# Rasagiline drug might slow Parkinson's

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Following one of the largest studies ever conducted in Parkinson's disease (PD), researchers at Mount Sinai School of Medicine report today in The *New England Journal of Medicine* that rasagiline, a drug currently used to treat the symptoms of PD, may also slow the rate of disease progression.

Known as ADAGIO (Attenuation of Disease Progression with Azilect Given Once Daily), the 18-month study used a novel design called the delayed start. In this type of study, patients are randomized to start active treatment early or late, and then researchers look to see if early treatment influences the outcome at final visit when patients in both groups are on the same treatment.

ADAGIO showed that previously untreated PD patients randomized to initiate therapy with rasagiline (Azilect(R)) 1 mg per day had benefits at 18 months that were not achieved when the same drug was initiated at nine months. These results are consistent with the possibility that the drug has a disease-modifying effect which slows disease progression. The study examined both 1- and 2-mg doses of rasagiline using a rigorous design that included three primary endpoints. The 1-mg dose met all three primary endpoints. The 2-mg dose did not.

C. Warren Olanow, MD, Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology, Mount Sinai School of Medicine, was the principal investigator of the trial.

"The finding that early treatment with rasagiline 1 mg per day provides

benefits that cannot be achieved with later administration of the same drug indicates that these benefits are not simply due to a symptomatic effect of the drug and are consistent with the possibility that the drug is disease-modifying," said Dr. Olanow, who is also a Professor in the Department of Neuroscience and Director, Robert and John M. Bendheim Parkinson's Disease Center, Mount Sinai School of Medicine. "If this can be confirmed, this would be the first drug determined to have a disease-modifying effect in PD, and that is exciting news for the PD community."

"The need for neuroprotective therapies that slow or stop disease progression represents a significant unmet medical need in PD," continued Dr. Olanow. "One of the obstacles in defining such a treatment has been the potential of such a drug to improve symptoms and thereby confound detection of a disease-modifying effect. The delayed-start design attempts to get around this problem and to eliminate confounding symptomatic effects."

"Dr. Olanow's use of a new clinical trial design appears to have provided a more definitive means to evaluate neuroprotection—something which had eluded researchers in the past," said Dennis S. Charney, MD, The Anne and Joel Ehrenkranz Dean of Mount Sinai School of Medicine and Executive Vice President for Academic Affairs of The Mount Sinai Medical Center. "It demonstrates what's possible when Mount Sinai clinicians, collaborating with regulators and kindred scientists, apply innovative thinking to advance medicine."

The first PD trial to use delayed start as its primary design, ADAGIO was one of the largest trials ever conducted in this disease and included 1,176 patients with very early PD in 14 countries and 129 medical centers. They were randomized to receive rasagiline 1 or 2 mg per day for 72 weeks (early start) or placebo for 36 weeks followed by rasagiline 1 or 2 mg per day for 36 weeks (delayed start).

"We think the findings with rasagiline 1 mg per day must have had something to do with a disease-modifying property of the drug that manifested during the trial's 36-week placebo-controlled phase," Dr. Olanow explained. "The failure to get similar results with the 2-mg dose may be due to the greater symptomatic effects of this dose masking an underlying disease-modifying effect. Indeed, a subgroup analysis of rasagiline 2 mg per day in the most severely affected patients in the study did show positive effects."

PD is a degenerative neurological condition that affects more than a million Americans. Early stages of the disorder are associated with impaired motor skills including tremor, stiffness, and slowness of movement. As the disease progresses, impairments become more severe and can include gait disturbance with falling and dementia.

The three primary endpoints used in this study were based on the Unified Parkinson's Disease Rating Scale (UPDRS), which is used to track PD progression in areas such as mental state, activities of daily life, and motor skills. The three endpoints were: 1) the rate of UPDRS deterioration between weeks 12 and 36 in the early start vs. placebo groups; 2) the change in UPDRS score between baseline and final visit (week 72) in the early treatment group compared to the delayed treatment group; 3) and a demonstration of non-inferiority of the early treatment group vs. the delayed start group in the rate of worsening of UPDRS score between weeks 48 and 72 (i.e., whether the benefit was enduring).

Source: The Mount Sinai Hospital