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Efficacy and Safety of Exenatide for the Treatment of Parkinson's Disease: A Systematic Literature Review

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Conclusion

- Exenatide has demonstrated neuroprotective and neurorestorative properties in clinical settings, which makes it a potential treatment for PD patients. Considering the limited RCTs identified in the SLR, the results of ongoing trials will help to draw firm conclusions about exenatide's effectiveness and safety

Background

- Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson's disease (PD)[1]
- The positive effects of exenatide on nerve cells raise the possibility that exenatide may slow down or stop PD degeneration
- In keeping with this belief, exenatide is being explored as a potential treatment for PD in clinical trials

Objective

- The systematic literature review (SLR) aimed to identify and summarise the evidence supporting the efficacy and safety of exenatide in PD

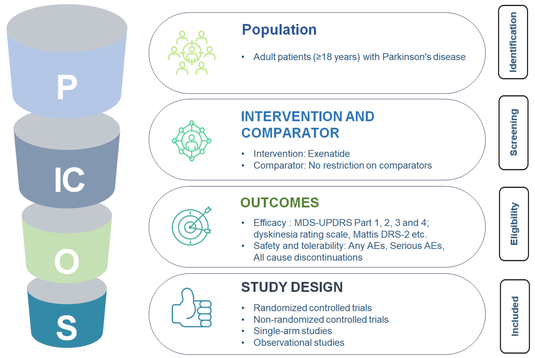
Methodology

- The review followed the standard methodology for conducting SLRs as per the guidelines provided by the National Institute for Health and Care Excellence (NICE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- Key biomedical databases (Embase, MEDLINE, Cochrane Central Trials Register, and clinicaltrials.gov) were searched for English language articles published from database inception to December 2022 to identify relevant studies in PD
- Two independent reviewers performed the screening and data extraction activities with conflicts resolved by a third independent reviewer
- The SLR included randomized controlled trials (RCTs), non-randomized controlled trials (nRCTs), single-arm, and observational studies assessing the efficacy and safety of exenatide in PD. The pre-defined PICOS criteria for study selection is presented in Figure 1

Results

- Two RCTs conducted in the United Kingdom finally met the eligibility criteria. The flow of publications through the entire SLR process is depicted in the PRISMA diagram (Figure 2)
- A total of 107 patients (mean age: 57.2 years; Hoehn and Yahr stage between 1 to 2.5) were randomized to either exenatide or conventional PD treatments (control group)
- At 48 weeks, a statistically significant improvement in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 (off-medication) scores was observed with exenatide vs. control in both RCTs (Aviles-Olmos 2013: CFB: -2.7 vs. +2.2, p=0.037; Athauda 2017: CFB: -2.3 vs. +1.7; p=0.0026) (Figure 3)
- Exenatide also suggested better improvement in MDS-UPDRS part 3 (on-medication) scores vs. control group (Aviles-Olmos 2013: -2.7 vs. +3.6 points) at 48 weeks, however, results were comparable in second RCT i.e., Athauda 2017 (+1.1 vs +1.3) (Figure 4)

Figure 1: PICOS eligibility criteria for selection of evidence



AE: Adverse Event: MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale

Figure 2: PRISMA diagram for the screening process

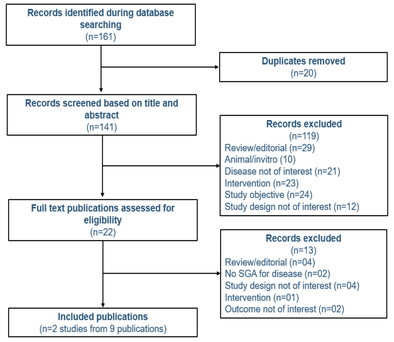


Table 1: Summary of efficacy outcomes reported across studies

Outcomes, Mean (SD)	Aviles-Olmos 2013				Athauda 2017			
	Baseline	24 weeks	48 weeks	CFB (48 weeks)	Baseline	24 weeks	48 weeks	CFB (48 weeks)
Blinded MDS-UPDRS part 3 "off-medication								
Exenatide	31.0 (11.2)	25.2 (9.0)	28.3 (9.9)	−2.7 (7.6)	32.8 (9·7)	30.6 (10·8)	30.2 (11·1)	−2·3
Conventional PD medication	34.0 (16.1)	34.4 (15.0)	36.2 (15.4)	2.2 (7.3)	27.1 (10·3)	28.5 (11·0)	28.8 (10·8)	1·7
MDS-UPDRS part 3 "on-medication								
Exenatide	23.5 (6.3)	22.9 (7.4)	20.8 (6.8)	−2.7 (7.7)	19.4 (8·4)	20.4 (9·7)	20.5 (9·5)	1·1
Conventional PD medication	25.3 (10.7)	29.3 (11.8)	29.0 (11.0)	3.6 (6.7)	14.4 (8·2)	16.0 (7·1)	15.7 (7·1)	1·3
MDS-UPDRS part 1								
Exenatide	10.4 (4.1)	8.8 (2.8)	10.6 (3.8)	0.2 (4.4)	9·8 (4·8)	8·3 (3·6)	8·8 (4·4)	−1·0
Conventional PD medication	11.6 (4.7)	11.5 (6.3)	14.3 (6.0)	2.8 (4.7)	9·2 (3·8)	8·9 (4·4)	9·7 (5·6)	0·5
MDS-UPDRS part 2								
Exenatide	10.2 (5.2)	9.2 (6.1)	9.6 (6.0)	−0.6 (3.9)	12·5 (6·7)	11·2 (7·4)	11·7 (6·3)	−0·7
Conventional PD medication	12.9 (6.2)	14.1 (6.6)	17.0 (7.4)	4.1 (4.4)	10·7 (5·3)	11·1 (6·0)	10·8 (5·6)	0·1
MDS-UPDRS part 4								
Exenatide	6.3 (2.4)	5.4 (2.9)	5.8 (3.3)	−0.5 (2.5)	4·7 (3·1)	4·2 (2·0)	4·9 (2·5)	0·3
Conventional PD medication	6.3 (3.4)	7.6 (4.0)	7.4 (3.5)	1.1 (2.6)	5·3 (3·0)	5·2 (3·2)	5·6 (3·0)	0·3
Dyskinesia rating scale, on medication								
Exenatide	2.3 (2.8)	2.5 (4.1)	3.3 (4.5)	1.0 (4.2)	5.4 (7·9)	4.4 (6·5)	5.1 (7·1)	−0.3
Conventional PD medication	2.6 (2.9)	3.5 (3.9)	2.5 (2.7)	−0.04 (2.7)	7.3 (9·4)	6.9 (9·8)	7.4 (10·7)	0.1
MATTIS Dementia Rating Scale-2								
Exenatide	140.1 (7.7)	142.4 (2.3)	142.3 (2.5)	2.2 (6.4)	138.0 (5·0)	139.5 (4·2)	139.7 (4·1)	1.7
Conventional PD medication	139.5 (4.5)	138.2 (5.1)	136.6 (6.1)	−2.8 (5.3)	139.8 (3·7)	139.7 (5·8)	140.2 (3·9)	0.4

CFB: Change From Baseline; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; PD: Parkinson's

Results (Cont'd)

- Similarly, a trend toward reduction of MDS-UPDRS part 1, 2 and 4 scores at week 24 and week 48 was observed with exenatide as compared with conventional PD treatments (Table 1)
- In comparison with conventional PD treatments, exenatide demonstrated improvement at week 24 and week 48 on both Dyskinesia Rating Scale and MATTIS Dementia Rating Scale-2 (Table 1)
- In terms of safety, both the clinical trials showed well-tolerance to exenatide, however, weight loss, constipation, and injection site reactions were common adverse events (AE) reported

Figure 3: Effect of exenatide on MDS-UPDRS part 3 off-medication score

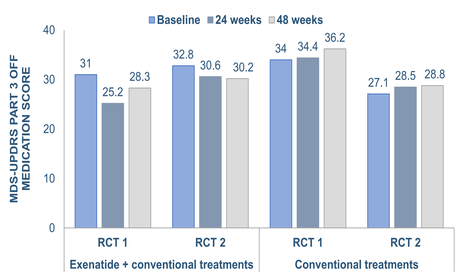
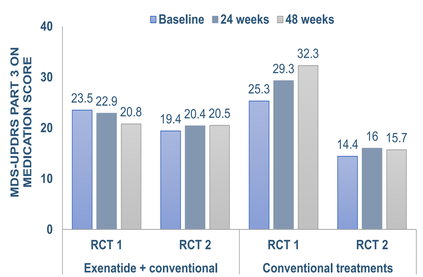


Figure 4: Effect of exenatide on MDS-UPDRS part 3 on-medication score



Results (Cont'd)

- Serious AEs were observed with exenatide, however, none of them were found related to the drug itself
- The findings of the SLR suggested a promising future of exenatide in PD where results of 5 ongoing phase II/III trials are expected in 2023/2024

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Disclosure

PR, SK, SP, and BS, the authors, declare that they have no conflict of interest

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