Exenatide has potential as a disease modifying agent in Parkinson's disease

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A follow-up study of patients with Parkinson's disease (PD) who participated in an earlier "proof of concept" clinical trial using exenatide showed that improvements persisted twelve months after discontinuing exenatide therapy. These data provide strong encouragement for the further study of this drug in patients with PD, report researchers in the *Journal of Parkinson's Disease*.

Several recent discoveries have highlighted common cellular pathways that potentially relate neurodegenerative processes with abnormal mitochondrial function and abnormal glucose metabolism.

Exenatide, a glucagon-like peptide-1 agonist (GLP-1 agonist) medication marketed as Byetta® and Bydureon® and used in the treatment of insulin resistance in patients with Type 2 diabetes, has been proposed as a disease modifying drug in PD. Earlier studies had shown that exenatide is neuroprotective and promotes functionally beneficial neuroplasticity in animal models of neurodegeneration. Furthermore, exenatide has a favorable safety profile, with only relatively mild gastrointestinal side effects (including nausea and weight loss) as frequent adverse events.

In an earlier "proof of concept" randomized controlled trial published in May 2013, participants were randomized to either self-administer exenatide in addition to their regular PD medications or to act as controls, i.e., receive their conventional PD treatment only. All of the participants had moderate severity PD. In total, 44 patients (20 in the exenatide group and 24 controls) completed the trial. After 12 months

the results showed significant and clinically meaningful differences in both motor and cognitive symptoms between those patients receiving exenatide and the controls. At 14 months, when the patients had discontinued exenatide for two months, the exenatide-treated and control groups still differed from each other. The authors concluded that the study supported potential disease-modifying benefits of exenatide in PD, while acknowledging the lack of a placebo arm.

All of the participants took part in a repeat assessment 12 months after the trial ended. The motor and cognitive advantages persisted in the exenatide group. Compared with the control group, those in the exenatide group had an advantage of 5.6 when using the blinded MDS-UPDRS motor subscale and 5.3 points on the Mattis Dementia Rating scale.

"We found that patients on exenatide appeared essentially unchanged throughout and beyond the trial period, while the control group had the expected rate of gradual decline in movement and cognitive ability," comments senior investigator Thomas Foltynie, MRCP, PhD, of the Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, UK.

The investigators did not find evidence in their data to suggest that glucose tolerance is different in PD patients who received exenatide for 12 months.

"Aside from the changes in MDS-UPDRS scores, there was also persistent divergence in cognitive performance between the groups, with significant differences which were sustained along the trial period, far beyond the 12-month period of drug exposure," says Foltynie. "These data provide continued support for formal double blind trials of GLP-1 agonists as disease modifying drugs in PD."

"The present study could represent a milestone if future controlled trials provide evidence supporting a disease-modifying effect of exenatide and could lead to a revolution in PD therapy," comment Tanya Simuni, MD, of Northwestern University Feinberg School of Medicine, Chicago, and Patrik Brundin, MD, PhD, of the Van Andel Research Institute, Grand Rapids, MI. Writing in the same issue, they warn however that: "Notwithstanding the promising nature of the results, it has to be emphasized that placebo effects can be highly significant and long-standing in PD. Therefore one should not jump to premature conclusions, While placebo effects ought to have diminished 12 months after drug withdrawal so that the exenatide-treated and control groups no longer differed, a lingering placebo effect cannot be excluded."

Tom Isaacs, Co-founder and President of The Cure Parkinson's Trust which funded the follow-up study, says: "Although we have to remain cautious on the estimation of these results, we are encouraged by the findings. This is the first time that I have come across a program that has the potential to make an enduring change for Parkinson's patients and we are excited by the potential of this scientific research."

More information: "Motor and Cognitive Advantages Persist 12 Months After Exenatide Exposure in Parkinson's Disease," by Iciar Aviles-Olmos, MD, PhD; John Dickson, PhD, Zinovia Kefalopoulou, MD, PhD; Atbin Djamshidian, MD, PhD; Joshua Kahan, BSc; Peter Ell, FmedSci; Peter Whitton PhD; Richard Wyse; Tom Isaacs; Andrew Lees, MD, FRCP; Patricia Limousin, MD, PhD; and Thomas Foltynie, MRCP, PhD (DOI: 10.3233/JPD-140364). Openly available at iospress.metapress.com/content … r458926/fulltext.pdf

Commentary: "Is Exenatide the next big thing in Parkinson's disease?" By Tanya Simuni, MD, and Patrik Brundin, MD, PhD (DOI: 10.3233/JPD-149001). Openly available at iospress.metapress.com/content … vj43342/fulltext.pdf . *Journal of*

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