

# Psychotic Episodes in Alzheimer's Disease

An expert interview with Clive Ballard

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## Clive Ballard

Clive Ballard received his medical degree at the University of Leicester (UK). He subsequently specialised in psychiatry of older adults and joined the Lewy Body Dementia Research Group. He was later appointed Professor of Age Related Disease and Director of the Biomedical Research Unit for Dementia at King's College London and is now the Executive Dean and Pro-Vice-Chancellor of the University of Exeter Medical School (UK). His key research interests include neuropsychiatric symptoms in dementia, clinical trials of drug and non-drug dementia therapies, genome wide association studies, non-Alzheimer dementias, and online intervention studies. He also leads drug discovery initiatives and clinical trials associated with Alzheimer's disease and non-Alzheimer's dementias.

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Psychotic episodes, particularly delusions, hallucinations, agitation, apathy, depression and sleep disturbance are characteristic and harmful effects of Alzheimer's disease (AD); they are often the first manifestation of the condition and frequently appear before dementia begins. Despite their importance, they are frequently unrecognised and are difficult to treat. There is currently much interest in the mechanisms causing these symptoms, their impact on the disease process and the possibility of new, more effective treatment approaches. In an expert interview, Clive Ballard of Exeter University discusses the current situation of psychosis in AD.

## Q: What are the prevalence and types of psychotic episodes in Alzheimer's disease (AD)?

Over 46 million people worldwide are estimated to live with dementia, of which approximately 75% are attributable to AD.<sup>1</sup> The prevalence of AD increases rapidly after 65 years of age. At any one time approximately 20–25% of people with AD experience psychotic symptoms, which become more common at later stages. Over the entire course of the disease, 50–60% of patients with AD experience at least one of these episodes.<sup>2</sup> In a study of 124 patients with dementia due to AD, 67% had psychotic symptoms occurring 2–6 times per week. For 32% of these patients, the symptoms lasted for 12 weeks and recurred in 50% within 12 months. The frequencies of psychotic episodes are greater in patients with Lewy bodies in brain neural cells. Hallucinations in AD tend to be visual rather than auditory, tactile or olfactory, which distinguishes AD and Parkinson's disease (PD), schizophrenia, psychotic depression or mania. Persecutory delusions occur earlier in AD than misidentification delusions; both types increase with dementia severity.

## Q: How does the incidence of psychotic episodes affect disease progression in AD?

Substantial evidence indicates that the presence of psychotic symptoms has a detrimental effect on the course of AD.<sup>2</sup> Psychotic symptoms are associated with more aggressive disease and a more rapid rate of decline. For example, this was demonstrated in two large cohort studies (n=335 and n=1,821) of patients with incident AD in which presence of clinically significant psychotic symptoms was strongly associated with progression from mild cognitive impairment to dementia (hazard ratios 1.47 and 2.68) and in one of these studies was associated with earlier death (hazard ratio 1.95).<sup>2</sup> Patients with psychotic symptoms are also more likely to be admitted to a nursing home. An unresolved question is whether this more rapid progression is simply the result of greater disease activity or whether it is caused by exposure to treatments for the symptoms, resulting in a range of severe adverse events that negatively impact the patient's condition.

### Q: What are the limitations of current treatment approaches to psychosis in AD?

The treatments evaluated for psychotic symptoms in AD have shown only moderate effects when comparing treated and untreated patients. Most of the outcome studies have evaluated atypical antipsychotics that were originally developed for schizophrenia and have been used to treat agitation and psychosis in people with dementia. Among 18 randomised controlled trials of at least 12 weeks' duration, all showed little or no benefit of treatment in reducing psychotic symptoms.<sup>2</sup> However, a meta-analysis combining these studies, revealed a slight overall effect. The Cohen's D effect size was 0.18 (a small effect would be indicated by  $\geq 0.2$  and a clinically meaningful effect would be  $\geq 0.4$ ). This indicates that the overall efficacy of current treatments is at best marginal and this may be offset by the risk of adverse events. A small number of trials that lasted beyond 12 weeks (6–12 months) have not shown any further benefit in psychosis treatment. These antipsychotics are associated with a near doubling in mortality rates, an approximate 3-fold increase in stroke and substantial increases in the risk of pulmonary embolism, deep vein thrombosis and pneumonia, in addition to more commonly associated adverse events such as parkinsonism, falls and fractures. Effective and well tolerated treatments for psychotic symptoms in AD therefore constitute an important unmet clinical need.

### Q: What outcome measures are important when assessing new therapeutic options for psychosis in AD?

The most widely used validated scale for the assessment of psychosis in AD in trials and clinical practice is the Neuropsychiatric Inventory<sup>3</sup> which comprises 12 subscales, two of which measure psychosis. Other validated scales include the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)<sup>4</sup> and the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSP-AD).<sup>5</sup> These scales cover a range of aspects including psychotic symptom type and severity, typically over a 4-week period, and the impact of these and the disease in general on patient status, functioning and quality of life. These scales are usually completed by informant interview with someone who has regular contact with the patient such as a carer or nurse. These outcome measures are useful in monitoring disease progression and identifying treatment needs.

### Q: What novel treatment approaches are currently under investigation?

A major challenge in the treatment of psychotic episodes in AD is the investigation of treatments other than selective serotonin reuptake inhibitors, but there have been too few studies evaluating such approaches. Approximately 15 years ago, the muscarinic agent

xanomeline showed some efficacy in treating delusions, but was very poorly tolerated due to severe gastrointestinal side effects and was consequently not developed further.<sup>6</sup> Some other novel muscarinic agents may have potential for treatment of psychotic episodes but none of this class are currently usable for these symptoms. Another compound with potential in this indication is the 5-hydroxytryptamine (5-HT)<sub>2A</sub> antagonist, pimavanserin. In a phase III clinical trial in the US (n=199), this drug demonstrated significant benefits in the treatment of psychosis in PD, showing a Parkinson's disease-adapted scale for assessment of positive symptoms compared with placebo of -3.06, (95% confidence interval -4.91 to -1.20; p=0.001; Cohen's D = 0.50).<sup>7</sup> The treatment was well tolerated with no significant safety concerns. Based on these results, pimavanserin was approved for this indication in the US. A UK clinical trial of pimavanserin for psychotic episodes is nearing completion and the results will be available soon. While one or two other classes of drug may offer future potential for psychosis in AD, currently only the atypical antipsychotics have an evidence base indicating that they provide efficacy benefits in this indication without a substantial risk of severe side effects.

In addition, visual hallucinations in AD can be triggered by cataracts.<sup>8</sup> The incidence of cataract rises with age and they are often not treated quickly. It would therefore be worthwhile investigating whether prompt treatment of cataract and other visual conditions would reduce the incidence and severity of hallucinations in patients with AD. Other novel treatments include non-drug approaches such as psychological and cognitive therapies, and physical exercise, but investigation of these specifically for psychotic episodes in AD has been limited.<sup>9</sup> The evidence supporting these approaches in AD is not strong, although some studies suggest that cognitive stimulation may be beneficial and that exercise can slow the rate of cognitive decline; however, further studies in larger patient populations are needed.<sup>9,10</sup>

For some years, progress in developing effective treatments for psychosis in AD has largely stalled. Current treatments are not satisfactory but few more effective and tolerable alternatives have emerged. The development of safer and more optimal treatments needs to be given greater priority. This should include both pharmacological and non-pharmacological approaches. While this situation may appear bleak, treatments are advancing, but not with the speed or resources that they need. With ageing populations worldwide, the prevalence of AD is certain to grow in the coming decades, and associated psychotic symptoms are likely to increase the heavy burden and worsen prognoses for patients with this disease. For this reason, greater efforts are needed to increase the pace of research in developing better means of managing this common and harmful consequence of AD. □

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