31 (0.27–0.35)	0.47 (0.42–0.52)
Recurrent/multiple psychosis		0.03 (0.02–0.05)	0.19 (0.16–0.22)	0.32 (0.27–0.36)
By diagnosis at study entry				
Psychosis	AD	0.12 (0.09–0.14)	0.35 (0.31–0.39)	0.52 (0.47–0.57)
	MCI	…[a]	0.04 (0.01–0.11)	0.12 (0.03–0.26)
Recurrent/multiple psychosis	AD	0.04 (0.02–0.06)	0.21 (0.18–0.25)	0.35 (0.30–0.40)
	MCI	…[a]	0.02 (0.00–0.08)	0.06 (0.01–0.20)
By sex				
Psychosis	Female	0.12 (0.09–0.15)	0.33 (0.28–0.38)	0.52 (0.45–0.58)
	Male	0.08 (0.05–0.11)	0.28 (0.22–0.33)	0.40 (0.33–0.48)
Recurrent/multiple psychosis	Female	0.04 (0.02–0.06)	0.22 (0.17–0.26)	0.34 (0.28–0.40)
	Male	0.02 (0.01–0.05)	0.15 (0.10–0.20)	0.28 (0.21–0.35)
By MMSE at study entry				
Psychosis	0–19	0.20 (0.15–0.26)	0.48 (0.40–0.55)	0.61 (0.52–0.69)
	20–24	0.08 (0.06–0.12)	0.33 (0.27–0.39)	0.48 (0.41–0.56)
	>24	0.04 (0.02–0.06)	0.14 (0.10–0.19)	0.34 (0.26–0.43)
Recurrent/multiple psychosis	0–19	0.07 (0.04–0.11)	0.33 (0.25–0.40)	0.48 (0.38–0.57)
	20–24	0.03 (0.01–0.05)	0.20 (0.15–0.25)	0.32 (0.25–0.39)
	>24	0.01 (0.00–0.04)	0.06 (0.03–0.10)	0.19 (0.12–0.26)

[a]No psychosis events reported during this interval.
Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

Figure 2. Cumulative Incidence of Psychosis and Recurrent/Multiple Psychosis



10.4% over 5 years. Consistent with the difference between MCI and AD subjects, psychosis incidence was strongly related to cognitive status at 1, 3, and 5 years (Table 2). Of interest, there was some evidence for a plateau in cumulative incidence of psychosis between 5 and 10 years of follow-up and in cumulative incidence of recurrent/multiple psychosis between 7.5 and 10 years of follow-up (Figure 2). Table 3 provides the incidence rates of psychosis and recurrent/multiple psychosis in a format that provides clinical utility by showing the rates for individuals within strata defined by combinations of MCI/AD status, sex, and MMSE score.

DISCUSSION

We examined the incidence of psychosis in a large cohort of outpatients diagnosed with MCI and AD who were participants in an Alzheimer's Disease Research Center. The 1-, 3-, and 5-year estimates of psychosis incidence were remarkably consistent, suggesting an overall annual incidence of 10%. Psychosis incidence was strongly related to cognitive status at all time points. However, there was a trend for the incidence rate to plateau during follow-up. Psychosis incidence after 5 years was 61% in individuals with moderate to severe AD, not significantly different from the incidence at 3 years in this group, 48%, and not significantly different from a 48% 5-year incidence in individuals who entered the study with mild AD.

To our knowledge, this is the largest cohort to be ascertained and followed longitudinally for psychosis incidence. Another notable strength of the current study was the inclusion of individuals with early AD and with MCI, as this latter syndrome is increasingly recognized as the earliest clinical manifestation of AD.[21,22] Although not all subjects with MCI will progress to AD, MCI is a common clinical presentation. Thus, the inclusion of these subjects also enhances the applicability of our incidence tables for many clinical settings. In addition, we evaluated the potential bias of ignoring the risk of death as a competing outcome, although the overall effect of this correction was modest.

An important potential limitation to this study is that the cohort was obtained from an outpatient AD research center and therefore may not be representative of the general population or of pertinent subgroups such as ethnic minorities or individuals in assisted living settings, neither of which are well represented in the current study. Indeed, the small numbers of ethnic minority subjects precluded generating separate incidence estimates for these subgroups.

Our finding of an annual rate of psychosis incidence of 10% is in general agreement with, although somewhat lower than, prior studies that observed a median annual incidence rate of 15.6% with a range from 7.6% to 25%

Table 3. One-Year, 3-Year, and 5-Year Cumulative Incidence (95% CI) of Psychosis and Recurrent/Multiple Psychosis: Stratified by Diagnosis, Sex, and Cognitive Impairment

Event	Sex	MMSE[a]	1-Year	3-Year	5-Year
Psychosis					
AD	Female	High	0.09 (0.06–0.13)	0.30 (0.24–0.36)	0.52 (0.43–0.59)
		Low	0.21 (0.15–0.28)	0.48 (0.39–0.57)	0.64 (0.52–0.73)
	Male	High	0.06 (0.03–0.10)	0.26 (0.19–0.33)	0.41 (0.32–0.50)
		Low	0.19 (0.11–0.29)	0.49 (0.35–0.63)	0.56 (0.40–0.69)
MCI	Female	High	…[b]	0.03 (0.00–0.14)	0.08 (0.01–0.25)
	Male	High	…[b]	0.05 (0.01–0.16)	0.14 (0.02–0.37)
Recurrent/multiple psychosis					
AD	Female	High	0.03 (0.01–0.06)	0.18 (0.13–0.24)	0.30 (0.23–0.37)
		Low	0.07 (0.03–0.12)	0.34 (0.25–0.43)	0.50 (0.39–0.61)
	Male	High	0.01 (0.00–0.04)	0.12 (0.08–0.19)	0.28 (0.20–0.36)
		Low	0.07 (0.02–0.15)	0.30 (0.17–0.44)	0.44 (0.27–0.59)
MCI	Female	High	…[b]	…[b]	0.09 (0.00–0.36)
	Male	High	…[b]	0.03 (0.00–0.14)	0.03 (0.00–0.14)

[a]High MMSE ≥ 20; low MMSE < 20.
[b]No psychosis events reported during this interval.
Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination.

(Supplementary eTable 1). A number of factors, including frequency of assessment, psychosis assessment instrument used, duration of follow-up, and case source, could contribute to this variability. However, the current study points more firmly to the mixture of the study population with regard to degree of cognitive impairment. Psychosis incidence in AD subjects with moderate to severe cognitive impairment was 2- to 3-fold higher than in AD subjects with mild impairments. An even larger difference in incidence rates was seen between AD subjects, regardless of degree of impairment, and MCI subjects.

Given the frequent occurrence of psychosis in AD and its associated poor clinical outcomes, estimates of the incidence of AD+P within subgroups of at-risk subjects could benefit clinical planning by allowing clinicians to target individuals at high risk for additional interventions. Although antipsychotic medications may not have a favorable risk-benefit ratio for prevention of AD+P, nonpharmacological interventions are well tolerated and may reduce psychotic symptoms in AD. For example, studies have found a reduction in hallucinations and delusions through the use of interventions such as education and training on how to cope with behavioral problems and through the use of person centered therapy.[36–38] In addition, music therapy, physical activities, art-cognitive activities, and orientation training had favorable outcomes on delusions and hallucinations.[39,40] Home-based cognitive rehabilitation programs for patients with mild to moderate AD have also been shown to significantly reduce delusions.[41] Thus, nonpharmacologic approaches, while not established as preventative, could be considered to prevent or delay psychosis onset in AD.[42]

CONCLUSIONS AND FUTURE DIRECTIONS

Psychosis in AD also shows evidence of a genetic causation and neurobiology that is distinct from that of AD itself.[1] Thus, it may ultimately be possible to refine the estimates of psychosis incidence provided here via inclusion of personal genetic information.[3,43] Alternatively, other biomarkers, such as cerebrospinal fluid tau[44] or brain imaging, may be useful to incorporate. For example, a recent study[45] found that psychosis in MCI and AD subjects was significantly correlated with atrophy of the lateral frontal, lateral parietal, and anterior cingulate cortices. Additionally, the rate of atrophy of the lateral frontal lobe was the strongest correlate of psychotic symptoms and/or the need for antipsychotic treatments.[45] The toxicity of currently available antipsychotic medications in AD subjects[46] precludes their use for prevention of psychosis if a personalized predictive algorithm can be developed. However, pending the development of more specific and better tolerated medications, nonpharmacologic approaches to psychosis prevention may have value and acceptable safety for individuals at risk.[42]

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Supplementary material: See accompanying pages.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Helen Lavretsky, MD, MS, at hlavretsky@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

Supplementary material follows this article.

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Supplementary Material

Article Title: Incident Psychosis in Mild Cognitive Impairment and Alzheimer's Disease Subjects

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List of Supplementary Material for the article

1. eTable 1 Studies Reporting on the Incidence of Psychosis in Alzheimer Disease

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eTable 1. Studies Reporting on the Incidence of Psychosis in Alzheimer Disease							
#	Manuscript	Sample Source	N	AD/MCI	Psychosis Assessment (frequency)	Observed Incidence	Identified Clinical Correlates / *Comments*
1	Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A: Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. Am J Psychiatry 1996; 153:1438–1443	Drug Study	181	AD (mild to moderate severity)	AD Assessment scale (3 month intervals for 1 year)	25%	AD+P presence (not incidence) was significantly associated with greater cognitive impairment, greater rate of cognitive decline, and greater age.
2	Ballard CG, O'Brien JT, Swann AG, Thompson P, Neill D, McKeith IG: The natural history of psychosis and depression in dementia with Lewy bodies and Alzheimer's disease: persistence and new cases over 1 year of follow-up. J Clin Psychiatry 2001; 62: 46–49	Case Register-UK	132	AD (severity not specified)	Columbia University Scale for Psychopathology in AD (Annual for 1 year)	Delusions:24% Misidentification Delusions: 12% Visual Hallucinations: 13% Auditory Hallucinations: 7%	
3	Caligiuri MP, Peavy G, Salmon DP, Galasko DR, Thal LJ: Neuromotor abnormalities and risk for psychosis in Alzheimer's disease. Neurology 2003; 61:954–958	ADRC-UCSD	54	AD (severity not specified)	Behave-AD (Annual for up to 2 years)	32.5% (Annualized 16.3%)	Increased incidence of AD+P in women
4	Chen JY, Stern Y, Sano M, Mayeux R: Cumulative risks of developing extrapyramidal signs, psychosis, or myoclonus, in the course of Alzheimer's disease. Arch Neurol 1991; 48:1141– 1143	Dementia Clinic	72	AD (severity not specified)	Psychiatric interview using DSMIII as a guide (Evaluated at least twice with a minimum interval of 6 months between evaluations)	29.6% (Annualized 10.2%)	
5	Haupt M, Kurz A, Janner M: A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. Dement	Outpatient Psychiatry Clinic	60	AD (mild to moderate severity)	Behave-AD (Annual for up to 2 years)	Delusions:29.7% (Annualized 14.9%) Hallucinations:	AD+P presence (not incidence) was significantly associated with greater functional

	Geriatr Cogn Disord 2000; 11:147–152					18.8% (Annualized 9.4%)	impairment
6	Paulsen JS, Salmon DP, Thal LJ, Romero R, Weisstein-Jenkins C, Galasko D, Hofstetter CR, Thomas R, Grant I, Jeste DV: Incidence of and risk factors for hallucinations and delusions in patients with probable AD. Neurology 2000; 54:1965–1971	ADRC-UCSD	254	AD (mild to moderate severity)	Diagnostic Interview Schedule for the DSM-III (Annual for up to 4 years)	Cumulative incidence Yr 1= 20.1% Yr 2= 36.1% Yr 3= 49.5% Yr 4= 51.3%	AD+P presence (not incidence) was significantly associated with greater cognitive impairment, greater rate of cognitive decline, and motoric impairments including parkinsonian gait
7	Sweet RA, Kamboh I, Wisniewski SR, Lopez OL, Klunk WE, Kaufer DI, DeKosky ST: Apolipoprotein E and alpha-1-antichymotrypsin genotypes do not predict time to psychosis in Alzheimer's disease. J Geriatr Psychiatry Neurol 2002; 15:24–30	ADRC-UPITT	253	AD (mild to moderate severity)	CERAD Behavioral Rating Scale (Annual)	18.6%	No effect of APOE*4 genotype on incident psychosis *Only 253 of 316 enrolled subjects were at risk.*
8	Wilkosz PA, Miyahara S, Lopez OL, Dekosky ST, Sweet RA. Prediction of psychosis onset in Alzheimer disease: The role of cognitive impairment, depressive symptoms, and further evidence for psychosis subtypes. Am J Geriatr Psychiatry. 2006 Apr;14(4):352-60.	ADRC-UPITT	288	AD (mild to moderate severity) MCI	CERAD Behavioral Rating Scale (6 month intervals for up to 3.7 years)	28.5% (Annualized 19%)	Greater cognitive impairment and antidepressant use risk factors for incident psychosis.

9	Wilkosz PA, Kodavali C, Weamer EA, Miyahara S, Lopez OL, Nimgaonkar VL, DeKosky ST, Sweet RA. Prediction of psychosis onset in Alzheimer disease: the role of depression symptom severity and the HTR2A T102C polymorphism. Am J Med Genet B Neuropsychiatr Genet. 2007 Dec 5;144B(8):1054-62.	ADRC-UPITT	324	AD (mild to moderate severity) MCI	CERAD Behavioral Rating Scale (6 month intervals for up to 4.8 years)	34.0% (Annualized 15.6%)	Greater cognitive impairment, higher education, and depression severity risk factors for incident psychosis. *Includes subjects in Study 8, above.*
10	Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Garre-Olmo J. Am J Geriatr Psychiatry. 2013 Nov;21(11):1135-43.	Memory Unit	455	AD (mild to moderate severity)	CAMDEX and NPI (6 month intervals for up to 2 years)	Cumulative incidence 6mo= 5.8% 12mo= 10.6% 18mo= 13.5% 24mo= 15.1%	Irritability, worsened expressive language and calculation skills were risk factors for incident psychosis. Preserved learning, memory, and perception were protective for incident psychosis.