Pilot study demonstrates safety of diabetes medication for patients with Alzheimer's disease

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A pilot study suggests the diabetes medication pioglitazone is generally well tolerated and may warrant further study as a treatment for patients with Alzheimer's disease, according to a report posted online today that will appear in the January 2011 print issue of *Archives of Neurology*.

"Alzheimer's disease is an immense and growing public health problem," the authors write as background information in the article. "Although prescription drug therapy for the symptoms of Alzheimer's disease has been available since 1993, these agents do not fundamentally alter the pathological expression of the disease or its progressive course. The failure of several recent treatment trials directed at the beta-amyloid peptide, a key pathological correlate of Alzheimer's disease, suggests a need to explore alternative approaches to Alzheimer's disease treatment that are not focused on beta-amyloid metabolism."

Another potential therapeutic target for the treatment of Alzheimer's disease is the nuclear receptor peroxisome proliferator-activated receptor gamma, PPAR-gamma, which acts to regulate glucose and lipid metabolism. A class of drugs known as thiazolidinediones, originally developed to reduce insulin resistance in patients with type 2 diabetes, are potent agonists (trigger a response) of PPAR-gamma. To evaluate the safety of one of these medications, pioglitazone, in patients without diabetes but with Alzheimer's disease, David S. Geldmacher, M.D., of the University of Virginia Health System, Charlottesville, and colleagues

conducted an 18-month, double-blind, placebo-controlled randomized controlled trial. Twenty-nine patients without diabetes but with probable Alzheimer's disease were randomly assigned to receive either pioglitazone (titrated to 45 milligrams daily) or matching placebo, along with 200 international units of vitamin E.

A total of 25 patients (12 taking pioglitazone and 13 taking placebo) completed 18 months of therapy. Two of the patients who discontinued participation in the study early had a change in caregivers status, and two withdrew their consent; no discontinuations were attributed to adverse events.

Peripheral edema, swelling of the legs and feet, was the main adverse event, affecting four patients in the pioglitazone group (28.6 percent) compared with none in the placebo group. "This is consistent with the known adverse event profile of pioglitazone," the authors write. "No group differences in laboratory measures were identified."

"No significant treatment effect was observed on exploratory analysis of clinical efficacy," they continue, noting that the study was not intended to determine treatment efficacy. Based on the results of sample size analyses, the researchers estimate that a study would need to enroll between 155 and 340 participants randomly assigned to placebo or pioglitazone to find treatment effects for patients with Alzheimer's disease. Given that trials leading to Food and Drug Administration approval of current drugs typically enrolled 250 to 500 patients, and that several ongoing trials will enroll more than 1,000, further studies to assess the clinical efficacy of pioglitazone would be feasible.

"Disappointing results of treatment trials based on the amyloid hypothesis, and the reasonable degree of safety identified in this trial, suggest that exploratory studies of thiazolidinediones remain warranted," the authors conclude. "Future studies of this class should focus on earlier

stages of disease progression and be augmented by biomarkers, such as nuclear imaging techniques, to measure changes in microglial activation associated with treatment."

More information: Arch Neurol. Published online September 13, 2010. doi:10.1001/archneurol.2010.229