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Psychosis of Alzheimer's disease: clinical characteristics and history

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Abstract

The concept of psychosis of Alzheimer's disease and dementia is developed with respect to prevalence, incidence, clinical characteristics, clinical course, and potential response to treatment. Psychosis frequently occurs subsequent to the onset of dementia. Published prevalence estimates of psychosis in patients with AD range from 10 to 73% with an overall median of 34% within clinic populations, and from 7 to 20% in community and clinical trials populations depending on definitions used. Among people with AD who have no psychotic symptoms there appears to be an annualized incidence of psychosis of about 20% in outpatients, and a much higher rate in nursing home patients. Female gender, somewhat greater cognitive impairment among outpatients, somewhat lesser cognitive impairment among nursing home patients, and physical aggression are more associated with psychotic signs and symptoms than not. Right frontal hypometabolism and greater frontal neuropsychological deficits occur in AD patients with psychosis in comparison to those without. Among nursing home patients with dementia who have clinically significant agitation, the substantial majority have delusions or hallucinations. Among patients in nursing homes with dementia and psychosis, nearly two-thirds have persistent symptoms over at least 12 weeks, and among outpatient studies, hallucinations and delusions may persist in approximately 40–50% over periods of 3 months to one year. There is some evidence that psychotic symptoms improve modestly with antipsychotic medication treatment. There is sufficient descriptive and empirical research to support the validity of a syndrome of psychosis of Alzheimer's disease.

Keywords: Alzheimer's disease; Psychosis; Dementia

1. Introduction

> Sometimes she greets the doctor as if he were a visitor…on other occasions she screams that he wants to cut her open…on others yet she fears him as a threat to her honor as a woman…she seems to have auditory hallucinations. Often she screams for many hours in a horrible voice. (A. Alzheimer, 1907).

This quote from the first histological clinical report of what is now known as Alzheimer's disease, describes the clinical presentation of the patient upon admission to the Frankfurt asylum (Alzheimer, 1987). Although the diagnostic criteria for Alzheimer's disease requires the presence of a dementia, emphasizing the amnesic and cerebral cortical deficits such as aphasia and apraxia (McKhann et al., 1984), other behavioral disturbances are common, occurring in the majority of patients during the course of their illnesses. Often, psychotic features such as delusions and hallucinations can be prominent.

There has been controversy about how to best characterize these disturbances. DSM-IV-TR (Association, 1994) recognizes dementia of the Alzheimer's type, as essentially the NINCDS-ADRDA criteria (McKhann et al., 1984) and then allows a modifier for the presence of "behavioral disturbance." Other clinical features are indicated by offering an additional Axis I diagnosis of a specific mental disorder "due to Alzheimer's disease." For example, "psychotic disorder due to Alzheimer's disease, with delusions" could be coded for a patient with psychosis, and "personality change due to AD, aggressive type," for a patient who is aggressive (pp. 154–158). As rational as this classification is, it presupposes distinct mental disorders "due to AD" to an

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extent not yet justified by current evidence. Moreover, no specific criteria are offered for the mental disorders assumed to be "due to AD." Thus, the characteristics, extent, severity, or persistence of psychosis is not described.

The non-specific construct "behavioral and psychological symptoms of dementia," BPSD, has been used in an undifferentiated way as any disruptive behavioral symptom occurring in people with dementia (Finkel, 2001; Finkel et al., 2000). In this case, a particular symptom or sign is treated as a syndrome or disorder, and distinctions between symptoms, such as wandering, aggression, depression, or psychosis is not made.

Clearly, these categorizations are inadequate for meaningful clinical use, or further clinical investigation. Such vague categorizations encourage clinicians to not further distinguish specific behaviors or possible syndromes of clinical importance, to not appreciate the importance of distinguishing different behaviors, and to lump them together as "agitation" or "BPSD." More recently, conceptualizations and criteria for a 'psychosis of dementia' or 'psychosis of Alzheimer's disease,' and for 'depression of dementia' have been proposed (Jeste and Finkel, 2000; Olin et al., 2002).

There has been even further interest in the construct of 'psychosis of Alzheimer's disease,' such that it was a subject of an FDA meeting as a possible target of a therapeutic claim (Psychopharmacological Drugs Advisory Committee, March 9, 2000, transcript http://www.fda.gov/ohrms/dockets/ac/cder00.htm. By this is meant that a medication could be developed, marketed, and receive labeling indications specifically for 'psychosis of AD' or possibly 'psychosis of dementia'. The FDA advisory committee at that time believed that the concept could be recognized as a distinct entity and potentially could be adequately defined as a reasonably homogeneous target of a clinical claim by use of criteria such as those offered above (Laughren, 2001).

This paper will further examine the idea of psychosis of Alzheimer's disease. It will example and discuss: (1) the prevalence and incidence of psychosis in dementia; (2) the association of psychotic symptoms with dementia diagnoses and other behavior symptoms; (3) the persistence and course of psychosis; (4) the distinction of 'psychosis of AD' from other psychoses; and (5) the potential responsiveness to medication. It is not meant to be a comprehensive review of the literature, but rather a selective garnering of evidence to support the validity of the concept.

2. Prevalence of psychosis in dementia

The prevalence of psychotic symptoms in patients with dementia or with Alzheimer's disease is quite substantial. In a review of descriptive studies performed over a decade ago, largely of clinic populations, the range of the proportion of people having delusions was from 10 to 73% and of hallucinations from 21 to 49% (Tariot and Blazina, 1994). In particular, in one clinic population patients with Alzheimer's disease and delusions comprised 60% of the population while those with hallucinations comprised 17% (Burns, 1997).

In nursing home populations, at least 15–21% of newly admitted dementia patients may have delusions or hallucinations (Morriss et al., 1990), (Ballard et al., 2001). The proportion of dementia patients with psychosis is even higher among those patients identified as significantly agitated and in need of an antipsychotic medication, over three-quarters of whom were found to have significant delusions or hallucinations (Schneider et al., 2003).

The prevalence in community samples may be more informative, however. The 18 month prevalence of a nearly 100% sample of people over the age of 65 in Cache County, Utah was the following: among people with dementia—19% had delusions and 14% had hallucinations of any degree; 6.5 and 2.6% had delusions or hallucinations, respectively, judged to be of moderate severity (Lyketsos et al., 2001).

In this population, there seems to be a different pattern of psychosis in patients with Alzheimer's dementia compared to those with vascular dementia. Delusions are more frequent in Alzheimer's dementia, 23 vs. 8% and agitation is less frequent, 23 vs. 33% (Lyketsos et al., 2000). With respect to individual delusions, patients with Alzheimer's disease are more likely to believe that they are in danger or that others are stealing from them than patients with vascular dementia.

3. Incidence

Up to 90% of patients with dementia develop significant behavioral problems during the course of their illness (Tariot and Blazina, 1994) substantial proportion of patients with AD develop delusions or hallucinations sometime over the course of their illness.

In preliminary data over the course of 18 months from the Cache County, Utah population, the incidences of delusions and hallucinations in people with dementia who did not have these symptoms at the beginning of the study were 27 and 16% respectively, an annualized rate of 18 and 11%, respectively (Lyketsos et al., 2001).

In a dementia clinic population, among 329 patients who did not have psychosis at initial evaluation, the overall incidence of onset of psychosis was 20% at 1 year, 36% at 2 years and 50% at 3 years (Paulsen et al., 2000). In this clinic population predictors of psychosis included the presence of a parkinsonian gate, bradypharenia, and exaggerated semantic memory decline.

In a clinical trials population of mildly to moderately impaired patients with Alzheimer's disease, 9% develop significant hallucinations or delusions after 5 months, and 12% had significant delusions or hallucinations at some time during the 5 months (Schneider and Kershaw, 2001).

4. Clinical characteristics and course

In contrast to schizophrenia where the delusions are frequently bizarre or complex, the delusions that occur in AD are typically paranoid type, non-bizarre and simple. Misidentification phenomena (e.g., of the caregiver) are much more common in AD (Jeste and Finkel, 2000). Typical delusions can include the belief that people are stealing things from them, that they are in danger and/or others are planning to harm them, that their spouse and/or other caregiver is an imposter (or not who they say they are), that their house is not their home, that their spouse is having an affair, that their family members are planning to abandon them, that unwelcome guests and/or television figures are actually present in the home, and other delusions of suspiciousness and paranoia (Reisberg et al., 1987). Hallucinations may be auditory or visual. Patients may hear voices, talk to people who are not there, see things that are not there (Reisberg et al., 1987).

Yet, even though this range of symptomatology is firmly established as typical of patients with AD, it may be artificially constrained by the limitations of the two main structured rating scales used to elicit symptoms of hallucinations and delusions, the Behave-AD and the Neuropsychiatric Interview (Reisberg et al., 1987; Cummings et al., 1994). Both, essentially enquire about the presence of the specific delusions mentioned above, so that these tend to be reported more often. The broader range of symptomatology has yet to be adequately described.

The persistence of psychosis of dementia can be better defined than it has been in the past. Although there has been clinical opinion that delusions and hallucinations tend to wax and wane in patients with dementia, current evidence suggests that as a rule this is not so. As examples, among nursing home patients with psychosis persisting for at least 2 weeks prior to randomization to placebo in a clinical trial, 62% had persistent psychotic symptomatology over the course of 12 weeks (Schneider et al., 2003). In another series, delusions persisted over the course of 1 year in 43% of patients with delusions admitted to nursing homes.

Among outpatients who had significant delusions or hallucinations prior to randomization to placebo, 39% had persistent psychosis over 3 months and 33% over 5 months (Schneider and Kershaw, 2002). Moreover, in a 12 month long trial 57% of outpatients with delusions or hallucinations at baseline had persistent symptomatology over the course of the year (Levy et al., 1996). In another clinical trial of AD patients with psychosis, 70% of patients with psychosis did not improve on a psychosis scale by more than 25% over the course of the 6 week study (Devanand et al., 1998).

All in all, a substantial proportion of patients with psychosis have persistent symptomatology over an indefinite period of time of at least 3 months to 1 year, as assessed by examining their responses to placebo in clinical trials. Indeed, the proportion is similar to other psychiatric syndromes such as late-life depression wherein placebo response rates of 30–40% imply that 60–70% of patients have persistence of depression over the 6–12 weeks of the trial.

5. Neuropsychological deficits

There is substantial evidence that patients with psychosis of AD have greater frontal lobe and executive function neuropsychological deficits than AD patients without psychosis. In one example, the performance of delusional and non-delusional Alzheimer patients was compared in one outpatient clinic population (Jeste et al., 1992). Although in this population, the delusional patients scored worse on the MMSE (13.9 (7.2 SD) vs 18.5 (6.3) and on the Mattis Dementia Rating Scale total score (89.8 (26.2) vs 101.4 (22.9)) much of the difference on the latter was due to greater deficits in conceptualization. Moreover, delusional patients fared worse on verbal fluency as assessed by the category portion of the Verbal Fluency Test. Thus, delusional patients were more impaired on tests requiring frontal/temporal function than those in the non delusional group.

6. Neuroimaging

Neuroimaging studies suggest that clinical symptoms associated with psychosis of dementia are tied to regional brain dysfunction. A florodeoxyglucose positron emission tomography study found that psychotic symptoms in AD were correlated with hypometabolic abnormalities in the right frontal cortex (Sultzer et al., 1995). Similarly, an association between psychosis in AD and hypoperfusion in the frontal lobes was reported using SPECT (Mega et al., 2000). This study also found disproportionate dysfunction within related subcortical and parietal structures in patients with psychosis.

The relationship between psychosis of AD and brain dysfunction has been explored more closely. A recent florodeoxyglucose study reported that delusions were related to hypometabolism, particularly in the right superior dorsal lateral cortex and anterior cingulate.

Moreover, hypometabolism in the right inferior frontal pole and orbital frontal areas correlated with clinical severity of delusions (Sultzer et al., 2003). Similarly, patients with delusional misidentification symptoms were found to have more severe frontal lobe atrophy and a lesser number of pyramidal cells in area CA1 than patients without such symptomology (Forstl et al., 1994). Thus, delusions in AD appear to be particularly correlated with frontal lobe dysfunction.

7. Psychosis and rate of cognitive decline

There is a substantial body of literature providing evidence that patients with psychosis of AD show a more rapid cognitive decline than AD patients without psychosis but who have similar cognitive deficits. For example, in a study following 135 patients with mild to moderate AD, the time to reach either of two cognitive endpoints (A MMSE score of 8, or a decline of 6 points) was shorter in patients with agitation and hallucinations or extrapyramidal signs (Chui et al, 1994). For patients who were mildly demented, the presence of hallucinations or agitation at study entry was associated with approximately three times the risk of reaching a six-point decline on the MMSE. Another study reported that patients with psychosis declined approximately 1.15 points per 6 mos interval more on the MMSE than those without psychosis (Stern et al., 1994). This can be very roughly thought of as a one-year greater rate of cognitive decline.

While psychotic symptoms are associated with accelerated decline, they do not appear to be associated with increased mortality (Drevets and Rubin, 1989; Rosen and Zubenko, 1991). Similarly, no significant effect of age, age of onset, cognitive performance, ventricular enlargement or severity of EEG at initial exam was observed, suggesting the faster progression associated with psychosis is independent of these factors (Forstl et al., 1994).

Although psychotic symptoms themselves seem to predict rapid cognitive decline, it is possible that treatment with antipsychotics does so as well. For example, in a case-control study, more rapid cognitive decline was observed in those patients treated with antipsychotic medication than in those without (McShane et al., 1998). MMSE scores deteriorated nearly twice as much over the 20 month interval (20.7(2.9) vs. 9.3 (1.3)). This effect, however, did not seem related to antipsychotic dose or to patients with dementia with Lewy bodies. The main predictors of MMSE cognitive decline were physical aggression, diurnal rhythm disturbance, persecutory ideas, and hallucinations. The multivariate analysis of these predictors and demographic characteristics suggested that both persecutory ideas and antipsychotic use best predicted rapid decline. It should be noted that conventional antipsychotics were used by patients in this study.

8. Proposed criteria

Characteristics of psychosis associated with AD and other dementia include simple delusions, misidentifications, hallucinations, frequent association with agitation, and aggression or depression. Provisional criteria have been proposed for identifying psychosis of AD (Jeste and Finkel 2000): Patients with AD must have the following: (a) characteristic delusions or hallucinations in the presence of the possible or probable AD; (b) onset of psychotic signs and symptoms after onset of other dementia symptoms, and which are present at least intermittently for at least 1 month; and (c) symptoms severe enough to disrupt patients' or others' functioning, (d) not better accounted for by another psychotic disorder, medical condition, or effects of a drug, and not occurring during the course of a delirium (Table 1). These criteria prove workable in systematically being able to define a more or less homogeneous group of patients. Key aspects to the criteria, are the psychosis occurs after the dementia, that there is some degree of persistence, and that symptoms are severe enough to be clinically important. One specific critique is that severity should not be based on the extent to which a patient's behavior affects others, but rather to the extent to which it affects the patient's functioning.

9. Response to treatment

One way of considering the validity of the construct of psychosis of dementia is to assess its response to treatment. Historically, antipsychotic medications have been frequently prescribed for agitation and psychotic features of dementia. Indeed, about 30% of total pre-

Table 1
Proposed criteria for psychosis of AD[a]

Characteristic delusions or hallucinations
Possible or probable AD
Onset of psychotic signs and symptoms after onset of other dementia symptoms
Symptoms present at least intermittently for at least 1 month
Symptoms severe enough to cause disruption in patient's functioning
Does not occur only during a delirium
Not better accounted for by another psychotic disorder, a medical condition, effects of a drug
Associated features such as agitation, negative symptoms, or depression should be identified

[a] Modified from Jeste and Finkel (2000). The main modifications are that the criteria are specific for AD; and severity is defined on the extent to which symptoms cause disruption of patient's functioning, and not the extent of disruption in others' functioning.

scriptions for atypical antipsychotics are used in elderly patients in long term care facilities as well as a substantial proportion of haloperidol use (Schneider, 2002).

Haloperidol and thioridazine have been subjected to clinical trials in nursing home populations in the past (Schneider et al., 1990), but subjects included had been heterogenous in terms of dementia diagnoses and behaviors. These trials generally suggested that antipsychotics conveyed a modest amount of efficacy, mainly on overall improvement, and with some adverse events. Haloperidol has been used as a comparator in more recent placebo-controlled trials of atypical antipsychotics, generally showing roughly equivalent efficacy but with the expected extrapyramidal signs and symptoms as adverse effects (e.g., De Deyn et al., 1999; Tariot et al., 2002).

Even so the currently approved and marketed atypical antipsychotics, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole have not been as well-studied in elderly patients with dementia as would be desirable. A growing body of clinical trials with atypical antipsychotics, however, is gradually better defining their efficacy, and in particular that of risperidone, in terms of overall improvement compared to placebo, and in some cases to both placebo and haloperidol, on various clinical rating scales. The few published methodologically sound, placebo-controlled clinical trials, tend to enroll mainly nursing home patients with dementia, not specifically AD, and with agitation and other heterogeneous behaviors, not specifically psychosis. More recent trials have begun to specify that only patients with dementia and delusions or hallucinations be enrolled.

Risperidone has been the most frequently studied of the atypical antipsychotics. There are three, published, placebo-controlled, multi-center trials, confirming the drug's benefit in reducing aggression and psychosis (Brodaty et al., 2003; De Deyn et al., 1999; Katz et al., 1999) (Table 2).

There is also a large, trial undertaken in Germany that has not yet been published. There is only one olanzapine trial in patients with dementia in nursing homes that has been published (Street et al., 2000a), but there are two dementia outpatient trials (Satterlee et al., 1995; Street et al., 2000b) and the Lilly medical letter, the latter comparing olanzapine with risperidone, that have not been fully published, and one European nursing home trial that is completed and unpublished.

There has been one quetiapine trial in nursing home patients, comparing it to haloperidol and placebo (Tariot et al., 2002), and one ariprazole trial (De Deyn et al., 2003) published in abstract form and presented as posters at a meeting, published or presented.

Table 2
Atypical antipsychotics placebo controlled trials in dementia

Reference	Population	*N*	Duration	Outcomes
Risperidone				
Katz et al. (1999) Study Ris-USA-63	Nursing home patients with AD or vascular dementia selected on basis of agitation; 75% had psychosis.	625	12 w	General improvement; improvement in psychosis and agitation.
DeDeyn et al. (1999) Study Ris-Int-24	Nursing home patients with AD or vascular dementia selected on basis of agitation.	344	13 w	Patients randomized to haloperidol also. Modest effects equivalent with haloperidol; differences in adverse events.
Brodaty et al. (2003) Study Ris-Aus-05	Nursing home patients selected on basis of AD and aggression	337	12 w	Improvement on an aggression score, and general improvements in psychosis and agitation
Olanzapine				
Satterlee et al. (1995); Street et al. (2000a) Study HGAO	Outpatients with psychotic manifestations of AD	238	8 w	Dosing was less than 5 mg/d no significant effects
Street et al. (2000b) Study HGEU	Nursing home AD patients with agitation or psychosis; 64% had hallucinations or delusions	206	6 w	Improvements in agitation and psychosis with 5 or 10 mg/d
Study HGGU	Outpatients			Completed, not fully reported
Kennedy et al. (2002) Study HGIV	Nursing home patients			Completed, not reported
Quetiapine				
Tariot et al. (2002) Study 039	Selected on the basis of psychosis and having AD	294	10 w	No significant effect on the primary NPI psychosis/agitation outcome obtained by interviewing caregiver. Significant effect on BPRS agitation factor obtained by direct patient evaluation.
Aripiprazole				
De Deyn et al. (2003) Study 006	Outpatients selected on the basis of having AD and psychosis	208	10 w	No significant effect on the primary NPI psychosis outcome. Significant effect on the BPRS psychosis outcomes.

Protocol RIS-USA-63 showed a modest benefit in reducing measures of both agitation and psychosis with 1 and 2 mg/day doses of risperidone (but not at 0.5 mg/d), compared with placebo (Katz et al., 1999). Adverse events were greater at 2 mg/d. A secondary analysis of only patients with psychosis of dementia, indicated a specific improvement in psychotic symptoms with treatment and not merely an improvement in agitation (Schneider et al., 2003). Moreover, 1 mg/d seemed to be maximally effective for delusions, while 2 mg/d was particularly more effective than 1 mg/d for agitation, implying that lower doses of antipsychotics may be ideal for treating the psychosis, and that higher doses or other approaches may be needed for agitation, not related to psychosis.

Another trial (De Deyn et al., 1999) was less clear: risperidone in flexible doses (average about 1.1 mg/d) improved measures of agitation but not psychosis, while haloperidol produced little effect on agitation, in 344 nursing home patients with dementia. A recently published trial (Brodaty et al., 2003) performed in Australia and New Zealand nursing homes, selected patients based on agitation. Most had AD, but some had vascular dementia. Overall, an average of 0.95 mg/d of oral risperidone concentrate improved agitation and psychotic symptoms.

One placebo-controlled trial of olanzapine in outpatients with dementia and psychotic features reported no differences in target symptoms between the drug and placebo groups (Street et al., 2000b; Satterlee et al., 1995). One speculation is that drug dosing may have been too low (below 3 mg/d) and that the patient population may have been too heterogeneous. Yet a nursing home trial in which approximately two-thirds of patients had psychotic symptoms, showed olanzapine at 5–10 mg/day to be effective (Street et al, 2000a).

Similarly, a nursing home study including 294 patients with psychosis and AD showed no significant effects for quetiapine on the main outcomes but some trends on psychosis-related subscales. In this trial wide-ranging but average doses of 113 mg/ day at improving psychotic symptoms and agitation compared to haloperidol and placebo (Tariot et al., 2002).

A 10 week long outpatient trial of aripiprazole in AD patients with psychosis, reported no significant effect on the primary outcome, the NPI summary of the delusion and hallucination items, an outcome obtained by interviewing the caregiver, but did find a significant effect on the psychosis item outcomes of the BPRS obtained by directly evaluating the patient.

Taken together, these trials suggest that atypical antipsychotic medications may be potentially effective in treating specifically psychotic signs and symptoms of AD or dementia. Considerably more work needs to be done, with respect to sample selection, dosing, and assessing outcomes, safety, and overall effectiveness. An additional consideration is that other classes of medications may be effective as well.

10. Discussion

Several comments can be made about patients with psychosis of AD: First, they can be distinguished from other patients with agitation alone, and patients with "uncomplicated" AD. Second, there is specificity and a continuing persistence of psychotic symptomatology among such patients; most patients with psychosis continue to fulfill criteria for psychosis of dementia over at least 3 months, and over a half may have psychotic symptoms persist over a year. Conversely about 20% of patients without psychosis of dementia develop it over a one year period. Third, patients with psychosis of dementia are different demographically and clinically from non psychotic patients in that they are more likely to be women, to be more verbal and ambulatory, and to be rated as having somewhat more anxiety symptoms (Schneider et al., in press). Lastly, there is some evidence that psychosis of dementia patients demonstrates a treatment response to atypical antipsychotics on both measures of psychosis symptoms and agitation, even as more work is needed to more directly assess the overall effectiveness on any response. Taken together, these observations provide evidence for the validity of the construct of psychosis of dementia.

Prospectively designed studies are needed to further confirm and describe the concept, clinical course and treatment responses.

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