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## REPORT

### DEPRENYL and Parkinson's The Answers are Unclear

In the May 1998 issue of *Life Extension*, we explored the role of deprenyl in protecting brain cells and even extending life span. In that context, the evidence is compelling. However, deprenyl's neuro-protective qualities are far from clear when applied to Parkinson's disease. Indeed, there is controversy over whether deprenyl protects neurons in a clinical setting, or merely treats the symptoms of Parkinson's disease. It isn't made any easier by the fact that different studies have produced alarmingly conflicting results.

Parkinson's disease is the second most common neuro-degenerative disease (after Alzheimer's disease), affecting about 2 percent of the population. The neuro-degeneration in this case is very selective-it is the brain's dopamine-producing neurons, in the pars compacta of the substantia nigra ganglia, that degenerate. Why is this important? Because dopamine, formed from an amino acid in the body called levodopa (L-dopa), acts as a neurotransmitter in the central nervous system; it helps carry signals through the brain. When dopamine-producing neurons degenerate, there is less dopamine to carry brain signals, producing the brain-impaired characteristics of Parkinson's disease.

To compensate for the loss, dopamine receptors in the striatum of the brain increase in number, leading to an increase in dopamine turnover and release. However, when dopamine in the striatum is depleted to 20 percent of the original level, compensation has reached its limit and symptoms of Parkinson's disease appear.

Treatment with levodopa-a form of the dopamine precursor that is administered to patients orally and converted to dopamine in the body-can alleviate Parkinsonian symptoms, but the degeneration continues. Within five to 10 years from the start of treatment, the effectiveness of levodopa begins to fail, while its side effects become intolerable. Those levodopa side effects may include nausea, vomiting, dry mouth, hand tremor, headaches, dizziness, confusion, hallucinations and delusions. Cardiac irregularities and palpitations have been reported, in addition to serious psychotic episodes and depression.

There is ample evidence that the neuron degeneration in the substantia nigra is due to free-radical oxidation, and most studies indicate a 30 to 40 percent increase of iron in the substantia nigra of Parkinson's patients. Aluminum, which can displace iron bound to protein and thereby increase reactivity, also is increased. Although Parkinson's symptoms can be induced in laboratory animals by injecting iron into the substantia nigra, this does not prove that iron accumulation is what ultimately causes Parkinson's disease.

Levels of glutathione-a naturally occurring compound in the body that destroys free radicals and other harmful substances-are lower in the substantia nigra in Parkinsonism, and there is evidence that this depletion occurs earlier than the increase in iron. However, there may be some earlier cause that precedes reduced glutathione. Therefore, acknowledging that oxidation contributes significantly to neuro-degeneration still may not provide an answer to what begins the Parkinsonian process.

Two large clinical trials, both consisting of about 800 Parkinson's patients, have served as a focus for the role of deprenyl as a neuro-protective agent in clinical practice. The first of these trials was DATATOP (Deprenyl And Tocopherol Antioxidant Therapy of Parkinsonism), a randomized, double-blind study at 28 U.S. and Canadian sites that tested the effectiveness of 2,000 international units (IU) a day of vitamin E and 10 mg a day of deprenyl in delaying the need for levodopa therapy in early stage Parkinson's patients.

Vitamin E was never shown to be of any benefit in Parkinsonism. But the first released results announced that deprenyl had delayed the need for levodopa therapy by 57 percent. A subsequent publication of DATATOP results was less enthusiastic. It acknowledged that at least part (and perhaps all) of the delayed need for levodopa was due to deprenyl relieving the symptoms of Parkinson's disease, while the underlying neuro-degeneration continued. A claim was made for neuro-protection, but the study design could not prove such protection.

After a few more years of patient follow-up, the conclusions ceased to be positive at all. The scientists noted, "Deprenyl does not provide an advantage in preventing or postponing complications from levodopa therapy." They added that, "By the end of the study, subjects receiving the different treatments had comparable degrees of Parkinsonian disability and were taking comparable amounts of levodopa."

The second large clinical trial, the PDRG-UK (Parkinson's Disease Research Group of the United Kingdom), contained a more devastating indictment of deprenyl. The startling conclusion: After five to six years of follow-up, patients taking a combination of levodopa and deprenyl had a 57 percent greater chance of dying than patients taking levodopa alone.

In the pooled results of seven other controlled long-term studies, the PDRG-UK patients receiving levodopa alone had death rates more than three times as great as the non-deprenyl-treated patients, and the levodopa/deprenyl patients had death rates more than five times as great as the deprenyl-only patients.

A storm of protest arose in the medical community, prompted by the fact that the results were counter to those found in nearly all previous studies. In fact, pooled results from many small studies showed opposite results from those of PDRG-UK...namely, slightly reduced mortality with deprenyl.

Why the controversy over the PDRG-UK trial? Fingers were pointed at methodology. The PDRG-UK trials had not been blinded at all, meaning patients knew their medications and could change groups at will. Nearly 50 percent of the subjects dropped out completely. Further skewing the results was the fact that, since the test was unblinded, the most seriously afflicted patients could have been the ones most earnest about receiving both medications. In addition, the fact that deprenyl was used only in combination with levodopa opens the possibility of levodopa/ deprenyl and Parkinson's disease interactions that might not be relevant to those taking deprenyl for longevity purposes.

Also, unlike other studies, PDRG- UK trial participants had not been excluded on grounds of excessive age, other diseases or other medications being taken. In defense, A.J. Lees and other representatives of PDRG-UK wrote that these conditions more accurately reflect true clinical practice than trials that screen participants more carefully. Lees and his associates also stated that their study design was superior to that of DATATOP and several others because mortality, rather than advent of levodopa therapy, was chosen as the end point.

A better interpretation is probably that the PDRG-UK study was able to command authority by having so many patients, but should be regarded with suspicion because of the poor controls that allowed the study to become so large.

Although causes of death due to deprenyl had not been well identified in the PDRG-UK paper, a subsequent paper co-authored by Lees concluded, "Therapy with deprenyl and levodopa in combination may be associated with severe orthostatic hypotension not attributable to levodopa alone." Orthostatic hypotension is a dramatic fall in blood pressure when standing, leading to blurred vision, dizziness or fainting.

A more carefully designed study that examined deprenyl alone, rather than in combination with levodopa, seemed to confirm a side effect of orthostatic hypotension for Parkinson's patients taking deprenyl. But, according to the DATATOP study, there was no significant treatment-related changes in blood pressure or pulse recordings, although a 2 percent incidence of non-life-threatening cardiac arrhythmias was reported for the deprenyl group.

Two subsequent trials tried to address the design flaws of DATATOP and PDRG-UK by being double-blind and placebo-controlled. One used mortality as the end point and the other used physical disability. Both concluded that deprenyl has neuro-protective action in clinical use. In support of this conclusion is another study that found more neurons in the substantia nigra of autopsied patients who had been taking deprenyl.

Even if 10 mg a day of deprenyl does lower blood pressure for some Parkinsonian patients-the orthostatic hypotension problem-it is questionable how relevant this result is for people without neuro-degenerative disease who are taking deprenyl in smaller doses for life-extension or cognitive-preservation purposes. Briefly elevated blood pressure is more often encountered in such cases, which is why morning dosing is common. And it should not be forgotten that Parkinsonian patients have already lost more than 80 percent of their substantia nigra neurons, with the remaining neurons typically in a degenerative state. Their reactions to therapy are going to differ from the reactions of healthy individuals.

Moreover, Parkinson's disease also attacks other midbrain nuclei, including the locus coeruleus, which produces most of the brain's norepinephrine. With norepinephrine (a major neurotransmitter) and serotonin (a vasoconstrictor, meaning it constricts blood vessels) at about 50 percent of normal levels, it is understandable that Parkinsonian patients might suffer from low blood pressure.

Until more is known, Parkinson's patients may want to restrict their deprenyl dosage to only one 5-mg tablet, taken three times a week with the approval of their physicians. This could provide significant protection without any of the potential risks that 10 mg of deprenyl a day could pose.

When it comes to healthy people over 40 who take deprenyl, these Parkinson's studies help to corroborate the recommendation of Dr. Joseph Knoll who has adamantly stated that, for the purpose of slowing brain aging, humans should take only two 5-mg deprenyl tablets a week. Knoll has published numerous articles showing that deprenyl protects the brain against numerous insults inflicted by normal aging. He also has conducted studies showing that animals supplemented with deprenyl have extended life spans.

For now, however, the jury may still be out on determining the impact of deprenyl on Parkinson's disease, and whether it has an effect on the base causes of the disease, or merely treats symptoms.

## Further Reading

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"Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease." A.J. Lees, et al. *British Medical Journal* 311:1602-1607 (1995)

"Selegiline and Mortality in Parkinson's Disease." C.W. Olanow, et al. *Annals of Neurology* 40:841-845 (1996)

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"Selegiline (deprenyl) treatment and death of nigral neurons in Parkinson's disease." J.O. Rinne, et al. *Neurology* 41:859-861 (1991)

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