

What's Hot in Parkinson's Disease

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Are Rasagiline (Azilect) and other Monoamine Oxidase Inhibitors Disease Modifying or Neuroprotective in Parkinson's Disease?

There has long been interest as to whether monoamine oxidase type B inhibitors may have disease modifying or neuroprotective benefits in Parkinson's disease¹⁻⁴. Disease modifying agents are thought to alter the course or progression of a particular disease. Neuroprotective therapies alternatively provide protection of neurons from neurodegeneration or other injuries²⁻⁴. No therapies to date have been proven to be disease modifying or neuroprotective in Parkinson's disease patients.

Monoamine oxidase (MAO) type B inhibitors were introduced over 70 years ago. MAO is a brain enzyme involved in the metabolism of catecholamines, which are specific chemicals present in all of our brains (dopamine, norepinephrine, serotonin)^{5,6}. These chemicals have been found to be critically low in Parkinson's disease, and use of a medication that blocks the enzyme known as MAO has the potential to make chemicals like dopamine more readily available to the brain. The MAO-A form of the enzyme is less selective than the B form of the drug. Additionally, the A form requires restriction of the diet (tyramine containing foods like cheese and wine) to prevent hypertensive crises and other untoward effects. Low doses of MAO-B inhibitors however, do not seem to have this effect, and are safe when mixed with cheese, wine, and even antidepressants⁷⁻¹⁰. MAO-B has therefore become an important part of the armamentarium in the treatment of Parkinson's disease.

The currently available MAO inhibitors include rasagiline tablets (Azilect), selegiline capsules (Eldepryl), and the selegiline orally disintegrating tablet (Zelapar)^{8,10-12}. All three drugs have been shown to have very modest symptomatic benefits on the motor symptoms of Parkinson's disease (e.g. tremor, stiffness, slowness, off time). There was a very large Parkinson Study

Group trial in the 1990's called DATATOP (Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism)¹³. There were 800 patients enrolled and until the ADAGIO (rasagiline) study it was the largest prospective early Parkinson's disease cohort ever investigated. According to information posted at PD-DOC (www.pd-doc.org), "the trial was carried out to determine whether long-term therapy with deprenyl (selegiline) and/or tocopherol would extend the time before advancing disability required the initiation of levodopa therapy in patients with early, untreated Parkinson's disease. Deprenyl, 10 mg/day, was found to significantly delay the initiation of levodopa. Tocopherol, 2000 IU/day, produced no benefits and there was no interaction of the two drugs." The DATATOP study was conclusive in showing a symptomatic benefit for selegiline, but was unable to prove a neuroprotective or disease modifying benefit.

At the American Neurological Association meeting in December 2008, results were released from the Attenuation of Disease Progression With Azilect Given Once-Daily (ADAGIO). The study was a randomized double-blind placebo-controlled trial and had 1176 early Parkinson's disease patients making it even larger than DATATOP. The study utilized a novel design called a delayed-start. The results revealed that the 1 mg dose of rasagiline may have had a disease modifying benefit. Specifically, the group randomized to the delayed start of rasagiline therapy failed to catch up to those randomized to the immediate start. Interestingly, unexpectedly and also without clear explanation the 2mg dose failed to reach study endpoints. The results were also recently presented at the 12th Congress of the European Federation of Neurological Societies, in Madrid, Spain.

Some of the controversy in interpretation has been centered around the study endpoints which were based on a common Parkinson's disease scale called the UPDRS. The impact of change from baseline of only 1.7 units (combined score with all UPDRS subscores), and the mystery as to why the 2mg dose failed, has drawn criticism from some experts in the scientific community. The novel study design has also been criticized as potentially falling short of proving the high bar of disease modification or neuroprotection. Finally, certain subtypes of Parkinson's disease may have fueled the statistical benefit, however we are not able at this time to tease these out (e.g. genetic, tremor predominant, etc.) The study ultimately revealed the 1mg dose to be safe and well tolerated, and because of the novel delayed start design it can be argued that rasagiline has a possible disease modifying effect.

There have not been similarly designed studies of plain selegiline or zelapar performed, but one may appropriately argue that the effects may be similar across the different MAO-B drugs in this class. It is therefore reasonably safe and there exists a reasonable rationale for patients and practitioners to use a MAO-B inhibitor as monotherapy (single drug), or as part of a more complex medication regimen. This class of therapy has the potential to improve symptoms and some experts will argue there is adequate evidence to support

disease modification (i.e. the delayed start group), however most experts will dismiss the notion of neuroprotection. It should be emphasized that the results of ADAGIO have not appeared in a peer reviewed paper form, and we await the scrutiny and interpretation of the full scientific community.

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