GLP-1, Parkinson's Disease, and Neuroprotection

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Parkinson's disease is a common and debilitating disorder. The best-known features are resting tremor, rigidity, and slowness, but recently a fuller picture of the associated complications has emerged, encompassing autonomic symptoms, sleep disorders, and cognitive impairment. A common experience of persons with Parkinson's disease is the relentless progression of symptoms and the resultant disability. The development of neuroprotective treatments, capable of slowing, stopping, or reversing neurodegeneration, has long been a priority in the field.[1] Indeed, James Parkinson expressed his optimism for such a treatment in his 1817 publication, *An Essay on the Shaking Palsy*,[2] noting that although the nature of the disease was unknown to him, "there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped." More than 200 years later, we are still waiting for this discovery.

In this issue of the *Journal*, Meissner et al. report on a trial of lixisenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist used to treat diabetes mellitus.[3] Diabetes is a risk factor for Parkinson's disease,[4] and treatment of diabetes with GLP-1 receptor agonists is associated with a reduction of more than 50% in the risk of new-onset Parkinson's disease.[5] GLP-1 receptor agonists are also protective in animal models of Parkinson's disease.[6] Although a variety of physiological effects are observed in response to GLP-1 receptor activation, a consistent finding is reduced inflammation in the brain, a process that is central to the pathophysiology of Parkinson's disease in humans.[7]

In the current trial, investigators studied participants with early clinical Parkinson's disease. All were already receiving treatment for Parkinson's disease symptoms with levodopa or other drugs. Participants were randomly assigned to either lixisenatide or placebo. After 12 months, the lixisenatide group had essentially no change in scores on the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, but the placebo group had worsening of Parkinson's disease symptoms (an increase of 3.04 points on the MDS-UPDRS part III, on which higher scores indicate greater motor disability). Taken at face value, these data suggest that lixisenatide completely prevented worsening of symptoms over the 12-month period, but this is probably an overly optimistic view. All the MDS-UPDRS scales, including part III, are composites with many components, and improvement in one feature may offset worsening of another. In addition, both trial groups may have benefited simply from participating in a clinical trial.[8] Still, the difference between the two trial groups appears genuine and supports an effect of lixisenatide on the symptoms, and potentially the course, of Parkinson's disease.

The trial participants did encounter adverse effects of treatment. The trialists set out to administer lixisenatide at the highest dose currently approved for diabetes but found that 36% of the participants had unacceptable side effects at that dose. Even with dose reduction, adverse effects of the treatment were common, with nausea reported in 46% of the participants and vomiting in 13% in the lixisenatide group (as compared with 12% and 3%, respectively, in the placebo group). The incidence of side effects may be a barrier to wider use of lixisenatide for Parkinson's disease, and further exploration of lower doses and other mitigation approaches would be valuable.

Previous trials have examined the effects of exenatide, a closely related GLP-1 agonist, in Parkinson's disease. In a 23-month, single-blind trial[9] and a 48-month, double-blind trial,[10] exenatide led to favorable differences in MDS-UPDRS scores similar to those observed in the current trial. All three trials also tested the effects of washing out the GLP-1 agonist for 2 to 3 months and showed that the benefits seemed to persist. A subsequent trial of a long-acting peglylated form of exenatide was negative.[11]

Producing a convincing demonstration of a disease-modifying, neuroprotective effect in Parkinson's disease is a difficult task. So far, technical measures such as imaging have not proven useful in tracking disease progression, and the focus has remained on assessing clinical signs and symptoms. In the current trial, the difference in scores on the MDS-UPDRS after 12 months of

treatment with lixisenatide was statistically significant but small. The importance of this finding is not the magnitude of the change but what it portends. Indeed, the primary concern of most patients with Parkinson's disease is not their present condition — it is the fear of progression of the disease. If a three-point improvement in score on the MDS-UPDRS is the most that can be achieved with lixisenatide, then the value of treatment with the drug may be limited (especially in view of the adverse effects). On the other hand, if the benefit of lixisenatide is cumulative, adding another three points each year over a period of 5 to 10 years or more, then this could be a truly transformative treatment. The next step is clearly trials of longer duration to see whether GLP-1 receptor agonists can live up to Dr. Parkinson's prediction.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Treating Acute Covid-19 — Final Chapters Still Unwritten

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Nirmatrelvir–ritonavir (Paxlovid [Pfizer]) is used as first-line therapy for nonhospitalized persons with Covid-19[1] on the basis of the results of the Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR) trial, which showed that this medication reduced the risk of hospitalization or death by 88%.[2] The EPIC-HR trial enrolled adults who had not received a SARS-CoV-2 vaccine and who were at high risk for progression to severe Covid-19. Given those results, the question arose as to whether nirmatrelvir–ritonavir conferred a benefit in persons who had been vaccinated or who did not have risk factors for severe disease.

The manufacturer-sponsored Evaluation of Protease Inhibition for Covid-19 in Standard-Risk Patients (EPIC-SR) trial, the results of which are reported in this issue of the *Journal*,[3] sought to answer these questions. Participants had symptom onset within 5 days before randomization and either were fully vaccinated and had risk factors for severe disease or were unvaccinated (or had not received a Covid-19 vaccine within the previous year) and had no risk factors. Participants received nirmatrelvir–ritonavir or placebo for 5 days.

The trial enrolled nearly 1300 persons: 57% had been vaccinated against Covid-19, and 50% had a risk factor for severe disease. The participants' median age was 42 years, and only 5% were 65 years of age or older. Other than obesity, smoking, and hypertension, risk factors for severe Covid-19 were uncommon; for example, less than 2% of the participants had heart or lung disease. In this relatively low-risk population, the time to sustained alleviation of symptoms (the primary end point) was similar in the nirmatrelvir–ritonavir group and the placebo group (median, 12 and 13 days, respectively). Although fewer participants were hospitalized for Covid-19 or died from any