PSYCHOSIS IN ALZHEIMER’S DISEASE

Based on a poster presentation by Schneider L1, with Kershaw P2

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As recently reviewed by Jeste and Finkel, the first patient described by Alois Alzheimer had psychotic symptoms including paranoid delusions and hallucinations.1,2 In fact, Alzheimer’s disease (AD) was initially referred to as presenile and later as senile psychosis. The most recent estimate of the frequency of psychotic symptoms in AD patients ranges from 30% to 50%, and the delusions can recur or persist in most patients for several years.3-9 The delusions and hallucinations are commonly associated with aggression, agitation, and disruptive behavior.10-13 Jeste and Finkel proposed diagnostic criteria for psychosis in AD that would distinguish these symptoms from those seen in schizophrenia.

This study is a post hoc analysis of a published study to further validate psychosis in AD. Subjects were participants in a 5-month, multicenter, parallel-group, double-blind, placebo-controlled trial of galantamine in the United States.14 Participants were required to cooperate with the study procedures at baseline, suggesting that behavioral impairment was not significant at that time.14

To review, diagnosis of AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria, including a history of gradual cognitive decline progressing over at least 6 months. Mild to moderate dementia was defined as a Mini-Mental State Examination (MMSE) score of 10 to 22 and a score of at least 18 on the AD Assessment Scale-cognitive subscale (ADAS-cog).14

Patients were assigned to 1 of 4 treatment groups: placebo, or galantamine at 8 mg/day, 16 mg/day, or 24 mg/day, following a 4-week, single-blind, placebo-run-in. The primary outcome measures, described previously, were cognitive abilities (ADAS-cog) and clinical global change. In addition, functional abilities and behavior were assessed.14 This post hoc analysis focused on the behavioral changes as measured by the Neuropsychiatric Inventory (NPI) in the placebo group to identify psychosis specifically related to AD. Clinically meaningful psychosis was defined as an NPI score of at least 4 (ie, distressing and disruptive hallucinations and delusions, present for the 4 weeks before baseline assessment).14

Of the 286 patients who received placebo, 285 had baseline NPI assessments. Of those 285 patients, 272 had assessments at 1 month, 249 at 3 months, and 238 at 5 months. The patients’ mean age was 77.1 years with a mean MMSE score of 18. Sixty-two percent of them were women.14

Of those patients who had at least 1 NPI assessment (N = 272), 12% (N = 33) had clinically meaningful psychosis at baseline. Of those 12%, the psychosis persisted for 1 month in 21 subjects (64%), for 3 months in 13 subjects (39%), and for 5 months in 11 subjects (33%), as diagramed in the figure.

Of the 239 patients who did not have clinically relevant psychosis at baseline, 4% (N = 9) had symptoms of psychosis at 1 month, 6% (N = 14) at 3 months, and 9% (N = 21) at 5 months, showing that the incidence of psychosis doubled during the duration of the study.

Of the 239 patients, 105 were labeled asymptomatic because they did not score higher than 3 on any NPI item at baseline. Of those 105 patients,
33% (N = 35) scored from 4 to 12 on any item of the NPI at the end of the 5-month study, the incidence of behavioral symptoms was 33%. Of these 35 patients, 2 developed hallucinations or delusions, 5 developed agitation and aggression (with no hallucinations or delusions), and 3 developed depression or dysphoria, indicating that the incidence increased by 5% and 4% over 5 months for aggression/agitation and depression, respectively. These results suggest that psychosis in patients with AD is a valid clinical entity, at least in patients with mild to moderate forms of the disease. The symptoms of psychosis persisted for at least 1 month in most subjects (postbaseline) and for the full 5 months in one third of the patients. The new incidence was 9% over 5 months, suggesting an annual incidence of 22%. These important results support the concept of psychosis during AD and provide a basis for further exploration of a psychotic syndrome with AD or dementia. The results also underscore the need for therapies that will address the associated behavioral problems such as aggression, agitation, and depression. The main results from the original study showed that galantamine significantly reduced behavioral problems by 16 mg/day and 24 mg/day, as assessed by NPI.13

REFERENCES

REMARKS
Reducing Anoma with Cholinergic Therapy
Based on a poster presentation by Fuller RH, Kendall DL Jr, Naudoo SE, Speeck AA, Heilman KM, and Gonzalez Bath L.13

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Acetylcholine is one of the key neurotransmitters involved in memory and learning. Because Alzheimer’s disease (AD) is associated with the relentless and ongoing loss of these cholinergic neurons, these patients display a debilitating memory and lose the ability to learn with the passage of time. Cholinergic compounds are now being used in AD patients to decrease these effects.

The Brain Rehabilitation Research Center, funded by the VA Rehabilitation Research and Development Service, is conducting numerous clinical trials that attempt to bridge pharmacotherapy with rehabilitative treatments for cognitive or motor impairments resulting from brain damage or degeneration. The center specializes in the development of innovative treatments for these conditions. The study reported here examined the effects of combining speech therapy targeting word retrieval practice with donepezil to improve lexical retrieval performance in a patient with AD. Word retrieval failure is one of the first signs of AD. Donepezil has been shown to be an efficacious acetylcholinesterase inhibitor that helps to maintain cognitive function, although the results are commonly not dramatic.

This was a within-subject study of a 72-year-old, right-handed woman with a diagnosis of probable AD 8 months prior to the study. She had been taking donepezil (5 mg/day) ... E, estrogen replacement therapy, and ginkgo biloba. She continued on these drugs throughout the course of this study.

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This was a within-subject study of a 72-year-old, right-handed woman with a diagnosis of probable AD 8 months prior to the study. She had been taking donepezil (5 mg/day) for 8 months and at the time of the study was also taking Vitamin E, estragon, replacement therapy, and ginkgo biloba. She continued on these drugs throughout the course of this study.

During the study, she was shown a collection of 50 pictures, which were divided into 3 lists. The patient met with the clinician once per day, 4 times per week, for 4 months. At the beginning of each session the full collection of pictures was shown to the patient, and she was asked to name the pictured item aloud. For the first 8 sessions, the patient responses were scored as correct or incorrect and the percentage correct was recorded. A stable baseline of naming performances on these lists was noted. She was noted to reliably produce only about 40% correct on each of the lists during this period when she only received the donepezil. From sessions 9 to 22, the patient participated in an “errorless learning” treatment of List 1 only. In this therapy the clinician provided the patient with the correct response before the patient’s attempt to answer, thus preventing her from producing an error and giving her practice at producing the correct name. From sessions 23 to 30, therapy focused on instituting a 3-second delay in the errorless learning process to increase her independence from the examiner in naming these practiced items. The percentage correct was recorded and the results show increased numbers of correct answers within these sessions during the errorless learning, and this progress was maintained during the delayed errorless learning phase. The percent correct for the untreated lists (Lists 2 and 3) remained unchanged during the treatment of List 1 thus suggesting that the improvement noted during this treatment phase was related to the treatment and not a generalized improvement resulting from unrelated influences.

From sessions 31 to 50, all 3 lists were probed daily again. However, the errorless learning treatment targeted only List 2 and stopped targeting List 1. From sessions 31 to 54, the delayed errorless learning began and from this point results again showed improved percentages of correct answers for List 2, which are maintained when the patient is tested 3 months after the treatment was discontinued. Scores for List 1 results also remained high months later.

These results show that drug alone does not result in improved word production because the percentage correct for List 3 (the list that was never the target of treatment) did not change throughout the study, but the combination of donepezil and word learning treatment did improve performance on Lists 1 & 2 when they were the target of treatment. The benefits were retained after word learning therapy ceased. This study design (a within-subject experiment design) offers the advantage of studying single patients while exerting experimental control. List 3 served as the “control group” because it was never the target of the experimental treatment and following performances on that list during the course of the two treatments on the
Galantamine has already demonstrated efficacy, safety, and good tolerability (especially with slow dose escalation) in randomized placebo-controlled trials in patients with mild to moderate AD.1-3

There are no standard treatments for vascular dementia and AD + CVD, so patients with vascular dementia often go untreated. Patients with AD + CVD may receive drug therapy for the AD. The study reported here is the first to examine the effects of a cholinergic drug (in this case, galantamine) in patients with AD + CVD or probable vascular dementia.

A randomized, double-blind, placebo-controlled, parallel group, 6-month study was conducted in centers throughout the world: Canada, Denmark, Finland, France, Germany, Israel, Poland, the Netherlands, and the United Kingdom. The 392 patients were randomized to receive either placebo (N = 196) or galantamine 24 mg/day (N = 396), following a 6-week escalation phase.

Participants were included if they had either probable vascular dementia according to the National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINCDS/ADRA) criteria or possible AD according to the NINCDS-AD/Alzheimer’s Disease and Related Disorders Association (ADRA) criteria. Computed tomography (CT) scans or magnetic resonance imaging (MRI) of patients with possible AD also showed significant evidence of cerebrovascular disease, ie, CVD. Discrepant data had mild to moderate dementia (as defined by Mini-Mental State Examination (MMSE) scores of 10 to 25, and a score of at least 12 on the cognitive subscale of the AD Assessment Scale-ADAS-cog). Informants for the patients provided parasagittal data, the Disability Assessment for Dementia (DAD) scale. And, finally, disease onset had to be between 40 and 90 years of age.

Both treatment groups had comparable demographic characteristics at baseline. Of note, half of the patients in both treatment groups had vascular dementia. For example, 23% of the patients had a history of cerebrovascular disease (CVD) or diabetes, in which vascular factors contribute to the clinical manifestations of dementia.11 Galantamine is a new pharmacotherapeutic that enhances cholinergic function by diastole mechanisms: competitively and reversibly inhibiting acetylcholinesterase (AChE) and potentiating cholinergic nicotinic neurotransmission by modulating nicotinic acetylcholine receptors.12,13 Galantamine has already demonstrated efficacy, safety, and good tolerability (especially with slow dose escalation) in randomized placebo-controlled trials in patients with mild to moderate AD.1,2

The primary end points were cognition (ADAS-cog) and global function. Secondary end points were activities of daily living (DAD) and behavior. Adverse events were also monitored. The statistical analyses for baseline characteristics and safety data included all randomized patients who received at least 1 dose of the trial medication. The primary statistical analyses of efficacy included data from patients who were randomized and available for evaluation at the designated assessment intervals—the observed case (OC) analyses. Intention-to-treat (ITT) analyses, using the last observation available for each patient who received treatment, were performed to test the robustness of the data.

Galantamine showed significantly greater efficacy than placebo on the ADAS-cog (P ≤ 0.001) for both OC and ITT analyses with final change in scores of 0.6 months of improvement of 1.7 (P < 0.001), and deterioration of 1.0 from baseline (P < 0.05), respectively. Improvement (ie, ≤ 0 point in both groups) was observed at 3 months, but more patients in the galantamine group maintained improvement at 6 months than in the placebo group (63.8% vs 50.6%, P ≤ 0.01). Also, more patients treated with galantamine responded by at least 4 points on the ADAS-cog than patients receiving a placebo (35.3% vs 22.2%, respectively; P ≤ 0.01). Similarly, the percentage of patients remaining stable or improving over 6 months in global functioning, as assessed by the Clinician’s Interview-Based Impression of Change plus caregiver input (CIBIC-plus), was greater for the galantamine group, as compared with the placebo group (74% vs 59%, P < 0.001).

For the activities of daily living, patients taking galantamine had significantly better outcomes at 6 months on the Neuropsychiatric Inventory (NPI), a measure of noncognitive behavioral symptoms of dementia, as compared with the placebo group (a difference of 2.2 points on the NPI, < 0.001). Also, more patients who started with baseline symptoms of behavioral disturbance had significantly better outcomes at 6 months on the Neuropsychiatric Inventory (NPI) (1.0 points on the NPI, < 0.001) and deterioration of 1.0 from baseline (P < 0.05), respectively. Improvement (ie, ≤ 0 point in both groups) was observed at 3 months, but more patients in the galantamine group maintained improvement at 6 months than in the placebo group (63.8% vs 50.6%, P ≤ 0.01). Also, more patients treated with galantamine responded by at least 4 points on the ADAS-cog than patients receiving a placebo (35.3% vs 22.2%, respectively; P ≤ 0.01). Similarly, the percentage of patients remaining stable or improving over 6 months in global functioning, as assessed by the Clinician’s Interview-Based Impression of Change plus caregiver input (CIBIC-plus), was greater for the galantamine group, as compared with the placebo group (74% vs 59%, P < 0.001).

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Galantamine was well tolerated as evidenced by the high number of patients completing the study (74% vs 83% in the placebo group). The adverse events were mild to moderate and mainly occurred during the titration period at a rate of 20% in both groups.

This study is important because it is the first to test the efficacy of a cholinergic drug in patients with AD + CVD and vascular dementia. A wide range of cognitive, behavioral, and functioning outcomes were measured and the benefit with galantamine was observed across the board. Future studies should focus on optimizing dose escalation and examining the clinical and economic benefits of using galantamine to treat these types of patients, in terms of both delayed institutionalization and reduced caregiver burden. -MGG

REFERENCES


