# Exenatide

- Impact of Y chromosome loss on the risk of Parkinson's disease and progression
- Glucagon-like peptide-1 receptor modulates cerebrospinal fluid secretion and intracranial pressure in rats
- Prognostic impact of glucagon-like peptide-1 receptor (GLP1R) expression on cancer survival and its implications for GLP-1R agonist therapy: an integrative analysis across multiple tumor types
- Exploring Analysis Approaches for Using the Dopamine Transporter Striatal Binding Ratio in Early- to Mid-Stage Parkinson's Disease Modification Trials
- Targeting microglial GLP1R in epilepsy: A novel approach to modulate neuroinflammation and neuronal apoptosis
- Comparing regional brain uptake of incretin receptor agonists after intranasal delivery in CD-1 mice and the APP/PS1 mouse model of Alzheimer's disease
- Corrigendum to "Pharmacokinetics and efficacy of PT302, a sustained-release Exenatide formulation, in a murine model of mild traumatic brain injury" [Neurobiology of Disease Volume 124 (2019) 439-453 /YNBDI_4338]
- Attenuating mitochondrial dysfunction and morphological disruption with PT320 delays dopamine degeneration in MitoPark mice

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Exenatide is a 39-amino-acid peptide; it is a synthetic version of exendin-4, a peptide found in the venom of the Gila monster.

### Indications

Exenatide, sold under the brand name Byetta among others, is a medication used to treat type 2 diabetes.

It is used together with diet, exercise, and potentially other antidiabetic medication. It is a treatment option after metformin and sulfonylureas. It is given by injection under the skin.

## Research

Glucagon-like peptide-1 receptor (GLP1R) agonist has gained interest as a potential treatment for Parkinson's disease (PD). However, the exact mechanisms responsible for the therapeutic effects of GLP-1R-related agonists are not yet fully understood.

Wang et al. explores the effects of early treatment with PT320, a sustained release formulation of the GLP-1R agonist Exenatide, on mitochondrial functions and morphology in a progressive PD mouse model, the MitoPark (MP) mouse.

The findings demonstrate that administration of a clinically translatable dose of PT320 ameliorates the reduction in tyrosine hydroxylase expression, lowers reactive oxygen species (ROS) levels, and inhibits mitochondrial cytochrome c release during nigrostriatal dopaminergic denervation in MP mice. PT320 treatment significantly preserved mitochondrial function and morphology but did not influence

the reduction in mitochondria numbers during PD progression in MP mice. Genetic analysis indicated that the cytoprotective effect of PT320 is attributed to a reduction in the expression of mitochondrial fission protein 1 (Fis1) and an increase in the expression of optic atrophy type 1 (Opa1), which is known to play a role in maintaining mitochondrial homeostasis and decreasing cytochrome c release through remodeling of the cristae.

The findings suggest that the early administration of PT320 shows potential as a neuroprotective treatment for PD, as it can preserve mitochondrial function. Through enhancing mitochondrial health by regulating Opa1 and Fis1, PT320 presents a new neuroprotective therapy in PD [1)]

There is growing interest in the use following the publication of the results of the Exenatide-PD trial.

## Case series

### 2017

In a randomized, double-blind, placebo controlled trial, patients with moderate stage Parkinson's disease treated with once-weekly subcutaneous injections of exenatide 2 mg (Bydureon) for 48 weeks, had a 3.5-point advantage over the placebo group in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (Part 3) in the practically defined OFF medication state, 12 weeks after cessation of the trial drug. In this article, we discuss some of the important issues of relevance to this trial, with regards to trial design, patient selection, choice of outcome measure and also place into context the implications these results have for patients with Parkinson's disease and the wider research community [2)].

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In a single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate Parkinson's disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. Eligible patients were aged 25-75 years, had idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing-off effects, and were at Hoehn and Yahr stage 2·5 or less when on treatment. Randomisation was by web-based randomisation with a two strata block design according to disease severity. Patients and investigators were masked to treatment allocation. The primary outcome was the adjusted difference in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3) in the practically defined off-medication state at 60 weeks. All efficacy analyses were based on a modified intention-to-treat principle, which included all patients who completed any post-randomisation follow-up assessments. The study is registered at ClinicalTrials.gov (NCT01971242) and is completed.

Between June 18, 2014, and March 13, 2015, 62 patients were enrolled and randomly assigned, 32 to exenatide and 30 to placebo. Our primary analysis included 31 patients in the exenatide group and 29 patients in the placebo group. At 60 weeks, off-medication scores on part 3 of the MDS-UPDRS had improved by 1·0 points (95% CI -2·6 to 0·7) in the exenatide group and worsened by 2·1 points (-0·6 to 4·8) in the placebo group, an adjusted mean difference of -3·5 points (-6·7 to -0·3; p=0·0318). Injection site reactions and gastrointestinal symptoms were common adverse events in both groups. Six serious adverse events occurred in the exenatide group and two in the placebo group, although none in either group were judged to be related to the study interventions.

Exenatide had positive effects on practically defined off-medication motor scores in Parkinson's disease, which were sustained beyond the period of exposure. Whether exenatide affects the underlying disease pathophysiology or simply induces long-lasting symptomatic effects is uncertain. Exenatide represents a major new avenue for investigation in Parkinson's disease, and effects on everyday symptoms should be examined in longer-term trials [3)].

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2)
Athauda D, Wyse R, Brundin P, Foltynie T. Is Exenatide a Treatment for Parkinson's Disease? J Parkinsons Dis. 2017 Aug 4. doi: 10.3233/JPD-171192. [Epub ahead of print] PubMed PMID: 28777758.
3)
Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, Hibbert S, Budnik N, Zampedri L, Dickson J, Li Y, Aviles-Olmos I, Warner TT, Limousin P, Lees AJ, Greig NH, Tebbs S, Foltynie T. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet. 2017 Aug 3. pii: S0140-6736(17)31585-4. doi: 10.1016/S0140-6736(17)31585-4. [Epub ahead of print] PubMed PMID: 28781108.