Cochrane Library

Cochrane Database of Systematic Reviews

GLP-1 receptor agonists for Parkinson's disease (Protocol)

Mulvaney CA, Duarte GS, Menon S, Handley J, Emsley HC

Mulvaney CA, Duarte GS, Menon S, Handley J, Emsley HC.
GLP-1 receptor agonists for Parkinson's disease.
Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD012990.
DOI: 10.1002/14651858.CD012990.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

GLP-1 receptor agonists for Parkinson's disease

Caroline A Mulvaney[1], Gonçalo S Duarte[2,3], Suresh Menon[4], Joel Handley[1,5], Hedley C.A. Emsley[1,6]

[1]Lancaster Medical School, Lancaster University, Lancaster, UK. [2]Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Lisboa, Portugal. [3]Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisboa, Portugal. [4]Department of Medicine, McMaster University, Hamilton, Canada. [5]Department of Neurology, Salford Royal Hospital, Salford, UK. [6]Department of Neurology, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK

Contact address: Caroline A Mulvaney, Lancaster Medical School, Lancaster University, Lancaster, LA1 4YG, UK. c.mulvaney@lancaster.ac.uk, caroline.mulvaney@nottingham.ac.uk.

Editorial group: Cochrane Movement Disorders Group.
Publication status and date: New, published in Issue 3, 2018.

Citation: Mulvaney CA, Duarte GS, Menon S, Handley J, Emsley HC. GLP-1 receptor agonists for Parkinson's disease. *Cochrane Database of Systematic Reviews* 2018, Issue 3. Art. No.: CD012990. DOI: 10.1002/14651858.CD012990.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the effectiveness and safety of GLP-1 receptor agonists for Parkinson's disease.

We will differentiate, as far as possible between neuroprotective and symptomatic effects.

BACKGROUND

Description of the condition

Parkinson's disease (PD) is the second commonest neurodegenerative disorder after Alzheimer's disease (AD), affecting approximately 0.5% of the population over 60 years of age in industrialised countries (Pringhseim 2014). It is caused by the loss of dopamine-producing nerve cells in the part of the brain called the substantia nigra. Dopamine functions as a neurotransmitter and plays a key role in motor control. It is not known what causes the loss of these dopamine-producing nerve cells.

PD is a long-term, progressive disorder which causes significant disability. The symptoms generally develop slowly, typically over 10 to 15 years. PD is characterised by motor features (problems with movement) that include a slowness of movement, shaking at rest, muscular rigidity and postural instability (Kalia 2015), and a variety of non-motor features which include a loss of sense of smell, and sleep and psychiatric dysfunction, including depression, anxiety and dementia. As the disease progresses and treatment-resistant motor and non-motor features dominate, falls, freezing of gait, choking, urinary incontinence and dementia are common (Hely 2005; Hely 2008).

PD shows an increasing incidence with age and is more common in men than women (Hirsch 2016). Risk factors for PD include exposure to pesticides and other environmental chemicals (often experienced by agricultural workers), high consumption of dairy products, a diagnosis of melanoma and traumatic brain injury (Ascherio 2016; de Lau 2006). Protective factors include the use of tobacco, consumption of coffee, caffeine and tea, higher plasma concentration of urates (salts of uric acid), physical activity and non-steroidal anti-inflammatory drugs (Ascherio 2016).

At present, there are no effective disease modifying or neuroprotective interventions: current therapies for PD treat the symptoms

only. Available therapies include levodopa which is converted in the brain (as well as in the periphery) to dopamine, and dopamine receptor agonists that stimulate dopamine receptors.

Typically, PD is defined pathologically by prominent dopaminergic neuron loss and the presence of Lewy bodies containing α-synuclein in the brain. It is increasingly recognised that the neurodegenerative process in PD is complex and multifactorial, and is also likely to involve mitochondrial dysfunction and oxidative stress (Abou-Sleiman 2006), inflammation (Collins 2012), blood-brain barrier dysfunction (Gray 2015), and neurovascular changes (Al-Bachari 2017). Such factors are likely to have treatment and prognostic implications. Vascular comorbidity (including prior stroke, TIA or more than two vascular risk factors), for instance, has recently been found to be significantly associated with cognitive and gait impairment in early PD (Malek 2016).

Description of the intervention

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of drugs that are licensed for the treatment of Type 2 diabetes (Baggio 2007; Campbell 2013; Doyle 2003; Holst 2004). An agonist acts by binding to a receptor (a protein molecule that is the target for the drug) which causes some form of cellular response (Pleuvry 2004). For people with Type 2 diabetes, GLP-1 receptor agonists work by stimulating the GLP-1 receptors in the pancreas, which triggers the release of insulin. However, GLP-1 receptors have also been found in the brain and thus GLP-1 receptor agonists may also have a role to play in the treatment of PD. Insulin signalling in the brain plays a key role in neuronal metabolism, repair and synaptic efficacy (Freiherr 2013; Ghasemi 2013; van der Heide 2006). Insulin activates growth factor receptors on neurons that control energy utilisation, cell repair, mitochondrial function, synapse growth and functionality. Several classic second messenger cell signalling pathways are activated while apoptotic (programmed cell death) cell signalling is inhibited (Holscher 2014). It has been shown that insulin signalling is desensitised in the brains of patients with PD (Aviles-Olmos 2013a; Moroo 1994; Morris 2011), which may explain why Type 2 diabetes has been identified as a risk factor for the development of PD (Hu 2007; Schernhammer 2011; Sun 2012; Wahlqvist 2012). GLP-1 receptor agonists are administered by subcutaneous injection.

How the intervention might work

GLP-1 activates the same key growth factor cell signalling cascades as insulin, and therefore compensates for the loss of insulin signalling (Jalewa 2016). Protease-resistant analogues of GLP-1 have shown neuroprotective effects in animal models of AD (Bomfim 2012; Li 2010; McClean 2011), and resensitise insulin signalling in the brain (Long-Smith 2013). Furthermore, previous studies found that GLP-1 receptor agonists also have neuroprotective effects in animal models of PD. The GLP-1 mimetic (molecule resembling GLP-1), exendin-4, protected motor activity, dopamine levels in the striatum, reduced chronic inflammation and oxidative stress (Harkavyi 2008; Li 2009; Liu 2015a; Zhang 2015). In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropypridine (MPTP) mouse model of PD, GLP-1 mimetics protected the brain from aspects of the MPTP-induced pathology, such as motor impairment, increase in α-synuclein levels, chronic inflammation in the brain, loss of dopaminergic neurons, oxidative stress and growth factor expression (Ji 2016; Li 2016; Liu 2015a; Liu 2015b; Zhang 2015). The GLP-1 mimetics liraglutide and lixisenatide are more effective than the first-generation drug exendin-4. The newer GLP-1 mimetics improve motor co-ordination and activity, and both drugs rescue the expression of tyrosine hydroxylase, a key enzyme in dopamine synthesis (Liu 2015a).

A challenge for clinical trials of neurodegenerative diseases such as PD is to differentiate between the disease-modifying effects and symptomatic effects of any therapeutic agent. Scales used in clinical assessment of PD to measure changes in, for example, motor impairment or quality of life, are unable to distinguish between symptomatic and disease-modifying effects of a treatment. Thus, in order for any novel, potential drug to demonstrate disease modification there needs to be evidence that the drug, when administered for a period of time, stops disease progression. This can be demonstrated in a clinical trial by an absence of deterioration in clinical outcome measures by comparison with a control or placebo group. leicestershire schools between treatment groups are indeed evidence of disease modification rather than symptomatic effects (McGhee 2013). Changes in relevant biomarkers, such as presynaptic striatal dopamine transporter (DAT) binding as assessed by [^{123}I]FP-CIT single photon emission CT (DaTSCAN) examinations, would provide additional evidence of disease modification. In addition, confounders may influence therapeutic effects. For example, while there is evidence that GLP-1 can cause weight loss (Vilsbøll 2012), it is known that the amount of levodopa and its maximum concentration in plasma are negatively correlated with body weight (Müller 2000), and consequently weight loss can lead to an increase in the effectiveness of levodopa. Thus an awareness of potential changes in weight loss due to GLP-1 and subsequent therapeutic effects on PD is essential in a study of GLP-1 receptor agonists.

Why it is important to do this review

Recent advances in understanding of the neuroprotective effects of incretin-based therapies, including GLP-1 receptor agonists, mean that there is considerable interest in their potential utility as repurposed treatments for several neurodegenerative disorders, including PD. People with PD treated with exenatide in an open-label clinical trial showed clinical benefit (Aviles-Olmos 2013b), with subsequent evidence of significant improvement in motor features 12 months after stopping exenatide (Aviles-Olmos 2014).

Similarly, a recent double-blind clinical trial of people with PD found that those treated with exenatide showed improved motor features 60 weeks after coming off the medication, while motor features for those on placebo had worsened (Athauda 2017). It is therefore timely to undertake this review of GLP-1 receptor agonists for PD, as this will provide a summary of the current state of the evidence, as well as providing a platform for updating the evidence base as future studies emerge.

OBJECTIVES

To evaluate the effectiveness and safety of GLP-1 receptor agonists for Parkinson's disease.

We will differentiate, as far as possible between neuroprotective and symptomatic effects.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished, parallel-designed, randomized controlled trials (RCTs). We will exclude non-parallel study designs, that is cross-over trials, due to uncertainty about whether this type of study design is appropriate to study people with PD (Higgins 2011).

Types of participants

We will include trials with a study population of adults (i.e. ≥ 18 years of age), in any setting, with a clinical diagnosis made by any physician, specialist or otherwise, of PD according to the UK Parkinson's Disease Society Brain Bank diagnostic criteria (Hughes 1992), or other equivalent clinical diagnostic criteria, or on the basis of clinical neurological assessment. We will include people at all stages of the disease. Participants may have medical conditions in addition to PD.

We will apply no restrictions based on the number of participants recruited to trials, or the number of recruitment centres.

Types of interventions

We will include studies that involve delivery of GLP-1 receptor agonists with no restrictions on dosage or duration of treatment. We will assess the following comparisons:

1. GLP-1 receptor agonists versus conventional PD treatment;
2. GLP-1 receptor agonists versus placebo intervention; and
3. GLP-1 receptor agonists versus no treatment.

Types of outcome measures

Primary outcomes

1. PD motor impairment measured using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) subscale Part III (Fahn 1987).
2. Health-related quality of life measured using a validated scale such as:
   i) Parkinson's Disease Questionnaire (PDQ-39) (Peto 1995), or short form PDQ-8 (Jenkinson 1997);
   ii) Parkinson's Disease Quality of Life Questionnaire (PDQL) (de Boer 1996); or
   iii) 36-item Short Form Health Survey (SF-36) (Ware 1992).
3. Adverse events, such as weight loss, measured as the number of participants with an adverse event associated with the intervention.

Secondary outcomes

1. PD motor impairment measured using a validated scale other than the UPDRS subscale Part III (Fahn 1987), such as the Unified Dyskinesia Rating Scale (UDysRS) (Goetz 2008)
2. Non-motor outcomes measured using validated scales including UPDRS Part I (Fahn 1987), and Non Motor Symptoms Questionnaire (NMSQuest) (Chaudhuri 2008)
3. Activities of Daily Living measured using scales such as the UPDRS Part II (Fahn 1987), and Schwab and England Activities of Daily Living (SEADL) (Schwab 1969)
4. Psychological outcomes such as dementia and depression measured using validated scales, for example, the Mattis Dementia Rating Scale (DRS) (Mattis 1976), or the Montogomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979)

These primary and secondary outcomes address key disease aspects identified as important by patients and clinicians; the outcomes classified as relating to participation, mobility and motor functioning were considered to be the most important (Hammarlund 2012), and are assessed using UPDRS Parts I and III respectively. We will report outcomes measured at the end of the intervention phase and, if data are available, at least three months post completion of the intervention. Reporting one or more of the outcomes listed will not be an inclusion criterion for trials considered for this review.

Search methods for identification of studies

Electronic searches

To identify studies considered for inclusion in this review, we have developed detailed search strategies for each database we will search. We will assess non-English language papers, translate them as necessary and evaluate them for inclusion.

Databases to be searched

We will search the following databases from inception for published trials in any language:

1. Cochrane Movement Disorders Group trials register;
2. Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library) (Appendix 1);
3. MEDLINE (OVID) (1946 to present) (Appendix 2);
4. Embase (1974 to present) (Appendix 3).

Searching other resources

We will search the following clinical trials registers:

1. WHO Portal (covers ClinicalTrials.gov; ISRCTN; Australian and New Zealand Clincal Trial Registry; Chinese Clinical Trial Register; India Clinical Trials Registry; German Clinical Trials Register; Iranian Registry of Clinical Trials; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register): www.who.int/trialsearch;
2. UK Clinical Trials Gateway: www.ukctg.nihr.ac.uk/default.aspx.

We will handsearch the abstracts of the 16th to 21st International Congresses of the Parkinson's Disease and Movement Disorders conference (2012 to 2017) and the meeting abstracts from the Association of British Neurology (2012 to 2017). As this therapy is relatively new, we are handsearching the more recent conference proceedings. We will screen reference lists of included trials and review articles.

We will cross-check the reference lists of both selected and potentially eligible studies for additional studies to be included.

Data collection and analysis

Selection of studies

We will merge the results of our searches and remove duplicates. Two review authors will independently screen titles and abstracts of studies identified by our search for potential inclusion in the review. We will search for full-text reports of all potentially relevant studies remaining after the initial assessment, and two review authors will independently assess these for inclusion in the review. We will resolve any disagreements between the two authors by consulting a third author. If any posters or conference abstracts are considered potentially relevant, we will seek full-text reports of the study and, if unsuccessful, we will contact study authors to seek further information. Where English translations for studies published in another language are not available at the screening stage, we will obtain full-text reports and translate them initially using an electronic translator. We will exclude studies according to a hierarchy based on the inclusion criteria, that is, wrong study design, wrong patient population and wrong comparator. We will record the reason for study exclusion as the first criterion not met. We will present reasons for excluding full-text reports in the 'Characteristics of excluded studies' table. We will produce a PRISMA flow chart showing how we selected our studies for inclusion in the review (Liberati 2009).

Data extraction and management

Two review authors will independently extract data from included studies using a standard data extraction form that we will customise for this review. We will pilot test the form. We will extract the data detailed below.

1. Publication details
2. Study eligibility criteria
3. Study details e.g. aim, study design, randomisation method, study location, start and end dates, ethics approval
4. Participant characteristics e.g. number of participants, age, sex, diagnostic criteria, study setting, baseline measurements
5. Description of intervention and comparator e.g. duration of treatment, timing, delivery, number of participants randomized to groups
6. Outcome data e.g. numerical data such as means and standard deviations, instruments used to assess outcomes of interest, time points of outcome assessment, withdrawals
7. Data on any relevant reported biomarkers
8. Funding sources and any conflicts of interest for authors

We will compare the extracted data and we will resolve any disagreements by consensus or by deferment to a third review author. One review author will input the data into Review Manager 5 (RevMan 2014), and these will be checked for accuracy by a second review author.

Assessment of risk of bias in included studies

Two review authors will independently assess each included study for risk of bias using the Cochrane tool for assessing risk of bias, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the risk of bias by examining the following six domains.

1. Random sequence generation (checking for possible selection bias): we plan to assess the method used to generate the allocation sequence as being at: low risk of bias (any truly random process, e.g. random number table; computer random

number generator); unclear risk of bias (method used to generate sequence not clearly stated). We will exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

2. Allocation concealment (checking for possible selection bias): we will assess the method used to conceal allocation to interventions prior to assignment to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as being at: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated); or high risk of bias (e.g. open list).

3. Blinding of participants and personnel (checking for possible performance bias): we will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess the methods as being at: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded, but does not provide an adequate description of how this was achieved). We will consider studies that are not double-blind as being at a high risk of bias.

4. Blinding of outcome assessment (checking for possible detection bias): we plan to assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as being at: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation, but lacks a clear statement on how it was achieved). We will consider studies where outcome assessment is not blinded as having a high risk of bias.

5. Selective reporting (checking for reporting bias): we aim to assess whether reported primary and secondary outcome measures were prespecified in a protocol. If the trial protocol is available from a trial registry, the reported outcomes should be consistent with those listed in the protocol if the protocol was registered before or at the time the trial began. We will assess selective reporting as being at: low risk of bias (studies reporting primary and secondary outcomes as specified in the original protocol); high risk of bias (not all prespecified outcomes reported, or only for certain data collection time points).

6. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data): we will assess the methods used to deal with incomplete data as being at: low risk (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).

We will resolve any disagreements by discussion or by deferment to a third review author. We will present our judgements in the 'Risk of bias' tables for each study and we will provide statements to justify our decisions, and appropriate quotes from the reports to support our decisions. We will provide figures summarising the risk of bias for all included studies.

Measures of treatment effect

Continuous data

We will analyse these data based on the mean, standard deviation (SD) and number of participants assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% confidence interval (CI). If more than one study measures the same outcome using different validated scales, we intend to calculate a standardised mean difference (SMD), standard deviation (SD) and 95% CI. We will calculate SMD as the difference in mean outcome between groups divided by the pooled SD of both groups. We will use change from baseline scores for continuous data.

Dichotomous data

We will analyse these data based on the number of events and the number of participants assessed in the intervention and comparison groups. We will use these data to calculate the risk ratio (RR) and 95% CI.

Unit of analysis issues

The unit of analysis will be the study participant with PD. For studies with more than two arms, we will include only those arms that meet the inclusion criteria of the review. We will analyse data on an intention-to-treat basis. In cases where multiple intervention groups of interest are present, we will combine all arms into a single pair-wise comparison, using the Review Manager 5 calculator (RevMan 2014), using the methods suggested by Cochrane (Higgins 2011).

Dealing with missing data

Where data are missing we will attempt to contact study authors to obtain missing data. We will make two attempts to contact authors. We will examine reports of studies with missing data and, where possible, we will report reasons for missing data.

Assessment of heterogeneity

Where we are able to undertake a meta-analysis, we will assess heterogeneity using the I^2 statistic that is included in the forest plot of a Cochrane Review. We will regard a level of heterogeneity above 50% as substantial or high as explained in *Cochrane Handbook for Systematic Reviews of Interventions* Section 9.5.2 (Higgins 2011). If heterogeneity exists, we will examine study reports to identify possible reasons for it. If there are sufficient studies, we will undertake subgroup analysis according to possible identified reasons for heterogeneity.

Assessment of reporting biases

If we are able to pool 10 or more trials in a single analysis, we plan to create and examine a funnel plot to explore possible small study and publication biases. We will test for asymmetry using Egger's test (Egger 1997). Where protocols are available we will compare outcomes reported in published trial reports with those listed in trial protocols to assess reporting bias.

Data synthesis

Where two or more studies report the same outcome, and are sufficiently similar in terms of treatments and participants, we will undertake meta-analyses using fixed-effect models. We will report pooled effect measures for dichotomous outcomes using the Mantel-Haenszel methods, and the inverse variance method for continuous outcomes. If there is considerable heterogeneity that cannot readily be explained, we will use random-effects models. Where it is not possible to pool the findings from studies in a meta-analysis, we will present the results of each study and provide a narrative synthesis of findings. We will perform statistical analysis using Review Manager 5 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

If sufficient data are available we will conduct the following subgroup analyses:

1. severity of PD: defined as severe, moderate or mild as scored on UDPRS subscale Part III (Fahn 1987);
2. clinical subtypes: tremor dominant, mixed, akinetic/rigid;
3. different dosages of GLP-1 receptor agonists;
4. different durations of treatment.

Sensitivity analysis

If we have sufficient studies we will repeat the analyses while excluding studies with a high risk of bias, for example, due to a lack of blinding.

Quality of the evidence

Independently, two reviews authors will assess the quality of the evidence for the three primary outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann 2013). We will use methods and recommendations as described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

To ensure the consistency and reproducibility of GRADE judgements, we will assess key outcomes using the criteria below for each of the five domains.

1. Study limitations: if a study suffers from major limitations, such as lack of blinding, these are likely to result in a biased assessment of the intervention effect.
2. Indirectness of the evidence: this may occur when the review intervention of interest is not compared directly with comparators of interest, or when trials that meet the inclusion criteria address a restricted version of the review question in terms of participants, intervention, comparator or outcomes.
3. Consistency of effect: studies may show differing estimates of effects, and thus we must look for explanations for heterogeneity.
4. Imprecision of results: this occurs if included studies have few participants or events and large confidence intervals.
5. Publication bias: this occurs if investigators do not report studies, usually those with no effect, or outcomes, typically harmful ones or those showing no effect.

The GRADE system uses the following criteria for assigning grade of evidence:

1. high: we are very confident that the true effect lies close to that of the estimate of the effect;
2. moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
3. low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
4. very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We plan to downgrade the GRADE rating by one (- 1) or two (- 2) levels if we identify:

1. serious (- 1) or very serious (- 2) limitations to study quality;
2. important inconsistency (- 1);
3. some (- 1) or major (- 2) uncertainty about directness;
4. imprecise or sparse data (- 1);
5. a high probability of reporting bias (- 1).

We will provide reasons for our decisions regarding the grading of the quality of evidence.

'Summary of findings' table

We will create a 'Summary of findings' table to summarize the key results of the three primary outcomes: PD motor impairment, health-related quality of life, and adverse events.
We will present our assessment of the quality of the evidence in this table. We will use GRADEpro software to prepare the table (GRADEpro 2015), importing the data from Review Manager 5 (RevMan 2014).

ACKNOWLEDGEMENTS

We thank Ema Roque, Managing Editor, Cochrane Movement Disorders Group for her help with this review. We thank Professor Christian Holscher for his help in writing this protocol.

REFERENCES

Additional references

Abou-Sleiman 2006
Abou-Sleiman PM, Muqit MM, Wood NW. Expanding insights of mitochondrial dysfunction in Parkinson's disease. *Nature Reviews. Neuroscience* 2006;**7**(3):207–19. DOI: 10.1038/nrn1868

Al-Bachari 2017
Al-Bachari S, Vidyasagar R, Emsley HC, Parkes LM. Structural and physiological neurovascular changes in idiopathic Parkinson's disease and its clinical phenotype. *Journal of Cerebal Blood Flow & Metabolism* 2017;**37**(10): 3409–21. DOI: 10.1177/0271678X16688919

Ascherio 2016
Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurology* 2016;**15**:1257–72. DOI: 10.1016/S1474-4422 (16)30230-7

Athauda 2017
Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease:a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;**390**:1664–75. DOI: 10.1016/S0140-6736(17)31585-4

Aviles-Olmos 2013a
Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. *Brain* 2013;**136**:374–84. DOI: 10.1093/ brain/aws009

Aviles-Olmos 2013b
Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Ell P, Soderlund T, et al. Exenatide and the treatment of patients with Parkinson's disease. *Journal of Clinical Investigation* 2013;**123**(6):2730–6. DOI: 10.1172/ JCI68295

Aviles-Olmos 2014
Aviles-Olmos I, Dickson J, Kefalopoulou Z, Djamshidian A, Kahan J, Ell P, et al. Motor and cognitive advantages persist 12 months after exenatide exposure in Parkinson's disease. *Journal of Parkinson's Disease* 2014;**4**(3):337–44. DOI: 10.3233/JPD-140364

Baggio 2007
Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007;**132**:2131–57. DOI: 10.1053/ j.gastro.2007.03.054

Bomfim 2012
Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. *Journal of Clinical Investigation* 2012;**122**:1339–53. DOI: 10.1172/JCI57256

Campbell 2013
Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metabolism* 2013;**17**:819–37. DOI: 10.1016/j.cmet.2013.04.008

Chaudhuri 2008
Chaudhuri KR, Martinez-Martin P. Quantitation of nonmotor symptoms in Parkinson's disease. *European Journal of Neurology* 2008;**15 Suppl 2**:2–7. DOI: 10.1111/ j.1468-1331.2008.02212.x

Collins 2012
Collins LM, Toulouse A, Connor TJ, Nolan YM. Contributions of central and systemic inflammation to the pathophysiology of Parkinson's disease. *Neuropharmacology* 2012;**62**(7):2154–68. DOI: 10.1016/ j.neuropharm.2012.01.028

de Boer 1996
de Boer AGEM, Wijker W. Quality of life in patients with Parkinson's disease: development of a questionnaire. *Journal*

of Neurology, Neurosurgery, and Psychiatry 1996;**61**:70–4. [PUBMED: 8676165]

de Lau 2006
de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurology* 2006;**5**(6):525–35. DOI: 10.1016/S1474-4422(06)70471-9

Doyle 2003
Doyle ME, Egan JM. Pharmacological agents that directly modulate insulin secretion. *Pharmacological Reviews* 2003; **55**:105–31. DOI: 10.1124/pr.55.1.7

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629. DOI: org/10.1136/bmj.315.7109.629

Fahn 1987
Fahn S, Elton R, Members of the UPDRS Development Committee. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M editor (s). *Recent Developments in Parkinson's Disease*. Vol. **2**, Florham Park (NJ): Macmillan Health Care Information, 1987:153-163, 293-304.

Freiherr 2013
Freiherr J, Hallschmid M, Frey WH 2nd, Brünner YF, Chapman CD, Hölscher C, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs* 2013;**27**(7):505–14. DOI: 10.1007/s40263-013-0076-8

Ghasemi 2013
Ghasemi R, Dargahi L, Haeri A, Moosavi M, Mohamed Z, Ahmadiani A. Brain insulin dysregulation: implication for neurological and neuropsychiatric disorders. *Molecular Neurobiology* 2013;**47**:1045–65. DOI: 10.1007/s12035-013-8404-z

Goetz 2008
Goetz CG, Nutt JG, Stebbins GT. The Unified Dyskinesia Rating Scale: presentation and clinimetric profile. *Movement Disorders* 2008;**23**(6):2398–403. DOI: 10.1002/mds.22341

GRADEpro 2015 [Computer program]
McMaster University (developed by Evidence Prime, Inc.). GRADEpro GDT. Version accessed 18 October 2017. Hamilton (ON): McMaster University (developed by Evidence Prime, Inc.), 2015.

Gray 2015
Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. *Journal of Cerebral Blood Flow & Metabolism* 2015;**35**(5):747–50.

Hammarlund 2012
Hammarlund CS, Nilsson MH, Hagell P. Measuring outcomes in Parkinson's disease: a multi-perspective concept mapping study. *Quality of Life Research* 2012;**21**(3):453–63. DOI: 10.1007/s11136-011-9995-3

Harkavyi 2008
Harkavyi A, Abuirmeileh A, Lever R, Kingsbury AE, Biggs CS, Whitton PS. Glucagon-like peptide 1 receptor stimulation reverses key deficits in distinct rodent models of Parkinson's disease. *Journal of Neuroinflammation* 2008;**5** (19):11–9. DOI: 10.1186/1742-2094-5-19

Hely 2005
Hely MA, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease:non-L-dopa-responsive problems dominate at 15 years. *Movement Disorders* 2005;**20**(2):190–9. DOI: 10.1002/mds.20324

Hely 2008
Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Movement Disorders* 2008;**23**(6):837–44. DOI: 10.1002/mds.21956

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hirsch 2016
Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of Parkinson's Disease:a systematic review and meta-analysis. *Neuroepidemiology* 2016;**46**:292–300. DOI: 10.1159/000445751

Holscher 2014
Holscher C. Insulin, incretins and other growth factors as potential novel treatments for Alzheimer's and Parkinson's diseases. *Biochemical Society Transactions* 2014;**42**:593–9. DOI: 10.1042/BST20140016

Holst 2004
Holst JJ. Treatment of type 2 diabetes mellitus with agonists of the GLP-1 receptor or DPP-IV inhibitors. *Expert Opinion on Emerging Drugs* 2004;**9**:155–66. DOI: 10.1517/eoed.9.1.155.32952

Hu 2007
Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. *Diabetes Care* 2007;**30**:842–7. DOI: 10.2337/dc06-2011

Hughes 1992
Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry* 1992;**55**:181–4. DOI: 10.4103/0972-2327.83083

Jalewa 2016
Jalewa J, Sharma MK, Holscher C. Novel incretin analogues improve autophagy and protect from mitochondrial stress induced by rotenone in SH-SY5Y cells. *Journal of Neurochemistry* 2016;**139**:55–67. DOI: 10.1111/jnc.13736

Jenkinson 1997
Jenkinson C, Fitzpatrick R, Peto V, Grenhall R, Hyman N. The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. *Psychology and Health* 1997;**12**:805–14. DOI: 10.1002/mds.10678

Ji 2016
Ji C, Xue GF, Li G, Li D, Holscher C. Neuroprotective effects of glucose-dependent insulinotropic polypeptide in

Alzheimer's disease. *Reviews in the Neurosciences* 2016;**27**: 61–70. DOI: 10.1515/revneuro-2015-0021

Kalia 2015

Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;**386**: 896–912. DOI: 10.1016/S0140-6736(14)61393-3

Li 2009

Li Y, Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, et al. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proceedings of the National Academy of Sciences of the United States of America* 2009;**106**:1285–90. DOI: 10.1073/pnas.0806720106

Li 2010

Li Y, Duffy K, Ottinger M, Ray B, Bailey J, Holloway H, et al. GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. *Journal of Alzheimer's Disease* 2010;**19**(4):1205–19. DOI: 10.3233/JAD-2010-1314

Li 2016

Li Y, Liu W, Li L, Holscher C. Neuroprotective effects of a GIP analogue in the MPTP Parkinson's disease mouse model. *Neuropharmacology* 2016;**101**:255–63. DOI: 10.1016/j.neuropharm.2015.10.002

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700. DOI: 10.1136/bmj.b2700

Liu 2015a

Liu W, Jalewa J, Sharma M, Li G, Li L, Holscher C. Neuroprotective effects of lixisenatide and liraglutide in the MPTP mouse model of Parkinson's disease. *Neuroscience* 2015;**303**:42–50. DOI: 10.1016/j.neuroscience.2015.06.054

Liu 2015b

Liu W, Li Y, Jalewa J, Saunders-Wood T, Li L, Hölscher C. Neuroprotective effects of an oxyntomodulin analogue in the MPTP mouse model of Parkinson's disease. *European Journal of Pharmacology* 2015;**765**:284–90. DOI: 10.1016/j.ejphar.2015.08.038

Long-Smith 2013

Long-Smith CM, Manning S, McClean PL, Coakley MF, O'Halloran DJ, Holscher C, et al. The diabetes drug liraglutide ameliorates aberrant insulin receptor localisation and signalling in parallel with decreasing both amyloid-beta plaque and glial pathology in a mouse model of Alzheimer's disease. *Neuromolecular Medicine* 2013;**15**:102–14. DOI: 10.1007/s12017-012-8199-5

Malek 2016

Malek N, Lawton MA, Swallow DM, Grosset KA, Marrinan SL, Bajaj N, et al. Vascular disease and vascular risk factors in relation to motor features and cognition in early Parkinson's disease. *Movement Disorders* 2016;**31**(10): 1518–26.

Mattis 1976

Mattis S. *Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians*. New York (NY): Grune and Stratton Inc, 1976.

McClean 2011

McClean P, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *Journal of Neuroscience* 2011;**31**:6587–94. DOI: 10.1523/JNEUROSCI.0529-11.2011

McGhee 2013

McGhee DJ, Royle PL, Thompson PA, Wright DE, Zajicek JP, Counsell CE. A systematic review of biomarkers for disease progression in Parkinson's disease. *BMC Neurology* 2013;**13**:35. DOI: 10.1186/1471-2377-13-35

Montgomery 1979

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* 1979;**134**:382–9. [PUBMED: 444788]

Moroo 1994

Moroo I, Yamada T, Makino H, Tooyama I, McGeer PL, McGeer EG, et al. Loss of insulin receptor immunoreactivity from the substantia nigra pars compacta neurons in Parkinson's disease. *Acta Neuropathologica* 1994;**87**:343–8. [PUBMED: 8017169]

Morris 2011

Morris JK, Bomhoff GL, Gorres BK, Davis VA, Kim J, Lee PP, et al. Insulin resistance impairs nigrostriatal dopamine function. *Experimental Neurology* 2011;**231**:171–80. DOI: 10.1016/j.expneurol.2011.06.005

Müller 2000

Müller T, Woitalla D, Saft C, Kuhn W. Levodopa in plasma correlates with body weight of parkinsonian patients. *Parkinsonism & Related Disorders* 2000;**6**(3):171–3. [PUBMED: PMID: 10817957]

Peto 1995

Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Quality of Life Research* 1995;**4**:241–8. [PUBMED: 7613534]

Pleuvry 2004

Pleuvry BJ. Receptors, agonists and antagonists. *Anaesthesia & Intensive Care Medicine* 2004;**5**(10):350–2. DOI: org/10.1383/anes.5.10.350.52312

Pringhseim 2014

Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders* 29;**13**:1583–90. DOI: 10.1002/mds.25945

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schernhammer 2011
Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, Ritz B. Diabetes and the risk of developing Parkinson's disease in Denmark. *Diabetes Care* 2011;**34**:1102–8. DOI: 10.2337/dc10-1333

Schwab 1969
Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC editor(s). *Third Symposium on Parkinson's Disease*. Edinburgh & London (UK): E & S Livingstone, 1969:152–7.

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editor (s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Sun 2012
Sun Y, Chang YH, Chen HF, Su YH, Su HF, Li CY. Risk of Parkinson disease onset in patients with diabetes: a 9-year population-based cohort study with age and sex stratifications. *Diabetes Care* 2012;**35**:1047–9. DOI: 10.2337/dc11-1511

van der Heide 2006
van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. *Progress in Neurobiology* 2006;**79**:205–21. DOI: 10.1016/j.pneurobio.2006.06.003

Vilsbøll 2012
Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2012;**344**:d7771. DOI: 10.1136/bmj.d7771

Wahlqvist 2012
Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with type 2 diabetes in a Taiwanese population cohort. *Parkinsonism & Related Disorders* 2012;**18**:753–8. DOI: 10.1016/j.parkreldis.2012.03.010

Ware 1992
Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;**30**(6):473–83. [PUBMED: 1593914]

Zhang 2015
Zhang YF, Chen YM, LI L, Hölscher C. Neuroprotective effects of (Val8) GLP-1-Glu-PAL in the MPTP Parkinson's disease mouse model. *Behavioural Brain Research* 2015;**293**:107–13. DOI: 10.1016/j.bbr.2015.07.021

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 Parkinson Disease:TI,AB,KY
#2 Parkinson*:TI,AB,KY
#3 #1 OR #2
#4 MESH DESCRIPTOR Glucagon-Like Peptide 1 EXPLODE ALL TREES WITH QUALIFIERS AA,AG
#5 ((glucagon like peptide* or GLP 1 or GLP1) ADJ3 (analog* or agonist*)):TI,AB,KY
#6 (exenatide or AC 2993 or ITCA 650):TI,AB,KY
#7 (liraglutide or NN 2211 or NN2211 or NNC 90 1170 or NNC90 1170):TI,AB,KY
#8 (albiglutide or GSK 716155):TI,AB,KY
#9 (elsiglutide):TI,AB,KY
#10 (lixisenatide or AVE 0010):TI,AB,KY
#11 (dulaglutide or LY2189265 or LY 2189265):TI,AB,KY
#12 (taspoglutide or BIM 51077 or BIM51077 or ITM 077 or ITM077 or R 1583 or R1583 or RO 5073031 or RO5073031):TI,AB,KY
#13 (semaglutide or NN 9535 or NN9535):TI,AB,KY
#14 (teduglutide or ALX 0600 or ALX0600):TI,AB,KY
#15 OR/#4-#14
#16 #3 and #15 in Trials

Appendix 2. MEDLINE search strategy

#1 randomized controlled trial.pt.
#2 controlled clinical trial.pt.
#3 randomized.ab.
#4 placebo.ab.
#5 clinical trials as topic.sh.
#6 randomly.ab.
#7 trial.ti.
#8 1 or 2 or 3 or 4 or 5 or 6 or 7
#9 animals.mh. not humans.mh.
#10 #8 not #9
#11 Parkinson Disease.mh.
#12 Parkinson*.ti,ab.
#13 #11 or #12
#14 exp Glucagon-Like Peptide 1/aa,ag [Analogs & Derivatives, Agonists]
#15 ((glucagon like peptide* or GLP 1 or GLP1) adj3 (analog* or agonist*)).tw.
#16 (exenatide or AC 2993 or ITCA 650).tw.
#17 (liraglutide or NN 2211 or NN2211 or NNC 90 1170 or NNC90 1170).tw.
#18 (albiglutide or GSK 716155).tw.
#19 (elsiglutide).tw.
#20 (lixisenatide or AVE 0010).tw.
#21 (dulaglutide or LY2189265 or LY 2189265).tw.
#22 (taspoglutide or BIM 51077 or BIM51077 or ITM 077 or ITM077 or R 1583 or R1583 or RO 5073031 or RO5073031).tw.
#23 (semaglutide or NN 9535 or NN9535).tw.
#24 (teduglutide or ALX 0600 or ALX0600).tw.
#25 OR/14-24
#26 #10 and #13 and #25

Appendix 3. EMBASE search strategy

#1 random$.tw.
#2 clinical trial:.mp.
#3 placebo$.mp.
#4 double-blind$.tw.
#5 1 or 2 or 3 or 4
#6 Parkinson*.ti,ab.
#7 Parkinson Disease/exp
#8 6 or 7
#9 ((glucagon like peptide* or GLP 1 or GLP1) adj3 (analog* or agonist*)).tw.
#10 (exenatide or AC 2993 or ITCA 650).tw.
#11 (liraglutide or NN 2211 or NN2211 or NNC 90 1170 or NNC90 1170).tw.
#12 (albiglutide or GSK 716155).tw.
#13 (elsiglutide).tw.
#14 (lixisenatide or AVE 0010).tw.
#15 (dulaglutide or LY2189265 or LY 2189265).tw.
#16 (taspoglutide or BIM 51077 or BIM51077 or ITM 077 or ITM077 or R 1583 or R1583 or RO 5073031 or RO5073031).tw.
#17 (semaglutide or NN 9535 or NN9535).tw.
#18 (teduglutide or ALX 0600 or ALX0600).tw.
#19 or/9-37
#20 5 and 8 and 19

CONTRIBUTIONS OF AUTHORS

The idea for the review was conceived by all authors. The protocol was drafted by all authors.

DECLARATIONS OF INTEREST

CAM: none known

GSD: none known

SM: none known

JH: none known

HCAE: none known

SOURCES OF SUPPORT

Internal sources

- Internal sources of support, Other.

No sources of support were received to write this protocol.

External sources

- External sources of support, Other.

No sources of support were received to write this protocol.