Clinical Practice Guideline for the Management of Patients with Parkinson's Disease

NOTE:

It has been 5 years since the publication of this Clinical Practice Guideline and it is subject to updating.

The recommendations included should be considered with caution taking into account that it is pending evaluate its validity.

CLINICAL PRACTICE GUIDELINES IN THE SPANISH NHS
MINISTRY OF HEALTH, SOCIAL SERVICES AND EQUALITY

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

RED ESPAÑOLA DE AGENCIAS DE EVALUACIÓN DE TECNOLOGÍAS Y PRESTACIONES DEL SISTEMA NACIONAL DE SALUD

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IACS Instituto Aragonés de Ciencias de la Salud

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This CPG is intended as an aid to decision-making in healthcare. The guidelines are not mandatory, nor do they take the place of the clinical judgement of healthcare staff.

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Table of Contents

Introduction

Documenting variability in clinical practice, analysing the causes thereof and adopting strategies Documenting the variability of clinical practices, analysing the causes, and adopting strategies aimed at eliminating it have been proven to be initiatives that encourage healthcare professionals to make effective, safe, and patient-centred decisions. One of these strategies is the preparation of Clinical Practice Guidelines (CPGs), which are "sets of recommendations based on the systematic review of the evidence and the assessment of the risks and benefits of the different alternatives, in order to optimise the healthcare for patients".

The priorities of the Ministry of Health, Social Services, and Equality include the consolidation of the preparation of CPGs, coordinated by GuíaSalud, within the framework offered by the Spanish Network of Agencies for the Assessment of Health Technologies and Services of the National Health System (NHS).

Parkinson's disease is the most common movement disorder and it has a significant impact on the social and health-related aspects of the quality of life of patients, family members, and caregivers. To effectively address the disease, a large number of healthcare professionals must work together, coordinated as an interdisciplinary team, in which the training, information, and participation of patients and their families plays a vital part.

This is the context that frames this **CPG for the Management of Patients with Parkinson's Disease**.

These guidelines are the product of the efforts by a team of professionals from different areas and healthcare disciplines, including the active participation of the Parkinson's Federation of Spain throughout the entire process of preparing them.

The Directorate General for Public Health, Quality and Innovation would like to thank all of these people for their work, and we hope that the guidelines will aid in the decision-making of professionals and patients, improving the suitability of treatments and the quality of life of those affected by Parkinson's disease.

JOSE JAVIER CASTRODEZA SANZ

Director General of Public Health, Quality and Innovation

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Declaration of interest: All members of the working group, as well as those who have participated in the expert collaboration and external review, have made a declaration of interest which is presented in Annex 5.

Key questions

PHARMACOLOGICAL TREATMENT

Motor symptoms

Antiparkinson drugs

1. Is non-oral administration of antiparkinson treatments used for motor symptoms (dopaminergics and anticholinergics) safer and more effective?

Management of problems related to antiparkinson medications

Drug-induced psychosis

2. Is it more effective and safer to add an atypical antipsychotic (for example: quetiapine) to antiparkinson medication or reduce/discontinue these antiparkinson drugs (anticholinergics, selegiline, amantadine) to control the drug-induced psychosis associated with this disease?

Sleep disorders

3. Which treatment is safest and most effective to reduce the sleep disorders associated with Parkinson's disease?

Impulse control disorders

4. Which treatment is safest and most effective in controlling the impulse control disorders associated with the treatment of Parkinson's disease using dopamine agonists?

Cognitive impairment

5. In adults with Parkinson's disease who develop initial cognitive impairment, is it safer and more effective to add an acetyl cholinesterase inhibitor, or modify dopaminergic treatment to improve cognitive functioning symptoms.

Non-motor symptoms

Sensory symptoms

6. Which treatment is safest and most effective in controlling the alterations with sensory symptoms associated with Parkinson's disease? (e.g. visual alterations; olfactory dysfunction; taste alterations; hypoacousia and other auditory disorders; pain and associated sensitivity symptoms)

Autonomic dysfunctions

7. Which treatments are safest and most effective in controlling the autonomic dysfunctions associated with Parkinson's disease? (e.g. orthostatic hypotension; constipation; fecal incontinence; nausea and vomiting; intolerance to heat; excessive sweating; nocturia; sexual dysfunction; weight loss; difficulty swallowing)

Depression as an associated comorbidity

8. Are selective serotonin reuptake inhibitors (SSRIs) safer and more effective than tricyclic antidepressants (TCAs) in controlling depression associated with Parkinson's disease?

NON-PHARMACOLOGICAL TREATMENT

Occupational and physical therapy

9. How effective is physical therapy in persons with Parkinson's disease?
10. How effective is occupational therapy in improving functional independence in persons with Parkinson's disease?

Speech therapy

Communication and language

11. How effective is speech therapy in improving communication and language in persons with Parkinson's disease?

Swallowing

12. How effective is speech therapy in improving swallowing in persons with Parkinson's disease?

Neuropsychology

13. How effective is rehabilitation of cognitive functions in persons with Parkinson's disease?

Nutrition and Diet

Vitamin D supplements

14. How effective and safe is supplementation with vitamin D in the prevention of falls and hip fractures in persons with Parkinson's disease who present a lack of renal synthesis of 1.25-dihydroxyvitamin D?

Weight loss

15. How effective are the different treatments aimed at weight loss in the treatment of obese and overweight persons with Parkinson's disease?

Modification of protein intake

16. What is the effect of the modification of protein intake in the necessary dose of Levadopa in persons recently diagnosed with Parkinson's and in persons with Parkinson's disease

Levels of evidence and recommendation grades

Table 1. SIGN Levels of evidence and grades of recommendation[1]

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High quality systematic reviews of case control or cohort or studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1++ directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1+ and showing overall consistency of results.
B	A body of evidence consisting of studies rated as 2++, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1 +.
C	A body of evidence consisting of studies rated as 2+ directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2++.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

Studies classified as 1- and 2- must not be used in the preparation of recommendations due to their high potential for bias.

Good clinical practice*

√	Recommended practice based on clinical experience and consensus of the editorial team.

** Sometimes the development group wishes to highlight an important practical aspect for which there is probably no supporting evidence. In general, these cases are related to an aspect of treatment generally accepted to be good clinical practice, and are evaluated as a point of good clinical practice. These messages are not an alternative to the evidence-based recommendations, but should be considered only when there is no other way of highlighting that aspect.*

Recommendations of the CPG

Pharmacological treatment

Motor symptoms

Antiparkinson drugs

B	The use of L-dopa/carbidopa intestinal gel (LCIG) is recommended only for the treatment of advanced Parkinson's disease (PD) with severe motor fluctuations and hyper/dyskinesia when the available combinations of the Parkinson's medications have not produced satisfactory results. This alternative may be cost-effective with the conditions established within the framework of usage of orphan drugs.
B	Evaluation of antiparkinson treatment with transdermal rotigotine is recommended for patients with early or initial PD, at the doses specified in the product sheet, when other alternatives are ineffective.
B	Intermittent injections of apomorphine can be used to reduce motor fluctuations ("on-off" phenomena) in patients with PD in which symptoms are not controlled sufficiently by oral antiparkinson medication.
D	Continuous subcutaneous infusions of apomorphine may be used to reduce *off* time and dyskinesia in persons with PD and severe motor complications. This should only be initiated in expert units with facilities to allow adequate supervision.

Management of problems related to antiparkinson medications

Drug-induced psychosis

D	All persons with PD and psychosis should receive a general medical evaluation, in order to exclude other treatable causes of psychosis.
D	Before considering the use of anti-psychotic medication, treatment for any precipitant condition is recommended.
D	The gradual discontinuation of antiparkinson medication that could trigger psychosis in persons with PD must be taken into account.
D	It may not be necessary to treat moderate psychotic symptoms in persons with PD if they are tolerated well by the patient and the caregiver.
D	Typical antipsychotics (such as phenothiazines and butyrophenones) should not be used with persons with PD because they may exacerbate the motor characteristics of PD.
D	Atypical antipsychotics may be considered for treatment of psychotic symptoms in persons with PD, although the evidence of its efficacy and safety is limited.

D	The use of clozapine at the minimum effective dose is indicated in patients who develop psychotic disorders over the course of their PD, in cases in which standard treatment has failed.
D	When treatment with clozapine is applied, weekly monitoring is recommended during the first 18 weeks of treatment, followed by monitoring for as long as the treatment is continued (at least once every 4 weeks). These analytical controls should be continued for 4 weeks after complete interruption of the treatment.
D	Treatment of psychotic symptoms in patients with PD with clozapine requires the mandatory registration of the monitoring scenario of the atypical anti-psychotic and of blood parameters (total white blood cell count and absolute neutrophil count). For more information, see the product sheet: http://www. aemps.gob.es/
D	The use of low doses of quetiapine may be considered as an alternative anti-psychotic to clozapine for the treatment of patients with psychosis in PD, when weekly routine blood monitoring is not possible, and within the framework of Royal Decree 1015/2009, dated 19 June, regulating the availability of medications in special situations.

Sleep disorders

D	The treatment of Excessive Daytime Sleepiness (EDS) must be aimed at finding a reversible cause, such as depression, poor sleep hygiene, or medications, associated with the altered sleep pattern.
D	Modafinil and melatonin are not recommended for the management of EDS associated with PD.
D	Modified-release Levadopa products may be used for nocturnal akinesia in patients with PD.
D	The sleep history of the patients with PD should be recorded to document the sleep disorder.
D	Proper sleep hygiene is recommended for persons with PD and any sleep disorder, including: • Avoid intake of stimulants in the afternoon (e.g. coffee, tea, etc.) • Establish a regular sleep pattern. • Comfortable bedroom temperature and setting. • Provide healthcare products, such as bed lifts or rails to assist with movement and turning, which helps make people more comfortable. • Restrict naps during the day. • Recommend regular and adequate exercise to sleep better. • Review all of the medication and avoid drugs that affect sleep or alertness, or that could interact with other medication (e.g. selegiline, antihistamines, H2 antagonists, antipsychotics, and sedatives).
D	Special care should be taken to identify and control sleep behaviour disorders, such as restless leg syndrome and the REM (rapid eye movement) phase in persons with PD and sleep disorders.

D	Persons with PD who have sleep attacks should be advised not to drive or expose themselves to occupational risks. An attempt should be made to adjust medication in order to reduce the occurrence of these attacks.
√	Patients should be advised to exercise caution with medication that could alter their ability to drive or operate machinery, and should read the information available on the packaging of this medication: the warning symbol or pictogram on the box (driving pictogram), which is supplemented by the information provided in the prospectus.
√	Persons with PD are recommended to maintain proper sleep hygiene, by doing physical exercise at least a few hours before going to sleep and using satin sheets to facilitate turning in bed.

Impulse control disorders

B	The management of impulse control disorders (ICD) in patients with PD should include the consideration of the reduction or discontinuation of the use of dopamine agonists, using a selective seratonin uptake inhibitor (SSRI), and probably psycho-social counselling and support.
B	Ergoline dopamine agonists should not be used as the first line of treatment of PD and ICD.
A	Switching between dopamine agonists in patients with PD and ICD is not recommended.
D	When ergoline dopamine agonists are used, patients should follow: • A baseline screening ecocardiograph and regular follow-up scans to identify cardiac abnormalities. • Baseline laboratory investigation (e.g. erythrocyte sedimentation rate, serum creatinine) and radiological investigation (chest x-ray) with regular follow-up monitoring to identify serosal fibrosis.
A	Patients should be warned of the potential of dopamine agonists to cause ICD and EDS, and should be informed of the effects on driving and management of machinery.
B	Special attention should be given to detect signs of ICD in young male patients with PD and a prior history of behavioural disorders or addictive behaviour.
√	Healthcare workers should discuss the possible complications of ICD with the patients with PD who are taking dopamine agonists.

Cognitive impairment

A	The use of the acetylcholinesterase inhibitor rivastigmine in patients with idiopathic PD who present mild to moderately severe dementia is recommended.

√	The evaluation of different intervention strategies, including cognitive stimulation is recommended to treat patients with PD who present an initial mild cognitive deterioration, before establishing specific pharmacological treatment with rivastigmine.
D	In patients with PD and cognitive impairment, the causes of dementia should be investigated, and if present, they should be treated.
D	The exclusion of any other non-parkinson medication that acts on the central nervous system should be considered, with the discontinuation of anticholinergic medication, amantadine, selegiline, and dopamine agonists.
√	A systematic review of the treatments prescribed for the management of the motor symptoms of PD is recommended, evaluating the indication, adherence, and interactions, in order to reduce the risk of adverse side-effects such as cognitive impairment, to reduce polypharmacy and agree upon treatments with the patient.

Non-motor symptoms

Sensory symptoms

√	It is advisable to inform patients of the possible alterations with sensory symptoms associated with PD, in order to work on them as a team (patients, family members, and caregivers, along with the healthcare professionals) and reduce the impact of those alterations on the lives of the people affected by this disease.

Autonomic dysfunctions

√	It is advisable to inform patients with PD to avoid the precipitating factors of orthostatic hypotension, such as sudden changes in posture, large meals, hot baths, and vasodilation medication.
√	Managing orthostatic hypotension in patients with PD is recommended, using non-pharmacological measures before initiating pharmacological treatment. Non-pharmacological measures include avoiding meals that are low in sodium and high in carbohydrates, increasing intake of water (2-2.5 l/d) and salt (>8 g or 150 mmol/d) in the diet, breaking up meals, exercise, elevating the head while sleeping, wearing compression stockings, or carrying out physical containment movements to increase blood pressure by increasing venous return and peripheral resistance, such as squatting, leaning forward, or crossing the legs at the onset of presyncopal symptoms. Get out of bed slowly and stay seated in bed for a few seconds before standing.
√	It is advisable to reconsider treatments that induce or aggravate orthostatic hypotension in patients with PD, including the review of all medications, taken with or without a prescription, and other products that could cause hypotension.
D	Persons with PD must be properly treated for the autonomic disorder that results in urinary dysfunction, weight loss, dysphagia, constipation, orthostatic hypotension, excessive sweating, and sialorrea.

√	It is advisable to consider the discontinuation of medication that could induce sialorrea, such as cholinesterase inhibitors, clozapine, or quetiapine.
B	Patients should be advised and treatments that could potentially produce sexual dysfunction (e.g. treatments for hypertension and depression) should be re-evaluated.
B	The use of sildenafil is not recommended for patients with PD and sexual dysfunction.
B	The evaluation of other comorbidities that could result in erectile dysfunction is recommended, such as depression or concurrent sexual dysfunction, especially low sex drive, as well as the deficiency of sex hormones, because the PD may not be the principal cause of the sexual dysfunction.
√	The evaluation of possible causes of urinary dysfunction in patients with PD, such as prostate hypertrophy or cancer, is recommended.
√	Changes in diet and physical activity are recommended for patients with PD and constipation. Increase intake of liquids and fibre, with fibre supplements and stool softeners, if necessary.
√	It is advisable to consider and evaluate treatments that frequently cause constipation (tricyclic antidepressants, loperamide, codeine and opiodes, antimuscarinics, and some antiparkinson drugs).
√	The preparation of an exhaustive pharmacotherapeutic sheet is recommended for patients with PD, in order to determine medications and products that could potentially interact with each other.
B	Domperidone is recommended for problems of gastrointestinal motility (anorexia, nausea, vomiting associated with treatment with Levadopa and dopamine agonists).
√	The use of metoclopramide is not recommended with patients with PD due to the aggravation of the motor symptoms.

Depression as associated comorbidity

D	The management of depression in persons with PD should be personalized, specifically taking into account concurrent treatments and any comorbidities that are present.
√	The selection of the treatment for depression will depend on the prior experience of the healthcare professional and the clinical condition of the patient.
B	Based on the comorbidities presented by the person affected by PD, tricyclic antidepressants may be chosen as a short-term treatment.
√	The evaluation of other non-pharmacological alternatives is recommended for the treatment of depression in persons with PD, such as psychotherapy.
√	A multi-discipline approach is recommended for the management of severe depression associated with PD.

Non-pharmacological treatment

Occupational and physical therapy

A	Offering persons newly affected by Parkinson's disease (PD) rehabilitation treatment based on physical therapy is recommended.
B	It would be advisable to include physical therapy techniques as part of the interdisciplinary approach to PD, placing special emphasis on the functional rehabilitation of the patient.
A	The use of exercise programmes for strengthening/stretching/functioning, supervised aerobic exercise, low-intensity treadmill running, and progressive endurance exercises are recommended in patients with PD.
√	There are other complementary techniques for patients with PD, which can be evaluated based on the characteristics of the patients and their environment, such as tai-chi, training with video games that involve physical exercise and dance.
B	Physical therapy must be available to persons with PD throughout the process of the disease. Special attention should be given to: • Re-education of walking, with improvement of balance and flexibility • Strengthen aerobic capacity • Improve initiation of movement • Improve functional independence, including mobility and activities of daily life • Give advice in regard to safety in the home.
C	The Alexander technique can benefit persons with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition, as well as the attitudes of the person who has PD.
D	Occupational therapy must be available for persons with PD. Special attention should be given to: • Maintaining jobs and family roles, instrumental and advanced daily life, domestic, and leisure activities • Improving and maintaining movement and mobility • Improving personal care activities such as eating, drinking, washing, and dressing. • The aspects of the environment to improve safety and motor functions. • Cognitive evaluation and appropriate intervention.
B	In patients mildly affected by PD, occupational therapy is recommended in order to improve the perceived functional capacity for the activities of daily life of these persons.

Speech therapy

Communication and language

D	Speech therapy should be made available to persons with PD. Special attention should be given to: • Improvement of voice volume and tone range, including speech therapy programs such as LSVT (speech therapy using the *Lee Silverman Voice Treatment* technique) • Teaching strategies to optimize intelligibility of language. • Guarantee that the effective instruments of communication are maintained over the course of the disease, including the use of assisting technologies. • Review and manage to support the safety and effectiveness of chewing and to minimize the risk of choking.
√	The evaluation of the use of the LSVT technique and the evaluation of the results of patients with PD affected by speech and language disorders, especially in the most clinically relevant variable, intelligibility of speech, is recommended.

Swallowing

√	The evaluation of the use of the LSVT technique for managing swallowing difficulties in persons with PD is recommended.
B	The evaluation of the use of video-assisted swallowing therapy (VAST) to improve swallowing in persons with PD is recommended.
√	The use of the chin-tuck technique together with thin liquids to reduce the incidence of pneumonia as a result of aspiration should not be considered as the first line of action in patients with PD and swallowing disorders.
√	A multi-discipline approach is recommended to manage swallowing disorders in persons affected by PD. It would be especially advisable to form coordinated work teams that include healthcare professionals specialized in endocrinology and nutrition, physical medicine and rehabilitation, hospital pharmacy, as well as speech therapists, dieticians-nutritionists, nurses, and occupational therapists, in order to promote the synergy among the tasks of rehabilitation, education, and nutritional support.

Neuropsychology

√	It is advisable to carry out neuropsychological evaluations of patients with PD in order to document baseline cognitive state and track its evolution.
√	Facilitating the improvement of cognitive functions in patients with PD using tools developed by multi-discipline teams is recommended.

Nutrition and Diet

Vitamin D supplements

B	Supplementation with vitamin D (as part of the diet, through enriched foods, food supplements, or medication) helps to prevent fractures in patients with PD who do not ingest a sufficient quantity, or who have a deficit of exposure to sunlight or have a greater need for vitamin D.
√	If an additional supplement of vitamin D is required in persons with PD, the association of calcium is recommended, provided that the patient does physical exercise or the daily calcium requirements are not covered by diet.
√	Food supplements should not be used as a substitute for a balanced diet in persons with PD and adequate nutrition and sufficient exposure to sunlight.

Weight loss

√	Persons affected by PD and who are overweight or obese are recommended to exercise moderately, receive a healthy diet, and develop a lifestyle that helps reduce the impact of this chronic disease and its associated comorbidities.

Modification of protein intake

√	It may be advisable to inform patients to keep protein intake within the recommended dietary requirements (≈ 0.8 g/kg/day) when beginning treatment with Levadopa. Routine dietary evaluation to ensure compliance.
√	The participation of healthcare professionals specialized in human nutrition and diet as part of the multi-discipline teams may help to achieve and maintain compliance in regard to the recommended daily protein intake.
√	Although there is no conclusive evidence, when motor fluctuations occur and drug-nutrient interaction is suspected, a diet with redistribution of proteins may be proposed to patients with PD who are mentally active, motivated, and highly cooperative, but the possible side effects must be considered and managed.

1. Introduction

Intravenous therapy (hereinafter, IVT) is the administration of liquid substances (used for It was Englishman James Parkinson who first described the disease, which he called "paralysis agitans" describing it as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured". This detailed definition is included in an essay titled *"An essay on the shaking palsy"*, published in London in 1817[2].

For many years, Parkinson's disease (PD) was described as a motor disease, characterized by a series of cardinal clinical signs that identify it: bradykinesia, rigidity, trembling and alteration of postural reflexes, requiring at least 3 of these 4 symptoms to establish the diagnosis of the disease.

Beyond these central core symptoms, the disease is associated with other clinical aspects that can also be considered to be motor, such as the phenomenon of "freezing", disorders related to writing (micrographia), or facial hypomimia, but also, in PD, other non-motor symptoms also appear, which can be grouped under three main headings:

- Neuropsychiatric and cognitive: depression, anxiety, psychosis, dementia, apathy, fatigue, and sleep disorders.
- Sensory: loss of smell, paraesthesia, dysesthesia, pain.
- Autonomic: hyperhidrosis, sialorrea, syncope, constipation, urinary dysfunction, and sexual dysfunction, among others.

PD is multifactor in origin and is slowly progressive, affecting primarily the dopamine neurons of the *pars compacta* of the substantia nigra, which produces a depletion of dopamine of the basal ganglia. It is currently described as a synucleinopathy, a multi-systemic disease that affects a particular type of predisposed cells and that advances in a specific manner and with a topographically determined sequence. In this determined or programmed progress, the components of the autonomic, limbic, and somatic-motor systems are damaged progressively. The affectation in PD begins at the level of the neurons of the olfactory bulb and enteric plexuses, which, upwards via the visceral-motor unmyelinated fibres, reach the dorsal nucleus of vagus nerve and later the Central Nervous System (CNS). This establishes a series of anatomical-pathological conditions of affectation with their corresponding clinical correlations[3-5].

The diagnosis of PD is primarily clinical, based on the characteristic symptoms mentioned above; nevertheless, the diagnosis of the autonomic dysfunction requires an objective exploration. Early diagnosis of autonomic affectation in Parkinson's is very important because initiating treatment early helps reduce the morbi-mortality of Parkinson's patients[6-7].

On the other hand, the affectation of the Autonomous Nervous System (ANS) is highly complex and diffuse, from the anatomical as well as the functional points of view, resulting in a superficial understanding of it, and disregarding how important its role is as the regulator of most of the organic functions and maintenance of homeostasis.

1. Patients with PD present an alteration of the ANS, in both the sympathetic and parasympathetic divisions.
2. The alteration of the ANS in patients with PD may appear in the early stages of the disease, regardless of whether patients manifest clinical symptoms of dysautonomia.
3. Patients with PD present a positive correlation between the evolution time and the severity of the disease with autonomic affectation.
4. Treatment with Levadopa helps to stabilize the functioning of the ANS.

The brain's dopamine circuits are vital in decision-making. The dopamine medication causes changes in decision-making in subjects with PD as well as in healthy controls. Consequently, the appearance of intercurrent diseases and neuropsychiatric comorbidities is frequent in these patients[8]. In addition to the classic tetrad of cardinal motor symptoms, the same patients with pharmacological treatments for it generate different alterations in other areas or spheres that are not exclusive to the disease's motor profile and sensory and autonomic symptoms appear, requiring an integrated response to the nosological entity as a whole through and interdisciplinary approach to the disease, which helps improve the management of patients with PD[9-10].

PD is the second most frequent neurodegenerative disease after Alzheimer's disease. It is a progressive neurodegenerative disorder with cumulative effects on patients, their families, and healthcare and social welfare systems.

In the most recent document published on mortality patterns in Spain, PD was one of the principal causes of death in Spain in 2011, with 3,274 deaths (0.8% of all deaths); an age-adjusted mortality rate per 100,000 persons of 3.4; an upward trend in the age-adjusted mortality age between the years 2001 and 2011, with an increase of 21.9%[11-12].

2. Scope and objectives

This Clinical Practice Guideline on Intravenous Therapy with Non-permanent Devices in Adults iThe purpose of these guidelines is to provide healthcare professionals and persons affected by PD with recommendations based on the best available scientific evidence to facilitate decision-making in the clinical management of the disease.

The target population of these guidelines is adults with PD, in any stage, of any age or gender, without restricting the presence of pluripathology or comorbidities. Secondary Parkinson's, which covers Parkinson's induced by neuroleptics and drug-induced Parkinson's is excluded. Other types of dementia that are similar to Parkinson's that are covered in the Clinical Practice Guidelines (CPG) on the comprehensive care of persons with Alzheimer's disease and other dementia, such as dementia with Parkinson's or dementia with Lewy bodies are also excluded13.

The principal users of this CPG are all primary-care healthcare professionals, as well as professionals providing specialised care and social-healthcare centres that provide healthcare to persons affected by PD. In short, all those medical professionals (specialists in neurology, psychiatry, geriatrics, family and community medicine, among others), as well as pharmacists, nurses, and other professions related to the care and rehabilitation of these patients from complementary approaches: psychology, physical therapy, speech therapy, occupational therapy, human nutrition and diet, etc.

The CPG is aimed in improving the treatment and rehabilitation of patients with PD. New methods of administration of antiparkinson treatments used in the management of motor symptoms and their place in therapy are covered. Recommendations also need to be prepared to address the disease's non-motor symptoms and comorbidities, and to evaluate the efficacy of the rehabilitation therapy. Surgical treatment of PD is not covered. The specific section on information for patients includes the training of patients and family members and the importance of associations for health education.

Recommendations of future lines of research that have been identified as gaps in current knowledge during the preparation of this guide are proposed. The formulation of recommendation takes into account the health benefits, side effects, and risks, as well as, whenever possible, the aspects of efficiency in the allocation of resources, with economic evaluation of the different alternatives.

The organization and planning of the different healthcare services is not covered in this guide.

Tools have been developed to improve the application of the recommendations presented in this guide, and to facilitate implementation, such as: summary guide, quick reference tools, educational material for patients, and digital versions.

3. Methodology

The methodology used in the preparation of this CPG is covered in the *Methodology Manual for the Preparation of CPGs in the National Health System*[1].

The steps followed were:

– Creation of the guideline working group (GWG), made up of primary-care and specialised professionals (medicine, pharmacy, nursing), specialists in neurology, psychiatry, physical therapists, speech therapists, dieticians-nutritionists for home hospitalization. The GWG did not include patients, family members, or caregivers; the Director General of the Spanish Parkinson's Federation was consulted as a collaborating expert. Potential users of the information aimed at patients were also consulted in the review of this content.

– Formulation of clinical questions, following the PICO format (Patient/Intervention/Comparison/*Outcome*).

– Bibliographic search in databases and other specialised sources: Medline (through PubMed), Embase (Elsevier), *The Cochrane Library, Centre for Reviews and Dissemination (CRD) of the University of York* (includes the DARE databases *(Database of Abstracts of Reviews of Effects)*, NHS EED *(National Health Service Economic Evaluation Database)*, and HTA *(Health Technology Assessment)*, Índice Bibliográfico Español en Ciencias de la Salud (IBECS) and Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS). In the question regarding occupational therapy, a search was done in the specialised database OTseeker, and in the question regarding physical therapy, the *Physiotherapy Evidence Database* (PEDro) was consulted. Languages: English and Spanish. Search period 10 years (2003 to 2013). Trial type filters: systematic reviews (SRs), CPG, and randomized controlled trials (RCT). The search strategies, accessible as additional material, were carried out combining terms in controlled language for each database ((MeSH, Emtree, DeCS) and free language. In the initial phase, a preliminary search was made of CPGs and systematic reviews in the aforementioned databases. These were included as a secondary source of CPG evidence, to respond to specific sections of the guidelines, in accordance with the methodology proposed in the asthma guidelines of the Basque Country14. The guidelines included were evaluated using the instrument AGREE II *(Appraisal of Guidelines Research and Evaluation)*[15]. The methodological material of the guidelines presents the scores obtained after applying the instrument AGREE II to two CPGs on PD consulted during the preparation of the guidelines *(National Institute for Health and Care Excellence –NICE-– 2006*[16]*,* and *Scottish Intercollegiate Guidelines Network* –SIGN-– 2010[17]).

– The minimum requirement established to constitute a source of evidence for this guideline was a score, using the AGREE instrument, higher than 60% in domains 1, 3, and 6. The level of evidence established for the RCTs and SRs specified in the CPGs was maintained. In the second phase, an expanded search of original trials (mainly RCTs) was done, and for some questions, www.clinicaltrials. gov was also consulted. A reverse search was done in the references of the articles identified and included in the CPGs. The authors of the studies were contacted directly when necessary. In addition, automatic e-mail alerts were defined for new studies included in Medline, Embase and *The Cochrane Library*.

– The search reports were evaluated by at least two members of the GWG. The screening was done initially by title and summary. In a second screening, the discarded studies were recorded

and the causes for exclusion were specified. The studies that were finally selected were evaluated using the critical reading tool of the Agency for Healthcare Technology Assessment of the Basque Country - OSTEBA[18].

– In the question regarding the efficacy of physical therapy in persons with PD, general physical therapy was evaluated, and a non-systematic review was done for other techniques, such as music and dance, martial arts or tai-chi, among others.

– Formulation of recommendations based on the "formal evaluation" or "justified opinion" of SIGN. The classification of the evidence and the grading of the recommendations were done using the SIGN system. Recommendations that were controversial or that lacked evidence were resolved by consensus in a meeting of the working group.

– The collaborating experts participated in the formulation of questions and the revision of the first draft of the guidelines. External reviewers participated in the revision of the second draft. The different Scientific Societies involved were contacted: Spanish Association of Physical Therapists (AEF), Spanish Association of Speech Therapy and Audiology (AELFA), Spanish Association of Neuropsychiatry (AEN), Spanish Professional Association of Occupational Therapists (APETO), Federation of Associations of Community Nursing and Primary Care (FAECAP), Spanish Parkinson's Federation (FEP), Spanish Foundation of Dieticians and Nutritionists (FEDN), Spanish Society of Primary Care Pharmacists (SEFAP), Spanish Society of Family and Community Medicine (SemFYC), Spanish Society of General and Family Physicians (SEMG), Spanish Society of Primary Care Physicians (SEMERGEN), Spanish Neurology Association (SEN), Spanish Society of Psychiatry (SEP), Spanish Society of Biological Psychiatry (SEPB), Spanish Society of Rehabilitation and Physical Medicine (SERMEF), which are also represented by the members of the working group, the collaborating experts, and external reviewers.

– Material is available at www.guiasalud.es that presents detailed information with the methodology of the CPG (search strategies for each clinical question, critical reading sheets of the selected studies, tables synthesizing the evidence, and formal evaluation tables).

– An update of the guidelines is planned within no more than three to five years, or sooner if new scientific evidence appears that could modify some of the recommendations in this guide. Updates will be made to the electronic version of the guidelines, available at the URL: http:www.guiasalud.es

4. Pharmacological treatment

4.1. Motor symptoms

4.1.1. Antiparkinson drugs

Question to be answered:

Is non-oral administration of antiparkinson treatments used for motor symptoms (dopaminergics and anticholinergics) safer and more effective?

The range of drugs available for the treatment of idiopathic Parkinson's disease (PD) is broader than for any other degenerative disease of the CNS. The management of individual patients requires careful consideration of a series of factors, including the signs and symptoms, the stage of the disease, the degree of functional disability and level of physical activity, and work situation. The classic treatment of PD includes the following as the principal drugs available for the motor symptoms of PD: Levadopa; dopamine agonists; MAO B inhibitors; anticholinergic agents; amantadine and COMT inhibitors Other CPGs, such as the one prepared by the *National Collaborating Centre for Chronic Conditions* for the *National Institute for Health and Clinical Excellence* (NICE) in 2006[16], or the one prepared by the *Scottish Intercollegiate Guidelines Network* (SIGN) in 2010[17], make recommendations for the management of the motor symptoms of PD through classic antiparkinson treatments. The objective of this question is not to revise or update these recommendations. When the disease is advanced, complications associated with long-term treatment with Levadopa appear and the management of the concomitant issues includes the management of excessive daytime sleepiness, hallucinations, and psychosis (as will be seen in other questions). The use of new pharmaceutical forms is proposed to address the pharmacological treatment of patients with PD with different complications and comorbidities, for which the efficacy, effectiveness, and safety must be established, in addition to the economic aspects, evaluating their efficacy.

In the context of this CPG, the new pharmaceutical forms refer specifically to those formulated for non-oral methods of administration, specifically: enteral administration for L-dopa/carbidopa gel, subcutaneous (sc) administration for apomorphine, and transdermal administration for rotigotine. Considering that there are new pharmaceutical forms whose novelty consists solely of the modification of the pharmacokinetics (controlled-release tablets or buco-dispersable tablets, among others) or of the incorporation of several active ingredients into a single tablet (L-dopa/carbidopa and entacapone, for example), it is considered necessary to compare the classic treatments with pharmaceutical forms administered by non-oral routes (enteral, sc, and transdermally).

Two systematic reviews (SRs) of randomized controlled trials (RCTs) were located and another SR of economic evaluations of health technologies (EEHT) that review the available evidence on the efficacy and safety of the new pharmaceutical forms in comparison with classic treatments of PD. There is also an RCT that compares the intrajejunal administration of an L-dopa/carbidopa gel with the same drug administered orally. One of the RCT SRs and the EEHT SR include the scientific evidence that is currently available that compares intestinal administration of L-dopa/carbidopa with classic treatments. The other RCT SR of average quality evaluates treatment of PD with rotigotine on a transdermal patch. No studies were found that compare the

efficacy and safety of subcutaneous administration of apomorphine in comparison with classic treatments of the motor symptoms of PD. In addition, the CPG on PD from the NICE in 2006 includes the question "What is the efficacy of apomorphine in comparison with standard oral treatment in advanced PD?".

Clarke *et al*. 2009[19] conducted a systematic review in order to assess the clinical efficacy and cost-effectiveness of the treatment options that are currently available for patients with PD and motor fluctuations in which the available combinations of oral medications have not generated satisfactory results or that are no longer effective. This is a low-quality systematic review. It only includes the results that are offered in the systematic review in relation to three high-quality RCTs for the L-dopa/carbidopa intestinal gel (LCIG). An RCT studies duodenal infusion of L-dopa/carbidopa compared with conventional oral therapy. The Levadopa infusion generates an 11% increase day in *"on"* state (p=0.03), and a reduction of 32% in immobile time in *"off"* state (p=0.03). Another RCT shows that LCIG produces an increase of 19% day in *"on"* state (p<0.01) in comparison with oral administration of controlled-release L-dopa/carbidopa. The third RCT with 24 participants compares LCIG with conventional oral therapy (oral Levadopa, other antiparkinson drugs, and in 8 patients, apomorphine sc and infusion). In this case, there were no changes in the *Unified Parkinson's Disease Rating Scale* (UPDRS). The review concludes that it is not possible to determine which of the compared treatment methods is more effective, better tolerated, or cost-effective.

SR
1-

Olanow *et al*. 2014[20] carried out the first double-blind RCT on LCIG, with double simulation (administering LCIG and oral placebo in the intervention group and immediate-release levalopa/carbidopa by p.o. and placebo by intestinal route in the control group) and two dose titrations (during the first 4 weeks), which demonstrates the benefits of continuous administration of the antiparkinson drug through a percutaneous intrajejunal tube. The motor fluctuations in patients with advanced PD, especially in terms of the reduction of the number of hours in the *off* state, improve significantly, with a difference in hours between the two groups of a change from baseline situation to the final visit of -1.91 hours (CI95% -3.05 to -0.76 h; p=0.0015). LCIG is a therapy option for patients with advanced PD who have *off* episodes and that cannot be satisfactorily controlled with standard medical therapy. The trial duration was 12 weeks, which is insufficient to evaluate safety, so in clinical practice, the symptomatic benefits of this treatment must be carefully weighed against its profile of adverse side effects. It is important to note that the problems in the control group resulted from the intrajejunal administration of the placebo.

RTC
1++

The objective of the review of Fox *et al*. 2011[21] was to update an earlier review on the efficacy and safety of the treatment of motor symptoms of PD published between 2002 and 2005. This update, which covered until December 2010, included new studies on rotigotine; but only one RCT (with 561 patients with early-stage PD) had an active comparator (ropinirole). When comparing 8 mg/d, administered transdermally for 33 weeks, with ropinirole 24 mg/d p.o. for 24 weeks, the differences between rotigotine and ropinirole were not found to show inferiority in the reduction of scores on the combined subscales UPDRS-II and III (which measure activities of daily life and motor response, respectively). A similar number of patients withdrew from both groups (rotigotine 17% and ropinirole 13%). The authors of the review concluded that the equivalence or superiority in the efficacy or safety of rotigotine versus ropinirole could not be established.

SR
1+

Reese *et al*. 2012[22] review the economic evaluation studies for patients in advanced stages of PD. Both the included economic evaluations as well as the systematic review itself have an average quality of the evidence. The economic evaluations included in the review carried out different cost-efficacy and cost-utility analyses (CAE and CUA, respectively), to compare LCIG with conventional therapy (TC; may be antiparkinson drugs by p.o. or apomorphine in sc injection or with infusion pump). In both cases, the point of view is that of the National Health System (British or Swedish, respectively) and the discount rates of costs and benefits are 3.5% and 3%, respectively.

SR
Econ.
Eval.

The second economic evaluation: LCIG 1.48 QALY, 562,000 SEK; TC 1.42 QALY, 172,000 SEK. ICER: 6.1 million SEK/QALY and in the sensitivity analysis, 500,000 SEK/QALY in 100% of the cases. SEK: Swedish krona (at the time of the review, defined as 1 € = 9.17 SEK).

The review concluded that in an economic evaluation, LCIG was evaluated to be an orphan drug, and that therefore must be considered to be cost-effective in the context of the United Kingdom, while in the other economic evaluation, the results of the CUA exceed the limit values of cost-effectiveness and willingness to pay (WTP).

Finally, the 2006 NICE CPG[16] indicates that three RCTs were found that evaluated the effectiveness of subcutaneous injections of apomorphine compared with a placebo. No trials of apomorphine compared with standard oral treatment were found, and no controlled trials on continuous subcutaneous infusion of apomorphine were found. With respect to intermittent sc injections of apomorphine, in regard to the correlation analysis, the dosage of levadopa (the single dose that produces the effect that equals the apomorphine responses) is not predictive of the dosage of apomorphine required. Also, the total daily dose of Levadopa is also not predictive of the dose of apomorphine ($p=0.32$) and the response of hospitalized patients correlated with and predicted the efficacy in outpatients ($p<0.001$). In regard to the overall clinical impressions, 86% of the people who completed the 8 weeks of monitoring with apomorphine (maintenance phase) indicated a "greater" or "much greater" improvement in the final visit, and none of the subjects indicated that they had worsened during the monitoring.

CPG
RCT
1+
CPG
Case
Series 3

In regard to dropout rates, reasons for withdrawal include: inability to demonstrate a significant response to the levadopa test, adverse events (nausea and vomiting, hypotension, rash), lack of motivation. And in regard to adverse events, the common events include: discomfort at the point of injection, sleepiness, yawning, dyskinesia, nausea or vomiting, sweating and hot flashes, dizziness, headache, and rhinitis. Other events include: nausea, dyskinesia, short-duration trembling of the legs, worsening of short-duration trembling, sweating and hot flashes, or lowered motor functioning at the end of the clinical effect compared with the basic level before the test. There are no significant changes in other safety measures (blood tests, electrocardiograph, and physical examination).

With respect to continuous sc injections of apomorphine, no RCTs were found. Nine retrospective studies and one prospective study were found that investigate the benefits of chronic treatment with apomorphine compared with pre-treatment evaluations.

CPG
RCT
1+
CPG
Case
Series 3

In regard to the overall clinical evaluation scales, when the patients were classified, none described an overall worsening; three noted no change; six experienced a slight improvement; and 16 had a significant improvement. According to the classification done by the physician, none of the patients worsened; two had no change (the same ones that described themselves as such); seven had slight improvement; and 16 showed clear improvement. In regard to the medication dose, higher doses of apomorphine produced a longer duration of the antiparkinson effects ($p<0.001$). Two studies examined the anti-dyskinetic effect of monotherapy, which means that these people did not receive antiparkinson treatment during the time that the apomorphine pump began in the morning until it turned off for the night. There is an overlap in the patient populations included in these studies.

In regard to motor complications, there is a maximum average reduction of dyskinesia per patient of 64% ($p<0.005$). Also, in relation to the management of the treatment, 25% of the persons managed their treatment independently, 50% managed it with family assistance, and 25% required nursing support. The success rate is higher (81%, $p<0.05$) among persons who handled the pump system independently, or with family assistance, than for those who required external assistance (e.g. by a nurse). In regard to neuropsychiatric problems, there was an improvement of 40% (especially in person with depression-type symptoms) ($p<0.05$), and with respect to adverse events, most of the patients developed subcutaneous nodules. Other effects included rhinorrhoea, nausea and hiccups, recurring diarrhoea, confusion, and mood swings, euphoria, dysarthria, worsening of dyskinesia, orthostatic hypotension, psychosis, hallucinations, intermittent illusions, confusion, drowsiness, vertigo, eosinophilia, increased appetite, increased sex drive, visual delusions, diurnal agitation, immune haemolytic anaemia, moderate self-limiting oedema in the legs, and positive Coombs test without associated haematological changes.

In regard to dropout rates, person withdrew due to side effects (psychiatric effects, insufficient therapeutic effects or adverse effects). In regard to the effects of the single dose of Levadopa and apomorphine in comparison with continuous apomorphine infusion before and after dyskinesia: Levadopa reduced dyskinesia after continuous infusion of apomorphine by at least 40% (AIMS and Goetz scales; in both $p<0.01$); apomorphine reduced dyskinesia after continuous apomorphine infusion by at least 36% (AIMS and Goetz scales; in both $p<0.01$).

The recommendations that were finally prepared in the 2006 NICE CPG with respect to apomorphine are: intermittent apomorphine injections can be used to reduce the time in *off* in persons with PD with severe motor complications. Continuous subcutaneous infusions of apomorphine may be used to reduce *off* time and dyskinesia in persons with PD and severe motor complications. This should only be initiated in expert units with facilities to allow adequate supervision.

The L-dopa/carbidopa intestinal gel (LCIG)[23] product sheet clearly establishes as an authorised therapeutic indication "the treatment of advanced Parkinson's disease (PD) with severe motor fluctuations and hyper/dyskinesia when the combinations of the medications available for Parkinson's have not produced satisfactory results. A positive test of the clinical response to Duodopa administered by a temporary nasalduodenal catheter is required before a permanent catheter is implanted".

Although the product sheet for the 1 and 3 mg/24 h transdermal rotigotine patch indicates that "Neupro is indicated for the symptomatic treatment of moderate to severe idiopathic restless leg syndrome in adults", for the rest of the presentations (2, 4, 6, and 8 mg/24 h) it is indicated for treatment of the signs and symptoms of the initial stage of idiopathic Parkinson's disease as monotherapy (in other words, without Levadopa) or in combination with L-dopa, in other words, over the course of the disease, during the final stages, when the effect of Levadopa is reduced or becomes incoherent and fluctuations in its therapeutic effect occur (end of dose or *"on-off"* fluctuations). In any case, for all presentations, the pharmacodynamic properties sections indicates that "rotigotine is a non-ergoline dopamine antagonist used for the treatment of the signs and symptoms of Parkinson's disease and restless leg syndrome".

Finally, in the case of apomorphine[23], the product sheet specifies as a therapeutic indication the treatment of motor fluctuations *"on-off"* phenomena) in patients with PD that are not sufficiently controlled by oral antiparkinson medication. It is also important to note that it is essential that the patient be in treatment with domperidone, normally with a 20 mg dose three times a day, at least two days before initiating the treatment. Also, treatment with apomorphine must be initiated in a controlled setting in a specialised clinical centre, and the patient must be supervised by a specialist with experience in the treatment of PD (e.g. a neurologist).

The economic evaluation studies presented in Reese *et al*. 2012[22] have the perspective of the National Health System (NHS) of the countries of each study (United Kingdom and Sweden), so the conclusions of the review in our NHS can be inferred.

The studies show heterogeneous results with different measurement scales, which do not allow firm and comparable conclusions to be drawn.

There is inconsistency in the cost-effectiveness studies. An important qualification is made in the economic evaluations on the cost-effectiveness of LCIG: in the context of an orphan drug (see glossary). In this case, and in the context of the United Kingdom, it is considered to be cost-effective. However, the second economic evaluation indicates that the results of the CUA are above the maximum values of cost-effectiveness and WTP.

The use of LCIG is limited by its therapeutic indications. It is a medication for hospital use, which requires specialised personnel in the process of selection, prescription, validation, dispensation, administration, and monitoring. Only the *CADD Legacy*® from Duodopa (CE0473) should be used as the healthcare product for administration. All of this, along with the need for a surgical operation to administer the medication, with the associated risks, modulates the grade of recommendation when the evidence from the studies Olanow *et al*. 2014[20] and Clarke *et al*. 2009[19] is extrapolated. After contacting the Spanish Parkinson's Federation to ask about the perception of the patients receiving this treatment, they indicated that it involves a significant change with a very positive impact on quality of life, although there are patients in whom the treatment does not work as expected, probably due to the divergence from the expectations generated.

It is important to note that in the study that compares rotigotine with ropinirole, the dose and duration of the alternatives are not comparable. In the case of ropinirole, the maximum dose of 24 mg/d was used for 24 weeks, and for rotigotine, 8 mg/d was used as the maximum dose for 33 weeks.

Summary of evidence

1-	Levadopa/carbidopa intestinal gel (LCIG) produces an increase in the time of day in the *"on"* state and a reduction of time of immobility in the *"off"*[19] state.
1++	The administration of LCIG produces a reduction in the number of hours in *off* (-1.91 h; CI95% -3.05 to -0.76 h; p=0.0015), between the baseline situation and the visit at week 12, in comparison with the administration of the same active ingredients administered orally[20].
Econ. Eval.	LCIG as an orphan drug can be considered to be cost-effective in the context of the United Kingdom[22].
Econ. Eval.	The results of the cost-utility analysis (CUA) for LCIG are above the maximum values of cost-effectiveness and willingness to pay (WTP)[22].
1+	Equivalence or superiority cannot be established between rotigotine 8 mg/d in transdermal patches and ropinirole 24 mg/d by oral route in terms of efficacy and safety[21].
CPG 1+	The single dose of levodopa is not predictive of the dose of apomorphine required. The total daily dose of levodopa is also not predictive of the apomorphine dose (p=0.32). The response in hospitalised patients to intermittent subcutaneous apomorphine predicts its efficacy in outpatients (p<0.001)[16].
CPG 1+	A "greater" or "much greater" improvement is achieved in 86% of the patients with apomorphine after 8 weeks. None of the patients indicated that they had worsened during the monitoring[16].
CPG 1+	The reasons for from intermittent subcutaneous apomorphine include: inability to demonstrate a significant response to the levadopa test, adverse events (nausea and vomiting, hypotension, rash), lack of motivation.
CPG 1+	The most common adverse events include: discomfort at the point of injection, sleepiness, yawning, dyskinesia, nausea or vomiting, sweating and hot flashes, dizziness, headache and rhinitis. Other adverse events include: short-duration trembling of the legs, worsening of short-duration trembling, lowered motor functioning at the end of the clinical effect compared with the basic level before the test. There were no significant changes in other safety measurements (blood tests, electrocardiograph, and physical examination)[16].
CPG 3	The classification in the descriptions of overall worsening with continuous subcutaneous apomorphine by the patient or by the physician are very similar: none of the patients worsened; 2 or 3 patients had no changes; 7 or 6 had a slight improvement; and 16 improved clearly[16].
CPG 3	Higher doses of continuous subcutaneous apomorphine produce a longer duration of the effect of the antiparkinson medications (p<0.001)[16].
CPG 3	There is a maximum average reduction of dyskinesia per patient of 64% with continuous subcutaneous apomorphine (p<0.005)[16].

CPG 3	25% of the persons managed their treatment independently, 50% managed it with family assistance, and 25% required nursing support. The success rate is higher (81%, p<0.05) among persons who handled the pump system for the continuous subcutaneous apomorphine independently, or with family assistance, than for those who required external assistance (e.g. by a nurse)[16].
CPG 3	There was an improvement of 40% with continuous subcutaneous apomorphine (especially in persons with depression-type symptoms) (p<0.05)[16].
CPG 3	Most patients developed subcutaneous nodules with continuous subcutaneous apomorphine. Other effects included rhinorrhoea, nausea and hiccups, recurring diarrhoea, confusion, and mood swings, euphoria, dysarthria, worsening of dyskinesia, orthostatic hypotension, psychosis, hallucinations, intermittent illusions, confusion, drowsiness, vertigo, eosinophilia, increased appetite, increased sex drive, visual delusions, diurnal agitation, immune haemolytic anaemia, moderate self-limiting oedema in the legs, and positive Coombs test without associated haematological changes[16].
CPG 3	Persons withdrew due to side effects caused by the administration of continuous subcutaneous apomorphine (psychiatric effects, insufficient therapeutic effects, or adverse effects)[16].
CPG 3	Levodopa reduced dyskinesia after continuous apomorphine infusion by at least 40% (AIMS and Goetz scales; in both p<0.01). Apomorphine reduced dyskinesia after continuous apomorphine infusion by at least 36% (AIMS and Goetz scales; in both p<0.01)[16].

Recommendations

B	The use of L-dopa/carbidopa intestinal gel (LCIG) is recommended only for the treatment of advanced Parkinson's disease (PD) with severe motor fluctuations and hyper/dyskinesia when the available combinations of the Parkinson's medications have not produced satisfactory results. This alternative may be cost-effective with the conditions established within the framework of usage of orphan drugs.
B	Evaluation of antiparkinson treatment with transdermal rotigotine is recommended for patients with early or initial PD, at the doses specified in the product sheet, when other alternatives are ineffective.
B	Intermittent injections of apomorphine may be used to reduce motor fluctuations (*"on-off"* phenomena) in patients with PD in which symptoms are not controlled sufficiently by oral antiparkinson medication.
D	Continuous subcutaneous infusions of apomorphine may be used to reduce *off* time and dyskinesia in persons with PD and severe motor complications. This should only be initiated in expert units with facilities to allow adequate supervision.

4.1.2. Management of problems related to antiparkinson medications

4.1.2.1. Drug-induced psychosis

Question to be answered:

Is it more effective and safer to add an atypical antipsychotic (for example: quetiapine) to antiparkinson medication or reduce/discontinue these antiparkinson drugs (anticholinergics, selegiline, amantadine) to control the drug-induced psychosis associated with this disease?

Psychosis is one of the principal neuropsychiatric aspects of PD and is associated with a significant degree of disability. Psychosis covers a wide range of symptoms, which include hallucinations, delirium, and paranoid beliefs. In the case of PD, visual hallucinations are the most prevalent manifestations (although audio hallucinations may also occur). Delirium may include matters of persecution, infidelity, and jealousy, but these are much less common.

It is therefore essential to explain the nature of these symptoms to the persons with PD, their family members, and caregivers, and evaluate which alternative could be the most effective and safe to manage the psychosis associated with antiparkinson medication.

No SRs, RCTs, or CPGs that study this question were found. The scientific literature is aimed at the use of atypical antipsychotics compared with placebo or non-intervention, and they do not evaluate the comparative effectiveness of these treatment in regard to reducing/discontinuing the antiparkinson medications that facilitate the development of drug-induced psychosis (mainly dopamine agonists)[24-27].

In this sense, the CPGs on PD from NICE[16] and SIGN[17] refer to the use of atypical antipsychotics in the management of patients with PD with drug-induced psychosis, because no studies that directly address this question were found.

CPG
SR of RCTs
1++

The 2010 SIGN CPG[17], identified two SRs related to the treatment of psychosis and the reduction of the risk of psychosis and hallucinations induced by medication in patients with PD. The first SR of the CPG includes seven RCTs with a total of 419 patients. The trials compare the antipsychotics clozapine, quetiapine, and olanzapine versus a placebo. One trial compared clozapine with quetiapine. Only the patients who received clozapine improved significantly more than the placebo group on the Clinical Global Impression (CGI) change scale (weighted mean difference, WMD, -1.1; CI95% -1.24 to -0.97; $p < 0.0001$). In the one-by-one comparison, no significant difference was detected between patients who received clozapine or quetiapine (WMD=0.20; CI95% -0.57 to 0.1). The conclusions of the other SRs are similar.

One RCT not included in the previous SRs compares the efficacy of quetiapine versus clozapine in the treatment of psychosis in 27 patients with PD. Both drugs are effective in the treatment of psychotic symptoms when measured with the CGI evaluation scale, although clozapine produces the greatest improvement in the specific measurements related to the frequency of hallucinations and delusions.

CPG
RCT
1CPG

Expert opinion 4

Clozapine has been associated with agranulocytosis, so regular monitoring of the total white blood cell count and the absolute neutrophil count is necessary for patients who are treated with this medication.

In short, olanzapine is not useful for improving psychosis in PD and worsens the motor symptoms. Clozapine is effective in the treatment of psychosis, and in some cases also improves motor function. Quetiapine produces some improvement in psychotic symptoms, without any benefits over clozapine. Quetiapine is not authorised for treatment of patients with psychosis in PD, while clozapine is. When patients are not bothered by the hallucinations, the clinical decision may be not to treat the symptoms or rationalize dopamine therapy, because the anti-psychotic medication may worsen motor symptoms[17].

The 2006 NICE CPG[16] indicates that five RCTs were found that evaluate the effectiveness of atypical antipsychotic therapies in comparison with a placebo or active comparator in the treatment of psychosis. Three were found that compare two atypical antipsychotics, and these were excluded by comparison between medication classes.

CPG
SR of RCTs
1+

With respect to the psychiatric results:

The RCTs that compare the effectiveness of clozapine versus a placebo showed statistically significant results in favour of clozapine on several scales.

The RCTs that evaluate the effectiveness of olanzapine versus a placebo and quetiapine versus a placebo did not show statistically significant differences between the groups in a battery of tests and scales.

In regard to adverse effects:

- A significant increase was reported in the following events in patients in treatment with clozapine: statistically significant increased average resting heart rate and body weight and increase in drowsiness (53% versus 18%) and worsening of Parkinson's (21.8% versus 4%). Dropouts were due to treatment failure or adverse effects.
- A significant increase in the following events was reported in patients in treatment with olanzapine: extrapyramidal syndrome, hallucinations, and increased salivation. Withdrawals were due mainly to the adverse side effects.
- There were no significant differences in the adverse events in the trial of quetiapine versus a placebo. There were no significant differences in the withdrawal rates.

Results were also reported with respect to motor results:

- Clozapine showed beneficial results on the UPDRS tremor subscale.
- Olanzapine worsened the results on the UPDRS scales and subscales.
- No differences were found between quetiapine and a placebo on the UPDRS scales.

The affirmations on the authorisations made in the aforementioned CPGs are also valid in Spain: only clozapine has an indication authorised by the Spanish Agency for Healthcare Products and Medications (AEMPS) for the psychotic disorders that appear in the course of PD. For quetiapine, whose product sheet does not include explicit authorisation of this indication, use may be considered in special situations (in compliance with Royal Decree 1015/2009 which regulates the availability of medications in special situations)[28]. Within this framework, and in regard to clinics, aripiprazole is being used for its partial antagonistic profile of D2 receptors with predominance of action in situations of apathy-aboulia and inactivity.

No studies related to the reduction/discontinuation of antiparkinson medication to reduce the psychosis induced by the drugs used in PD were found.

The two CPGs reach similar conclusions with respect to the use of atypical antipsychotics based on different SRs and RCTs.

Due to the problems related to the use of clozapine (mainly agranulocytosis and also myocarditis) the analytical resources necessary for weekly monitoring during the first 18 weeks of treatment, followed by monitoring for as long as the treatment is continued (at least once every 4 weeks), must be available. These analytical controls should be continued for 4 weeks after complete interruption of the treatment. Medications that contain clozapine are indicated in "psychotic disorders that appear in the course of Parkinson's disease, in which standard treatment has failed" and its use is limited to patients who must initially present normal leukocyte values (white blood cell count ≥ 3500/mm^3 (3.5x109/l), and absolute neutrophil counts, ≥ 2000/mm^3 (2.0x10^9/l)). For more information, see the product sheet[23].

Quetiapine: The use of quetiapine as a treatment for the psychosis induced by the dopamine agonists used in patients with PD is not explicitly indicated in the product sheet. However, it should be noted that the specialists in this area emphasize the quetiapine is currently the drug that is used most widely in clinical practice for this indication, proposing the use of higher doses.

The product sheets of medications that contain olanzapine indicate that olanzapine is not recommended for the treatment of the psychosis induced by the dopamine agonists used in patients with PD. In the clinical trials, a worsening of the Parkinson's symptoms and hallucinations was reported, very frequently and with greater frequency than with the placebo, and olanzapine was not more effective than the placebo in the treatment of psychotic symptoms.

The product sheets of typical antipsychotic medications specify PD in the contraindications, warnings, and special precautions for use, because it can reduce the antiparkinson effects of levodopa, exacerbating the symptoms of the diease[23].

These clinical trials required the prior stabilisation of patients with the lowest effective antiparkinson dose (dopamine antagonist) and continue with the same dose and antiparkinson medication for the duration of the trial. The initial dose of olanzapine was 2.5 mg/day and the increase up to a maximum of 15 mg/day in the opinion of the investigator was evaluated. See product sheet[23].

Summary of evidence

CPG 1++	Only the patients who received clozapine improved significantly more than the placebo group on the CGI change scale (WMD, -1.1; CI95% -1.24 to -0.97; p < 0.0001).
CPG 1++	In the one-by-one comparison, no significant difference was detected between patients who received clozapine or quetiapine (WMD -0.20; CI95% -0.57 to 0.1).

CPG 1-	Clozapine produces the greatest improvement in the specific measurements related to the frequency of hallucinations and delusions[17].
CPG 4	Clozapine has been associated with agranulocytosis, so regular monitoring of the total white blood cell count and the absolute neutrophil count (ANC) is necessary for patients who are treated with this medication.
CPG 1+	A statistically significant improvement of efficacy of the treatment of psychiatric symptoms with clozapine versus a placebo was found. No statistically significant differences were found in the treatment of psychiatric symptoms between the groups that evaluated the effectiveness of olanzapine versus a placebo and olanzapine versus a placebo[16].
CPG 1+	In the treatment of patients with clozapine, a significant increase was reported in the following adverse events: increased average resting heart rate and body weight and increase in drowsiness (53% versus 18%) and worsening of Parkinson's (21.8% versus 4%). Withdrawals were due to treatment failure or adverse effects. With olanzapine, an increase in the following adverse effects was reported: extrapyramidal syndrome, hallucinations, and increased salivation. Withdrawals were due mainly to the adverse side effects. There were no significant differences in the adverse events in the trial of quetiapine versus a placebo. There were no significant differences in the withdrawal rates[16].
CPG 1+	Clozapine showed beneficial results on the UPDRS tremor subscale. Olanzapine worsened motor results on the UPDRS scales and subscales. No differences were found between quetiapine and a placebo on the UPDRS scales16.
CPG 4	An improvement of psychiatric symptoms was achieved in patients with PD by the general medical evaluation, with evaluation of the different causes of psychosis and precipitating conditions[17].
CPG 4	Better health results are obtained if, in the management of psychotic symptoms in patients with PD, the impact of these psychotic symptoms on quality of life is evaluated, because treatment of these symptoms may not be required. Also, the evaluation of the need to gradually discontinue the treatments that cause the symptoms (especially antiparkinson treatments), or the need to actively treat the precipitating causes with medications that do not increase the motor problems in patients with PD can improve health results[16].
CPG 4	The use of typical antipsychotics (phenothiazines and butyrophenones) in patients with PD may exacerbate symptoms and worsen the disease[16].

Recommendations

D	All persons with PD and psychosis should receive a general medical evaluation, in order to exclude other treatable causes of psychosis.
D	Before considering the use of anti-psychotic medication, treatment for any precipitant condition is recommended.

D	The gradual discontinuation of antiparkinson medication that could trigger psychosis in persons with PD must be taken into account.
D	It may not be necessary to treat moderate psychotic symptoms in persons with PD if they are tolerated well by the patient and the caregiver.
D	Typical antipsychotics (such as phenothiazines and butyrophenones) should not be used with persons with PD because they may exacerbate the motor characteristics of PD.
D	Atypical antipsychotics may be considered for treatment of psychotic symptoms in persons with PD, although the evidence of its efficacy and safety is limited.
A	The use of clozapine at the minimum effective dose is indicated in patients who develop psychotic disorders over the course of their PD, in cases in which standard treatment has failed.
D	When treatment with clozapine is applied, weekly monitoring is recommended during the first 18 weeks of treatment, followed by monitoring for as long as the treatment is continued (at least once every 4 weeks). These analytical controls should be continued for 4 weeks after complete interruption of the treatment.
D	Treatment of psychotic symptoms in patients with PD with clozapine requires the mandatory registration of the monitoring scenario of the atypical anti-psychotic and of blood parameters (total white blood cell count and absolute neutrophil count). For more information, see the product sheet[23]. http://www.aemps.gob.es/
B	The use of low doses of quetiapine may be considered as an alternative anti-psychotic to clozapine for the treatment of patients with psychosis in PD, when weekly routine blood monitoring is not possible, and within the framework of Royal Decree 1015/2009, dated 19 June, regulating the availability of medications in special situations.

4.1.2.2. Sleep disorders

Question to be answered:

Which treatment is safest and most effective to reduce the sleep disorders associated with Parkinson's disease?

Sleep alterations are one of the comorbidity problems associated with PD[29]. These sleep disorders occur in a high percentage of patients with PD, especially in advanced stages. The associated disorders include a wide range of alterations: insomnia, hyperinsomnia, REM sleep behaviour disorder, restless leg syndrome, akathisia, and period leg movements. Insomnia is the most frequent disorder predominating over sleep maintenance insomnia. Hypersomnia, classified as excessive daytime sleepiness (EDS) and sleep attacks may also occur. EDS is frequent in patients with PD. The sudden onset of sleep, a phenomenon known as sleep attacks, has been described. EDS and sleep attacks can be dangerous for patients with PD while they drive. The aetiology appears to be multi-factor, involving the death of dopamine cells, an altered night-time sleep architecture, and the effects of antiparkinson medications[30].

Consequently, it is clear that sleep disorders have a direct impact on the quality of life of the persons affected by PD and the family members who live with them, and it may create significant problems with the coexistence at home, with possible life-threatening consequences. Consequently, the available evidence on the safest and most effective treatment to reduce the sleep disorders associated with PD will be evaluated[31-32].

No studies that address this question were identified. Only one healthcare technology assessment report regarding the use of pitolisant for the treatment of hyperinsomnia and narcolepsy in patients with PD was found[34]. However, this was a preliminary results report, pending the final results, so it was not analysed.

The SIGN[17] and NICE[16] CPGs address very similar questions.

The SIGN 2010[17] CPG asks, "Is there an effective pharmacological treatment to reduce daytime sleepiness in patients with PD? (e.g. modafinil, amantadine, selegiline)". This CPG describes an RCT that examined the effect of modafinil (200 – 400 mg/d) for seven weeks in 20 patients with PD, and found a non-significant improvement in the treatment of Excessive Daytime Sleepiness (EDS) in PD in comparison with the control.

CPG
RCT
1++

A second RCT used modafinil in doses of 100 mg and 200 mg in patients with EDS. Although there was an improvement on the Epworth subjective sleepiness scale (ESS) in the treatment group compared with a placebo (ESS of 3.42 ± 3.9 versus 0.83 ± 1.99), there were no changes in the objective polygraph of the maintenance of wakefulness test (p=0.14). This was a study with a small number of patients (12 completed the trial) and a short duration (two blocks of 2 weeks)[17].

CPG
RCT
1+

The third RCT used a treatment dose of modafinil of 200 mg per day and examined 21 patients with PD over a treatment period of 3 weeks. The ESS values (average ± standard deviation) for the placebo group worsened from (16.0 ± 4.2) to (17.0 ± 5.1) and for the modafinil, they improved from (17.8 ± 4.2) to (14.4 ± 5.7) (p=0.039). There were no significant differences in change CGI[17].

CPG
RCT
1-

One crossover RCT evaluated the effect of melatonin (dose of 5 mg and 50 mg) in 40 subjects with idiopathic PD and sleep disorders for a period of 10 weeks (two treatment periods of 2 weeks). Although there was an improvement on the daytime sleepiness subscale of the General Sleep Disorder Scale (GSDS) in patients treated with 5 mg of melatonin (p<0.05), no change was observed on other scales that were examined (ESS and the Stanford Sleepiness Scale (SSS)[17].

CPG
RCT
1++

The second RCT evaluated the effect of 3 mg of melatonin at night in 20 patients. This was a brief study and there was no pharmacological effect on EDS[17].

CPG
RCT 1-

The NICE 2006[16] CPG did not formulate a specific question to evaluate which treatment was most effective and safe to reduce the sleep disorders associated with PD. However, it does address aspects such as EDS and nocturnal akinesia in PD. In regard to EDS, the same RCTs covered in the SIGN CPG are included. In regard to nocturnal akinesia, a double-blind RCT was found (*The UK Madopar CR Study Group* 1989) that compares controlled-release levodopa and immediate-release levodopa in the treatment of nocturnal and daytime disability. The RCT was a multi-centre study that included 103 persons in 11 centres in the United Kingdom. The average age of the people included in the trial was 68, with an average duration of the disease of 8 years. Immediate-release and controlled-release levadopa/benserazide were administered in a dose of 125 mg/day at night immediately before going to bed. No significant differences were observed in nocturnal and morning disability[16].

CPG
RCT
1+

The product sheets of the medications that have modafinil as the active ingredient, in the therapeutic indications section, specify that it "is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy. Excessive sleepiness is defined as difficulty in maintaining wakefulness and an increase in the probability of falling asleep in inappropriate situations". Also, in the posology and administration sections, it indicates that "treatment must be initiated by a physician specialised in sleep disorders or under the physician's supervision". The diagnosis of narcolepsy must be made in accordance with the International Directive for the Classification of Sleep Disorders (ICSD-2). Patients must be monitoring periodically, including the clinical evaluation of the need for the treatment".

With these requirements defined in the product sheet itself, it should be noted that in our NHS, the Sleep Units or reference centres are distributed throughout the country, although this may have an impact on the work load of the professionals involved (with the consequent waiting lists), as well as the inconvenience caused by the travel of patients, along with their family members and caregivers.

In regard to treatment with melatonin, the European Commission issued a marketing authorisation valid for the entire European Union for the medication Circadin® a *Rad Neurim Pharmaceuticals EEC Limited* on 29 June 2007. The on-line Information Centre of the Spanish Agency for Healthcare Products and Medications (AEMPS _ CIMA) indicates that in Spain, it is marketed under the name Circadin 2 mg extended-release tablets, and is a medication that requires a prescription from a physician. Circadin is indicated, in monotherapy, for the short-term treatment of primary insomnia (very light sleep) in patients 55 years of age and older.

It should be noted that the packaging of some antiparkinson medications, as well as their respective summaries of product characteristics and patient information leaflets, mention the potential problems in regard to driving vehicles and management hazardous machinery as a result of the appearance of these sleep disorders. Specifically, the AEMPS[35] website provides a list of active ingredients and the addition of the driving pictogram to the subgroup of antiparkinson medications (N04) of the TCA classification of the WHO, updated by the Spanish Agency for Healthcare Products and Medications (AEMPS) on 03/05/2011.

At the time this CPG for the management of patients with PD was prepared, a trial is being carried out on pitolisant in the management of hyperinsomnia and narcolepsy in patients with PD[34].

There are antiparkinson medications, such as rotigotine, as well as other therapeutic groups, that may have an impact on sleep disorders in patients with multiple pathologies. The pharmacotherapeutic information of these patients, in which the information regarding

polypharmacy, its side effects and interactions is collected, may be especially relevant in reducing these sleep disorders.

It should be noted that there are studies that evaluate the efficacy of transdermal rotigotine in the management of sleep disorders[36]. The product sheet or summary of product characteristics does not include this therapeutic indication, and its warnings and special precautions for use indicate that the use of rotigotine has been associated with drowsiness and episodes with sudden onset of sleep. Also, some of the frequent adverse reactions include: sleep attacks/sudden sleep episodes, insomnia, sleep disorders, abnormal dreams, among others. The revalidation of the product (AEMPS) was carried out on 17/02/2011, and revised, in the public evaluation report, of the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA), in March 2013.

Based on the experience of occupational therapy, it was observed that the use of satin sheets facilitates turning over in bed. Falling asleep is also improved by physical exercise up to 2 hours prior to going to bed.

Summary of evidence

CPG 1++	Modafinil (200 – 400 mg/d) improves EDS in patients with PD but not significantly[17].
CPG 1+	Modafinil (100 – 200 mg/d) improves on the Epworth subjective sleepiness scale, but not in the objective polygraph of the maintenance of wakefulness test[17].
CPG 1-	Modafinil (200 mg/d) improves on the Epworth sleepiness scale, but there are no significant differences in the *Clinical Global Impression*[17].
CPG 1++	Melatonin (5 to 50 mg) improves on the daytime sleepiness subscale of the General Sleep Disorder Scale (GSDS). No change was observed in the ESS and the Stanford Sleepiness Scale[17].
CPG 1-	Melatonin (3 mg/d) has no effect on EDS[17].
CPG 1+	No significant differences were observed in nocturnal and morning disability when administering controlled-release and immediate-release levodopa[16].
CPG 4	The recording of sleep history, documenting possible disorders, and the adoption of sleep hygiene measures, which include diet-related measures, as well as the review of medication, lead to a reduction in sleep disorders in patients with PD[16].

Recommendations

D	The treatment of Excessive Daytime Sleepiness (EDS) must be aimed at finding a reversible cause, such as depression, poor sleep hygiene, or medications, associated with the altered sleep pattern.
D	Modafinil and melatonin are not recommended for the management of EDS associated with PD.
D	Modified-release Levadopa products may be used for nocturnal akinesia in patients with PD.

D	The sleep history of the patients with PD should be recorded to document the sleep disorder.
D	Proper sleep hygiene is recommended for persons with PD and any sleep disorder, including: • Avoid intake of stimulants in the afternoon (e.g. coffee, tea, etc.) • Establish a regular sleep pattern. • Comfortable bedroom temperature and setting. • Provide healthcare products, such as bed lifts or rails to assist with movement and turning, which helps make people more comfortable. • Restrict naps during the day. • Recommend regular and adequate exercise to sleep better. • Review all of the medication and avoid drugs that affect sleep or alertness, or that could interact with other medication (e.g. selegiline, antihistamines, H2 antagonists, antipsychotics, and sedatives).
D	Special care should be taken to identify and control sleep behaviour disorders, such as restless leg syndrome and the REM (rapid eye movement) phase in persons with PD and sleep disorders.
D	Persons with PD who have sleep attacks should be advised not to drive or expose themselves to occupational risks. An attempt should be made to adjust medication in order to reduce the occurrence of these attacks.
√	Patients should be advised to exercise caution with medication that could alter their ability to drive or operate machinery, and should read the information available on the packaging of this medication: the warning symbol or pictogram on the box (driving pictogram), which is supplemented by the information provided in the prospectus.
√	Persons with PD are recommended to maintain proper sleep hygiene, by doing physical exercise at least a few hours before going to sleep and using satin sheets to facilitate turning in bed.

4.1.2.3. Impulse control disorders

Question to be answered:
Which treatment is safest and most effective in controlling the impulse control disorders associated with the treatment of Parkinson's disease using dopamine agonists?

One of the complications that may occur as a result of the pharmacological treatment of PD (mainly with dopamine receptor agonists in high doses) are impulse control disorders (ICDs)[37]. The essential characteristic of ICDs is the failure to resist an impulse, tendency, or temptation to carry out an act that is harmful to others or the individuals themselves. Persons with ICDs experience a greater impulse to carry out the action prior to the action, as well as greater pleasure, gratification, or release of tension at the moment the act is committed.

Examples of ICDs include pyromania, compulsive gambling (ludopathy), and trichotillomania (compulsive pulling of the hair), or kleptomania, among others. There is growing concern for the comorbidity of a range of ICDs, especially in patients with advanced PD, such as ludopathy, compulsive eating, compulsive shopping, the phenomenon of *punding* (stereotyped behaviour that includes automatic motor rituals for no purpose), and hypersexuality or libido disorders[38].

Some of these disorders can have an enormous impact on the quality of life of patients with PD and their family members (generating serious situations, in some cases with dramatic or catastrophic consequences).

The clinical management of the symptoms of ICDs normally consists of modifications in the dopamine replacement therapy (DRT), mainly of the dopamine agonists[39-40], with discontinuation or changing of pharmacotherapy, although the use of other therapeutic alternatives, including antidepressants, antipsychotics, and other medications, is also proposed. In addition, these disorders may mimic primary psychiatric conditions.

It is therefore necessary to evaluate which treatments will be most effective and safe for the management of the impulse control disorders associated with this disease, taking into consideration aspects such as agonists withdrawal syndrome.

Two low-quality systematic reviews were found[41-42] that address the treatment alternatives for these ICDs associated with the pharmacotherapy of PD. The management of these ICDs is also addressed in question 12 of the SIGN 2010[17] CPG for PD.

Antonini *et al*. 2009[41] summarises the current evidence (until December 2008) on the epidemiology of behavioural disorders in PD, including reflections on the neurobiological basis, and discusses strategies for management and prevention of the disorders. The different treatments proposed to reduce ICDs in patients in DRT include: reducing or discontinuing the medications involved, specifically dopamine agonists; adjuvant psychiatric medication; evaluation of symptoms of dopamine dysregulation syndrome. SR 1-

The review proposes the use of selective serotonin reuptake inhibitor antidepressants (SSRIs) for the management of ICDs, and indicates that "proven" results have been found for the treatment of ludopathy with fluvoxamine, but not with paroxetine or sertraline. Promising results for escitalopram were found in two open trials in small cohorts. In the case of fluoxetine, they mention its use for eating disorders.

The use of mood stabilizers (lithium, valproate, and topiramate) or opioid receptor antagonists (naltrexone and nalmefene) has not been studied in patients with PD and ICD, so they should be used with caution.

Atypical antipsychotics: ludopathic patients with PD respond to low doses of risperidone, quetiapine, and olanzapine, and clozapine can be used to reduce hypersexuality in PD, but it is not effective on ludopathy.

Antiglutamate drugs: the efficacy of acetylcysteine in the treatment of ludopathic patients has been postulated.

Behavioural therapies: currently, the role of psychotherapy to advise and support patients with PD and addictive behaviours (ICB and dopamine dysregulation syndrome) is limited to a small number of cases with variable results.

For the prevention of ICDs in patients with PD, they indicate that several recent studies suggest that some specific clinical aspects, which include male gender, young age at the time of appearance of PD, premorbid traits of impulsiveness and impulsive behaviour, depression, and personal or family history of alcohol or drug abuse are associated with increased risk of developing addictive behaviours. The clinics must identify the patients with PD who are vulnerable and monitor behavioural aspects during treatment with dopamine medication, especially when using dopamine agonists. The instruments *Barratt Impulsiveness Scale* and *Minnesota Impulsive Disorders Interview* may be useful for identifying high-risk patients before initiating treatment.

Management should include the consideration of the reduction or discontinuation of dopamine agonists, using an SSRI, and probably psycho-social counselling and support.

Callesen *et al*. 2013[42] present the prevalence rate and discuss functional neuroanatomy, the impact of the interactions of dopamine-seratonin, and the cognitive symptoms associated with ICDs in PD. They also present and discuss the prospects for future investigation in the management of ICDs in PD. The reduction of dopamine agonists is the primary strategy in the management of ICDs in PD, but it is normally associated with the development or deepening of depression, anxiety, or apathy, which is normally found to occur in up to 19% of the patients during the discontinuation of dopamine agonists.

SR 1-

The following are used for the pharmacological management of ICDs in PD: zonisamide, donepezil, used to treat cognitive disorders and dementia in PD; valproate, which has been shown to be effective in the treatment of ludopathy in patients without PD and in patients with ICDs in PD; SSRIs, at least in the subgroup of patients with ICDs who present comorbidity with depressive symptoms; atomexitine, a noradrenalin reuptake inhibitor that leaves the ventral striatal dopamine system intact; the opioid antagonist nalmefene. The use of sustained-release dopamine agonists has been proposed for future investigation. The involvement of the seratonergic system is emphasised. Tools for evaluating the risk of ludopathy are presented. The association of the dopamine receptor agonists D_2/ D_3 in behavioural complications is emphasised.

The SIGN 2010[17] CPG on PD poses the question: in patients with PD, what evidence is there of the adverse effects associated with ergoline dopamine agonists (e.g. bromocriptine, pergolide, lisuride, and cabergoline) *vs*. non-ergoline dopamine agonists (e.g. ropinirole and pramipexole) and levodopa? In addition to ICDs, they include fibrotic effects (moderate to severe cardiac valvulopathy and serosal fibrosis) and sleep disorders as adverse effects to be taken into consideration (see the corresponding question of this CPG).

CPG RCT 1+

CPG Case Series 3

They found a relationship with the adverse effects (ICDs) associated with dopamine agonists:

Dopamine agonists can be classified as ergoline (bromocriptine, pergolide, and cabergoline) or non-ergoline (apomorphine, pramipexole, ropinirole, and rotigotine). Ergoline and non-ergoline dopamine agonists are associated with an increased risk of: ICDs, which include ludopathy, binge eating, and hypersexuality; a survey indicated a lifetime risk of ICDs of 13.7% in patients in treatment with dopamine agonists; young males and persons with a history of behavioural disorders, alcohol abuse, or obsessive-compulsive disorder are especially vulnerable. There is no solid evidence that ergoline and non-ergoline agonists differ in this sense, or that a specific medication is associated with a higher risk, so normally the changing between agonists to control ICDs is not normally recommended.

The professionals involved in the detection of these disorders should receive specific training. In general, patients with PD may require assistance by specialised care resources, which is the area in which psychiatric and clinical psychology professionals work, who presumably have the most experience in the detection of these impulse control disorders.

Active dispensation in pharmacies might be encouraged, so that they advise patients and caregivers to take the risks associated with the use of these antiparkinson medications into consideration. For example, this active dispensation could also mention aspects such as the recommended time for the administration of the medications, or whether or not medications should

be taken with food (e.g., the product sheet for bromocriptine indicates that it should preferably be administered at night and that dopamine agonists should always be taken with food).

In conclusion, the initiatives and resources needed to provide training and information in all of the areas involved should be planned and facilitated.

Finally, it should also be noted that pergolide is not marketed.

The studies agree that different parameters, especially those related to behavioural aspects, should be monitored during treatment of PD with dopamine agonists, in order reduce the dose if necessary. Non-conclusive results were presented regarding the efficacy of valproate in patients with ICD and PD. The results on the efficacy of SSRIs in patients with PD and ICD point in the same direction, especially in the subgroup of patients with PD with ICD who show comorbidity of depressive symptoms. Only one study indicated that there are results that point towards the use of specific drugs from this subgroup for specific impulse control disorders (e.g. fluvoxamine and pathological gambling).

Primary prevention actions help reduce the incidence of the disease, because they act before it occurs, by reducing the risk factors in healthy individuals. Therefore, if professionals, patients, family members, and caregivers are instructed in regard to the risks associated with the use of antiparkinson medications, and focus is placed on the screening of the impulse control disorders that may appear in patients at risk, this helps reduce the clinical impact of this intercurrent problem.

The focus to date has been mainly theoretical or conceptual. The studies found were low quality. However, due to the serious consequences that the ICDs associated with antiparkinson medications may have on the quality of life of the patients, it is considered helpful to highlight several recommendations.

Summary of evidence

CPG 1+	Ergoline and non-ergoline dopamine agonists are associated with an increased risk of: impulse control disorders, which include ludopathy, binge eating, and hypersexuality[13].
CPG 3	A survey indicated a lifetime risk of ICDs of 13.7% in patients in treatment with dopamine agonists[17].
CPG 1+ and 1-	The following are some of the variables that may be associated with an increased risk of developing addictive behaviours: male gender, young age at the time of appearance of PD, premorbid traits of impulsiveness and impulsive behaviour, depression, and personal or family history of alcohol or drug abuse[17-41].
CPG 1+	There is no solid evidence that ergoline and non-ergoline agonists differ in this sense, or that a specific medication is associated with a higher risk[17].
1-	The role of psychotherapy to counsel and support patients with PD and ICDs is limited to a small number of cases with variable results[41].
1-	The discontinuation of dopamine agonists in the management of ICDs in PD is associated with the development or deepening of depression, anxiety, or apathy in up to 19% of the patients[42].
1-	Ludopathic patients with PD respond to low doses of atypical antipsychotics (risperidone, quetiapine, and olanzapine). Clozapine may be effective in patients with PD and hypersexuality[41].

CPG 1+ and 3	An increase in the risk of moderate to severe cardiac valvulopathy and serosal fibrosis (pleural, pericardial, and retroperitoneal) has been observed in the use of ergoline dopamine agonists[17].

Recommendations

B	The management of impulse control disorders (ICD) in patients with PD should include the consideration of the reduction or discontinuation of the use of dopamine agonists, using a selective serotonin uptake inhibitor (SSRI), and probably psycho-social counselling and support.
B	Ergoline dopamine agonists should not be used as the first line of treatment of PD and ICD.
A	Switching between dopamine agonists in patients with PD and ICD is not recommended.
D	When ergoline dopamine agonists are used, patients should follow: A baseline screening ecocardiograph and regular follow-up scans to identify cardiac abnormalities. Baseline laboratory investigation (e.g. erythrocyte sedimentation rate, serum creatinine) and radiological investigation (chest x-ray) with regular follow-up monitoring to identify serosal fibrosis.
A	Patients should be warned of the potential of dopamine agonists to cause ICD and EDS, and should be informed of the effects on driving and management of machinery.
B	Special attention should be given to detect signs of ICD in young male patients with PD and a prior history of behavioural disorders or addictive behaviour.
√	Healthcare workers should discuss the possible complications of ICD with the patients with PD who are taking dopamine agonists.

4.1.2.4. Cognitive impairment

Question to be answered:
In adults with Parkinson's disease, who develop initial cognitive impairment, is it safer and more effective to add an acetyl cholinesterase inhibitor, or modify dopaminergic treatment to improve cognitive functioning symptoms?

Dementia is a common aspect in advanced PD, affecting up to one out of every four patients with PD. There are nuances in the classification of these patients, depending on the grade of dementia. This means that there are patients who have PD and clinically significant cognitive impairment, but who have not been formally diagnosed with dementia. Other situations that appear in day-to-day clinical practice are cases in which patients have dementia with Lewy bodies, or present PD with dementia.

Also, the use of cholinesterase inhibitors has been suggested as part of the pharmacotherapeutic arsenal that is available for the treatment of this cognitive impairment, but it should be noted that

within this group, rivastigmine is the only drug authorised for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic PD.

In some studies, the use of dopamine agonists has been found to possibly be involved in the appearance of a worsening of cognitive function, although there are no known well-designed studies that make it possible to unequivocally establish this causal relationship.

In conclusion, the prior information available is not conclusive to orient the management of patients with PD who develop initial cognitive impairment, which makes it necessary to identify the scientific knowledge that is currently available, in order to establish a well-guided recommendation either towards the addition of a acetylcholinesterase inhibitor, or the modification of antiparkinson drugs which could be involved in the worsening of the cognitive function symptoms.

The protocol of a placebo-controlled double-blind RCT was found, the objective of which was to demonstrate the superiority of donepezil hydrochloride (5 mg capsules or 10 mg of donepezil) versus a placebo in the improvement of cognitive function, neuropsychiatric load, and functional ability in persons with PD and moderate dementia after 24 months of treatment. The study (*MUSTARDD-PD: Multicentre UK study of the acetylcholinesterase inhibitor donepezil in early dementia associated with Parkinson's disease)* is still in the period of patient recruitment (although it has a duration of 60 months, and it was registered in 2009). The RCT identification information is: EudraCT: 2009-015170-35; www.isrctn.com: ISRCTN30151023; Clinicaltrials.gov: NCT01014858. According to Clinicaltrials.gov the study will not be completed until May 2017, and at http://www.nets.nihr.ac.uk/programmes/nta they indicate that no results will be published until the start of 2018.

One high-quality systematic review (SR)[43] and one low-quality SR[44] were found. Also, an economic evaluation study with moderate quality[45], which analyses the cost-effectiveness of rivastigmine in patients with PD and dementia. In addition, question 18 of the SIGN[17] CPG on PD (in the section on the modification of dopamine treatment) helps provide a partial response to the question, because for the addition of an acetylcholinesterase inhibitor, several of the studies agree with the ones found in the aforementioned SRs. In addition, as mentioned before, one RCT was found that was underway at the time this guide was prepared[46].

The objective of the SR Rolinski *et al.* 2012[43] was to evaluate the efficacy, safety, and tolerability of cholinesterase inhibitors in patients dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), and cognitive impairment not dementia in PD (CIND-PD) (this is considered to be a separate phenomenon and also grouped together with the Lewy bodies disease). It evaluates treatment with cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine) at any dose and any treatment duration, compared with a placebo. Coexistence of Alzheimer's disease was not an exclusion criterion in the SR. The magnitude of the effect of the combined studies was presented (results from individual studies, or highly heterogeneous combined studies, or results with no statistically significant differences are not shown). The evidence that is currently available supports the use of acetylcholinesterase inhibitors in patients with dementia in PD (and cognitive impairment not dementia in patients with PD), with a positive impact on the global evaluation scales, cognitive function, behavioural alterations, and activities of daily life.

SR 1++

The scale *Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change* (ADCS-CGIC) was used for the global evaluation, finding a standardised mean difference (SMD) of -0.38 (CI95% -0.56 to -0.24; p<0.0001). For cognitive function, the *Mini-Mental State Examination* (MMSE) or *Alzheimer's Disease Assessment Scale Cognitive* (ADASCog) was used SMD -0.34 (CI95% -0.46 to -0.23; p<0.00001); MMSE weighted mean difference (WMD) PDD 1.09 (CI95% 0.45 to 1.73; p=0.0008); PDD and CIND-PD 1.05 (CI95% 0.42 to 1.68; p=0.01). In the measurement of behavioural alteration; SMD -0.20 (CI95% -0.36 to -0.04; p=0.01). For the activities of daily life; ADCS and *Unified Parkinson's Disease Rating Scale* (UPDRS) SMD -0.20 (CI95% -0.38 to -0.02; p=0.03). SR 1++

In regard to safety and tolerability, when the group in treatment with acetylcholinesterase inhibitors was compared with the placebo group, the patients in treatment with cholinesterase inhibitors experienced more adverse effects (AE) 318/452 *vs*. 668/842; OR 1.64 (CI95% 1.26 to 2.15; p=0.0003) and there were more dropouts during the study 128/465 *vs*. 45/279; OR 1.94 (CI95% 1.33 to 2.84; p=0.0006). When compared with a placebo, the AEs were more common in patients in treatment with rivastigmine 357/421 *vs*. 173/240; OR 2.28 (CI95% 1.53 to 3.38; p<0.0001). In regard to the AEs of donepezil, 311/421 *vs*. 145/212; OR 1.24 (CI95% 0.86 to 1.80; p=0.25). Finally, Parkinson's symptoms (tremors) appeared more frequently in the treatment group than in the control group: 64/739 *vs*. 12/352; OR 2.71 (CI95% 1.44 to 5.09; p=0.002). In regard to deaths, there were fewer deaths in the treatment group than in the placebo group 4/465 *vs*. 9/279; OR 0.28 (CI95% 0.09 to 0.84; p=0.03). The conclusions are that the evidence currently available supports the use of cholinesterase inhibitors in patients with PDD (and CIND-PD), with a positive impact on the global evaluation scales, cognitive function, behavioural alterations, and activities of daily life. The effect on DLB was uncertain (it was evaluated in one small study only). There is currently no disaggregated data to recommend the use of acetylcholinesterase inhibitors in CIND-PD.

Van-Laar *et al*. 2011[44] evaluates the efficacy, tolerability, and safety of cholinesterase inhibitors in patients with PD and dementia (PDD). Unlike the previous SR, in this case, the quality of the evidence of the review is low, the patients already had the diagnosis of dementia (with PD) established, and the studies included did not address galantamine and tacrine; only rivastigmine and donepezil. In regard to the magnitude of the effect of rivastigmine, the SRs indicate that in comparison with the placebo, it improved on different scales: total scale *Mattis Dementia Rating Scale* (MDRS) 5.8 points; ADAS-cog (2.9), ADCS-CGIC (0.5), ADCS-ADL (2.5), NPI (2.15), MMSE (1.0), *Cognitive Drug Research Power of Attention test* (294.84 msec), *Verbal fluency test form the Delis-Kaplan Executive Function System test battery* (D-KEFS) (2.8), *Ten Point Clock-Drawing test* (1.1). SR 1-

Also, with respect to donepezil, different studies were found that demonstrated that its produces improvement on several scales in comparison with a placebo: MMSE (1.8); *Clinician's Interview-Based Impression of Change plus caregiver input* (CIBIC-plus) (0.8), memory scale component MDRS (5.32), another study indicates that it improves on the MMSE scale (2.3), CGI (0.37), with no differences on the ADAS-cog, MDRS, *Brief Psychiatric Rating Scale* (BPRS). SR 1-

Other studies indicate that donepezil improves on MMSE, *Brief Test of Attention* (BTA), D-KEFS, CIBIC-plus but does not provide numerical data, and indicates that there was no significant improvement on ADAS-cog, DAD, *Neuropsychiatric Inventory* (NPI). In terms of conclusions, the two long RCTs on rivastigmine and donepezil, and the three small RCTs on donepezil that have been done to date present at least one result on the difference with treatment in comparison with a placebo with statistical significance, although not all of the donepezil studies achieve the primary objectives. Rivastigmine is now approved by the regulatory authorities for symptomatic treatment of moderate to severe PDD, based on the positive results observed in the RCTs on this cholinesterase inhibitor. Donepezil and galantamine are not approved for this indication.

Willan *et al*. 2006[45] analyse the cost-effectiveness of rivastigmine 3-12 mg/d in patients who have developed mild to moderate dementia at least 2 years after receiving the clinical diagnosis of PD. The study was done on the data from the EXPRESS trial (*EXelon in PaRkinson's disEaSe dementia Study*). The quality of the evidence is moderate. The time horizon is 24 weeks and the they use the social perspective as the point of view for the analysis. In terms of the results of the incremental analysis, for the scope of Canada (*Canadian Price Weights*) the ICER is 7249 $Can/QALY, and the probability that it is cost effective (CE) with different willingness to pay (WTP) (WTP values between 50,000 and 100,000 $Can/QALY) are in the range between 56% and 63%. In the scope of the United Kingdom (*UK Price Weights*), the ICER is 3403 £/QALY, and the CE probability with different WTP (between 20,000-40,000 £/QALY) would range between 55% and 59%. These calculations must take into consideration that the cost data is updated to values for the year 2004 using the healthcare component of the CPI. The conclusions of the pharmaco-economic study establish that rivastigmine can improve care in this study population. A small improvement was observed in the quality-adjusted life years (transformed from the scores on the MMSE scale). No differences were observed in the costs. Econ. Eval.

Also, the SIGN[17] CPG on PD poses the question: "In patients with PD who develop initial cognitive impairment, is there any evidence that starting treatment with a cholinesterase inhibitor or discontinuing dopamine therapy leads to a symptomatic improvement in cognitive function?". Dementia is a common aspect in advanced PD, with an estimated prevalence of between 24-31%. One longitudinal study of 126 patients with PD found that over period of three to five years, 10% developed dementia, while 57% also showed some degree of impairment in neuropsychological tests. Some medications used in the treatment of the motor symptoms may have harmful effects on cognition due to their anticholinergic effects. There is no evidence that specifically identifies the effect of the discontinuing of antiparkinson therapies on dementia, but best practices recommend that the first line of action in regard to the treatment of dementia in patients with PD be to rule out other causes of cognitive impairment (infection, dehydration, electrolyte imbalance, or subdural haemorrhage). This is especially relevant for patients who present *delirium* (sudden appearance of confusion or symptoms of psychosis), but it is also important in relation to any patients who present new symptoms of confusion.

CPG
Case Series 3
CPG
Expert opinion 4

One small RCT investigates the effect of the discontinuation of dopamine medication on patients in home care with advanced Parkinson's, and they concluded that the discontinuation of dopamine medication may be a feasible way to reduce polypharmacy and the potential adverse effects related to the medication, with a minimal risk of worsening motor deterioration. The small sample size and difference in baseline levels of dementia and motor dysfunction among the control and experimental groups limit the conclusions that can be drawn from this study[17].

CPG
RCT 1-

Special consideration must be given to the exclusion of medications that act at the level of the CNS that are not anti-parkinson's medications, such as antidepressants with antimuscarinic properties (e.g. tricyclic antidepressants) and benzodiazepines. The discontinuation of anticholinergic medications, amantadine, selegiline, and dopamine agonists may also be considered, along with optimisation of therapy with levodopa (without causing psychosis). The objective is to maximize motor control, but minimize the impact on cognition[17].

CPG
Expert opinion 4
CPG SR of cohort studies 2++

In regard to cholinesterase inhibitors, there is evidence that suggests a correlation between the pathological changes in the cholinergic neurotransmission system in PD and the level of cognitive impairment or presence of dementia, suggesting a possible therapeutic benefit of the use of cholinesterase inhibitors. Several different cholinesterase inhibitors have been studied in patients with PD, although most of studies have used rivastigmine as the drug[17].

CPG SR 1++
CPG
Expert opinion 4

Four reviews concluded that rivastigmine can be considered in patients with moderate to severe dementia (*Mini-Mental State Examination*, MMSE, 10 to 24) and PD, but it should be noted that the magnitude of the benefit is small, and it may exacerbate tremors and increase vomiting. The larger study (541 patients) found small but statistically significant increases in performance on the *Alzheimer's Disease Assessment Scale-Cognitive* scale (ADAS-cog; p<0.001) and on the *Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change* (ADCS-CGIC; p=0.007). In terms of activities of daily life (ADL), the *Alzheimer's Disease Cooperative Study-ADL scale*, there was a significant benefit (p=0.02) in the rivastigmine group, but the magnitude of the effect was small/moderate. Three small RCTs examined the effects of donepezil. Two showed statistically significant improvements on the MMSE scale (p=0.013 and p=0.0044, respectively) and one did not (but it did find a significant improvement on the *Dementia Rating Scale*). The studies vary in terms of frequency of the adverse side effects of donepezil. Two studies concluded that donepezil was well tolerated and did not worsen the symptoms of PD, while one indicated very poor tolerance. The evidence is insufficient to determine the effectiveness of galantamine or any other cholinesterase inhibitor drug. The recommendations indicate that in patients with PD and cognitive impairment, the causes of dementia should be investigated, and if present, they should be treated. The exclusion of any other non-parkinson medication that acts on the CNS should be considered, with the discontinuation of anticholinergic medication, amantadine, selegiline, and dopamine agonists[17].

CPG SR 1++
CPG Expert opinion 4
RCT 1+
RCT 1-

In regard to the material resources, only rivastigmine is authorised for the indication of symptomatic treatment of mild to moderately severe dementia in patients with idiopathic PD. The effectiveness (including economic costs) was evaluated only for this drug, whose efficacy has been proven.

During the process of revising the CPG, a new SR was published that included studies of the investigation groups mentioned earlier in the prior references, which evaluated the treatment of dementia with PD and/or Lewy bodies disease, with cholinesterase inhibitors and memantine[47]. The authors concluded, in the same line as the earlier studies, that only cholinesterase inhibitors improved cognitive function, behavioural symptoms, and the activities of daily life.

The reduction in cognitive function has an enormous impact on the quality of life related to patient health, family members, and caregivers. For this reason, all measures aimed in improving symptoms of the cognitive function, including cognitive stimulation, will have a large impact.

Summary of evidence

1++	The evidence that is currently available supports the use of acetylcholinesterase inhibitors in patients with dementia in PD (and cognitive impairment, not dementia in patients with PD), with a positive impact for the treatment group versus the control group, measured as the standardised mean difference on the global evaluation scales ADCS-CGIC -0.38; p<0.0001), cognitive function (weighted mean difference in favour of treatment, which improved on the MMSE scale 1.09; p=0.0008), behaviour alterations (weighted mean difference in continuous data combined on several scales for the assessment of behavioural disorders -0.20; p=0.01) and activities of daily life (combined data on ADCS and UPDRS scales -0.20; p=0.03)[43].

1++	There is currently no disaggregated evidence to recommend the use of acetylcholinesterase inhibitors in patients with cognitive impairment, not dementia and PD[43].
1-	Rivastigmine is now approved by the regulatory authorities for symptomatic treatment of moderate to severe PD with dementia, based on the positive results observed in the RCTs on this cholinesterase inhibitor[44].
1-	Donepezil and galantamine are not approved for the indication of dementia in patients with PD[44].
Econ. Eval.	Rivastigmine can improve care in patients who have developed mild to moderate dementia at least two years after receiving the clinical diagnosis of PD. A small improvement was observed in the quality-adjusted life years. Not cost differences were observed[45].
CPG 3	One longitudinal study of 126 patients with PD found that over period of three to five years, that 10% developed dementia, while 57% also showed some degree of impairment in neuropsychological tests[17].
CPG 4	Some medications used in the treatment of the motor symptoms of PD may have harmful effects on cognition due to their anticholinergic effects. There is no evidence that specifically identifies the effect of the discontinuing of antiparkinson therapies on dementia, but best practices recommend that the first line of action in regard to the treatment of dementia in patients with PD be to rule out other causes of cognitive impairment (infection, dehydration, electrolyte imbalance, or subdural haemorrhage). This is especially relevant for patients who present *delirium* (sudden appearance of confusion or symptoms of psychosis), but it is also important in relation to any patients who present new symptoms of confusion[17].
CPG 1-	The discontinuation of dopamine medication in patients in home care with advanced Parkinson's may be a feasible way to reduce polypharmacy and the potential adverse effects related to the medication with a minimal risk of worsening motor deterioration[17].
CPG 4 and 2++	Medications that act at the level of the CNS and are not antiparkinson medications and that could produce cognitive impairment, such as antidepressants with antimuscarinic properties (e.g. tricyclic antidepressants) and benzodiazepines are used. Anticholinergic medication, amantadine, selegiline, and dopamine agonists also present negative effects on cognitive function[17].
CPG 1++ and 4	Rivastigmine in patients with moderate to severe dementia (*Mini-Mental State Examination*, MMSE, 10 to 24) and PD, shows a magnitude of benefit that is small and may exacerbate tremors and increase vomiting. There were small but statistically significant increases in performance on the *Alzheimer's Disease Assessment Scale-Cognitive* scale (ADAS-cog; $p<0.001$) and on the *Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change* (ADCS-CGIC; $p=0.007$). In terms of activities of daily life (ADL), measured with the *Alzheimer's Disease Cooperative Study-ADL scale*, there was a significant benefit ($p=0.02$) in the rivastigmine group, but the magnitude of the effect was small/moderate[17].

CPG 1+ and 1-	Donezepil has shown statistically significant improvements on the MMSE scale (p=0.013 and p=0.0044, respectively) but no statistically significant improvement on the MMSE scale was found (however, a significant improvement was found on the *Dementia Rating Scale*). The studies vary in terms of frequency of the adverse side effects of donepezil. Donepezil was well tolerated and did not worsen the symptoms of PD in two studies, while one indicated very poor tolerance[17].
CPG 4	The evidence is insufficient to determine the effectiveness of galantamine or any other cholinesterase inhibitor drug in the treatment of patients with PD[17].

Recommendations

A	The use of the acetylcholinesterase inhibitor rivastigmine in patients with idiopathic PD who present mild to moderately severe dementia is recommended.
√	The evaluation of different intervention strategies, including cognitive stimulation is recommended to treat patients with PD who present an initial mild cognitive deterioration, before establishing specific pharmacological treatment with rivastigmine.
D	In patients with PD and cognitive impairment, the causes of dementia should be investigated, and if present, they should be treated.
D	The exclusion of any other non-parkinson medication that acts on the central nervous system should be considered, with the discontinuation of anticholinergic medication, amantadine, selegiline, and dopamine agonists.
√	A systematic review of the treatments prescribed for the management of the motor symptoms of PD is recommended, evaluating the indication, adherence, and interactions, in order to reduce the risk of adverse side-effects such as cognitive impairment, to reduce polypharmacy and agree upon treatments with the patient.

4.2. Non-motor symptoms

4.2.1. Sensory symptoms

Question to be answered:

Which treatment is safest and most effective in controlling the alterations with sensory symptoms associated with Parkinson's disease? (e.g. visual alterations; olfactory dysfunction; taste alterations; hypoacousia and other auditory disorders; pain and associated sensitivity symptoms).

Sensory disorders can be defined as any deficiency related to an alteration in one or more of the sense organs. In the case of PD, the following are considered to be the fundamental sensory disorders: visual alterations, olfactory dysfunction, taste alterations, hypoacousia and other auditory disorders, as well as pain and associated sensitivity symptoms[48].

Pain is a frequent symptom in patients with PD. James Parkinson himself, in the first description of the disease, noted the "rheumatic pain" ipsilateral to the extremity affected[2]. There are different classifications of pain in PD. One of the classifications of pain in PD classifies it into the following types: muscular-skeletal, neuropathic radicular, primary or central neuropathic, dystonic, and akathisic[48].

Parkinson's patients suffer from an alteration of the sense of smell (hyposmia or anosmia), which is early, frequent, and not clearly related to the motor symptoms of the disease. It appears that it may be an early marker of the disease, and it is an alteration for which no effective treatment has been found to date.

Patients with PD may also present different visual alterations, such as accommodation deficit, due to the generalized slowness of the muscles, which also involves the extraocular muscles, and even with complications such as visual hallucinations[48].

Consequently, despite the evident methodological difficulties that are posed by the search for studies that address these questions, and which were already mentioned in the NICE CPG on PD[16], the search, evaluation, and synthesis of the available scientific evidence is pertinent in order to help guide professionals and the patients themselves in their decision-making, due to the impact that these alterations with sensory symptoms associated with PD have on the quality of life of persons with the disease.

Three RCTs with low quality[49-50] or moderate quality[51] specifically related to the management of pain in patients with PD were found.

The study by Gerdelat-Mas *et al*. 2007[49] uses an open quasi-experimental design to compare the effects of levodopa on the objective pain threshold in patients with PD who are free of pain and in healthy subjects. The conclusions that it reaches are that levodopa significantly increases the objective pain thresholds of patients with PD who are free of pain, but not in healthy subjects; and that the patients with PD have an objective pain threshold that is lower than in the threshold in healthy subjects. The quality of the evidence is low, because it is a non-randomized controlled study with 23 participants. ECA 1-

Another study, Lim *et al*. 2008[50], compared the change in pain sensitivity after the administration of L-dopa among stable responders (12 patients), fluctuating responders without dyskinesia (15 patients), and dyskinetic patients (23 patients), also comparing sensitivity to pain among healthy subjects (20 patients) and patients with PD. The threshold and tolerance to pain caused by cold was studied, concluding, with low evidence quality, that L-dopa improves the response to pain in patients with PD and dyskinesia. ECA 1-

Dellapina *et al*. 2011[51] carried out a double-blind placebo-controlled crossover trial which evaluated the effect of apomorphine (a dopamine antagonist) versus a placebo, on the objective and subjective pain thresholds during experimental nociceptive stimuli in patients with PD. In this case, with moderate evidence quality, they concluded that, in comparison with a placebo, apomorphine has no specific effect on pain thresholds in patients with PD. RCT 1+

Only studies that were aimed specifically at pain in patients with PD were evaluated. In this sense, the Spanish healthcare system has good professionals in the Pain Units (mainly at the specialised care level) who address this disorder from different disciplines. However, other sensory alterations (specifically hypoacousia and visual deficits), for which studies were not found, within the NHS are addressed mainly as part of the portfolio of primary care services.

Two of the low-quality RCTs concluded that levodopa improved the response to pain in patients with PD (without pain or with dyskinesia, respectively), while a third study, on the other hand, established that another antiparkinson drug, apomorphine, has no specific effect on the pain threshold in patients with PD. It should be noted, as pharmacodynamic properties of the dopamine antagonist apomorphine, that it is a direct stimulant of the dopamine receptors, and although it does possess antagonist properties for both D_1 and D_2 receptors, it does not share the transport or metabolic paths of levodopa.

One person in the GWG highlighted a study that suggests the possibility of using transdermal rotigotine in the management of pain associated with the disease[36]. This is included as one of the future lines of research.

Summary of evidence

1-	Levadopa significantly increases the objective pain threshold in patients with PD who are free from pain, but not in healthy subjects[49].
1-	Patients with PD have an objective pain threshold that is lower than that of healthy subjects[49].
1-	Levadopa improves the response to pain in patients with PD and dyskinesia[50].
1+	In comparison with a placebo, apomorphine has no specific effect on pain thresholds in patients with PD[51].

Recommendations

√	It is advisable to inform patients of the possible alterations with sensory symptoms associated with PD, in order to work on them as a team (patients, family members, and caregivers, along with the healthcare professionals) and reduce the impact of those alterations on the lives of the people affected by this disease.

4.2.2. Autonomic dysfunctions

Question to be answered:

Which treatments are safest and most effective in controlling the autonomic dysfunctions associated with Parkinson's disease? (e.g. orthostatic hypotension; constipation; fecal incontinence; nausea and vomiting; hypersalivation; intolerance to heat; excessive sweating; nocturia; sexual dysfunction; weight loss; difficulty swallowing).

In patients with advanced PD, it is the non-motor symptoms that may determine disability to the greatest extent[26]. Orthostatic hypotension is one of these non-motor symptoms that appears most frequently in PD[52-53]. The symptoms of upper and lower gastrointestinal dysautonomia (sialorrea, dysphagia, and constipation) are common in PD and create physical and social difficulties for patients. Sialorrea appears commonly in patients with PD, presenting a problem for some. Oropharyngeal dysphagia is a disorder frequently associated with PD that significantly reduces quality of life. However, a proactive clinical approach is needed to ask patients about this disorder, because patients may not always report their difficulties swallowing unless they are asked directly.

The symptoms of urinary incontinence have harmful effects on physical and mental health, and are a serious concern of patients with PD due to their impact on their quality of life[54].

In general, patients with PD have a body mass index (BMI) lower than that of healthy patients, with weight decreasing as the disease worsens[55-57]. Lower body weight is associated with negative effects on health and a more negative prognosis.

To approach all of these questions, it is necessary to evaluate which interventions are the safest and most effective in the management of these autonomic dysfunctions associated with the disease.

Three SRs were located (Perez-Lloret *et al*. 2013; Seppi *et al*. 2011; Lombardi *et al*. 2012)[26-58-59] which review different alternatives for different sections of the question, as well as one moderate-quality RCT (Chinnapongse *et al*. 2012)[60], which evaluated the safety, tolerability, and efficacy of botulinum toxin type B in the treatment of sialorrea in patients with PD. Different treatments for the postural hypotension that is symptomatic in patients with PD were also found in the 2010 SIGN CPG[17]. The 2006 NICE CPG[16] addresses different autonomic disorders without carrying out a systematic search. Some of the aspects of autonomic dysfunction are included in multiple SRs. Specifically, the RS by Seppi *et al*. 2011 is included in Perez-Lloret *et al*. 2013. However, some of the intervention alternatives are only considered in the original review of Seppi *et al*. 2011, which is another reason for a critical reading of the original article.

Perez-Lloret *et al*. 2013[58] review the scientific literature in order to summarise the safety and efficacy of the treatments available for the autonomic dysfunctions in PD: orthostatic hypotension, sialorrea, sexual dysfunction, urinary dysfunction, and constipation. SR 1-

For orthostatic hypotension, they propose intervention with midodrine and fludrocortisone. The conclusions that the authors of the RS reach are: to reconsider treatments that induce or aggravate hypotension; warn patients to avoid the precipitating factors, such as sudden changes of posture, large meals, warms baths, and vasodilating medication; other non-pharmacological methods include the addition of salt to the diet, exercise, compression stockings, or physical manoeuvres to increase blood pressure by increasing venous return and peripheral resistance.

In regard to sialorrea, the use of botulinum toxin A (50 units in each parathyroid gland) was evaluated, achieving a 40% reduction on the sialorrea evaluation scale and a 31% reduction on the sialorrea frequency and severity scale. The evaluation of the use of botulinum toxin type B achieved a reduction of 40% in EVA scores and reduced oral saliva by 50%. A reduction was also achieved on the scale of frequency and severity of sialorrea (from 77 points to 40 points). With gycopyrrolate 1 mg/8 h an improvement of ≥ 30% was achieved in 39.1% of patients treated, as opposed to 4.3% of the placebo group. It was concluded that the discontinuation of medications that induce sialorrea, such as cholinesterase inhibitors, clozapine, or quetiapine, is the best option.

For sexual dysfunction, they evaluate sildenafil, tadalafil, and vardenafil as pharmacological alternatives. Other options include: intracavernous injections, intraurethral alprostadil, vacuum constriction products, and prosthetic penile implants. The conclusions of the review include: advising patients and re-evaluating treatments that could potentially produce sexual dysfunction (eg. certain treatments for hypertension and depression). SR 1-

In regard to urinary dysfunction, anticholinergic or antimuscarinic drugs were evaluated as intervention alternatives: fesoterodin, tolterodine, oxybutynin, solifenacin and trospium. No evidence was found for these treatments and it concluded with the recommendation that external causes such as prostate hypertrophy or cancer be considered. In the case of neurogenic hyperactivity of the detrusor, they also propose stimulation of the tibial nerve or behavioural therapy.

Finally, to address constipation, the proposed interventions are laxatives (osmotic agents such as laculose or PEG-macrogol and stimulants, such as bisacodyl or sodium picosulphate), prucalopride, lubiprostone, and linaclotide, obtaining a relative risk (RR), in the comparison with a placebo, as results: laxatives RR=0.52 (CI95% 0.46 to 0.60); prucalopride RR=0.82 (CI95% 0.76 to 0.88); lubiprostone RR=0.67 (CI95% 0.56 to 0.80); linaclotide RR=0.84 (CI95% 0.80 to 0.87). In the evaluation of macrogol, 7.3 g of isosmotic solution with electrolytes, obtained as a result a response rate of 80% versus 30% for the placebo. They conclude saying that macrogol, an osmotic laxative, and lubiprostone, an activator of chlorine channels, have shown some degree of efficacy. Other prokinetics, such as mosapride, should probably be used with caution, in light of the potential cardiovascular safety issues. They also recommend changes in diet and physical activity; increased intake of liquids and fibre, if necessary with fibre supplements and stool softeners; review of treatments that often cause constipation (tricyclic antidepressants, loperamide, codeine and opioids, antimuscarinics and some antiparkinson medications). Other proposed approaches include osmotic laxatives, mosapride, neutrophin 3, prebiotics, and biofeedback therapy.

The objective of Seppi *et al*. 2011[26] was to review the safety and efficacy of the treatments available for the autonomic dysfunctions in PD: orthostatic hypotension, sialorrea, sexual dysfunction, urinary dysfunction, constipation and gastrointestinal motility problems. SR 1-

In regard to orthostatic hypotension, they concluded that pragmatic treatment with non-pharmacological measures can be applied: sleeping with the head elevated, breaking up meals into smaller meals, physical containment manoeuvres. These manoeuvres include actions such as squatting, leaning forward, or crossing the legs at the onset of the presyncopal symptoms. They propose avoiding meals that are low in sodium and rich in carbohydrates, increasing intake of water (2-2.5 l/d) and salt (>8 g or 150 mmol/d), and wearing support stockings before initiating adjuvant treatment with anti-hypotension agents.

In regard to sexual dysfunction, the use of sildenafil in patients with PD was evaluated, but the evidence was insufficient to recommend sildenafil in the treatment of erectile dysfunction in patients with PD. It also has adverse side effects such as headache, shortness of breath, and dyspepsia. It is contraindicated in patients being treated with nitrates for cardiac coronary disease. SR 1-

For other problems of gastrointestinal motility (anorexia, nausea, and vomiting associated with treatment with levodopa and dopamine agonists), they noted that domperidone is possibly effective and that there is insufficient evidence to support the efficacy of metoclopramide, in addition to unacceptable risk (it worsens motor symptoms).

2011; Lombardi *et al*. 2012[59] systematically review the studies that evaluate the phosphodiesterase type 5 inhibitor (PDE5) sildenafil in individuals with diseases of the CNS and erectile dysfunction. They include three studies which evaluate, respectively, 50-100 mg of sildenafil; 25-100 mg of sildenafil; and 50 mg of sildenafil in a fixed dose. The conclusions of the review are that the PDE5 inhibitors are the first-line therapy only in males with erectile dysfunction with spinal cord injuries. For the rest of the diseases of the CNS, neurological pathology is not the principal cause of the erectile dysfunction: there are other comorbidities, mainly depression or concurrent sexual dysfunction, especially low sex drive, as well as the deficiency of sex hormones. There is also a high risk of side effects. SR 1+

The study by Chinnapongse *et al*. 2012)[60], with moderate evidence quality, evaluates the safety, tolerability, and efficacy of botulinum toxin type B (1,500 UI, 2,500 UI, and 3,500 UI) in the treatment of sialorrea in patients with PD. This was a double-blind placebo controlled RCT, with single treatment with escalating doses of botulinum toxin type B, with first injection in sub-mandibular glands, and later in parotid glands. By measuring the change in the scores on the sialorrea severity and frequency scale (measured by the investigator) from the baseline to week 4, it was found that each botulinum toxin type B group showed a significant improvement in comparison with the placebo group ($p<0.05$). Significant improvements were observed in total scores on the sialorrea severity and frequency scale that also persisted in week 8. RCT 1+

A reduction in the speed of salivary flow was also found, with statistically significant reductions observed in weeks 1, 2, 4, 8, and 12 in the groups 1,500 UI and 2,500 UI versus the placebo group ($p\leq0.0207$). In the 3,500 UI group, the speed of saliva flow reduced significantly from the baseline in weeks 2 and 4 in comparison with the placebo group ($p<0.0033$), with no significant differences detected later.

In the CGI, the botulinum toxin type B groups also improved in comparison with the placebo group, achieving statistical significance in weeks 1, 2, 4, 8, and 12. In regard to adverse effects (AEs), in the intervention groups, the following percentages presented at least one AE: 1,500 UI 50%, 2,500 UI 58.3%, 3,500 UI 61.5%. In the placebo group, 53.3% reported at least one AE. Gastrointestinal AEs occurred more frequently with the botulinum toxin type B group than with the placebo group (12/39 (31%) of subjects, in comparison with 1/15 (7%) of subjects, respectively). The study indicates that intraglandular injection of botulinum toxin type B (total dose of 1,500 to 3,500 UI) is well tolerated and significantly improves sialorrea in patients with PD. RCT 1+

In the 2010 SIGN SPG[17] posed the question "What is the effectiveness of treatments for symptomatic postural hypotension in patients with PD?" The alternatives that are proposed in the question are: raise the pillow, fludrocortisone, midodrine, or other adrenergic drugs, pyridostigmine or domperidone. CPG 1+

No studies related to the elevation of the pillow or head of the bed were referenced.

In regard to domperidone, it antagonizes the peripheral D_2 receptors and has been proposed as a treatment for orthostatic hypotension (OH). An RCT with a small sample (n=13) investigated the use of domperidone and fludrocortisone. Patients were assigned randomly to receive 10 mg of domperidone 3 times a day, or 0.1 mg of fludrocortisone in the morning, and two placebo tablets at lunch and dinner. After three weeks of treatment, and a one-week washout, the patients were crossed to the alternative therapy. The patients who took 10 mg of domperidone 3 times a day demonstrated a significant change in COMPASS-OD (*Composite Autonomic Symptom Scale, orthostatic domain*). The results, expressed as an average ± standard deviation (SD) are: (7 ± 2) compared with the non-pharmacological therapy ([9 ± 3]; p=0.04).

Fludrocortisone is a synthetic mineralocorticoid with few glucocorticoid effects It increases renal reabsorption of sodium and increases plasma volume through the renin-angiotensin-aldosterone system. In the previous RCT, patients who received 0.1 mg/day of fludrocortisone showed a significant change on the COMPASS-OD scale (6 ± 3) in comparison with the non-pharmacological therapy ([9 ± 3]; p=0.02).

Midodrine is a vasopressor with anti-hypotension properties. One RCT (n=171) showed that 10 mg of midodrine 3 times a day elevates systolic blood pressure (SBP) significantly in the upright position in patients with OH compared with a placebo (p<0.001). This is associated with an improvement in orthostatic dizziness (p=0.001). The midodrine group experienced adverse effects (mainly pilomotor reactions, itching, paraesthesia, urinary retention, and supine hypertension) more frequently than in the placebo group (p=0.001). The trial duration was short (6 weeks).

Another RCT (n=97) showed that 10 mg of midodrine increased upright SBP by 22 mm Hg in comparison with a placebo (28%, p<0.001). Midodrine improved the following symptoms of OH compared with a placebo: vertigo/dizziness, weakness/fatigue, syncope, low energy level, weakened ability to withstand and feel the drop in pressure (p<0.005). The adverse effects (mainly itching of the scalp) were reported in 22% of the placebo group versus 27% of the midodrine treatment groups. Hypertension in the supine decubitus position was documented in 8% of the patients treated with midodrine, in comparison with 1% of the patients taking a placebo. The trial duration was short (4 weeks). CPG 1+

Pyridostigmine is the cholinesterase inhibitor that improves sympathetic activity by increasing acetylcholine in the sympathetic synapses, which means that it strengthens baroreflexes by increasing systemic resistance. One RCT (n=58) evaluated the efficacy of a single dose of 60 mg of pyridostigmine alone, or in combination with 2.5 and 5 mg of midodrine, in comparison with a placebo. It was unclear whether any of the subjects in the study had PD, but 17 patients had multiple systemic atrophy. The primary objective of lowering the systolic BP while standing was reduced significantly with the treatment in comparison with the placebo (p=0.02). There was a significant reduction in the lowering of diastolic BP with pyridostigmine alone (lowering of BP by 27.6 mm Hg vs. 34.0 mm Hg with the placebo; p=0.04) and pyridostigmine with 5 mg of midodrine hydrochloride (BP lowered by 27.2 mm Hg vs.34 mm Hg with a placebo; p=0.002). No significant differences were noted in the measurements of BP in the supine decubitus position, in either the systolic (p=0.36) or diastolic pressure (p=0.85), indicating that the pyridostigmine does not increase BP in the supine decubitus position.

They did not make any recommendations, and commented that there is insufficient evidence (due to the small number of studies, small sample sizes, and short durations) to make any recommendations regarding the use of domperidone, fludrocortisone, midodrine, or pyridostigmine to treat OH.

The 2006 NICE CPG on PD[16] does not contain a specific question, but point 9.5 addresses different autonomic disorders. These include different gastrointestinal dysfunctions: weight loss, dysphagia, constipation, genito-urinary dysfunction, urinary dysfunction, sexual dysfunction, orthostatic hypotension, excessive sweating, and sialorrea. As a recommendation, it indicates that persons with PD should be treated as needed for the autonomic disorder of urinary dysfunction, weight loss, dysphagia, constipation, orthostatic hypotension, excessive sweating, and sialorrea, although it does note that since the symptoms of autonomic disorders are frequent, and since a systematic search of treatment trials has not been done in this area, different crucial aspects that are specific to PD were identified by the GWG as recommendations for best practices in the original CPG.

At this time (December 2014), the laxative lubiprostone is not marketed in Spain. As of this same date, the laxative linaclotide is authorised for the therapeutic indication of the symptomatic treatment of irritable bowel syndrome with moderate to severe constipation in adults. In the case of tegaserod, the drug has been withdrawn from the market.

All of the medications that contain botulinum toxin, both type A and type B, as the active ingredient are drugs for hospital use, so they may only be prescribed by physicians who are assigned to hospital departments and only hospital pharmacies can dispense them. None of these include sialorrea as an authorised indication.

In regard to weight loss, it should be highlighted that in-home enteral nutrition can be used, because the list of pathologies included as clinical situations of the patient that would justify the

need for this in-home enteral nutrition (regulated by Annex VII, section 8.B, of Royal Decree 1030/2006, dated 15 December, establishing the portfolio of common services of the National Health System and the procedure for updating it[61]) includes the severe degenerative processes of the CNS, such as PD, as a neurological disease that progresses with aphasia or severe dysphagia in patients with neuromotor disorders that prevents swallowing or passage, and that requires intubation.

The approach of the NHS must give special emphasis to the involvement of different professionals, including specifically speech specialists (in the section for sialorrea and difficulty swallowing) and rehabilitation measures for performing exercises and nutritional therapy for several sections.

In the case of sialorrea, the RCT by Chinnapongse *et al*. 2012[60] concluded that intraglandular injection of botulinum toxin type B (total dose of 1,500 to 3,500 UI) is well tolerated and significantly improves sialorrea in patients with PD. However, there is possible funding bias. The SR by Perez-Lloret *et al*. 2013[58] in relation to sialorrea concludes that it is advisable to discontinue the medications that cause it, such as cholinesterase inhibitors, clozapine, or quetiapine.

There are physicians who propose rehabilitation therapy as an initial measure, using speech therapy, because patients who speak well and vocalize well, working on phonation, do not normally present problems with sialorrea, and other measures should be reserved for special situations.

With metoclopramide, patients with PD who receive this D_2 receptor antagonist have an unacceptable risk, because it worsens motor symptoms and generates other additional adverse effects. The authorised indications of domperidone, as indicated in the basic product information sheet from the company for the original product, include nausea and vomiting induced by dopamine agonists (such as L-dopa and bromocriptine) used to treat PD.

In terms of the non-pharmacological measures for persons with PD, experience indicates that slowly raising the bed and remaining seated in bed for several seconds before standing improve the management of orthostatic hypotension.

Summary of evidence

CPG 1+ and 1-	The evidence on the efficacy of the use of domperidone, fludrocortisone, midodrine, or pyridostigmine in the treatment of orthostatic hypotension in PD is insufficient (due to the small number of studies, small sample sizes, and short study durations)[17-26].
CPG 1+	0.1 mg/day of fludrocortisone showed a significant change on the COMPASS-OD scale (average 6 ± SD 3) compared with the non-pharmacological therapy ([average 9 ± SD 3]; p=0.02)[17].
CPG 1+	Patients who take 10 mg/day of domperidone 3 times a day showed a significant change on the COMPASS-OD scale (average 7 ± SD 2) compared with the non-pharmacological therapy ([average 9 ± SD 3]; p=0.04)[17].
CPG 1+	10 mg of midodrine 3 times a day elevates SBP in the upright position significantly in patients with OH compared with a placebo (n=171; p<0.001). This is associated with an improvement in orthostatic dizziness (p=0.001). The principal adverse effects presented were pilomotor reactions, itching, paraesthesia, urinary retention, and hypertension in the supine decubitus position placebo (p=0.001)[17].

CPG 1+	10 mg of midodrine increased standing SBP by 22 mm Hg in comparison with a placebo (28%, p<0.001). Midodrine improved the following symptoms of OH compared with a placebo: vertigo/dizziness, weakness/fatigue, syncope, low energy level, weakened ability to withstand and feel the drop in pressure (p<0.005). The adverse effects (mainly itching of the scalp) were reported in 22% of the placebo group versus 27% of the midodrine treatment groups. Hypertension in the supine decubitus position was documented in 8% of the patients treated with midodrine, in comparison with 1% of the patients taking a placebo[17].
CPG 1+	The efficacy of a single dose of 60 mg of pyridostigmine alone, or in combination with 2.5 and 5 mg of midodrine, compared with a placebo resulted in a significant reduction in the drop in standing diastolic BP: alone (reduction of BP of 27.6 mm Hg *vs*. 34.0 mm Hg with the placebo; p=0.04); with 5 mg of midodrine hydrochloride (BP lowered by 27.2 mm Hg *vs*. 34 mm Hg with a placebo; p=0.002). No significant differences were noted in the measurements of BP in the supine decubitus position, in either the systolic (p=0.36) or diastolic pressure (p=0.85), indicating that the pyridostigmine does not increase BP in the supine decubitus position[17].
1-	The administration of botulinum toxin A (50 units in each parathyroid gland) is evaluated, achieving a 40% reduction on the sialorrea evaluation scale and a 31% reduction on the sialorrea frequency and severity scale[58]. For botulinum toxin type B, the reduction in the scores on the visual analogue scale (VAS) was 40% and the reduction of oral saliva 50%, and a reduction on the sialorrea frequency and severity scale (77 to 40 points)[58]. With gycopyrrolate 1 mg/8 h an improvement of ≥ 30% was achieved in 39.1% of patients treated, as opposed to 4.3% of the placebo group[58].
1+	Intraglandular injection of botulinum toxin type B (total dose of 1,500 to 3,500 UI) is well tolerated and significantly improves sialorrea in patients with PD[60].
1-	The relative risk (RR) of constipation in patients with PD decreases with laxatives (osmotic agents such as lactulose or PEG-macrogol and stimulants such as bisacodyl or sodium picosulphate) compared with a placebo. RR=0.52 (CI95% 0.46 to 0.60); prucalopride RR=0.82 (CI95% 0.76 to 0.88); lubiprostone RR=0.67 (CI95% 0.56 to 0.80); linaclotide RR=0.84 (CI95% 0.80 to 0.87). In the treatment of constipation, a response rate of 80% was achieved with macrogol 7.3% isosmotic solution with electrolytes versus 30% for the placebo[58].
1-	Domperidone is possibly effective in the treatment of the problems of gastrointestinal motility associated with PD26.
1-	Metoclopramide presents an unacceptable risk/benefit profile in the treatment of nausea and vomiting associated with the treatment of PD with levodopa and dopamine agonists, because it worsens motor symptoms[26].
1+	In patients with PD, the neurological pathology is not the principal cause of the erectile dysfunction: there are other comorbidities, mainly depression or concurrent sexual dysfunction, especially low sex drive, as well as the deficiency of sex hormones. There is also a high risk of side effects caused by sildenafil[59].

Recommendations

√	Patients with PD should be advised to avoid the precipitating factors of orthostatic hypotension, such as sudden changes in posture, large meals, hot baths, and vasodilation medication.
√	Managing orthostatic hypotension in patients with PD is recommended, using non-pharmacological measures before initiating pharmacological treatment. Non-pharmacological measures include avoiding meals that are low in sodium and high in carbohydrates, increasing intake of water (2-2.5 l/d) and salt (>8 g or 150 mmol/d) in the diet, breaking up meals, exercise, elevating the head while sleeping, wearing compression stockings, or carrying out physical containment movements to increase blood pressure by increasing venous return and peripheral resistance, such as squatting, leaning forward, or crossing the legs at the onset of presyncopal symptoms. Get out of bed slowly and stay seated in bed for a few seconds before standing.
√	It is advisable to reconsider treatments that induce or aggravate orthostatic hypotension in patients with PD, including the review of all medications, taken with or without a prescription, and other products that could cause hypotension.
D	Persons with PD must be properly treated for the autonomic disorder that results in urinary dysfunction, weight loss, dysphagia, constipation, orthostatic hypotension, excessive sweating, and sialorrea.
√	It is advisable to consider the discontinuation of medication that could induce sialorrea, such as cholinesterase inhibitors, clozapine, or quetiapine.
B	Patients should be advised and treatments that could potentially produce sexual dysfunction (e.g. treatments for hypertension and depression) should be re-evaluated.
B	The use of sildenafil is not recommended for patients with PD and sexual dysfunction.
B	The evaluation of other comorbidities that could result in erectile dysfunction is recommended, such as depression or concurrent sexual dysfunction, especially low sex drive, as well as the deficiency of sex hormones, because the PD may not be the principal cause of the sexual dysfunction.
√	The evaluation of possible causes of urinary dysfunction in patients with PD, such as prostate hypertrophy or cancer, is recommended.
√	Changes in diet and physical activity are recommended for patients with PD and constipation. Increase intake of liquids and fibre, with fibre supplements and stool softeners, if necessary.
√	It is advisable to consider and evaluate treatments that frequently cause constipation (tricyclic antidepressants, loperamide, codeine and opiodes, antimuscarinics, and some antiparkinson drugs).
√	The preparation of an exhaustive pharmacotherapeutic sheet is recommended for patients with PD, in order to determine medications and products that could potentially interact with each other.

B	Domperidone is recommended for problems of gastrointestinal motility (anorexia, nausea, vomiting associated with treatment with Levadopa and dopamine agonists).
√	The use of metoclopramide is not recommended with patients with PD due to the aggravation of the motor symptoms.

4.3. Depression as associated comorbidity

Question to be answered:

Are selective serotonin reuptake inhibitors (SSRIs) safer and more effective than tricyclic antidepressants (TCAs) for controlling depression associated with Parkinson's disease?

Depression is one of the most common psychiatric disorders observed in PD and it affects a large number of patients with PD. The depression associated with this disease is generally mild or moderate, but can be severe. There is no clear consensus regarding the use of antidepressants to treat depression in patients with PD.

Bradykinesia in patients with PD treated with L-dopa may improve after administration of selective serotonin reuptake inhibitors (SSRIs) in depressed persons with PD[62]. However, there are two possible problems with the use of antidepressants to treat depression in patients with PD. These are the possibility of extrapyramidal symptoms (such as dystonia, akathisia, tremors, and parkinsonism), and the possibility of an adverse interaction with selegiline, an MAO B inhibitor sometimes used in the treatment of PD. Although the use of SSRIs in PD with or without selegiline appears to be safe, caution is recommended when introducing these drugs.

Another therapeutic option for managing depression are tricyclic antidepressants (TCAs), with which there is extensive experience. However, the anticholinergic side effects of TCAs, which may include cognitive impairment and orthostatic hypotension, with an increased risk of falls, may cause many problems within the scope of PD. Also, for patients who do not improve with treatment with SSRIs, TCAs are a reasonable option when tremors are the dominant symptom and the potential benefit is thought to outweigh the risk of anticholinergic side effects.

In the absence of a clear primary option for the treatment of depression associated with PD, the selection of medication to manage depression in patients with PD must be based on the potential advantages in comparison with the potential side effects.

The evaluation of the efficacy and safety of SSRIs in comparison with TCAs is therefore of special interest, because the different pharmacodynamic targets of TCAs make it possible to generate hypotheses regarding its additional activity to resolve other complications or comorbidities (pain or sleep disorders, among others).

Two moderate-quality SRs were found[63-64], that address pharmacological treatment of depression associated with PD using SSRIs or TCAs

A third SR was found (Liu *et al*. 2013)[65], which compares the efficacy and acceptability of the therapeutic methods in the treatment of depression in patients with PD. This SR did not include new studies with respect to the previous two SRs, so it was not included as a source of evidence. The conclusions of these SRs are along thesame lines as the previous SRs: they indicate that there is insufficient evidence to support the anti-depressive efficacy of SSRIs, pramipexole,

pergolide, and serotonin–norepinephrine reuptake inhibitors (SNRIs). TCAs could be the first-line antidepressant medications in patients with PD because they have the most favourable balance between benefits and acceptability, followed by pramipexole and SNRIs, with SSRIs as the last alternative.

Rocha *et al*. 2013[63] carried out a systematic review with the objective of studying the efficacy of antidepressants in patients with idiopathic PD with depression. One RCT compared the administration of sertraline (SSRI) against venlafaxine (SNRI) over the course of 9 weeks in 32 patients. A reduction of at least 50% in the baseline symptoms on the *Hamilton Rating Scale Depression* 17-items (HRSD-17) was achieved: sertraline 14/16 (87.5%); venlafaxine 12/16 (75%). Another RCT compares the SSRI paroxetine (24±11 mg/d) with the SNRI venlafaxine (121±75 mg/d) in 76 participants over the course of 12 weeks. The response obtained in terms of reduction ≥50% on the HRSD-17: paroxetine 23/42 (55%); venlafaxine 16/34 (47%). For the response of remission on the HRSD-17 (sub-threshold score on a depression scale ≤7 on the HRSD 17-item scale) the following results were obtained: paroxetine 15/42 (36%); venlafaxine 11/34 (32%). In the improvement of depression status (analysing the association using relative risk -RR), no statistically significant differences were found between paroxetine and venlafaxine: RR=0.86 (CI95% 0.64 to 1.16). A meta-analysed estimator of two RCTs was shown, with significant differences found in the analysis by sub-groups (TCAs *vs*. SSRIs): RR=1.78 (CI95% 1.06 to 2.99). On the other hand, no specific class of anti-depression treatment is superior to the placebo: SSRI RR=1.20 (CI95% 0.57 to 2.52) in five studies; TCA RR=1.20 (CI95% 0.57 to 2.52) in two studies. The results of this moderate-quality RS point towards higher effectiveness of TCAs in comparison with SSRIs. The authors concluded that antidepressant treatments are tolerated well and they may be effective in the treatment of depression in patients with PD. SR 1+

The review by Skapinakis *et al*. 2010[64] evaluated the efficacy of SSRIs for depression in PD, with the secondary objectives of comparing SSRIs against TCAs and examining safety and tolerability in the use of SSRIs. The following were compared: citalopram 20 mg/d with desipramine 75 mg/d, for 4 weeks; continuous release paroxetine (average dose 28.4 mg/d) with nortriptyline (average dose 48.5 mg/d) for 8 weeks; and fluvoxamine (average dose 78 mg/d) with amitriptyline (average dose 69 mg/d) for 16 weeks. The response was defined as a reduction ≥50% on the MADRS scale (*Montgomery-Asberg Depression Rating Scale*) with respect to the baseline level (scale that measures depression severity): SSRI 8/15 *vs*. TCA 11/17; RR 0.82 (CI95% 0.46 to 1.49) p=0.52. In two studies, depression severity was measured on the HDRS (*Hamilton Depression Rating Scale*): SSRI 2/18 *vs*. TCA 9/17; RR 0.21 (CI95% 0.05 to 0.84) p=0.03. SSRI 12/20 *vs*. TCA 15/27; RR 1.08 (CI95% 0.66 to 1.77) p=0.76.

In the meta-analysis: raw response rate of SSRI 41% (22/53); raw response rate of TCA 57% (35/61); RR (randomized effects) 0.75 (CI95% 0.39 to 1.42) (p=0.37) in favour of TCAs. The authors concluded that the use of TCAs can be considered at least as often as SSRIs (in two of the three studies included, the investigators prefer to use TCAs). The quality of the evidence of this SR was moderate, because in the RCTs included, the doses of SSRIs are heterogeneous, as well as the treatment duration. Also, patients with severe depression were excluded, and one of the studies included in the meta-analysis is only published as a summary. It is important to note the number of withdrawals in both groups (30% for the SSRI group and 31% for the TCA group). SR 1+

This RS excludes Antonini *et al*. 2006[66] due to the low doses of amitriptyline in the comparator group (25 mg/d) and Serrano-Duenas *et al*. 2002[67] due to methodological limitations that pose a high risk of bias (they do not document the selection criteria, there are masking issues, the directives in the CONSORT statement are not followed, among others)[64].

The NHS has the resources to carry out this intervention (in terms of healthcare professionals involved, as well as the medication prescribed).

The results presented are directly applicable to our population. The review of Skapinakis *et al*. 2010[64], specifies that patients with severe depression were excluded, although the treatments are the same.

The results of the SRs found were not conclusive, although both point towards the equivalence between the two treatment alternatives (SSRIs and TCAs).

The SR by Rocha *et al*. 2013[63] concluded that antidepressant treatments are well tolerated, although it should be noted that there was a high number of dropouts from both groups. They also emphasise that no specific class of anti-depression treatment is superior to the placebo. The magnitude of the relative effect is therefore minimal, and the evaluation of other treatment alternatives is recommended, as well as working with other tools in a multi-discipline team.

The selection of the anti-depression treatment must be conditioned by the comorbidities in the patient, because some of the adverse effects of these medications, mainly due to the anticholinergic effects, may be used to treat these comorbidities (insomnia, pain, etc.). There are difficulties in the diagnosis of moderate depression in persons with PD because there are clinical aspects of depression that are superimposed on the motor aspects of PD.

The opinions of the experts of the NICE CPG on PD[16] regarding the individualized management of patients with PD who present depression as an associated comorbidity are included, along with the need for a holistic approach that evaluates the pharmacotherapy of both diseases.

The GWG emphasizes that the dose of venlafaxine and other antidepressants are probably infratherapeutic in the case of severe depression.

Summary of evidence

1+	No specific class of anti-depression treatment is superior to the placebo in the short term[63].
1+	The results point towards higher effectiveness of TCAs in comparison with SSRIs in the short term[63].

1+	The use of TCAs can be considered at least as often as SSRIs, in short periods of time[64].
1+	Antidepressant treatments are tolerated well, at least in the short term, and they may be effectivein the treatment of depression in patients with PD[63].
CPG 4	It was observed that the individualized management of depression in persons with PD, which particularly considers coexistent therapy, makes it possible to achieve better health results[16].

Recommendations

D	The management of depression in persons with PD should be personalized, specifically taking into account concurrent treatments and any comorbidities that are present.
√	The selection of the treatment for depression will depend on the prior experience of the healthcare professional and the clinical condition of the patient.
B	Based on the comorbidities presented by the person affected by PD, tricyclic antidepressants may be chosen as a short-term treatment.
√	The evaluation of other non-pharmacological alternatives is recommended for the treatment of depression in persons with PD, such as psychotherapy.
√	A multi-discipline approach is recommended for the management of severe depression associated with PD.

5. Non-pharmacological treatment

5.1. Occupational and physical therapy

Question to be answered:
How effective is physical therapy in persons with Parkinson's disease?

Parkinson's disease (PD) has serious implications with an enormous impact on the lives of patients and their families[68-69]. Traditionally, management of PD has focused on pharmacological treatment, but even with optimum administration of antiparkinson drugs, patients continue to experience a gradual deterioration in body function, and a progressive decrease in activities, participation, and mobility. This can lead to greater dependency on others, inactivity, and social isolation, all of which reduce quality of life. There is a growing trend to include rehabilitation therapies to supplement pharmacological and neurosurgical treatment, and a transition towards the inter-disciplinary management of patients with PD[70-71].

The physical therapist is a member of this interdisciplinary team, whose goal is to maximize functional capacity and reduce complications through the rehabilitation of movement and function in the context of education for health and the support of the person as a whole.

Physical therapy in people affected by PD is aimed at six essential specific areas: transference, posture, functioning of upper extremities (reaching and holding), balance (and falls), walking and physical capacity, and (in)activity. They also use attention orientation strategies, cognitive movement strategies, and exercise to maintain or increase independence, safety, and quality of life related to health. Historically, rates of referral to physical therapy for persons with PD have been low due to the weak evidence base and limited availability of physical therapy services[72-74].

However, thanks in part to initiatives such as PEDro (*Physiotherapy Evidence Database*), different studies and work groups have been developed to support the evidence backing the inclusion of physical therapy in the treatment of PD, with an increase, especially in the last five years, in the number of randomized controlled trials (RCTs) and systematic reviews (SRs).

The evidence that is currently available on the effectiveness of physical therapy in persons with PD needs to be evaluated, along with the contribution that this discipline can make to improving the quality of life of these people.

One high-quality systematic review (SR) (Tomlinson *et al*. 2012)[75], one moderate-quality RS (Lau *et al*. 2011)[76], and one moderate-quality economic evaluation study(Fletcher *et al*. 2012)[77], four moderate-quality RCTs (McGinley *et al*. 2012; Schenkman *et al*. 2012; Shulman *et al*. 2013; Corcos *et al*. 2013)[78-81] and one low-quality pilot study (Frazzitta *et al*. 2012)[82] were found. There is a wide variety of techniques used in physical therapy for the management of patients with PD. The Alexander technique is included in the NICE CPG on PD[16].

The objective of the high-quality RS by Tomlinson *et al*. 2012[75] was to evaluate the effectiveness of physical therapy in comparison with non-intervention in patients with PD (of any age, disease duration, and antiparkinson medication). Different physical therapy techniques, with any duration of the physical therapy, were compared with each other. The search period extended to December 2010, and includes 33 RCTs with a total of 1,518 participants. The interventions compared are: general physical therapy, exercise, treadmill, responses to instructions, dance, and martial arts. The results compare the different physical therapy techniques, but we present the magnitude of the overall effect of physical therapy (magnitude of effect expressed as the mean difference, with their respective 95% confidence intervals (CI95%) in parentheses, with the number of randomized controlled trials and number of participants in brackets [N° RCTs, N° participants]). The SRs evaluate the improvement in patients with PD through physical therapy, using parameters that measure the functions of walking, mobility, and balance, falls, and disability and clinical deterioration. The results obtained are indicated below, in favour of the intervention group (physical therapy) in comparison with the control group, for each one of these variables, and expressed in the corresponding units as the mean difference. Walking: distance covered in 2-6 min (m): 16.40 (CI95% 1.90 to 30.90) [4, 172]; time to cover 10-20 m (sec): 0.40 (CI95% 0.00 to 0.80) [4, 169]; speed (m/sec): 0.05 (CI95% 0.02 to 0.07) [11, 629]; cadence (steps/min): -1.72 (CI95% -4.01 to 0.58) [6, 327]; distance covered in two consecutive steps (m): 0.03 (CI95% -0.02 to 0.09) [5, 202]; stride (m): 0.03 (CI95% 0.00 to 0.06) [3, 239]; questionnaire on blocking of movem ent: -1.19 (CI95% -2.54 to 0.16) [3, 246]. For mobility and balance: Timed up & go (sec): -0.61 (CI95% -1.06 to -0.17) [7, 495]; functional reach (cm): 2.16 (CI95% 0.89 to 3.43) [4, 393]; Berg balance scale (scale from 0 to 56 points, with higher risk at lower scores): 3.36 (CI95% 1.91 to 4.81) [4, 361]; confidence in balance (0% no confidence and 100% totally confident): 2.40 (CI95% -2.78 to 7.57) [3, 66]. For falls: fall scale (inverse correlation between values; scores ≥ 70 indicate that there is fear of falling): -1.91 (CI95% -4.76 to 0.94) [4, 353]. Finally, the results in favour of the intervention for disability and clinical deterioration are measured on the Unified Parkinson's Disease Rating Scale (UPDRS): UPDRS total (0 to 176): -4.46 (CI95% -7.16 to -1.75) [2, 105]; UPDRS mental (0 to 16): -0.44 (CI95% -0.98 to 0.09) [2, 105]; UPDRS ADL (0 to 52): -1.36 (CI95% -2.41 to -0.30) [3, 157]; UPDRS motor (0 to 108): -4.09 (CI95% -5.59 to -2.59) [9, 431]. For these values, only the overall results are shown if there are no heterogeneity problems ($I^2 \leq 50\%$). No adverse effects were described. The conclusions reached by the authors are that physical therapy offers short-term benefits in the treatment of PD.

SR 1++

The objective of the review by Lau *et al*. 2011[76] was to determine whether whole body vibration (WBV) improves sensorimotor performance in persons with PD. The included population consisted of persons with idiopathic PD, with average age ranging between 63.1 and 75.0. It is important to note that they presented highly heterogeneous Hoehn & Yahr (H&Y) stages. The following interventions were evaluated: Acute WBV (single session) in four studies, the effects after a single session of WBV (5 series with a duration of 1 minute and 1 minute of rest between each) were evaluated. Vibrating platform to provide the WBV treatment (standing, with knees slightly bent). In one study, a physio-acoustic system was used (recline in a chair with a computer and multiple speakers that produce sound vibrations). The use of chronic WBV (multiple sessions over the course of 3 to 5 weeks) was also evaluated: one study with 2 sessions of WBV/day, 5 days/week for 3 weeks (2 series of 15 minutes each), and another study with 12 sessions distributed over 5 weeks. The frequencies of the vibration signals are between 6 and 25 Hz, and the amplitude of the signals between 3 and 14 mm. Conventional therapy (balance platform or walking for 15 minutes) or non-intervention (rest) was used for comparison. In terms of results, two studies found favourable results for acute WBV that were statistically significant on UPDRS tremor and rigidity scales; Conflicting results on UPDRS scales for walking and posture, bradykinesia, and cluster of cranial symptoms. No evidence that WBV is effective in the improvement of knee proprioception and other clinical measurements of sensorimotor performance (such as balance and mobility). For chronic WBV: two studies showed that compared with conventional exercise, WBV has non-significant effects on the UPDRS motor scale. In one study, WBV showed that, compared with conventional exercises, they have a tendency to improve performance on dynamic posturography tests (studies posture control through the movements of the centre on a dynamometer platform and is used to evaluate overall balance function) but not in other clinical measurements of walking and balance. Most of the studies showed no statistical significance in UPDRS measurements and other measurements of sensorimotor performance. Despite the fact that the question in the SR is formulated in a disaggregated manner in PICO format, and that the quality of the studies is evaluated with the scale proposed in the *Physiotherapy Evidence Data-base* (PEDro), the protocols and results are very heterogeneous, so the quality of the evidence in the SR is moderate. The authors concluded that evidence is insufficient to demonstrate or refute the effectiveness of WBV in the improvement of sensorimotor performance in persons with PD. More high quality studies are needed to establish the clinical efficacy of WBV in the improvement of sensorimotor function in persons with PD.

SR 1+

Econ. Eval.

Fletcher *et al*. 2011)[76] carried out a moderate-quality economic evaluation study. The objectives of the cost-utility analysis (CUA) were to evaluate the costs of exercise therapy for the prevention of falls in patients with PD, and determine whether this intervention was cost-effective in terms of QALY (Quality-adjusted life years). The evaluated intervention consisted of 10 weeks with one session/week of exercises in a group (maximum 6 people) to prevent falls in patients with PD and two sessions/week of additional exercises at home (strengthening and balance). After the intervention, there were 10 more weeks of monitoring. The comparison was customary care. The point of view for the analysis perspective was the *National Health Service and Personal Social Services* of the United Kingdom (funder). No updates were done for the discount rates of costs or benefits. According to the results presented, in regard to the costs, benefits, and synthesis of both: total cost 10 weeks of exercise intervention 4,883 £ (rental of space 448 £; time physical therapist 3,900 £; physical therapist travel 335 £; equipment 200 £). This corresponds to an average cost of 76 £ per participant (assuming that all of the participants attended the intervention; an average of 4 participants per exercise group). There were no statistically significant gains in the average QALY from the baseline to the follow-up in the participants of the intervention group compared with the controls (0.03 QALY; CI95% -0.02 to 0.08). An incremental analysis was done using the study of the ICER. The ICER for total costs in healthcare services was approximately -4,900 £ per QALY and the ICER for the total costs in social and healthcare services was approximately -1,400 £ per QALY. There were no statistically significant differences between the groups in total healthcare costs, combined costs of healthcare and social services, or QALY at the week-20 follow-up. The probability that the intervention would be more cost effective at 20,000 £ was 85% considering the costs of healthcare services, and 81% using the combined costs of healthcare and social services. A sensitivity analysis was carried out. The conclusions of the study were that exercise therapy is relatively inexpensive and is therefore probably cost-effective if a small improvement in health is demonstrated. The results support the cost-effectiveness of intervention with exercises aimed at reducing falls, but are not statistically significant enough to establish a definitive conclusion. It is important to note that the study duration was short, focused on costs, and that of the initial randomization of 130 patients, the EuroQoL questionnaires (the questionnaire that evaluates quality of life in relation to health), 37 (28.5%) were not returned, which and for these reasons, the evidence was considered to be of moderate quality.

In regard to the different RCTs, in the first place, McGinley *et al*. 2012[78] carried out a single-blind study with 210 participants to evaluate the effectiveness of two methods of physical therapy combined with education on falls. The objectives of the study were to document the safety, dropouts, adherence, and compliance rates of physical rehabilitation to reduce falls and the improvement of mobility of persons with PD. The interventions in the experimental group were a progressive strengthening training program (PST) or a movement strategy training (MST) program. The PST program consisted of 7 exercises to strengthen the principal muscles of the lower extremities and torso, according to the principles of PST. The exercises progressed adjusting the number of series and repetitions, adding more weight to the vest and increasing the resistance of the elastic band (*Theraband*®) and adjusting the height of the step or chair. The objective of the MST program was to improve movement performance, balance, and mobility, and prevent falls, according to the principles defined by Morris. External verbal attention instructions are used while functional tasks such as sitting down or standing up, moving from chair to chair, standing up and reaching, or walking and returning are carried out, individually or in pairs. The intervention in the control group consisted of guided discussion sessions on aspects related to PD, such as the impact of PD on the individual and the family, managing fatigue, relaxation, medication, communication, and community services. The control session included the teaching of "life skills" and did not include any content related to education on falls, exercises, walking, or balance. The results were grouped based on the proposed objectives (safety, dropouts, adherence, and compliance). In regard to safety: in the PST group (70 patients), new pains lasting more than 48 h appeared in 25 patients, 18 participants reported new pains, one fall occurred during the therapy session with no after-effects, and during the intervention, 10 patients fell, with a range of frequency of falls 0-7, and a median time to the first fall of 14 days. In the MST group (69 patients), new pains lasting more than 48 h appeared in 11 patients, 10 participants reported new pains, there were two cases of dizziness during the therapy session with no after-effects, and during the intervention, 24 patients fell, with a range of frequency of falls 0-24, and a median time to the first fall of 9 days. In the control group (71 participants): no new pains or incidents during the therapy session, during the intervention, 24 participants fell, with a frequency range of falls 0-52, and a median time of first fall of 9 days. In regard to dropouts, in the PST group: baseline evaluation 70 participants, 1 week after the week of intervention 69 patients remained, 3 months after the intervention phase, 67, and 12 months after the intervention phase, 65. In regard to the MST group: baseline evaluation, 69 participants, 1 week after the week of intervention 68 patients, 3 months after the intervention phase, 64, and 12 months after the intervention phase, 63.

RCT 1+

Finally, in the control group: baseline evaluation, 71 participants, 1 week after the week of intervention 59 patients, 3 months after the intervention phase, 54, and 12 months after the intervention phase, 56. In regard to adherence, in the PST group: 70 participants attended at least one intervention session, 90% went to between 6 and 8 sessions, and 4% went to fewer than 5 sessions. In total, patients attended 82.5% of the available sessions. In the MST group: 67 participants attended at least one intervention session, 93% went to between 6 and 8 sessions, and 3% went to fewer than 5 sessions. In total, patients attended 90.5% of the available sessions. In the control group: 65 participants attended at least one intervention session, 78% went to between 6 and 8 sessions, and 9% went to fewer than 5 sessions. In total, patients attended 80.7% of the available sessions. The compliance in the PST group was 89% of the participants, who completed the 7 exercises proposed in the 2-hour sessions. The remaining 11% completed 6 exercises. The most common form of progression was to increase the number of repetitions or series (97%). 80% of the participants wore weight vests during the appropriate exercises. The step platform and elastic bands were used by all participants. The resistance of the elastic band was increased with 57% of the participants. In the MST group: 86% of the participants were able to complete 6 or 7 of the activities in the 2-hour period. The most common method of progressing in the program was to increase the number of series and repetitions, along with increasing the difficulty of the tasks. The conclusions of the RCT, which were of moderate quality, were that in combination with a program for education on falls, progressive strength training and movement strategy training can be safely implemented in a community sample of persons with idiopathic PD. Programs on social skills for life and education are also effective control interventions. It is important to note that neither the level of education of the patients nor prior physical activities were taken into account. The life skills control group is developed by occupational therapists and social workers. One resource for education on falls to use as material for patients is: *Commonwealth of Australia, Don't Fall for It. Falls Can Be Prevented!; A Guide to Preventing Falls for Older People, Commonwealth of Australia, Canberra, ACT, Australia, 2007*. Available at:

RCT 1+

http://www.health.gov.au/internet/main/publishing.nsf/Content/phd-pub-injury-dontfall-cnt.htm

The study by Schenkman *et al*. 2012[80] compares the short-term (4 month) and long-term (10 and 16 month) responses to two supervised exercise programs and one exercise control program carried out in the home. The intervention in the experimental group consisted of supervised flexibility/balance/functioning (FBF) exercises 3 days/week for 4 months (followed by participation once a month, with patients encouraged to repeat the prescribed exercises 5 to 7 days a week for the 16 months). This FBF group completed 2 months of individual flexibility training with physical therapy, followed by 2 months of exercises in small groups (up to 6 participants), which included flexibility, balance, and functional exercises. On the other hand, the supervised aerobic exercise (SAE) group had sessions with 5 to 10 minutes of warmup, 30 minutes of exercises between 65% and 80% of maximum heart rate, and 5 to 10 minutes of stretching. Treadmills were mainly used, but stationary bicycles and elliptical trainers were also allowed. The intervention in the control group consisted of the *Fitness Counts* program of the *National Parkinson Foundation* which was carried out in the participants' home. In regard to the results (the results are presented for the mean difference between groups, with their respective 95% confidence intervals in parentheses), the results on the *Continuous scale-physical functional performance test* (CS-PFP indicated primary effects in favour of intervention; scale of 5 domains; total range 0 to 12): after 4 months: FBF group *vs*. control 4.3 (CI95% 1.2 to 7.3); SAE group *vs*. control 1.2 (CI95% -2.0 to 4.3); FBF group *vs*. SAE 3.1 (CI95% 0.0 to 6.2). There were no differences between groups after 10 and 16 months. There were no differences on the *Functional reach test* (FRT). In regard to oxygen consumption (VO2), after 4 months, SAE group *vs*. FBF group -1.2 ml/kg/min (CI95% -1.9 to -0.5). After 10 months: SAE group *vs*. FBF group -1.21 ml/kg/min (CI95% -1.92 to -0.49). After 16 months, SAE group *vs*. FBF group -1.7 ml/kg/min (CI95% -2.5 to -1.0) SAE group *vs*. control group -1.3 ml/kg/min (CI95% -2.0 to -0.6). As secondary results, they used PDQ-39 (a 39-item questionnaire on quality of life with PD): with no differences between groups; *Unified Parkinson's Disease Rating Scale* (UPDRS), motor subscale: no differences between groups; UPDRS ADL subscale: after 4 months, FBF group *vs*. control group -1.47 (CI95% -2.79 to -0.15). After 16 months FBF group *vs*. control group -1.95 (CI95% -3.84 to -0.08). With respect to adverse effects: 3 falls occurred without injury (one in each group), 2 patients showed discomfort or pain (both in the SAE group). 24 non-serious adverse events were reported: 2 sprains/dislocations (1 in FBF group, 1 in SAE group), 22 discomfort/injury (9 FBF group, 9 in SAE group, 4 in control group). The conclusions of the study are that from a clinical perspective, these results suggest that the FBF program and the SAE program can be important for persons with initial or intermediate PD (however in the study, the years of time since diagnosis of PD are: FBF group 4.9; SAE group 3.9; control group 4.5).

RCT 1+

RCT 1+

The primary objective of the single-blind study by Shulman *et al*. 2013[81] was to compare three types of physical exercises to improve walking, physical aptitude, and strength in patients with PD (high intensity treadmill; low intensity treadmill; stretching, and resistance). The secondary objectives of the study were to investigate the efficacy of exercise to improve disability and non-motor symptoms in PD. The interventions in the experimental group consisted of 3 sessions/week for 3 months (36 sessions in total). In the high intensity treadmill training group, the intervention consisted of: 15 minutes with heart rate at 40% to 50% of maximum capacity. The intensity and duration was increased by five minutes, 0.2 km/h and 1% incline every 2 weeks up to 30 minutes at 70% to 80% of heart rate capacity. The intervention in the low intensity training group consisted of: 15 minutes, 0% incline. The speed and incline were constant during the 3 months. The duration was increased 5 minutes every 2 weeks up to 50 minutes between 40% to 50% of maximum heart rate. For the control group, a stretching and resistance training group was formed: resistance exercises (muscular strengthening of the muscles of the lower part of the body, followed by stretching of the upper and lower parts of the body. The resistance exercises included to series of 10 repetitions with each leg with 3 resistance machines. The stretching exercises included one series of 10 repetitions with rotation of the torso, hip abduction, and stretching of hamstrings, quadriceps, calves, and ankles. The results obtained are presented grouped according to evaluation of walking, peak VO2, muscle strengthening, severity of the disease and disability, non-motor evaluation, and the adverse effects are documented. For the evaluation of walking: in the high intensity treadmill training group, this increased 6% (increase of 23 meters, $p = 0.07$); in the low intensity treadmill training group, it increased 12% (increase of 48 meters) $p = 0.001$); and in the stretching and strength group, it increased 9% (increase of 32 meters, $p < 0.02$). In the evaluation of peak VO_2 (ml O_2/kg/min): high intensity treadmill training groups there was an increase of 7% ($p=0.03$) with respect to peak VO_2; in the low intensity treadmill training group, an increase of 8% ($p=0.04$); and no effect in the stretching and strength group. In the evaluation of muscular strengthening: the high and low intensity treadmill training groups: led to an increase in strength of 2% and 8%; in the stretching and resistance group, the strength increase was 16% ($p<0.001$). In regard to the severity of the disease and disability, no changes were observed on the total UPDRS scale with either of the treadmill groups.

The stretching and resistance group: improvement -3.5 points ($p<0.05$) on the UPDRS motor subscale. No changes in non-motor assessment. Finally, in regard to adverse effects, no serious adverse events occurred. The exercise sessions never had to be interrupted and there were no changes in antiparkinson medication. Dropouts due to medical conditions included orthostatic hypotension, back pain, or fracture of the sacrum after a fall at home. The authors concluded that the three types of physical exercises improved walking and mobility. However, each type of exercise generates a different benefit profile. The low intensity treadmill training exercise was the most effective training exercise for walking and physical aptitude. The benefits in walking, physical aptitude and muscular strength were not accompanied by improvements in disability and quality of life.

The objective of the single-blind RCT by Corcos *et al*. 2013[79] was to determine the effects of progressive resistance exercises (PRE) in the improvement of signs of PD. The intervention was carried out two times/week for 24 months. The first 6 months with a certified personal trainer, and after, with a trainer only one time/week. The PREs consisted of 11 strengthening exercises (pectorals and dorsals on machines, inverted butterfly, press with both legs, hip extension, shoulder press, bicep curls, calves (plantar flexing of the ankle), triceps extension, seated quadriceps extension, and back extension). In the intervention with the control group, called the mFC group, because the strengthening exercise program (*Modified Fitness Counts*, the exercise program recommended by the *National Parkinson Foundation* was used, doing stretching, balance exercises, breathing and non-progressive strengthening. The programs were identical in regard to duration of exercise, number of exercise sessions, time with personal trainer, except for the specific exercises. In regard to the magnitude of the effects, the results in favour of the intervention, expressed in brackets as the mean difference (MD), with their respective 95% confidence intervals (CI95%) and the p value, between the PRE group and the mFC group. A distinction was made between *on* medication and *off* medication: in the case of *off* medication, the evaluation was done in the morning, after 12 hours had elapsed overnight without the patient taking medication; in the case of onmedication, after taking the medication and eating breakfast, participants waited 60 minutes and the evaluation was repeated. Motor signs and medication status were evaluated using the UPDRS-III scale. The score with *off* medication is presented first: from baseline to 6 months: [MD -1.0; CI95% -4.5 to 2.5; p=0.55]; after 12 months [MD -4.1; CI95% -7.6 to -0.5; p=0.02]; after 18 months [MD -3.8; CI95% -7.6 to -0.3; p=0.03]; after 24 months [MD -7.3; CI95% -11.3 to -3.6; p<0.001].

For the *on* medication: after 6 months [MD 0.7; CI95% -2.4 to 3.7; p=0.66]; after 12 months [MD -0.3; CI95% -3.5 to 2.6; p=0.78]; after 18 months [MD 0.2; CI95% -3.4 to 2.9; p=0.87]; after 24 months [MD -1.0; CI95% -4.7 to 1.8; p=0.39]. The equivalent dose of L-dopa was also evaluated: variation from baseline to 24 months [MD -75 mg; CI95% -200 to 62 mg; p=0.29]. Increase in L-dopa equivalents by 229.6 ± 283.3 mg (mFC group) and 155.8 ± 193.3 mg (PRE group). In regard to strength and speed of movement, and the comparison between the PRE group and the mFC group: flexing of the elbow with *off* medication [MD 3.7 Nm; CI95% -0.8 to 8.3 Nm; p=0.1]; after 12 months [MD 7.6 Nm; CI95% 3.2 to 12.5 Nm; p=0.001]; after 18 months [MD 7.9 Nm; CI95% 3.7 to 13.2 Nm; p<0.001]; after 24 months [MD 14.3 Nm; CI95% 9.3 to 19.3 Nm; p<0.001]; after 24 months, the mFC group was weaker -5.3 parentheses (expressed as the average ± standard deviation) than at the baseline by -5.3 ± 9.5 Nm; the PRE group was stronger by 9.0 ± 6.9 Nm. Flexing of the elbow with *on* medication: after 12 months [MD 8.6 Nm; CI95% 2.9 to 14.3 Nm; p=0.003]; after 18 months [MD 9.6 Nm; CI95% 3.9 to 15.5 Nm; p=0.001]; after 24 months [MD 6.2 Nm; CI95% 0.3 to 12.3 Nm; p=0.04]. For the results of speed of movement of flexing of the elbow, *off* medication: from the baseline to 6 months, the mean difference between the mFC group *vs*. PRE [MD -9.2 degrees per second; CI95% -34.6 to 16.4; p=0.48]; after 24 months PRE group faster than mFW [MD 43.5 degrees per second; CI95% 9.2 to 64.7; p=0.009]. In regard to physical function: no differences between groups after 6 months [MD -1; CI95% -3 to 1; p=0.209] and after 24 months [MD 0.5; CI95% 0 to 4; p=0.1]. Finally, in terms of the adverse effects that were noted: one case of wrist pain in one session due to maximum voluntary contraction; one adverse event possibly related to mFC (convalescence) and six possibly related to PRE (bilateral hip replacement, two unilateral hip replacements in the same patient, knee surgery to remove detritus, foot surgery, and hospitalization after a fall). The conclusions of the study were that the PRE has greater benefits than mFC in PD signs, muscle strength of upper limbs, and speed of movement after 24 months. The PRE was also found to reduce falls, which is a vital concern in the management of PD. RCT 1+

A pilot study was also found (Frazzitta *et al*. 2012)[82] whose objectives were to test whether intensive rehabilitation treatment (IRT) is effective to improve motor development and autonomy in activities of daily life compared with a control group in a monitoring period of 12 months; to investigate whether a second cycle of rehabilitation (RHB) administered after one year had the same efficacy as the first cycle; and to verify whether the treatment reduces the need for increasing doses of levodopa. The 25 participants in the intervention group received on cycle of 4 weeks, 5 d/w, of physical therapy, with 3 daily sessions (2 in the morning and 1 in the afternoon), with each session lasting 1 hour. Total 15 h/w x 4 weeks. RCT 1

RCT 1

The 1st session consisted of cardiovascular warmup activities; relaxation exercises, muscle stretching (scapular, hip flexor, tendons, and gastrocnemius muscles [calves]; exercises to improve functionality of abdominal muscles and posture changes in the supine position. In the 2nd session: exercises to improve balance and walking, using a platform to measure stability with visual indications and training on a treadmills associated with auditory and visual indications (treadmill plus). In the 3rd session: occupational therapy to improve autonomy in activities of daily life: transference from sitting to standing, changing from supine to sitting position, and from sitting to supine position, dressing, use of tools, and exercises to improve functions and skills with the hands (e.g. screwing and unscrewing). After completion, the patients were instructed to continue doing the exercises that they had learned in order to maintain functional activity of the joints of the back, scapula, and pelvis, along with the instruction to walk for at least 30 minutes/day. The customary care (pharmacological treatment) was given in the intervention in the control group. The results were as follows, expressing the magnitude of the effect as and average ± standard deviation; p value, for the IRT group *vs*. control group: UPDRS II: at baseline (13 ± 5) *vs*. (14 ± 4), and after one year (14 ± 6) *vs*. (19 ± 6). UPDRS III: baseline (21 ± 6) *vs*. (22 ± 7), and after one year (21 ± 6) *vs*. (28 ± 7). total UPDRS: baseline (21 ± 13) *vs*. (40 ± 11), after one year (41 ± 12) *vs*. (49 ± 13). The data is also provided for the first and second completion for the scales UPDRS II, III, and total for the IRT group (e.g. on the total UPDRS scale), 28 ± 11 (reduction 11.6 points; p <0.0001) in the first completion and in the second completion 31 ± 11 (reduction 9.6 points; p <0.0001). Equivalent dose of levodopa (mg/d) in the IRT group *vs*. control group, baseline (653 ± 322) *vs*. (617 ± 239), after one year (602 ± 268) *vs*. (647 ± 245). The average value decreased by 52 mg (p=0.04) in the IRT group and increased 30 mg (p=0.015) in the control group.

The conclusions were that the results suggest that the natural worsening of the symptoms associated with PD and the parallel increase in medication dosages can be counteracted by well-designed RHB treatment. It recommends the consideration of the addition of periodic cycles of IRT to pharmacological treatment to improve motor development and autonomy in activities of daily life, and to delay the increase in medication doses and prevent possible adverse effects. The external validity of the study is limited because the inclusion criteria specified that patients not have comorbidities, be able to walk without physical assistance, MMSE ≥ 26, not have vestibular/visual dysfunction that limited locomotion or balance, and be in stable antiparkinson treatment for > 4 weeks.

CPG SR of RCTs 1+ and RCT 1+

Lastly, the NICE CPG on PD[16], posed the question: "What is the effectiveness of physical therapy in comparison with standard medical therapy or a placebo in the treatment of PD?". They found a Cochrane review that evaluates the efficacy of physical therapy versus standard medical therapy in persons with PD. An RCT was also found that investigated an aerobic exercise program (with only 8 patients, so it is not included in the synthesis of the evidence). Also, a study to evaluate the effectiveness of the Alexander technique in comparison with no therapy or massage therapy. The SR includes 11 RCTs; four of which present significant results in regard to the treatment of persons with PD with physical therapy, with a total of 280 people. For conventional physical therapy techniques, one RCT (with 20 patients) evaluated the effectiveness of physical therapy to improve activities of daily life measured using: Barthel index post-intervention p=0.05; and after 5 months p=0.045. NUDS post-intervention not significant (NS); after 5 months p=0.018. Measurement functional index post-intervention p=0.048; 5 months p=0.016. Clinical assessment scales: total UPDRS post-intervention p<0.001; 5 months p<0.001. Webster assessment scale post-intervention NS; and after 5 months p=0.011. In another RCT (with 30 patients), it is used as an instrument for Parkinson's evaluation in home visits: 8 months p<0.05. Two RCTs (44 patients) evaluated motor disability by walking speed and stride length. For walking speed: post-intervention p ≤ 0.002; 5 months p=0.006. For stride length, post-intervention p=0.019; 5 months p=0.44. Another RCT (51 patients), considers motor disability: spinal rotation post-intervention p=0.019. A fifth RCT (88 patients) includes the Alexander technique: scale for self-assessment of PD disability at the best time of day post-intervention *vs*. controls p=0.04; at the worst time of day post-intervention *vs*. controls p=0.01; 6 months *vs*. controls p=0.01. BDI score post-intervention *vs*. controls p=0.03; 6 months *vs*. controls NS. Attitudes on self-assessment scale: post-intervention *vs*. controls NS; 6 months *vs*. controls p=0.04. In regard to the changes in medication in this RCT: the rate of medication changes was statistically favourable to treatment with the Alexander technique in comparison with the control (p=0.001). Fewer participants in the Alexander technique group changed their medication, but despite this, they did not experience worsening of symptoms (p=0.047). The following recommendations are defined: physical therapy should be available for persons with PD. Special attention should be given to: re-education for walking, with improvement of balance and flexibility; increase aerobic capacity; improve initiation of movement; improve functional independence, including mobility, and activities of daily life; provide advice regarding safety in the home. The Alexander technique could be offered to benefit persons with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition, as well as the attitudes of the person who has PD.

Physical therapy professionals provide the care that is characteristic of their discipline in primary care and specialised care of the NHS, through treatments with physical agents and resources, aimed at facilitating the recovery and rehabilitation of persons with somatic dysfunctions or disabilities, and to prevent them.

The results are consistent in the positive evaluation of the effects of physical therapy on persons affected by PD, especially in the short term. The results are not consistent in the case of medium and long-term evaluation, which could be conditioned by issues of adherence or continuity in the intervention, as well as the evolution of the disease itself.

The impact will be conditioned by the number of professionals involved and the techniques used, as well as by the population treated. No physical therapy intervention is free of the risk of

injury, but data indicates that the benefits may outweigh the possible risks of physical therapy.

There are other techniques that do not form part of the academic training of physical therapy. The SR search strategy did not include the specific terms of different techniques, such as tai-chi, dance, or the use of video game consoles in physical therapy as techniques for patients with PD. The search process found two moderate-quality RCTs (Li *et al*. 2012[83]; Pompeu *et al*. 2012[84]) aimed at the techniques of tai-chi and Wii-Fit®, respectively, and one low-quality RCT (Duncan *et al*. 2012[85]) that evaluated the efficacy of tango with these patients.

The primary objective of the controlled study by Li *et al*. 2012[83] was to examine whether a tai-chi program could improve posture stability in patients with PD. The intervention alternatives were compared: tai-chi, resistance training, and stretching. The intervention in the experimental group consisted of 60-minute classes 2 times/week for 24 weeks. Six tai-chi movements were done, integrated into a routine with 8 forms. The program emphasised rhythmic movements, shifting of weight, taking symmetrical steps, and controlled movements close to the limits of stability. It examined whether tai-chi could be more effective in the improvement of postural stability in tasks close to the limits of stability than a regime of exercises based on resistance or low-impact stretching (control). The first 10 weeks were focused on perfecting the simple forms through multiple repetition, and the following weeks focused on repetitions to improve balance and increase locomotion. For resistance training: at week 10, resistance (with weight vests and ankle weights) was introduced. Use of weight vests began with 1% of body weight and increased approximately 1 to 2% body weight every 5 weeks, up to 5% body weight. Use of ankle weights began with 0.45 kg per leg, gradually increasing to 1.36 kg. The routine included 8 to 10 exercises with steps forward and to the sides, crouching, squats to the front and sides, standing on toes, done in 1 to 3 sessions with 10 to 15 repetitions. For the intervention in the control group, participants did stretching while seated and standing, including the upper torso (neck, upper back, shoulders, chest, and arms) and lower limbs (quadriceps, hamstrings, calves, and hips), and with smooth extension of the joint and bending and rotating the torso. As the magnitude of the effect, expressed as the mean difference (CI95%; p value), as primary results, two indicators of posture stability are presented: maximum excursion and directional control. In regard to maximum excursion after six months with tai-chi, the average increase from the baseline was 9.56%. In the comparison between tai-chi *vs*. resistance training, a difference between groups in the average change from the baseline of 5.55% was achieved (CI95% 1.12 to 9.97; p=0.01). Tai-chi *vs*. stretching 11.98 (CI95% 7.21 to 16.74; p<0.001). In regard to directional control after 6 months with tai-chi, the average increase from the baseline was 8.02%. Tai-chi *vs*. resistance training 10.45% (CI95% 3.89 to 17.00; p=0.002). Tai-chi *vs*. stretching 11.38 (CI95% 5.50 to 17.27; p<0.001). In terms of secondary results (only those that are statistically significant are shown): stride length (cm) in the comparison of tai-chi *vs*. resistance training 5.9 (CI95% 1.5 to 10.4; p=0.01). Tai-chi *vs*. stretching 12.3 (CI95% 8.3 to 16.4; p<0.001). In walking speed (cm/sec) tai-chi *vs*. stretching 14.9 (CI95% 9.8 to 20.1; p<0.001). For maximum twisting in knee extension (Nm) tai-chi *vs*. stretching 13.5 (CI95% 3.4 to 23.6; p=0.01). For maximum twisting in knee flexing (Nm) tai-chi *vs*. stretching 7.7 (CI95% 1.9 to 13.6; p=0.01). Functional reach (cm) Tai-chi *vs*. resistance training 2.8 (CI95% 0.6 to 5.0; p=0.01). Tai-chi *vs*. stretching 4.9 (CI95% 3.0 to 6.9; p<0.001). *Timed up & go* (sec) Tai-chi *vs*. stretching -1.03 (CI95% -1.58 to -0.47; p<0.001). UPDRS III scale tai-chi *vs*. stretching -5.02 (CI95% -6.90 to -3.13; p<0.001). In regard to falls: the incidence rate of falls with tai-chi (0.22 falls/participant-month) was lower than with resistance (0.51) and stretching (0.62). The ratio of the incidence rates of falls tai-chi *vs*. stretching is 0.33 (CI95% 0.16 to 0.71) [67% fewer falls occur with tai-chi *vs*. stretching]. The ratio of the incidence rates of falls tai-chi *vs*. resistance (0.47; CI95% 0.21 to 1.00). Ratio of incidence rates 3 months post-intervention tai-chi group *vs*. stretching (0.31; CI95% 0.14 to 0.67; p=0.003). Ratio of incidence rates 3 months post-intervention tai-chi group *vs*. resistance [0.40; (CI95% 0.18 to 0.88; p=0.02)]. Finally, the number of events in each group was recorded as adverse effects, emphasising in-class

events (a record of adverse effects that occur outside of class was also recorded): number of falls in each group (2 tai-chi, 4 resistance, 5 stretching); discomfort or muscle pain (1 tai-chi, 4 resistance, 5 stretching); dizziness or fainting (0 tai-chi, 3 resistance, 2 stretching); symptoms of hypotension (0 tai-chi, 3 resistance, 1 stretching). The conclusions are that tai-chi training appears to reduce the deterioration of balance in patients with mild to moderate PD, with the additional benefits of improving functional capacity and reducing falls. Tai-chi appears to be effective as an independent behavioural intervention designed to improve postural stability and functional ability of persons with PD.

The objective of the single-blind parallel group RCT by Pompeu *et al*. 2012[84] was to verify whether patients with PD can improve their performance in Wii Fit® games and compare the effects of cognitive and motor training based on the Wii with balance exercise therapy in the independent performance of activities of daily life in patients with PD. This was a study with 32 participants (16 per group) in which the intervention in the experimental group consisted of 14 individual training sessions with a duration of one hour, 2 times/week for 7 weeks (in the on period of dopamine replacement therapy. The sessions were divided into 30 minutes of body exercises and 30 minutes of balance exercises. The body exercises included: 10' of warmup, stretching, and active exercises; 10'of resistance exercises for the limbs; 10' of exercises in diagonal patterns of the torso, neck, and limbs. 30' of balance exercises from the motor and cognitive training group based on Wii: play 10 Wii Fit® games (5 games per session, 2 attempts at each game). An addition session was given 60 days after the end of the training (follow-up). The games were divided into 3 groups: static balance (*Single Leg Extension and Torso Twist*); dynamic balance (*Table Tilt, Tilt City, Soccer Heading, and Penguin Slide*); walking in place (*Rhythm Parade, Obstacle Course, Basic Step and Basic Run*). For the intervention in the control group, the entire sequence was identical except for the 30' of therapy with balance exercises. This therapy has the same movements and time for each game in each test: 10 exercises (5 per session, 2 tests each session) which are equivalent in terms of motor requirements to those in the experimental training group, but without giving external instructions, feedback, and cognitive stimulation. In regard to the results, the magnitude of the effect before and after the training is presented (values expressed as MD (SD) [CI95%]). Note that only the results that are statistically significant, or almost statistically significant are shown. In regard to UPDRS II, in the control group MD -1.0 (SD 1.7) [CI95% -1.9 to -0.1]; for the Berg balance scale, in the experimental group MD 1.4 (SD 2.6) [CI95% 0.0 to 2.8]; control group MD 1.1 (SD 2.1) [CI95% 0.0 to 2.2]; 6 months (follow-up); control group MD 1.1 (SD 2.2) [CI95% 0.0 to 2.3]. In the *Unipedal Stance* with eyes open, for the experimental group MD 9.5 (SD 10.5) [CI95% 3.9 to 15.0]; 6 months (follow-up); experimental group MD 7.8 (SD 12.6) [CI95% 1.0 to 14.5]. *Unipedal Stance* with eyes closed, in the control group MD 1.2 (SD 2.1) [CI95% 0.0 to 2.3]; 6 months (follow-up), in control group MD 1.5 (SD 2.0) [CI95% 0.4 to 2.5]. For the Montreal cognitive evaluation with the values expressed as the mean difference before *vs*. after training, experimental group MD 1.6 (SD 2.7) [CI95% 0.1 to 3.1]; control group MD 1.4 (SD 1.9) [CI95% 0.4 to 2.4]. Expressing the values as the MD between before training and after 6 months (follow-up): experimental group MD 1.2 (SD 2.4) [CI95% 0.0 to 2.5]; control group MD 1.6 (SD 2.5) [CI95% 0.2 to 2.9]. Based on these results, the authors concluded that both types of training facilitate improvement in performance of activities of daily life, balance, and cognition in patients with PD, supporting the possibility of therapeutic use of balance exercise therapy and cognitive and motor training based on the Wii. Patients with PD were able to improve their performance in the three groups of games; cognitive and motor training based on the Wii improves the independent performance of participants in their activities of daily life, balance, and cognition, and this improvement was maintained 60 days after the end of the training; the improvement was similar to that obtained by participants who did the balance exercise therapy; none of the types of training produced a significant improvement in balance in the double task (*Unipedal Stance* with eyes open and verbal fluidity). The external validity

of the study may be limited because the patients included were in good condition, with good visual and auditory perception, and did not present other neurological or orthopaedic diseases or dementia (MMSE ≥ 23), or depression (GDS15 ≥ 6). It should be noted that this tool could be used to empower individuals, promote health, as well as active ageing, because the study itself highlighted that it could improve motivation and adherence in the rehabilitation of this chronic disease.

The objective of the RCT by Duncan *et al*. 2012[85] was to determine the effects of a long-duration community-based dance program in persons with PD. The intervention in the experimental group consisted of 12 months of Argentine tango class based in the community, with a duration of 1 hour, 2 times per week (with changes between the roles of leader and follower, switching partners, learning new steps, and integration of steps learned previously into new choreographies). Exercise was not prescribed in the control group and they were instructed to continue with their normal life. The results are presented as magnitude of the effect [average ± standard error (CI95%)]. The severity of the disease was studied using the *Unified Parkinson's Disease Rating Scale*. UPDRS-III tango group baseline 44.5 ± 2.3 (CI95% 37 to 53), 3 months 39.9 ± 2.3 (CI95% 28 to 45), 6 months 34.2 ± 2.2 (CI95% 28 to 38), 12 months 31.7 ± 2.4 (CI95% 24 to 36). UPDRS-III control group: Baseline 48.0 ± 1.8 (CI95% 45 to 56), 3 months 45.6 ± 1.8 (CI95% 38 to 49), 6 months 45.2 ± 1.9 (CI95% 41 to 50), 12 months 45.0 ± 1.9 (CI95% 39 to 48). No differences in UPDRS-II (activities of daily life) or UPDRS-I (non-motor symptoms). Nor were differences observed in tremors, rigidity, bradykinesia, walking disorder/postural instability. For balance while walking, there were no significant differences on the FOG_Q scale and the distance walked in 6 minutes. In the study of upper extremity function, numerical data for the 9HPT was not provided. In the study of the adherence of participants, it was notable that the dropout rate in the tango group was 50% (of 32 initial participants in the intervention group, 16 finished the study after 12 months, attending 78.5% ± 3% of all the classes) and a dropout rate of 37% in the control group. 11 continued to attend the classes after the 12 months of the RCT. Based on these results, the authors of the study concluded that long-term participation in community-based dance exercises benefits persons with PD. They also indicated that exercises that are fun and attractive, based on abilities, can help promote long-term participation.

These other techniques used by physical therapy professionals, as well as aqua-therapy, the Bobath concept, and other that may be developed in the future, have been left for future updates to this CPG.

Before the publishing of the CPG, a Cochrane systematic review was published, comparing different physical therapy techniques for PD[86]. It was prepared by the same group as the Cochrane review included in the clinical question, and was an update to an early review from 2001. The conclusions of the authors were reaffirmed in the same sense: "there is insufficient evidence to support or refute the effectiveness of one physical therapy intervention over another in PD".

Summary of evidence

1++	Physical therapy offers short-term benefits in the treatment of patients with PD (significant in the variables of speed, 2 or 6-minute walking tests, *Timed Up & Go*, functional reach test, Berg balance scale, and the UPDRS scale scored by the physician)[75].

1+	Evidence is insufficient to demonstrate or refute the effectiveness of Whole Body Vibration (WBV) in the improvement of sensorimotor performance in persons with PD. More high quality studies are needed to establish the clinical efficacy of WBV in the improvement of sensorimotor function in persons with PD[76].
Econ. Eval.	Physical therapy is relatively inexpensive and is therefore probably cost-effective if a small improvement in health can be demonstrated. The results support the cost-effectiveness of intervention with exercises aimed at reducing falls, but are not statistically significant enough to establish a definitive conclusion[77].
1+	Progressive strength training and movement strategy training, combined with a program for education on falls, can be safely implemented in a community sample of persons with idiopathic PD. Programs on social skills for life and education are also effective control interventions[78].
1+	From the clinical perspective, the results suggest that the strengthening/stretching/functional program and the supervised aerobic exercise program may be important for persons with initial or intermediate PD[80].
1+	The 3 types of physical exercise (high-intensity treadmill, low-intensity treadmill, and stretching and resistance) improve walking and mobility. However, each type of exercise generates a different benefit profile. The low intensity treadmill training exercise was the most effective training exercise for walking and mobility. No improvement was obtained on the total UPDRS scale to measure disability or quality of life[81].
1+	Progressive resistance exercises (PRE) have greater benefit than the strengthening exercise program (mFC) on motor symptoms of PD (significant with *off* medication, after 12, 18 and 24 months), strength and speed of movement of elbow flexing maintained after 24 months. The PRE was also found to reduce falls, which is a vital concern in the management of PD[79].
1-	The results on the scales UPDRS II, III, and total suggest that the natural worsening of the symptoms associated with PD and the parallel increase in medication dosages can be counteracted by well-designed rehabilitation treatment. The consideration of the addition of periodic cycles of intensive rehabilitation therapy (IRT) to pharmacological treatment is recommended, to improve motor development and autonomy in activities of daily life, and to delay the increase in medication doses and prevent possible adverse effects[82].
CPG 1+	Physical therapy improves the activities of daily life after the intervention p=0.05; and after five months p=0.045. On the *Northwestern University Disability Scale* (NUDS) 5 months p=0.018. In the measurement of the functional index post-intervention p=0.048; 5 months p=0.016. Improvement on clinical assessment scales: total UPDRS post-intervention p<0.001; 5 months p<0.001. On the Webster assessment scale 5 months p=0.011. For motor disabilities: walking speed: post-intervention p ≤ 0,002; 5 months p=0.006. Stride length, post-intervention p=0.019; 5 months p=0.44. Spine rotation post-intervention p=0.019[16].

CPG 1+	With the Alexander technique: scale for self-assessment of PD disability at the best time of day post-intervention *vs*. controls p=0.04; at the worst time of day post-intervention *vs*. controls p=0.01; 6 months *vs*. controls p=0.01. BDI score post-intervention *vs*. controls p=0.03; 6 months *vs*. controls NS. Attitudes on self-assessment scale: post-intervention *vs*. controls not significant; 6 months *vs*. controls p=0.04. The rate of medication changes was statistically favourable to treatment with the Alexander technique in comparison with the control (p=0.001). Fewer participants in the Alexander technique group changed their medication, but despite this, they did not experience worsening of symptoms (p=0.047)[16].

Recommendations

A	Offering persons newly affected by Parkinson's disease (PD) rehabilitation treatment based on physical therapy is recommended.
B	It would be advisable to include physical therapy techniques as part of the interdisciplinary approach to PD, placing special emphasis on the functional rehabilitation of the patient.
A	The use of exercise programmes for strengthening/stretching/functioning, supervised aerobic exercise, low-intensity treadmill running, and progressive endurance exercises are recommended in patients with PD.
√	There are other complementary techniques for patients with PD, which can be evaluated based on the characteristics of the patients and their environment, such as tai-chi, training with video games that involve physical exercise and dance.
B	Physical therapy must be available to persons with PD throughout the process of the disease. Special attention should be given to: • Re-education of walking, with improvement of balance and flexibility • Strengthen aerobic capacity • Improve initiation of movement • Improve functional independence, including mobility and activities of daily life • Give advice in regard to safety in the home.
C	The Alexander technique can benefit persons with PD by helping them to make lifestyle adjustments that affect both the physical nature of the condition, as well as the attitudes of the person who has PD.

Question to be answered:

How effective is occupational therapy in improving functional independence in persons with Parkinson's disease?

The function of occupational therapy (OT) and its objective with persons affected by PD is to prevent and reduce loss of functions and dependence. People holding certificates or university degrees in occupational therapy are responsible for applying techniques and carrying out occupational activities aimed at strengthening or supplementing reduced physical or mental functions or losses, and to guide and stimulate the development of those functions. To do this, these professionals generally use technological devices, environmental adaptations, and techniques to facilitate the activities of daily life for patients. Patients with PD have motor, cognitive, and emotional difficulties. Occupational therapists can provide added value in the treatment of patients with PD whose day-to-day functioning has been compromised, as well as for their immediate caregivers. These professionals work with different procedures that include motor coordination, relaxation and breathing techniques, the execution of activities of daily life, and the development of procedures for the capabilities that have been conserved, to minimize the resulting impact of the evolution of the disease, the involvement of family members and caregivers in the application of the changes proposed by the occupational therapists is vital[87-88].

The effectiveness of the strategies applied by occupational therapy healthcare professionals in the improvement of functional independence in persons affected by PD is evaluated.

One SR with moderate quality[89] and another low-quality SR[90] were found. A pilot study done by Clarke *et al*. 2009[91] was also found and was included to comment on the lines of future research, as well as a multi-centre RCT, which was initially pending results[92], so the principal investigator was asked directly for more information on the results of the study, which was later published as a moderate-quality RCT[93].

The objective of the review by Dixon *et al*. 2007[89] was to compare the efficacy and effectiveness of OT with a placebo or non-intervention (control group) in patients with PD. 84 patients with PD with any duration, age, pharmacotherapy, and treatment duration were included. Two studies were located: one compared group or individual therapy 12 hours a month with crafts, drawing, basket-weaving, songs, dances, and games, versus individual physical therapy sessions in both groups. The results of this study favoured the use of OT in patients with PD, indicating better scores on the specific scales for Parkinson's, and on the measurement of speed, activities of daily life, and quality of life: -0.2 points measured using the UPDRS scales I, II, and III (evaluation of disability, mental aspects, activities of daily life, and motor aspects, respectively); improvement in walking speed of 0.04 m/s; improvement in activities of daily life (personal care and daily activities): -6.5 on the Brown scale; improvement in health-related quality of life. *Nottingham Health Profile* -2.5. The second study, with 20 patients, compares the intervention [groups of 8 patients, with 20 hours of activities over a period of 5 weeks for mobility (including visual and auditory instructions), dexterity (games and writing), functional activities and educational sessions (with occupational therapists, physical therapists, speech therapists, social workers, dieticians, and nurses)] with the control (no intervention or placebo). The results show that, for activities of daily life, measured after one year with the Barthel index (designed to evaluate geriatric patients in nursing homes, on a scale of 100 points), the scores of patients who did not receive OT dropped an average of 4.6 points on this scale. The conclusions of the SR are that, although both RCTs reported positive results for OT, the methodological problems in both studies, and the small sample size in both RCTs prevent firm conclusions from being drawn in regard to the efficacy and effectiveness of OT on PD. The heterogeneity of the two studies is very high.

SR 1 +

The objective of the review by Rao 2010[90] was to evaluate the effectiveness of OT in patients with PD. It included the following possible interventions: 1st, training in tasks related to OT (6 or 8 therapy sessions for 8 weeks in 2 RCTs and 12 sessions for 4 weeks in 1 RCT); 2nd, functional training with external visual and auditory instructions (RCT with 9 therapy sessions for 3 weeks and an RCT with 18 therapy sessions for 6 weeks); 3rd, OT as part of multi-discipline intervention [study without control group (pre-test and post-test) with 4 therapy sessions for 4 weeks, RCT with therapy sessions for 6 weeks, and an RCT with 6 therapy sessions for 6 weeks]. The effects of the interventions are presented descriptively. For intervention 1, improvement on NEADL and PDQ-39; improvement on the UPDRS ADL and PD-Q scales; improvement on the ADL scale and quality of life; for intervention 2, scales: posture and stride, stride speed, and stride length, and efficacy of falls, improved by the effects did not last after 6 and 12 weeks; improvement UPDRS ADL and motor section at the end of the treatment, but 6 weeks after the treatment, only the group with indications had maintained the improvement; finally, for intervention 3, improvement on SIP-68, walking speed, and UPDRS ADL scales after 6 weeks, maintained after 24 weeks; improvement in the stand-walk-sit test and scale for quality of life related to disability after 6 months; quality of life related to mobility, discourse, and depression improved after 4 weeks. Despite the heterogeneity of the interventions, the following conclusions can be drawn: 1st, that OT is tolerated well in patients with PD (in individual and group sessions) and leads to improvement in motor function and quality of life, at least during the therapy;

SR 1

Lastly, the objective of the multi-centre RCT by Sturkenboom *et al*. 2013[92] was to evaluate the effectiveness and cost-effectiveness of OT according to the Dutch guidelines for OT with PD. A variety of possible strategies or advice aimed at addressing individual needs were used with the experimental group. As a general approach, they applied *coaching* skills, with information and training. The interventions on patients were: alternative and compensation strategies to improve the development of functions (e.g. use of indications, reorganise complex functional sequences, focused attention, cognitive strategies, such as management of temporary stress); advice to optimise daily routines and simplify activities; advice on appropriate assistance and adaptations of the environment to improve independence, efficiency, and safety. Interventions with caregivers: providing information (impact of the disease on daily functioning of the patient, available care resources, assistance, and adaptations); training in supervision skills. The study intended to specify the sample size and design of an RCT to evaluate the effectiveness of OT in improving the activities of daily life in PD. Information on the trial is available at Clinicaltrials.gov: NCT01336127, although the critical reading of the work was done by the Sturkenboom group[93], which was ultimately published *on-line* on 09/04/2014 as an open multi-centre randomized controlled clinical trial (with evaluator masking). Its objective was to evaluate the efficacy of OT based on the Dutch practice guidelines for OT in PD. 191 patients were included post-randomization, with an intervention group of 124 patients (117 caregivers for this group also participated in the study) and a control group of 67 patients (along with 63 caregivers). The control group did not receive OT intervention during the study period (6 months); they were later allowed to receive OT in accordance with the Dutch intervention protocol. The characteristics are comparable between patient groups in terms of: age, sex, advanced studies, paid work, disease duration, H&Y stage, UPDRS III, MMSE, levodopa equivalence units, and physical therapy. Also in regard to *Canadian Occupational Performance Measure* [COPM] <5 *vs*. ≥5. The characteristics of the caregivers were comparable between groups in regard to: age, sex, educational level, and paid work. The intervention consisted of advice or training strategies in activities, adaptation of tasks, daily routines, or environment (e.g. using assistance devices). The duration of the intervention was 10 weeks (1-hour sessions approximately).

RCT 1+

The total maximum duration could not exceed 16 hours. Results were measured using a semi-structured interview in which patients identified and prioritized between three and five significant daily activities in which the patients perceived performance problems. Patients later rated each activity on a scale of 10 points in terms of the perceived performance capacity (COPM-P; where 1 = cannot do it at all, and 10 = capable of doing it very well). In the same way as for performance satisfaction (COPM-S). The follow-up period was 3 and 6 months. The primary results of the study measure the perceived performance capacity (COPM-P) as the adjustment mean difference between the intervention group and the control group with respect to the baseline after 3 months: 1.2 (CI95% 0.8 to 1.6) p<0.0001. A *post-hoc* found a clinically relevant improvement in COPM-P (increase of ≥ 2 points): 32% (39/122) of the intervention group and 10% (6/63) in the control group (p=0.001). The secondary results showed adjusted mean differences between the intervention and control groups in: perceived performance capacity (COPM-P) with respect to the baseline after 6 months: 0.9 (CI95% 0.5 to 1.3) p<0.0001. In performance satisfaction (COPM-S), from the baseline after 3 months, 1.1 (CI95% 0.7 to 1.5) p<0.0001, and after 6 months, 0.9 (CI95% 0.5 to 1.3) p<0.0001. A post hoc analysis found, among the adverse effects, a clinically relevant deterioration (drop in COPM ≥ 2 points) in 1% (1/124) of the intervention group and in 3% (2/67) of the control group. Masking (dropout): after 3 months: 11/185; and after 6 months: 18/182 (7 more cases). The conclusion of the study is that in the home, individualized OT led to an improvement in the perceived performance capacity for the daily activities of patients affected with mild PD. | RCT 1+

The questions, described in the section on non-pharmacological treatment (rehabilitation) of this CPG, present different interventions developed by professionals in the fields of Physical Therapy, Occupational Therapy, Speech Therapy, Psychology, and Human Nutrition and Diet. All of these are healthcare professions covered in Act 44/2003 on the organisation of healthcare professions. The services provided by these professionals are included in Royal Decree 1030/2006, which establishes the portfolio of common services of the National Health System and the procedure for updating it[61]. It is also important to indicate Medical professionals specialised in Physical Medicine and Rehabilitation, as a medical specialisation that is concerned with the diagnosis, evaluation, prevention, and treatment of disability, aimed at facilitating, maintaining, or returning the greatest possible degree of functional capacity and independence.

All of the studies point in the direction that OT contributes to the improvement of the functional independence of persons with PD.

The objective of the RCT by Clarke *et al*. 2009[91] was to carry out a pilot study on OT to optimise functional independence in PD in order to evaluate the cumulative/dropout rates, acceptability, measurements of results, and present information on the calculation of the size of the sample. This was an RCT pilot study with masked evaluation of standard community-based individual OT aimed at mobility and functional independence *vs*. normal care of the British NHS, with OT delayed until the end of the RCT. Patients, who did not present dementia, but who did have difficulty carrying out activities of daily life, in the experimental group received intervention that consisted of 6 sessions lasting 45 minutes for 2 months covering specific tasks (eating, moving) in the patient homes and the techniques used included the practice of specific tasks (dressing, mobility training); reducing task complexity or demands, and/or altering the environment by providing assistance or adaptations; information and advice for patients and caregivers, and referral to other healthcare professionals when appropriate. When time permitted, secondary interventions were covered, such as managing fatigue, leisure therapy, communication and language interventions, and relaxation techniques. The results obtained are presented as the

mean difference between the results obtained from the baseline after 2 months, and from the baseline after 8 months, with their respective CI95%. A negative change in the results on the *Nottingham Extended ADL* (NEADL), *Rivermead* and EuroQol scales indicated a deterioration from the initial value. A positive change on the *Parkinson's Disease Questionnaire* 39 (PDQ-39), *Unified Parkinson's Disease Rating Scale* (UPDRS) *Activity of Daily Living* (ADL) and *Hospital Anxiety and Depression Scale* (HADS) scales indicated a deterioration from the initial value. The results found showed a positive difference in the average of NEADL, *Rivermead* and EuroQol in favour of the delayed therapy, while positive results in favour of immediate therapy were found in PDQ-39, UPDRS ADL and HADS. The results from the baseline after 2 months were: NEADL 0.04 (CI95% -4.74 to 4.82); *Rivermead* mobility index -0.46 (CI95% -1.89 to 0.97); UPDRS ADL -1.46 (CI95% -5.36 to 2.44); PDQ-39 summary index 1.69 (CI95% -5.17 to 8.55); EuroQol EQ5D scale -0.01 (CI95% -0.17 to 0.16); HADS anxiety scale 1.53 (CI95% -0.72 to 3.78); HADS depression scale -0.50 (CI95% -2.31 to 1.30). From the baseline after 8 months: NEADL 3.50 (CI95% -3.24 to 10.24); Rivermead mobility index -0.70 (CI95% -2.87 to 1.47); UPDRS ADL Scale 0.39 (CI95% -3.32 to 4.10); PDQ-39 summary index 3.82 (CI95% -4.94 to 12.57); EuroQol EQ5D scale 0.08 (CI95% -0.04 to 0.21); HADS anxiety scale 1.44 (CI95% -1.20 to 4.09); HADS depression scale -1.42 (CI95% -3.66 to 0.82). This pilot study was not intended to present definitive data on the effectiveness of OT for the problems of activities of daily life in PD. It provides information on the design of the RCT (which uses NEADL, PDQ-39, and cost-effectiveness as results measurements) and the sample size (approximately 750 patients).

The functional improvement in these patients has an enormous impact on their quality of life.

The studies that are included in the SR by Dixon *et al*. 2007[89] are included in the NICE CPG on PD[16]. Consequently, it is not included as a source of evidence in this CPG, but does help to modulate the grade of each one of the recommendations.

Once the information on our area has been collected, there are professionals who differentiate it into the activities of daily life, between basic, instrumental and advanced activities, which is an aspect that is not taken into account in the review by Dixon *et al*. 2007.

According to Act 39/2006, of 14 December, on the promotion of personal autonomy and attending to dependant persons[94], the catalogue of services includes the social services to promote personal independence and to attend to dependants, which only lists the services for the prevention of dependant situations and services for the promotion of personal independence. The regulation, organisation, and management of the social services corresponds to each Region and the Local Entities.

Summary of evidence

1+	The use of occupational therapy in patients with PD improved scores on different scales, in comparison with a placebo or non-intervention: UPDRS I, II & III (evaluation of disability, in mental aspects, activities of daily life, and motor activities, respectively): -0.2; walking speed (m/s) 0.04; activities of daily life (personal care and activities of daily life) Brown -6.5; and quality of life measurements *Nottingham Health Profile* -2,5[89].
1+	The results measured on the scale of the Barthel index were maintained for more than one year in the patients with PD treated with OT. The group with no OT intervention lost an average of 4.6 points (on a total scale of 100)[89].

1-	For patients with PD, OT produces an improvement in functional independence. The results for each OT technique evaluated were: training OT-related tasks (between 6 and 12 sessions) improvement on NEADL and PDQ-39, UPDRS-ADL and PD-Q, ADL and quality of life scales. Functional training with external visual or auditory instructions (between 9 and 18 sessions) did not maintain the improvements in parameters such as posture, speed and length of stride, after 6 and 12 weeks. OT as a part of a multi-discipline intervention (between 4 and 12 sessions) managed to maintain the improvements in walking speed and on the SIP-68 and UPDRS-ADL scales after 24 weeks[90].
1+	In the home, individualized OT led to an improvement in the perceived performance capacity (COPM-P) for the daily activities of patients affected with mild PD, measured as adjusted mean difference between groups with respect to the baseline after 3 months: 1.2 (CI95% 0.8 to 1.6) p<0.0001. A *post-hoc* found a clinically relevant improvement in COPM-P (increase of ≥ 2 points): 32% (39/122) of the intervention group and 10% (6/63) in the control group (p=0.001)[93].

Recommendations

D	Occupational therapy must be available for persons with PD. Special attention should be given to: • Maintaining jobs and family roles, instrumental and advanced daily life, domestic, and leisure activities. • Improving and maintaining movement and mobility. • Improving personal care activities such as eating, drinking, washing, and dressing. • The aspects of the environment to improve safety and motor functions. • Cognitive evaluation and appropriate intervention.
B	In patients mildly affected by PD, occupational therapy is recommended in order to improve the perceived functional capacity for the activities of daily life of these persons.

5.2. Speech Therapy

5.2.1. Communication and language

Question to be answered:

How effective is speech therapy in improving communication and language in persons with Parkinson's disease?

Idiopathic PD produces voice and speech disorders that lead to changes in communication[95-96]. These disorders are common and increase in frequency and intensity as the disease progresses[97]. Dysarthria is the collective name of a group of speech conditions that results from disorders in the muscle control mechanisms of speech as a result of damage to the CNS. The characteristics of dysarthria in PD are monotony in tone and volume (dysprosody), reduction of articulation tension, imprecise articulation, variations in speech speed which results in inappropriate silences as well as acceleration of speech speed, as well as stuttering and trembling, and choppy hoarseness of voice (hypotony) with nasal or monotone voice, which reflects the difficulty in the patient to synchronize speech and breathing. Many of these characteristics are attributed to hypokinesia (limitation of movement) and rigidity, which are considered to be two of the cardinal characteristics of PD. Patients with PD frequently suffer mild cognitive impairment, which leads to difficulties with language selection, language comprehension, coordination of multiple tasks (speaking and walking), as well as disorders involving emotional comprehension in communication. Persons affected by PD tend to give fewer non-verbal signals, such as facial expressions and gestures with the hands. As mentioned before, these disabilities tend to increase as the disease progresses, and can lead to serious communication problems. The approach by speech therapy professionals includes work on the voice and articulation, and also focuses on cognitive-linguistic alterations. Other sections of the CPG for the management of patients with PD also cover the role played by speech therapists in the management of the disorders of dysphagia, swallowing, and salivary control.

The goal of speech therapy is to improve the intelligibility of speech using behavioural treatment techniques and instrumental assistance. The efficacy of speech therapy in patients with PD in the improvement of communication and language needs to be evaluated. The techniques used in speech therapy to improve communication and language in persons with PD that are covered in this question include breathing exercises, prosodic exercises, voice treatment methods (*Lee Silverman Voice Treatment* in its different versions), and others, such as communication devices, which may include: alphabet boards, or stimulation, voice amplifiers, digitized voice output systems, recorded voice messages, delayed auditory feedback, or feedback devices via laptop computer.

Two low-quality SRs were found (Herd *et al*. 2012a; Herd *et al*. 2012b). The first SR98 compares the efficacy and effectiveness of the new speech therapy techniques in comparison with the standard speech therapy approach to treat language and communication problems in patients with PD. The second SR99 compares the efficacy of speech therapy in comparison with a placebo or non-intervention for voice and language problems in patients with PD. Both SRs were prepared by the Cochrane movement disorders group.

Herd *et al*. 2012a[98] compares the efficacy and effectiveness of the new speech therapy techniques in comparison with the standard speech therapy approach to treat language and communication problems in patients with PD. It includes six RCTs, with a total of 159 patients. As interventions, they compare one speech therapy technique with another: *Lee Silverman Voice Treatment* (LSVT) *vs*. Respiratory exercises (RE); LSVT-ARTIC (modified version of LSVT) *vs*. LSVT-LOUD (standard version of LSVT); Delayed Auditory Feedback (DAF) *vs*. Traditional Therapy (TT); LSVT *on-line vs*. face-to-face LSVT. For the results, the statistically significant effects are highlighted (values expressed as mean difference in decibels [dB], indicating the respective 95% confidence intervals). In the first comparison, LSVT *vs*. RE, the following results were obtained in favour of LSVT: sound level when reading 3.62 (CI95% 2.36 to 4.89) (there is statistical significance initially, but this is lost in the 12 and 24 month follow-ups); sound level in monologue 2.49 (CI95% 1.22 to 3.76); frequency variability in monologue 0.57 (CI95% 0.28 to 0.85); frequency variability in reading 0.24 (CI95% 0.08 to 0.41); communication improvement (SIP) -13.88 (CI95% -25.80 to -1.96); hoarseness -17.20 points (CI95% -34.29 to -0.11); sigh -23.80 points (CI95% -45.50 to -2.10); sound level in sustained phonation in improvement of speech volume 11.12 (CI95% 9.43 to 12.81) (the heterogeneity between studies $I^2 = 68\%$). SR 1

In the comparison of the techniques LSVT-LOUD *vs*. LSVT-ARTIC, results in favour of LSVT-LOUD were obtained: intelligibility of pre/post speech -12.46 points (CI95% -22.15 to -2.77); sound level of pre/post reading -5.03 (CI95% -8.32 to 1.74). For the comparison of DAF *vs.* TT, the results in favour of DAF were: conversation rate while reading pre/post -0.73 syllables/second (CI95% -1.33 to -0.13); conversation rate while reading pre/follow-up 6 weeks -0.83 (CI95% -1.43 to -0.23). In the same comparison DAF *vs.* TT, the following results were in favour of TT: intelligibility of reading pre/post -23.89 points (CI95% -44.46 to -3.32). In the comparison of the techniques LSVT *on-line vs.* LSVT face-to-face, the following results were in favour of face-to-face LSVT: vocal phonation sustained in sound level-10.01 (CI95% -12.85 to -7.17); harshness 9.20 points (CI95% 1.49 to 16.91). Finally, the following were found to be non-statistically significant results: voice volume, monotonicity, intelligibility, sound level when reading and in monologue, fundamental reading frequency, frequency variability in monologue, frequency variability in reading, fundamental frequency in monologue, Beck depression index (BDI), sickness impact profile (SIP) in communication and social interaction, snoring, sighing, sustained sound level in phonation, diagnostic test of rhyming, with and without noise, conversation rate while reading, intelligibility in reading, and in monologue with follow-up. No studies that present results on the following were found: activities of daily life, quality of life, adverse effects, results on caregivers, or studies that make economic evaluations. The authors highlight the following conclusions: considering the small number of patients in these RCTs, the evidence is insufficient to indicate or refute the efficacy of any type of speech therapy over another to treat language problems in patients with PD. There is limited evidence in favour of LSVTLOUD over LSVT-ARTIC and RE and supporting the non-inferiority of the *on-line* version of LSVT compared with the use of the same technique face to face. The most clinically relevant result is the improvement in intelligibility. All of the RCTs included evaluate intelligibility and virtually none of the results are statistically significant. Despite the better rate of articulation to a greater degree with DAF than with TT, DAF is less satisfactory than TT in the improvement of intelligibility of language. It should be noted that the sample sizes are small, with different interventions and highly heterogeneous results; problems with heterogeneity ($I^2 > 50\%$) are highlighted. SR 1

The second systematic review by Herd *et al*. 2012b[99] covers 3 RCTs with 63 participants for the qualitative synthesis, although the analysis (with quantitative synthesis and meta-analysis) is done on only 2 RCTs (with a total of 41 participants), because Robertson *et al*. 1984 does not provide data on participants. Patients with PD of any age, PD duration, drug, and treatment duration were included. The speech therapies were compared applying: the *Lee Silverman Voice Treatment* (LSVT) technique or visual feedback (VF) compared with non-intervention or placebo (as in the previous SR, the values are expressed as mean difference in decibels [dB] with their respective 95% confidence intervals). Specific for LSVT versus VF: sound level in monologue pre/post: LSVT-VF 6.17 (CI95% 3.57 to 8.77) ($I^2 = 53\%$); LSVT 5.40 (CI95% 2.60 to 8.20); VF 11.0 (CI95% 3.98 to 18.02). Sound level during reading pre/post: LSVT-VF 7.18 (CI95% 4.65 to 9.71); LSVT 6.30 (CI95% 3.50 to 9.10); VF 11.0 (CI95% 5.15 to 16.85). Specific for LSVT versus placebo: sound level in monologue pre/follow-up 6 months 3.5 (CI95% 0.88 to 6.12); sound level during reading pre/follow-up 6 months 4.5 (CI95% 1.91 to 7.09); sound level during sustained phonation pre/post 12.10 (CI95% 8.85 to 15.35); sound level during sustained phonation pre/follow-up 6 months 9.40 (CI95% 6.24 to 12.56); sound level describing a painting pre/post 5.2 (CI95% 2.02 to 8.38); sound level describing a painting pre/follow-up 6 months 9.40 (CI95% 6.24 to 12.56); sound level /i/ 8.40 (CI95% 5.15 to 11.65); sound level /u/ 5.2 (CI95% 1.83 to 8.57); sound level /a/ 7.5 (CI95% 3.53 to 11.47); F2u (Frequency of second formant /u/) -96.0 Hertz (Hz) (CI95% -233.51 to 41.51); F2i/F2u 0.18 Hz (CI95% -0.02 to 0.38); good vocalization /i/ 15.20 (CI95% 7.12 to 23.28); good vocalization /u/ 12.20 (CI95% 5.34 to 19.06); Good vocalization /a/ 7.4 (CI95% 0.19 to 14.99). Specific for VF versus placebo 29.0 points (CI95% 13.66 to 44.34); tone range pre/post 66.1 Hz (CI95% -4.44 to 136.64); volume range pre/post 23.7 (CI95% 9.30 to 38.10); fundamental frequency -65.4 Hz (CI95% -133.18 to 2.38). The authors concluded that although some improvements in language complications were observed in these studies thanks to s, due to the small number of patients evaluated, methodological limitations, and the possibility of publication bias, the evidence was insufficient to support or refute the efficacy of speech therapy in language problems in PD. Any problems of heterogeneity of the studies ($I^2 > 50\%$) were indicated. This SR includes few studies and few patients, which do not provide intelligibility data. VF appears to be more effective than LSVT.

SR 1

The NHS has professionals in the field of speech therapy who carry out the activities of prevention, evaluation, and recovery from disorders involving hearing, phonation, and language, using the therapeutic techniques available in their discipline.

The point in the direction of a relative contribution of speech therapy in the improvement of communication and language in persons with PD, although the evidence is not conclusive.

The improvement in communication and language in persons with PD is a result that has a clear impact on health-related quality of life.

The NICE CPG on PD[16] evaluates the effectiveness of physical therapy in comparison with standard medical therapy or a placebo in the treatment of language problems in persons with PD. The 2006 CPG is not included as an information source, because the studies found are the same ones that are also covered by the more recent SR by Herd *et al*. 2012b[99]. The recommendation prepared by the experts of the CPG is adopted.

Summary of evidence

1	The evidence is insufficient to support or refute the efficacy of speech therapy in language problems in PD compared with non-intervention or placebo[99].
1	The evidence is insufficient to indicate or refute the efficacy of any type of speech therapy over another to treat language problems in patients with PD[98].
1	There is evidence that supports LSVT-LOUD over LSVT-ARTIC and respiratory exercises in patients with PD and language and communication difficulties[98].
1	Equivalence was found in the comparison between the *on-line* version of LSVT with the use of the LSVT technique and respiratory exercises carried out face to face in patients with PD and language and communication difficulties[98].
1	The most clinically relevant result is the improvement in intelligibility in patients with PD and language and communication difficulties. Intelligibility results in favour of TT in comparison with DAF were obtained[98].
1	A better rate of articulation is achieved to a greater extent with DAF than with TT[98].
CPG 4	Speech therapy applied in patients with PD improves the volume and intelligibility of language, and consequently improves the speech and communication of these persons[16].

Recommendations

D	Speech therapy should be made available to persons with PD. Special attention should be given to: Improvement of voice volume and tone range, including speech therapy programs such as LSVT (speech therapy using the *Lee Silverman Voice Treatment* technique). Teaching strategies to optimize intelligibility of language. Guarantee that the effective instruments of communication are maintained over the course of the disease, including the use of assisting technologies. Review and manage to support the safety and effectiveness of chewing and to minimize the risk of choking.
√	The evaluation of the use of the LSVT technique and the evaluation of the results of patients with PD affected by speech and language disorders, especially in the most clinically relevant variable, intelligibility of speech, is recommended.

5.2.2. Swallowing

Question to be answered:

How effective is speech therapy in improving swallowing in persons with Parkinson's disease?

According to the dictionary definition, swallowing is the act of causing or allowing food or any solid or liquid substance to pass from the mouth to the stomach. Dysphagia is defined as the difficulty or inability to swallow. Dysphagia is a problematic and sometimes dangerous trait of PD. Oropharyngeal dysphagia can have a negative impact on quality of life, and increases the risk of pneumonia due to aspiration, and may often be a cause of death in patients with PD[101]. Patients affected by PD have hyperkinetic dysarthria, drooling, and dysphagia as the most common oral and motor disorders associated with PD. The estimate the incidence of oropharyngeal dysphagia in patients with PD is 80% during the initial stages of the disease, increasing to 95% in the advanced stages. The rigidity and bradykinesia for swallowing may be due to incomplete cricopharyngeal relaxation, smaller cricopharyngeal opening, and a delay in the initiation of the swallowing reflex. Some traits commonly found in patients with dysphagia caused by PD are delayed oropharyngeal transition time, decreased muscular strength, and increased risk of aspiration.

Dysphagia in patients with PD is currently treated by speech therapy specialists. This treatment is normally given one or two times per week over the course of several months or years, and includes oral motor exercises, manoeuvres to protect

Respiratory function, correction of posture to facilitate the transition of the bolus, or thermo-tactile stimulation. The techniques applied are varied and the different techniques need to be evaluated to verify the efficacy of speech therapy in the improvement of swallowing in persons with PD.

Three low-quality SRs were located (Smith *et al*. 2012; Ashford *et al*. 2009; Baijens *et al*. 2009)[102-104] and one moderate-quality RCT (Manor *et al*. 2013)[105].

The review by Smith *et al*. 2012[102] provides an overview of the different treatments of dysphagia in patients with PD. The objective of the SR is to critically review the available literature on the compensatory or rehabilitation practices used by speech therapy professionals in the management of oropharyngeal dysphagia in PD. The SRs evaluated treatments with an impact in oropharyngeal swallowing in patients with idiopathic PD that are not pharmaceutical or surgical treatments or treatments for lower gastrointestinal dysphagia. The following are included as compensatory treatments: thin and pudding-like thickness for bolus consistency, tucked chin position with nectar bolus consistency or honey thickness, thermo-tactile stimulation. The comparison was made with rehabilitation treatments, which include: swallowing exercises, *Lee Silverman Voice Treatment* (LSVT), forced swallowing in combination with biofeedback and training to strengthen expiratory musculature. The most notable results in relation to compensatory treatments were: pudding thickness consistency results in significant increase in the time in oral transit and the number of thrusts with the tongue, and the penetration-aspiration (P-A) score is significantly lower in comparison with thin consistency. For all patient groups, the chin-tuck posture is less effective at preventing aspiration and honey consistency is most effective. Significantly fewer participants evaluated the honey consistency as easy/enjoyable in comparison with the chin-tuck posture and the nectar consistency. Neither the chin-tuck posture nor thickened liquids were found to be superior in preventing pneumonia, death, or other adverse results of dysphagia. A significant reduction was achieved in pharyngeal transit time, pharyngeal delay time, and total transit time of liquids. A significant reduction was is also achieved in pharyngeal transit time and total transit time for pasta. In regard to rehabilitation treatments, the following results are presented: pre-motor times significantly improved for the group of patients with PD, but not for healthy volunteers, and subjective reports of improved swallowing in 8 of the 10 participants with PD. A significant reduction was found in oral transit time and in the estimation of oral residue in some bolus volumes and consistencies, and some motility disorders decreased, while others increased. SR 1

Scores for efficiency in oral pharyngeal swallowing significantly improved when drinking from a cup. Decrease in the number of participants with swallowing complications. Pressure measurements significantly higher. Significant decrease in P-A scores and significant increase in maximum expiratory pressure and overall effectiveness of cough (acceleration of cough volume). Significant increase in average P-A score for the active treatment group but not for the placebo group. Significant reduction in hyoid movement for the placebo group but not for the active treatment group. Hyoid displacement increased for the active treatment group and hyoid displacement decreased for the placebo group (not always at significant levels). Improvement in the SWAL-QOL score (questionnaire on quality of life in relation to swallowing) in both groups. In terms of conclusions, they indicate that compensatory approaches may have the potential benefit of producing immediate relief of symptoms of dysphagia, but these methods can do little to improve long-term quality of life and do nothing to resolve the problem of swallowing. The rehabilitation approaches have the potential to reduce or resolve dysphagia itself, which could improve safety and quality of life, but with slower gains. SR 1

Ashford *et al*. 2009[103] included patients with dysphagia secondary to neurological disorders (e.g. brain accident, cerebral infarction, PD, and dementia) in the review population. The objective was to evaluate the effectiveness of behavioural intervention in individuals with neurologically-caused dysphagia on swallowing physiology, and functional results of swallowing and pulmonary health. The studies on patients with PD were evaluated, but only to controlled trials that fulfilled a series of minimum methodological requirements were included (one trial was disregarded because it was a case series). In relation to one RCT, the results showed: chin tuck *vs*. liquids with honey density produce a relative risk reduction (RRR) of -0.22 (CI95% -0.18 to -0.27); Chin tuck *vs*. nectar density liquids RRR -0.07 (CI95% -0.11 to -0,001). The results of another RCT indicated that the chin-tuck technique achieved an RRR of 0.02 (CI95% -0.04 to 0.07). The conclusions were that: the first study indicates that tucking the chin protects against aspiration in just 41% of the patients with PD. The use of this posture with thin consistency liquids is less effective in the prevention of aspiration in comparison with the use of thick liquids alone. This finding is surprising given that tucking the chin is widely accepted in clinical practice. The second study concluded that the chin-tuck posture when used with thin-consistency liquids does not effectively reduce the incidence of pneumonia in populations with PD and dementia. SR 1

The objective of the review by Baijens *et al*. 2009[104] was to evaluate the effects of rehabilitation therapies (swallowing training) on oropharyngeal dysphagia in PD. This was a low-quality review, because it included non-randomized trials with few patients. In the SR, other treatments not included in our question are also included (surgical treatment, pharmacological treatment, and others). The study population consisted of patients with PD (also including Parkinsonian syndromes and secondary PD). Four rehabilitation techniques were evaluated as the intervention: *Lee Silverman Voice Treatment* (LSVT); 5 swallowing training exercises (tongue movement exercises, resistance exercises, exercises to increase the adduction of vocal cords, Mendelsohn manoeuvre of motor exercises in the neck, torso, and shoulders); verbal instruction while lifting a spoon to the mouth; modification of the bolus in three ways: a) fluid liquid and pudding-consistency bolus; b) honey density and nectar density, and c) postural changes (chin tuck). Different variables were recorded to measure the results: Numerical data was not offered in several studies. In the case of LSVT: identification of oropharyngeal motility disorders; timed swallowing variables; oropharyngeal swallow efficiency. In the case of the 5 training exercises: premotor time (motor phase *on*). For verbal instruction: directing breathing immediately before and after swallowing; N° of swallows; duration oral part; duration pharyngeal part (motor phase *on*). Finally, qualitative and quantitative results are presented for the modification of the bolus: a) significant differences in the oral transit time, n° tongue movements and qualitative swallow variables: greater with denser bolus; b) 39% of participants aspirated with the three interventions. 12% aspirated with 2 out of the 3 interventions. 17% aspirated with 1 out of the 3 interventions. 32% aspirated with none of the 3 interventions. The conclusions of the SR are that, for LSVT: the incidence of swallowing mobility disorders is significantly reduced after LSVT and some timed swallow variables increased significantly. For swallow training, there is a significant decrease in premotor time. Verbal instructions achieved a significant reduction in the duration of the oral part, with no impact on the duration of the pharyngeal part. In regard to modification of the bolus: more investigation is required on the use of thickening agents for liquids in regard to their effectiveness on certain types of dysphagia. It is important to note that a large number of patients in the study did not benefit from any of the interventions studied. SR 1

Lastly, the primary objective of the moderate-quality double-blind randomized prospective controlled study by Manor *et al*. 2013[105] was to evaluate the effect of video-assisted swallowing therapy (VAST) on objective swallow function post-intervention in patients with PD, and as a secondary objective, to evaluate the effect of VAST on patient perception of the swallowing function, their quality of life, and the degree of pleasure of eating compared with the responses of the control group. The intervention in the experimental group was VAST, a video-assisted tool used in each therapy session, to educate patients and help them to understand the structure of the swallowing mechanism, and how it works. Each group received five 30 minute sessions of therapy for two weeks, followed by a sixth session four weeks after the fifth. Both interventions included swallow exercises and compensatory therapy techniques for patients in their baseline evaluation using fibre-optic endoscopic evaluation of swallowing. The RCT presents the magnitude of the effect measured by the (*Swallowing Disturbances Questionnaire* or SDQ) and eating pleasure as results. In the case of the SDQ, for the value in the VAST group *vs*. control group, they present first immediately post-intervention and later, at the 1-month follow up. The values (expressed as average ± standard deviation) in each one of the moments indicated, and for each group are: (12.73 ± 7.6) *vs*. (13.43 ± 7.03); (9.05 ± 5.30) *vs*. (13.08 ± 7.20). The SWAL-QOL (quality of life questionnaire that measures swallowing) scores after 4 weeks and after 6 months were significantly favourable to the VAST group in 5 variables: load, desire to eat, social function, mental health, and frequency of symptoms. The effectiveness of the speech therapy advice was evaluated immediately post-treatment using the SWAL-CARE averages (questionnaire that measures the quality of care in swallowing) and scores were significantly better for the VAST group (26.26 ± 5.86) than for the control group (22.34 ± 5.7). In regard to the pleasure of eating, immediately post-treatment and at the 4-week follow-up, for the VAST group *vs*. control group: (7.95 ± 1.56) *vs*. (7.24 ± 1.79); (8.52 ± 1.36) *vs*. (7.38 ± 1.74). The authors concluded that in patients with PD without cognitive alterations, who have swallowing disorders, VAST was associated with better quality of life with swallowing and decreased pharyngeal residue. It is important to note that it is a new technique and appears to be effective (on the subjective scale).

A comprehensive view of different intervention strategies was given, but with a high degree of heterogeneity, little consistency, and inconclusive results.

The intervention proposals were very heterogeneous, making it impossible to establish overall relevance and clinical impact.

Summary of evidence

1	There is insufficient evidence to support or refute the efficacy of speech therapy in the improvement of swallowing in persons with PD[103].
1	Compensatory approaches (thin bolus consistency and pudding thickness, chin tuck, and nectar consistency and honey thickness, thermo-tactile stimulation) may have the potential benefit of producing immediate relief of symptoms of dysphagia, but these methods can do little to improve long-term quality of life and do nothing to resolve the problem of swallowing[102].

1	Rehabilitation approaches (swallowing exercises, LSVT, forced swallowing in combination with biofeedback, training to strengthen expiratory muscles) have the potential to reduce or resolve dysphagia itself, which could improve safety and quality of life, but with slower gains[102].
1	The incidence of swallowing mobility disorders is significantly reduced after LSVT and some timed swallow variables improved significantly[104].
1	The use of the chin-tuck posture with thin consistency liquids is less effective in the prevention of aspiration in comparison with the use of thick liquids alone; it does not effectively reduce the incidence of pneumonia in populations with PD and dementia[103].
1+	In patients with PD without cognitive alterations, who have swallowing disorders, video-assisted swallowing therapy (VAST) was associated with better quality of life with swallowing and decreased pharyngeal residue[105].

Recommendations

√	The evaluation of the use of the LSVT technique for managing swallowing difficulties in persons with PD is recommended.
B	The evaluation of the use of video-assisted swallowing therapy (VAST) to improve swallowing in persons with PD is recommended.
√	The use of the chin-tuck technique together with thin liquids to reduce the incidence of pneumonia as a result of aspiration should not be considered as the first line of action in patients with PD and swallowing disorders.
√	A multi-discipline approach is recommended to manage swallowing disorders in persons affected by PD. It would be especially advisable to form coordinated work teams that include healthcare professionals specialized in endocrinology and nutrition, physical medicine and rehabilitation, hospital pharmacy, as well as speech therapists, dieticians-nutritionists, nurses, and occupational therapists, in order to promote the synergy among the tasks of rehabilitation, education, and nutritional support.

5.3. Neuropsychology

Question to be answered:

How effective is rehabilitation of cognitive functions in persons with Parkinson's disease?

Cognitive deterioration is a non-motor characteristic of PD, which contributes to a significant degree to disability, the load on the caregiver, and decreased quality of life over the course of the disease. It is well-established that cognitive changes occur with PD, including especially deterioration of memory, attention, processing speed, executive and visuospatial functions. The cognitive changes in PD can manifest themselves in different ways depending on the patient, and may vary from preservation of cognitive functions, presence of cognitive impairment in some cognitive functions, to the presence of dementia. With the advances in medical and surgical

interventions for motor symptoms, persons with PD have a longer life-expectancy, which consequently means an increase in the prevalence of disability related to the presence of cognitive alterations. This leads to a greater need to treat these cognitive changes. However, at present, there are no definitive treatments for the cognitive impairment in PD. Trials with medication, aimed at slowing the progression of cognitive impairment or improving cognitive performance, have met with varying degrees of success in reducing functional deterioration. Cognitive rehabilitation may have the potential to reduce disability and improve quality of life in persons with PD and their caregivers[106].

Originally developed to improve cognitive function after brain injuries, neuropsychology rehabilitation programs have recently been adapted for other neurological disorders. However, there is no consensus regarding which strategies offer the most beneficial results when applied to patients with PD. Rehabilitation of cognitive functions, a treatment focus for persons with impairment, is designed to optimise cognitive performance and reduce functional deterioration in the activities of daily life. Although there are variations between the programs, the essential elements of cognitive function rehabilitation are focused on the skills needed for adequate cognitive performance in daily life, at the personal, professional, and social levels. The different rehabilitation programs are aimed at improvements in specific cognitive domains, such as attention, memory, executive and visuospatial functions, which are cognitive abilities that are essential for completing the tasks of daily life. The programs can also promote strategies to improve self-management, such as problem-solving, time management, and compensation of memory loss. It is therefore necessary to examine which cognitive function rehabilitation strategies have the greatest positive impact on adaptive abilities for the lives of persons with PD, so that it can serve as the first step in the evaluation of the viability and utility of cognitive function rehabilitation programs in this population.

One moderate-quality RS (Braun *et al*. 2013)[107], and another low-quality RS (Calleo *et al*. 2012)[108] were found.

The objective of the review by Braun *et al*. 2013[107] was to investigate the benefits and adverse effects of an intervention with mental practice (MP) on cognition activities and emotions of patients after brain accidents, patients with PD, or patients with multiple sclerosis. As an intervention, it evaluates MP added to therapy (e.g. using recorded instructions), inserted into therapy (e.g. problem-solving strategies in which open movements are combined with mental practice during occupational or physical therapy), or administered as an independent intervention. The SR included two RCTs. In one, the intervention period was 12 weeks, with 60 minutes of physical therapy 2 t/w; in a 3-part protocol (15-20 minutes) that included callisthenics, crucial motor tasks, and relaxation exercises. The other study had an intervention. Of 6 weeks (groups 60 minutes 1 t/w or individual 30 minutes 2 t/w of physical therapy in accordance with the Dutch PD guidelines). Both studies use images with kinaesthetic and visual symbolism. The comparison in both studies is customary therapy with focus on physical exercises and relaxation (Jacobson: 30 minutes treadmill and progressive muscle relaxation). Numerical data was not offered in several studies. According to the first RCT, MP showed significant differences in the *timed up & go* (TUG), getting up from a chair and from the supine decubitus position, number of steps taken to complete a lap, and the mental section of the UPDRS scale. At the cognitive level, significant differences were found in the *Stroop test* part B, with an increase in attention and concentration (in the intervention group and control group). It is suggested that image symbolism may increase motivation and excitation, and reduce depression. In the second RCT, no differences were observed between groups in regard to short-term and long-term physical recovery (6 and 12 weeks). One intervention with mental practice added to regular therapy had facts similar to those of regular therapy with relaxation. In terms of negative side effects, it was documented that MP required a lot of effort to carry it out (dropouts). They also indicate that thinking of the motor actions is excessively challenging (dropouts). The authors concluded that firm conclusions cannot be established based on the available evidence in regard to the effectiveness of mental practice in patients with PD.

SR 1+

Calleo *et al.* 2012[108] reviewed the types of cognitive disabilities on which rehabilitation of cognitive function in PD may be focused, and they compared the content and methods of administration in cognitive rehabilitation interventions applied to patients with PD. The proposed interventions were cognitive training (CT) or cognitive rehabilitation. Two RCTs were included. In the first RCT, 10 sessions of memory training tasks were given (searches, matrices, puzzles, speeches, complete drawings, and storytelling). The second RCT used computer software and exercises with paper and pen. The comparison in the first study is standard rehabilitation (occupational therapy, physical therapy, and physical treatment), and in the second study, speech therapy.

SR 1

Numerical data is also not offered in the results of this SR. For the first RCT, the CT group showed significant improvement in *Behavioural Assessment of Dysexecutive Syndrome* (BADS). For the second RCT, an improvement was documented in the CT group on different scales, such as *Digit Span Forward, Stroop Word Test, ROCFT, Semantic fluency, Trail Making Band TOL*. There were no differences in PDQ-39 or CDS. The conclusions of the SR are that cognitive rehabilitation programs are being recognized as a beneficial alternative or adjuvant therapy to medication to improve specific aspects of cognitive disabilities in patients with neurological disorders or to maintain patients at their current levels; however, the evidence on the effectiveness in cognitive rehabilitation in PD is limited.

SR 1

The applicability of the intervention is limited by the number of hours required to apply it, which complicates its inclusion into customary practice. In addition, they are techniques that require specific training of the professionals. Rehabilitation of cognitive functions can be done in primary care and specialized care, with coordination between mental health services and social services.

The professionals involved in the provision of services for the rehabilitation of cognitive functions may be persons holding official advanced university degrees in psychology, clinical psychology specialists, and academic certification in neuropsychology. They may provide their assistance within the scope of the health care and socio-healthcare system, including social services for the promotion of personal independence and care of dependence Institute for Senior Citizens and Social Services (IMSERSO).

Different techniques were used, with heterogeneous results. Calleo *et al*. 2012[108] points towards a series of positive effects of cognitive training in comparison with standard rehabilitation. The mental practice evaluated by Braun *et al*. 2013[107], is a technique that is different from the ones mentioned above, and its conclusions are not firm.

In ageing, the progression of this disease and the pharmacotherapy used to treat it, as well as the associated comorbidities, may produce cognitive impairment. In this sense, and addition to evaluating the relative benefit that cognitive function rehabilitation may have in patients with PD, the possible intervention using pharmacological treatment of the initial cognitive impairment in patients with PD must be evaluated, such as the use of acetylcholinesterase inhibitors (for more information, see the corresponding question in the chapter on pharmacological treatment).

Summary of evidence

1+	There is no evidence available regarding the benefits of mental practice added to customary therapy in patients with PD in comparison with customary therapy with relaxation[107].
1	Cognitive rehabilitation programs are being recognized as a beneficial alternative or adjuvant therapy to medication to improve specific aspects of cognitive disabilities in patients with neurological disorders or to maintain patients at their current levels; however, the evidence on the effectiveness in cognitive rehabilitation in PD is limited[108].

Recommendations

√	It is advisable to carry out neuropsychological evaluations of patients with PD in order to document baseline cognitive state and track its evolution.
√	Facilitating the improvement of cognitive functions in patients with PD using tools developed by multi-discipline teams is recommended.

5.4. Nutrition and Diet

5.4.1. Vitamin D supplementation

Question to be answered:

How effective and safe is supplementation with vitamin D for the prevention of falls and hip fractures in persons with Parkinson's disease who present a lack of renal synthesis of 1.25-dihydroxyvitamin D?

Vitamin D, or calciferol, is a prohormone that is essential for the maintenance of calcium homeostasis. The adverse effects from deficient renal synthesis of vitamin D on the skeleton are well established. The enzyme 25-hydroxyvitamin D1-hydroxylase converts stored 25-hydroxyvitamin D (25 [OH] D) to the biologically active form of vitamin D, 1.25-dihydroxyitamin D. The end of the synthesis of vitamin D takes place in the skin after exposure to UV-B radiation in sunlight, or it can be obtained from the diet[109,110]. Since vitamin D is stored in the body, the supplementation of vitamin D or its active metabolites is relatively simple, requiring small daily doses or large doses spaced out over time[111].

In addition, the elderly, with neurodegenerative diseases in general, and PD specifically, have a higher prevalence of vitamin D insufficiency[112-114]. A systematic review was carried out on the efficacy and safety of supplementation with vitamin D for the prevention of falls and hip fractures in persons with Parkinson's disease who present a lack of renal synthesis of 1.25-dihydroxyvitamin D.

No RCTs or SRs were found in the systematic search, but in the inverse search of references included in the articles identified in the first screening from the years 2003 to 2013, one moderate-quality RCT (Sato *et al*. 1999)[115] was found.

Sato *et al*. 1999[115] is a double-blind placebo RCT. The objective of the study was to determine the effect of supplementation with 1.25-OH-D_2 on bone mass and on the incidence of hip fractures and other non-vertebral fractures in patients with PD. To achieve this objective, it compared the administration of a daily oral dose of 1.0 microgram of 1-alpha-(OH)-D_3 for 18 months with a placebo. In regard to results (relevant for the question in the guideline, because in addition, the measurement of bone-mineral density by bone densitometry, or serum concentration of 1.25-OH-D_2), it indicates that of the 40 patients in the placebo group, 8 had fractures from falls (6 hip fractures and 2 radius and ankle fractures) and in the treatment group, 1/40 had a hip fracture. The *Odds Ratio* (OR) of the probability of non-vertebral fracture among the patients in the placebo group compared with those in the vitamin D_3 group was 9.8 in favour of D_3 (CI95% 4.7 to 20.2). Then number of non-vertebral fractures per 1000 patients-year: 17 in the treatment group and 167 in the placebo group. There were no significant differences between the two groups in the number of falls per subject over the 18 months: treatment group 1.4 (SD 1.8) and placebo group 1.3 (SD 1.9). The authors conclude that among elderly patients with PD who completed the 18 months of the study, the number of hip fractures and other non-vertebral fractures was 17.5% lower in the intervention group (vitamin D_3) in comparison with the placebo group. The incidence of non-vertebral fractures during the 18 months in the placebo group reached 20.0%, indicating a fracture rate of 167/1000 patients-year. They concluded by indicating that 1-alpha-(OH)-D_3 prevents non-vertebral fractures in PD. The following exclusion criteria were applied in the selection of the sample population: other causes of osteoporosis such as hyperparathyroidism or renal osteodystrophy; deterioration of renal, cardiac, or thyroid function; prior treatment with corticosteroids, estrogens, calcitonin, etidronate, calcium, or vitamin D during 3 months in the 18 months prior to the study (including short-duration treatments in the two months immediately prior to the study). Also patients with Hoehn & Yahr stage 5 and a history of non-vertebral fractures. The external validity of the study is compromised since the study population lives in the Kahanzan district (Japan) and with different variables (physical activity and exercise, muscle strength, vitamin D deficiency, low body weight, hyperhomocystenaemia, lifestyles...).

RCT 1+

The hygiene-diet measurements may have a highly favourable risk/benefit balance, in addition to being a low-cost intervention. It should be noted that vitamin D deficiency can alter normal bone metabolism, which can lead to osteomalacia or osteoporosis in adults. However, it should be noted that ingestion of excessive amounts of vitamin D may cause large quantities of calcium in urine and blood, as well as calcification of soft tissues, such as blood vessels and some organs.

It is important to consider that there are vitamin and mineral substances that may be used in the production of food additives, and that they can be added to foods. In the case of vitamin D, colecalciferol and ergocalciferol are used.

Vitamin D can be obtained from natural sources. According to National Dietary Intake Survey (ENIDE) done by the Spanish Nutrition and Food Safety Agency (AESAN) in 2009 and 2010, in the section on the nutritional evaluation of micronutrients, in regard to the contribution of food groups to vitamin D intake, the group of fish, shellfish, crustaceans, and derivatives is responsible for 68% of the intake of vitamin D in the diet, followed by eggs and derivatives (20%).

In addition, for the active synthesis of vitamin D by the ultraviolet B radiation from the sun, it should be noted that Spain is a country with a Mediterranean climate, with social and cultural characteristics that facilitate this exposure to sunlight, which decreases the probability of the occurrence of a deficiency of vitamin D.

Summary of evidence

1+	The number of hip fractures and other non-vertebral fractures was 17.5% lower in the intervention group (vitamin D_3) in comparison with the placebo group[115].
1+	The incidence of non-vertebral fractures during the 18 months in the placebo group reached 20.0%, indicating a fracture rate of 167/1000 patients-year[115].
1+	1-alpha-(OH)-D_3 slows bone-mass loss and prevents non-vertebral fractures in PD[115].

Recommendations

B	Supplementation with vitamin D (as part of the diet, through enriched foods, food supplements, or medication) helps to prevent fractures in patients with PD who do not ingest a sufficient quantity, or who have a deficit of exposure to sunlight or have a greater need for vitamin D.
√	If an additional supplement of vitamin D is required in persons with PD, the association of calcium is recommended, provided that the patient does physical exercise or the daily calcium requirements are not covered by diet.
√	Food supplements should not be used as a substitute for a balanced diet in persons with PD and adequate nutrition and sufficient exposure to sunlight.

5.4.2. Weight loss

Question to be answered:

How effective are the different treatments aimed at weight loss in the treatment of obese and overweight persons with Parkinson's disease?

Obesity and weight gain in relation to Parkinson's have been limited mainly to patients who have been subjected to deep brain stimulation, although dopamine agonists have sometimes been associated with weight gain as well. PD and obesity are two of the chronic multi-morbidity conditions that have the greatest effect on results for health-related quality of life. Although the relationship between obesity, or even diabetes or arterial hypertension, and the risk of PD is still controversial, the evaluation of obesity in patients with PD could help to improve the understanding of the reality of PD and could also create an opportunity to study the impact of excess weight in the clinical picture of PD as a chronic disease in the context of other comorbidities and pluripathology[116].

No randomized controlled trials, systematic reviews, or published clinical practice guidelines that address this question were found. One study (Barichella *et al*. 2007)[117] was found, but it had an insufficient number of patients (6 patients, 3 per group) and number of days of the study (14 days) to make any recommendations. Also, depending on the body mass index (BMI) the majority were subjects with normal weight (BMI<25) and weight loss was not evaluated in the study.

Another intervention option was to promote exercise, especially the type of physical exercise that is adapted to this population, so that it helps to provide greater control over weight. In this sense, the proposed exercises in the question on the efficacy of physical therapy in patients with PD could serve as the basis for the intervention.

Hygiene-diet measures and other actions aimed at acquiring healthy life habits should also be noted.

Moderate exercise, a nutritionally-balanced diet, and the acquisition of healthy habits could help patients with PD to lose weight and reduce obesity.

Summary of evidence

No suitably-designed studies to provide an answer to the question posed in this section were found.

Recommendations

√	Persons affected by PD and who are overweight or obese are recommended to exercise moderately, receive a healthy diet, and develop a lifestyle that helps reduce the impact of this chronic disease and its associated comorbidities.

5.4.3. Modification of protein intake

Question to be answered:

What is the effect of the modification of protein intake in the necessary dose of L-dopa in persons recently diagnosed with Parkinson's and in persons with Parkinson's disease.

Patients with PD in treatment with levodopa may experience pharmaco-nutrient interactions, with the consequent post-prandial motor blocking. In particular, the early hours of the afternoon are often the worst hours in terms of mobility for these patients, due to motor blocking after lunch. This finding is due mainly to the ingestion of large neutral amino acids in protein-rich foods, which compete with the levodopa for the same type of active transport in the membrane of the intestinal mucosa as well as of the blood-brain barrier. Diets with changes in protein ingestion at dinner, maintaining the daily protein intake at the recommended daily allowance (RDA) have translated into improvement in motor fluctuations and increase in the duration of the *on* phase, so these changes are sometimes recommended for the management of PD[117].

In this so-called protein-redistribution diet, patients are advised to consume most of their protein-rich foods (meat, fish, dairy products, eggs, or legumes) at dinner. The consumption of grain-based products (bread, pasta, cookies), fruits and vegetables, which are relatively low in proteins, is also permitted at breakfast and lunch. A reduction in protein intake during the first part of the day can also be achieved by substituting some common foods with special low-protein products (LPP). These products were originally formulated for patients with chronic renal insufficiency, in which the renal disease in the terminal phase requires a low-protein diet.

The effect of the modification of protein intake, either through redistribution of daily intake, or by using special low-protein products, on levodopa absorption needs to be evaluated.

One low-quality systematic review was found (Cereda *et al*. 2010)[118].

SR 1

The objective of the SR by Cereda *et al*. 2010[118] was to evaluate intervention studies that investigated the neurological results of low-protein diets (<0.8 g/kg ideal bodyweight/day) and redistribution of proteins in patients with PD who experience motor fluctuations during treatment with levodopa. The proposed intervention consisted of a protein-redistribution diet, with 7 grams of protein before dinner (up to a total protein intake of 0.8-1.0 g/kg ideal weight/day) or 12 to 15 g of protein before dinner (maintaining protein intake at 0.8-1.0 g/kg ideal weight/day), in comparison with a low-protein diet (< 0.8 g/kg ideal weight/day). The review included 16 studies, but only the two with sufficient patients (30 and 20 patients) and study duration (4 weeks and 3 months, respectively) were evaluated. To measure the results, in terms of the magnitude of the effects, the two studies examined the effects of the protein redistribution diet. In the first study, they found that the acceptability of the intervention was 100%; and that a reduction of 3.5 h/d in *off* time was achieved (n=14); improvement in maximum motor performance (n=8); no change on UPDRS scale; response rate to the diet intervention 60.7%; 10 patients continued to follow the diet for 6 months (they lost an average of 0.32 kg of weight (with a range from a drop of 5 kg to an increase of 4 kg). In the second study, the acceptability of the intervention was 57.6% (11 patients dropped out: 9 were unable to adapt to the habits of the diet or prepare the food, 1 dyskinesia, and 1 did not respond). There was a decrease of 10.5 h/day in *off* time; and increase of 6.4 points on the AIMS (*Abnormal Involuntary Movements Scale*) at the moment of peak dyskinesia of the dose; and the response rate to the diet intervention was 66.6%.

The characteristics of the people who responded to the protein-redistribution diet were: shorter duration of PD, shorter duration of treatment with levodopa, higher age at the onset of the disease, and shorter duration of fluctuations.

The conclusions of the authors of the review are that robust conclusions cannot be drawn in regard to the evaluated alternatives (protein-redistribution diet or use of special low-protein products). They propose that patients be advised to keep protein intake within the recommended dietary requirements (0.8 g/kg/day) when beginning treatment with levodopa, and that routine dietary evaluation could ensure compliance. They also indicated that when motor fluctuations occur, a diet with redistribution of proteins may be proposed safely to patients with PD who are mentally active, motivated, and highly cooperative, but the possible side effects must be considered and managed.

The proposed interventions do not need to be carried out in the NHS only. Nutritional habits may also be conditioned from other areas.

The two studies selected from the review point in the same direction. The protein-redistribution diet reduces *off* time by between 3.5 and 10.5 hours a day.

With the protein-redistribution diet, the following complications or side effects were detected: severe dyskinesia (which led to a reduction of the levodopa dose), moderate weight loss, and hunger before dinner. The following hypotheses of long-term complications were presented in the SR: protein malnutrition, loss of lean body mass, deficiencies of vitamins (niacin, [B_1] and riboflavin [B_2] and minerals (calcium, phosphorus, and iron).

Summary of evidence

1	Redistribution of protein intake achieved a reduction of 3.5 h/d in *off* time (n=14); improvement in maximum motor performance (n=8); no change on UPDRS scale; response rate to the diet intervention 60.7%; 10 patients continued to follow the diet for 6 months (they lost an average of 0.32 kg of weight (with a range from a drop of 5 kg to an increase >4 kg)[118].
1	With the protein-redistribution diet, there was a decrease of 10.5 h/day in *off* time; and increase of 6.4 points on the AIMS at the moment of peak dyskinesia of the dose; and the response rate to the diet intervention was 66.6%[118].
1	The patients who were the oldest at the onset of the disease, shorter duration of PD, shorter duration of treatment with levodopa, and shorter duration of fluctuations may respond better to the diet[118].

Recommendations

√	It may be advisable to inform patients to keep protein intake within the recommended dietary requirements (≈ 0.8 g/kg/day) when beginning treatment with Levadopa. Routine dietary evaluation to ensure compliance.
√	The participation of healthcare professionals specialized in human nutrition and diet as part of the multi-discipline teams may help to achieve and maintain compliance in regard to the recommended daily protein intake.
√	Although there is no conclusive evidence, when motor fluctuations occur and drug-nutrient interaction is suspected, a diet with redistribution of proteins may be proposed to patients with PD who are mentally active, motivated, and highly cooperative, but the possible side effects must be considered and managed.

6. Dissemination and Implementation

Clinical practice guidelines (CPGs) are tools to assist professionals and users to make decisions regarding the most appropriate healthcare treatment. To improve the implementation of a CPG, in other words, its introduction into the clinical environment, it is helpful to design a series of strategies aimed at overcoming possible barriers to adoption[1].

The plan for the implementation of this CPG for the management of patients with PD includes the following strategies:

- Presentation of the CPG by the healthcare authorities to the communication media.
- Presentation of the CPG to the different national associations and societies for neurology, family and community medicine, physical therapy and medicine, pharmacy, nursing, physical therapy, occupational therapy, speech therapy, psychology, human nutrition and diet, etc.
- Presentation of the CPG to the pertinent regional associations.
- Collaboration with scientific societies that have participated in the preparation of this CPG, to promote distribution.
- Sending and distribution of the CPG to the different databases that collect information on CPGs, for evaluation and inclusion.
- Contact with the Spanish Parkinson's Federation (FEP) and other associations of interested persons to present the guidelines to them.
- Free access to the different versions of the GPC at the GuíaSalud website, http:// www.guiasalud.es.
- Distribution of information on the CPG at scientific activities (conferences, congresses, meetings) related to neurology, family and community medicine, physical therapy and medicine, pharmacy, nursing, physical therapy, occupational therapy, speech therapy, psychology, human nutrition and diet, etc.
- Information on the CPG in medical journals and magazines for the specialisations involved.
- Publicising the existence and objectives of the CPG by means of mailing lists for professionals who would be potentially interested in it.
- Translation of the complete version into English.

A study of the barriers and facilitators in the implementation of the CPG is recommended, with interventions in the area of the healthcare professionals (skills, attitudes, opinions, motivation for change or individual characteristics), social context (patients and colleagues), factors related to the system (organization and structure, or economic measures), and aspects related to the CPG itself.

7. Lines of future investigation

This chapter covers the proposals for future investigation included in the different sections of the guidelines.

4.1.1. Pharmacological treatment of motor symptoms: antiparkinson medications

Investigate the efficacy of transdermal rotigotine compared with conventional levalopa/carbidopa treatment.

4.1.2.1. Pharmacological treatment of problems related to antiparkinson medications: management of drug-induced psychosis

Conduct adequate studies in order to evaluate whether the modification of the dosage guidelines for antiparkinson medication (dosage and frequency of administration) is effective for reducing drug-induced psychosis.

Randomized controlled trials are needed to evaluate whether the modification of the dosage, substitution, or withdrawal of the medications used in the treatment of PD which could cause psychosis, could be an effective and safe alternative before commencing treatment with an atypical antipsychotic.

Conduct experimental trials on which to base the order to discontinue the medications involved in the appearance of drug-induced psychosis that are used in the treatment of PD.

Conduct qualitative research trials to evaluate the repercussions that psychosis may have on patients and caregivers, both before the initiation of the treatment as well as after, and to determine their preferences in regard to the management of these disorders.

4.1.2.3. Pharmacological treatment of problems related to antiparkinson medications: management of impulse control disorders (ICDs)

Conduct experimental trials to evaluate the effectiveness and safety of atypical antipsychotics on patients with PD and ICD.

Conduct randomized controlled trials with sufficient patients to evaluate the efficacy of psychotherapy to provide advice and support to patients with PD and ICD.

It would be helpful to carry out qualitative research studies to determine the preferences of patients with PD and their caregivers, in regard to the management of the ICDs.

4.2.1. Pharmacological treatment of non-motor symptoms: management of alterations with sensory symptoms

More studies with adequate design and sufficient sample size are needed to be able to establish the efficacy and safety of treatment of pain using antiparkinson medications in patients with PD.

Well-designed randomized controlled trials are needed to establish the efficacy and safety of the different pain treatment alternatives, with analgesics as well as with non-pharmacological methods (mainly physical therapy).

4.2.2. Pharmacological treatment of non-motor symptoms: management of autonomic dysfunctions

Conduct properly-designed studies to analyse the efficacy and safety of treatment of orthostatic hypotension in patients with PD, because there is insufficient evidence to make a recommendation on the use of domperidone, fludrocortisone, midodrine, or pyridostigmine.

Investigate the effectiveness and safety of botulinum toxin for the management of sialorrea in patients with PD.

Conduct well-designed studies to evaluate the pharmacotherapy alternatives for urinary incontinence in PD that include anticholinergics and antimuscarinics (fesoterodin, tolterodine, oxybutynin, solifenacin, and trospium). Evaluate stimulation of the tibial nerve and behavioural therapy.

Evaluate the use of osmotic laxatives, mosapride, neutrophin 3, prebiotics, and feedback therapy in patients with PD and constipation.

5.1. Non-pharmacological treatment: occupational therapy and physical therapy

Conduct randomized controlled trials to evaluate the medium and long-term effects of physical therapy on persons affected by PD.

Well-designed studies are needed to establish the efficacy of occupational therapy in patients with PD.

5.2.1. Non-pharmacological treatment: speech therapy to improve communication and language

Well-designed studies are needed to establish the effectiveness of speech therapy in improving communication and language in persons with PD.

Investigation to improve the techniques and instruments used to diagnose language and communication problems in patients with PD.

5.2.2. Non-pharmacological treatment: speech therapy to improve swallowing

Well-designed studies are needed to establish the effectiveness of speech therapy in improving swallowing in persons with PD.

5.3. Non-pharmacological treatment: neuropsychology

Well-designed randomized controlled trials are needed in order to evaluate the effectiveness of the rehabilitation of cognitive functions in persons with PD.

5.4.1. Non-pharmacological treatment: nutrition and diet - vitamin D supplementation

Well-designed randomized controlled trials that control possible biases and other variables (sun exposure, activity, and exercise, proper and balanced diet, interactions between foods and medications, diseases and disorders, among others) that provide evidence on the role of vitamin D in patients with PD are needed.

5.4.2. Non-pharmacological treatment: nutrition and diet - Weight loss

Future lines of investigation should include the question regarding the effectiveness of the different weight-loss diets in the treatment of obese and overweight persons with PD, developing well-designed studies with samples that are adequate both qualitatively and quantitatively, with follow-up times that are sufficient to establish scientifically proven evidence on which to base the formulation of recommendations.

5.4.3. Non-pharmacological treatment: nutrition and diet - Modification of protein intake

Conduct well-designed studies, with a sufficient number of patients and with prolonged follow-up, in order to evaluate the effects of modification of protein intake on the absorption of L-dopa in persons affected by PD, and define the characteristics of the patients who respond to the dietary modifications.

Annexes

Annex 1. Scales used in the studies included in the CPG

The following section presents the different scales that are used in the studies that evaluate the efficacy and safety of the pharmacological and rehabilitation treatment interventions for PD. The first group includes clinical scales for PD, followed by other scales for evaluating health-related quality of life, and lastly, other scales included in the studies included in the CPG.

Clinical scales for Parkinson's disease

Several of the most commonly used scales for the evaluation of PD are described below.

Hoehn & Yahr Classification (H & Y)[119]

Standard reference in the comprehensive evaluation of the severity of patients with PD. (motor function and progression of the disease). The original version classifies from I to V.

- Stage I indicates unilateral disease
- Stage II indicates bilateral disease without postural instability
- Stage III indicates postural instability
- Stage IV indicates considerable disability, but the ability to walk independently is maintained.
- Stage V indicates dependence on a wheelchair or that walking is possible with assistance

The UPDRS included a modified version of the H & Y scale 0; 1; 1.5; 2; 2.5; 3; 4 and 5) with satisfactory acceptability and a moderate or high correlation with other measurements of PD.

Schwab and England Scale, SES

Based on an interview, evaluates the overall functional capacity and the degree of dependence of the patient in regard to motor aspects of PD. The score is expressed as a percentage, from 0 (normal state) to 100 (confined to bed and with vegetative alterations). Included, along with the H & Y scale, as a complementary scale of the UPDRS.

This scale is widely used in clinical practice and investigation, but it lacks standardization, which can lead to problems in its application. It also does not evaluate the impact of key aspects of PD, such as dyskinesia and non-motor symptoms.

Unified Parkinson's Disease Rating Scale, UPDRS

Scale used to measure the severity of PD, derived from other earlier scales, consisting of 42 items grouped into four sub-scales:

- UPDRS I Evaluation of mental state, behaviour, and mood (4 items)
- UPDRS II Activities of daily life (13 items)
- UPDRS III Exploration of the motor system (14 items)
- UPDRS IV Treatment complications (11 items)

The subscales are scored by an evaluator, through an interview and physical examination. The range of scores for the first three sections is from 0 (normal) to 4 (serious). On subscale IV, some items are scored from 0 (absence) to 1 (presence) and others from 0 to 4. The total UPSRS

score is obtained as the sum total of the subscales. Higher scores indicate greater disability. The UPDRS is complemented by the modified 8-item Hoehn and Yahr (H & Y) classification (called UPDRS V) and the 20-item Schwab and England scale of activities of daily life (SES) (resulting in the section UPDRS VI), with which it forms a battery of evaluation tests.

The UPDRS evaluates different aspects of PD (mental alterations, disability, motor alterations, complications). This is the most widely-used scale in both investigation and clinical practice, the one with the largest number of validation studies, and the reference scale for international regulatory entities (such as the FDA or EMA).

A new version of the scale was developed by the Movement Disorder Society (MDS), called the MDS-UPDRS.

Evaluation of health-related quality of life

Generic measurements and specific measurements can be used to determine health-related quality of life (HRQoL) of patients with PD, in the broadest sense, combining aspects of physical, mental, and social well-being. The following standardized questionnaires have been applied especially for the generic scales: *Sickness Impact Profile* (SIP), *36-item Short-Form Health Survey* (SF-36) and EuroQol-5D (EQ-5D). All of these provide information on general health aspects, can be applied to healthy individuals and to patients with different processes, and they allow comparisons between different diseases and health situations. On the other hand, its content may have littler relation to the manifestations present in patients with PD, and therefore it may have minimal sensitivity to change.

The generic scales SIP, SF-36 and EuroQol-5D are presented below:

Sickness Impact Profile, SIP

The sickness impact profile is a general quality of life scale. It consists of 136 items that measure 12 different domains of quality of life. The participants identify the statements that describe their experience. Higher scores represent more dysfunction.

Short Form 36 (SF-36)

Evaluates the functioning and well-being of any group of participants with a chronic illness. The 36 items are divided into 8 domains, which cover the functional state, well-being, and an overall evaluation of health. The scores range from 0 to 100, with higher scores indicating better self-perceived state of health.

EuroQol-5D (EQ-5D)

A questionnaire that provides a simple description of the profile and the isolated index value of the state of health. The questionnaire also includes a visual analogue scale (VAS) to allow patients to indicate their state of health. On this scale, selecting 100 indicates the best possible state of health.

The specific scales are presented below, since the disadvantages indicated for the generic health-related quality of life measurements do not occur with the specific measurements, although they do not provide information on general health aspects and they cannot be used populations other than those for which they were designed. The following are some of the most widely-used quality of life scales (all are self-evaluated).

Parkinson's Disease Questionnaire, PDQ-39

Self-administered questionnaire that includes 39 items divided into eight health domains for which the participants feel have been negatively affected by the disease: mobility (10 items),

activities of daily life (6 items), emotional well-being (6 items), stigmatization (4 items), social support (3 items), cognitive state (4 items), communication (3 items), and pain (3 items). The time frame explored is the last month and each item presents five response options (from 0 [never] to 4 [always or unable to do it]). The score for each domain is calculated by dividing the sum of the scores of the items by the maximum possible score for that dimension, and expressing it as a percentage. The scores range from 0 to 100, with lower scores indicated better self-perceived state of health.

The sum index of the PDQ-39 and the total score on the short form of the questionnaire (PDQ-8) are calculated as the arithmetic mean of the scores of the eight dimensions or eight items, respectively. The results are presented in 8 domain scores, and also as one total score.

Parkinson's Disease Quality of Life Questionnaire (PDQL)

This consists of 37 items divided into four dimensions: Parkinson's symptoms (14 items), systemic symptoms (7 items), social function (7 items), and emotional function (9 items). The score of each item varies from 1 (all the time, continually), to 5 (never). The total score is obtained by directly adding the items.

Parkinson's Disease Quality of Life Instrument (PDQUALIF)

Questionnaire containing 32 items grouped into seven domains: social function/role (9 items), self-image/sexuality (7 items), sleep (3 items), perspectives (4 items), physical function (5 items), independence (2 items), and urinary function (2 items). The score of each dimension is obtained by adding the scores of the items and transforming them to a percentage out of the maximum possible score. The total score ranges from 0 to 128, with lower scales indicating better quality of life.

Activities of daily life (ADL)

Measurement of the impact of PD in 14 categories; each category is scored on a scale from 0 to 4, with higher scores indicating greater disability and the need for assistance. The overall score ranges from 0 to 56.

Other scales used in the studies included in the CPG

The different scales used in the studies included in the CPG are presented below.

Alzheimer's disease assessment (ADAS-cog)

A test to measure cognitive function in people suffering from dementia using a cognitive scale sub-score. The scale has a range between 0 and 70, with higher scores indicating more serious disability and lower scores indicating improvement.

Alzheimer's disease cooperative (ADCS-CGIC)

Test to evaluate the change in the study condition - with overall clinical impression (e.g. better, worse, or no change) of the change in the person who suffers dementia, as judged by the physician. The scores are in the range of 1 to 17, with a score of 1 indicating a significant improvement and a score of 7 indicating a significant worsening.

Barthel Index

Measurement of the impact of PD in 10 categories of "activities of daily life". The scores range from 0 to 100, with higher scores indicating better functionality.

Beck depression inventory (BDI)

A test used to measure the manifestations and severity of depression. This is a self-scored depression scale with 21 items. Each item comprises 4 statements (classified from 0 to 4), describing an increase in the severity of the corresponding abnormality.

Brief psychiatric rating scale (BPRS)

An 18-item scale for measuring psychiatric symptoms. Some of these items can be scored simply by observation, while other items include a self-reported element. There are 24 symptom constructs; each one scored on a 7-point scale of severity, from "not present"(1) to "extremely severe"(7).

Clinical global impression (CGI)

Participant score the change in their illness over time on a scale of 1 (much better) to 7 (much worse). A three-item scale is used (severity of the disease; overall improvement; and efficacy index) to evaluate the response to treatment of the participants.

Delis-Kaplan executive function system (D-KEFS)

Evaluates fundamental areas of cognitive function, fluidity in verbal resolution, flexibility of thought, deductive reasoning test, spatial knowledge and verbal communication. Higher scores indicate better performance.

Dementia rating scale (DRS)

Test to evaluate cognitive function in elderly adults with a total score of neurological disability. The test provides a measurement of attention, initiation, construction, conceptualization, and memory.

Berg balance scale

This is a test that was originally developed to determine people's capacity to maintain their balance. There are 14 steps that must be completed, and the results are based on the time taken to complete the specific tests and how well the tasks are carried out. Each test is scored on a scale from 0 to 4, when the patient achieves a perfect score, the final score obtained is 56. Patients who score between 0-20 are considered to require a wheelchair; if the score is between 21-40, they can walk with assistance, and between 41-56, the person is independent.

Epworth subjective sleepiness scale (ESS)

Subjective scale on which participants rate the probability that they will fall asleep or become drowsy during sedentary diurnal activities (e.g. watching television). Each question receives a score of 0 to 3, with a total maximum score of 24.

Frenchay dysarthria assessment

Tool developed to diagnose dysarthria, quantitatively evaluating speech for a range of parameters, including movements of orofacial muscles and a measurement of intelligibility.

Hamilton Depression Rating Scale (HDRS)

Observer-scored scale on 17 items to assess the presence of depression and the severity of depressive states. A score of 11 normally indicates a diagnosis of depression.

Mini-Mental State Examination (MMSE)

Scale to evaluate overall cognitive function, with scores ranging from 0 to 30. Higher scores indicate better brain function; <23 normally indicates cognitive impairment.

Montgomery-Asberg Depression Rating Scale (MADRS)

A scale for the classification of depression, used to monitor the depressive state over time on a patient-scored scale. The scores range from 0 to 60, with higher scores indicating a higher degree of depression.

Neuropsychiatric Inventory (NPI)

Test that evaluates dementia-related behaviours. The scores on the 10 items (NPI-10) range from 1 t0 120, with higher scores indicating greater severity or higher frequency of behavioural problems.

New York University Parkinson's Disease Scale (NYUPDS)

Determines clinical efficacy, classifying patients on an illness scale with 5 symptoms, using a 5-point scale, with a range from 0 (normal functioning) to 4 (significant worsening).

Northwestern University Disability Scale (NUDS)

Evaluates the activities of daily life on a disability scale for 6 categories, with a scale ranging from 0 (normal functioning) to 10 (notable disability).

Scales for Outcomes of Parkinson Disease – Sleep (SCOPA-S)

Scale for the evaluation of night-time sleep disorders and diurnal hypersomnia in PD. It consists of two sub-scales: nocturnal sleep (5 items) and diurnal hypersomnia (6 items). The scores range from 0 (never) to 3 (frequently). It also includes one item to evaluate the quality of nocturnal sleep, scored from 1 (very good) to 7 (very bad), which does not form part of the total score.

Trail Making Test

The test consists of two parts: part A, in which participants connect, the numbers 1 to 25 in order in the shortest time possible. Part B requires participants to connect the numbers and letters in an alternating pattern (in other words, 1-A-2-B) in the shortest time possible.

Annex 2. Information for patients

Table of contents of the version of the CPG for the Management of Patients with Parkinson's Disease intended for patients, family members, and caregivers

1. Definition of Parkinson's disease. Concept

Parkinson's disease (PD) is a disorder produced by the deterioration and death of a type of brain cells. These cells produce the molecule dopamine, which participates in the coordination and generation of muscular movements.

Parkinson's disease is a chronic, progressive, and degenerative process that falls within the group of movement disorders.

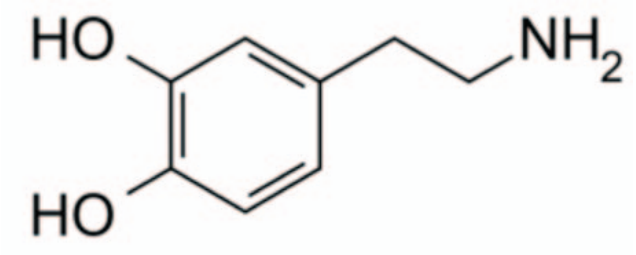

Image 1. Structure of the dopamine molecule.

The cause of PD is not known, although it probably depends on several factors that are mainly genetic and environmental in nature. There is no test that is able to distinguish this disease from other disorders with similar clinical presentations. Consequently, diagnosis is mainly clinical, and is based on a set of questions, the patient's medical history, and a physical examination. Patients with PD have a series of characteristic symptoms which are: slowness in voluntary and involuntary movements (bradykinesia), mainly with difficulty to initiate and finish these movements (dyskinesia), rigidity in the extremities, tremors, and loss of balance. PD may start asymmetrically.

It is important to note that the consumption of certain medications can produce symptoms similar to those of PD

Although PD is essentially a movement disorder, persons affected by it frequently develop other alterations, including mental problems such as depression and dementia. As the disease progresses, alterations may appear, including pain, that evolve into a serious disability that affects the quality of life of patients, their family members, and caregivers.

2. Dimension of Parkinson's disease. Participation of patients, family members, and caregivers

Worldwide, PD is the second most common disease that affects the brain after Alzheimer's disease. 10% of the cases of Parkinson's disease are explained by genetic factors, with the cause unknown in the remaining 90%.

As in the case of other countries, several studies carried out in Spain have found that the number of cases of PD increases with age. The disease appears to affect men more than women.

Participation of patients, family members, and caregivers in decision-making regarding the management of the different alterations associated with the disease or its treatments.

As in any medical action intervention, when the study, treatment, or care of persons with PD begins, the patient, as well as the patient's family members or caregivers, have the right to be fully informed.

As patients, they are entitled to receive be treated with respect, sensitivity, and understanding, and they will be given simple and clear information about PD. The information will include details on the possible benefits and risks of the treatments and the tests that will be programmed.

Patients are advised to ask questions regarding any aspects related to PD, attempting to resolve potential doubts that may arise during while the treatment is being provided or after. Some examples of frequently asked questions proposed by the European Association European Parkinson's Disease Association are shown in Table 2:

Table 2. FAQs by patients with PD

– What is Parkinson's disease?
– Where does the name of the disease come from?
– What causes the disease?
– Can the disease be prevented?
– How common is Parkinson's disease?
– Whom does it affect?
– What are the symptoms?
– What causes the symptoms?
– Is Parkinson's disease hereditary?
– Does the disease produce mental effects?
– Is Parkinson's disease fatal?
– How is Parkinson's disease diagnosed?
– What treatments are available?
– Does it matter how soon treatment begins after diagnosis?
– What are some of the most common medications?
– Does it matter how treatment of Parkinson's disease begins?
– Is there an effective operation against Parkinson's disease?
– Should a special diet be followed?
– Is there any good practical advice on Parkinson's disease?
– Is there any investigation underway on Parkinson's disease?
– Examples of famous people with Parkinson's disease
– Where can I easily find more information on Parkinson's disease?

Likewise, the religious, ethnic, and cultural needs of the family environment, as well as difficulties related to language -related difficulties must be taken into account so that the explanations that are provided take these aspects into consideration.

If information on the disease and its treatment is consulted on the Internet, it is advisable to use reliable sources of information with proven quality. The last section of the Annex with information for patients includes some of describe some of the resources that are currently available on the Internet.

It is only possible to make informed decisions after receiving correct information.

3. Recognizing the symptoms

At the onset of symptoms, close to 60% of the cells that produce dopamine have already then lost, reducing dopamine levels by 80%.

The characteristic symptoms of PD are: tremors, slow movements, and rigidity. Postural disorders generally present themselves in the advanced stages of the disease. Become bilateral

as the disease progresses, in addition to other manifestations that affect memory, language, the ability to make decisions and carry out calculations, and other alterations that affect the senses.

Sometimes, PD may begin to manifest itself in an unspecific manner, with general discomfort, rapid tiring, subtle changes in personality, pain, urinary symptoms, sleep abnormalities, loss of smell, and emotional alteration such as depression and anxiety. However, none of these symptoms is able to predict the appearance of PD in the future with a high degree of precision.

Principle symptoms of PD:

1. *Rest tremor:* this symptom is present in approximately 70% of patients. It normally presents itself before the initiation of movement, and disappears when a posture is adopted or an action is carried out. It especially affects the arms, and less frequently, the legs, lips, tongue, chin, etc. Tremors of the head are rare in PD. As in the case of all tremors, the symptom worsens with tiredness, anxiety, and drugs that stimulate the nervous system. During the day, the intensity and amplitude of the tremors varies, decreasing or disappearing during sleep.

It is important to note that there are many other causes that can generate tremors, which means that not all people with tremors have Parkinson's disease

2. *Slowness of movement or bradykinesia:* this symptom may manifest itself in the initial stages of the disease, especially during activities that involve small, precise movements, and movements that require a certain degree of skill, such as writing, sewing, shaving, etc. However, as the disease progresses, it may become more evident and appear in activities that require less precision, such as buttoning a button or peeling a piece of fruit.
3. *Rigidity or increase in muscle tone:* this refers to the resistance offered by the arms and legs when a physician attempts to bend or extend them. This rigidity may not initially be noticed by the patient, and may be described as a slight pain in the neck, back, or shoulders, or even as muscle cramps due to the static and bent position of the joints. This rigidity is normally more evident in the more distant parts of the arms and legs (wrists and ankles) although it is also observed in intermediate zones (such as elbows or knees).
4. *Postural disorders:* these normally appear in the advanced stages of the disease (although they may also appear in the early stages). The patient's normal posture has a tendency to bend at the torso, neck, and the four extremities. Walking is also altered, with an involuntary tendency to move or fall forward, and to take short steps. In advanced periods of the disease, the patient may present blockage of walking, with small steps and minimal movement, and with a high degree of instability when turning. These blockages of walking can easily result in falls. Postural and walking disorders increase in narrow areas (corridors, door thresholds) and improve in open and uncrowded spaces.

These symptoms do not always appear together, any combination of them may occur. The association of two or more of these symptoms is called parkinsonism. Other associated or secondary symptoms are:

- Changes in voice tone, which becomes weaker.
- Less expressiveness in the face.
- Psychological symptoms: anxiety, depression, and reduced sex drive.
- Sleep disorders: insomnia, fragmented sleep, and vivid dreams.
- Sensitive symptoms: cramps, tingling, and even pain in an extremity.
- Minor disorders of the Autonomic Nervous System (ANS): constipation and increased sweating.
- Cutaneous alterations: increase in skin fat, which affects mainly the skin of the face and scalp.
- Reduced sense of smell.

Other symptoms of PD:

1) Neuropsychiatric symptoms

The most common neuropsychiatric symptoms are depression, dementia, and psychosis Depression affects up to 65% of patients with PD, and may precede the typical symptoms of PD. Dementia may be present in up to 31% of patients with PD, and normally occurs after the first year following the start of the symptoms. It manifests itself as a loss of functions for the execution of commands, learning, and verbal fluidity. It affects the performance in the activities of daily life, and along with psychosis, is the most common cause of the need for care in the home and nursing supervision. Psychosis affects between 20% and 40% of patients with antiparkinson medication, and although all of the antiparkinson drugs may produce psychosis, it has been demonstrated that there is a greater risk of visual hallucinations with medications that simulate the action of dopamine.

2) Sleep problems

Sleep problems are alterations that are frequently associated with PD, and affect up to 88% of patients. The most common symptoms are fragmentation of sleep and early waking. There are several different causes, including nocturia (more frequent urination during the night), difficulty turning over in bed (nocturnal akinesia), cramps, nightmares, and pain (especially in the neck and back). Vivid dreams and nightmares may also be side effects of antiparkinson treatment. PD may also be associated with vigorous and often violent movements (kicking or punching, that appear during one of the phases of sleep. Patients may injure themselves or their partner, and it may be difficult to wake them during the episode. This affects between 15% and 47% of patients with PD. These symptoms may appear in the initial phases of the disease, even before the typical symptoms. Another important disorder, which affects between 33% and 76% of patients, is excessive daytime sleepiness (problems to stay awake during the day, which, along with sleep attacks, pose a significant risk for the safety of persons with

PD, especially while driving. All of the antiparkinson medications, specifically those which simulate the effect of dopamine, may cause excessive daytime sleepiness, or hypersomnia.

3) Fatigue

This is a frequent reason for visits to the physician in PD, often in the earliest stages of the disease. Although fatigue is associated with depression and sleep problems, a large number of persons with PD and fatigue without these symptoms have also been found.

4) Alteration of involuntary functions

This is a broad group of disorders that affect the system that is responsible for coordinating involuntary functions at different levels, including a lack of control over blood pressure, which results in falls or fainting due to sudden changes in the position of the body, generally when sitting up, and others, such as constipation, swallowing problems, difficulty chewing, or swallowing food or liquids, and urinary and sexual alterations, mainly.

5) Digestive symptoms

In relation to digestive symptoms, weight loss affects half of patients with PD, and affects women more than men, and is associated significantly with the presence of problems swallowing food or liquids, and complications such as involuntary movements. More than 70% of patients experience sialorrea (excessive salivation), aggravated by a decrease in the frequency and efficiency of swallowing. Difficulty swallowing has been documented in up to 82% of patients with PD, and may compromise oral, pharyngeal, or oesophageal function, with the passage of contents from the digestive tract to the respiratory tract representing one of the most feared complications, due to the risk of pneumonia or even asphyxiation. Another one of the most common digestive symptoms is constipation, present in between 20% and 79% of the cases.

6) Urinary symptoms

Urinary alterations affect up to 75% of patients with Parkinson's, and they are most frequent during the advanced stages of the disease. The increase in frequency of urination during the night is often the first manifestation, followed by daytime urgency, and urinary incontinence. The decrease in bladder capacity is the most common finding during the urodynamic evaluation.

7) Sexual dysfunction

This may range from hyposexuality to hypersexuality. The latter is present more frequently in men as a side effect of treatment, rather than an intrinsic characteristic of PD. Also, difficulty to achieve erection and alteration of ejaculation have been reported in up to 79% of men, as well as decreased sex drive in 44%. It women, decreased sex drive is most common (70%), and is usually accompanied by a lack of pleasure and sexual relations.

8) Pain

Pain affects almost half of the patients with PD, and it may appear during any stage of the disease. There are several different types, from very sharp pain, with a tingling sensation or numbness. This mainly affects the face, abdomen, genitals, and joints.

4. Evolution of Parkinson's disease

The life expectancy of Parkinson's patients is similar to that of the unaffected population, but their state of health worsens more significantly over the years. PD is classified into different stages depending on the degree of affectation. Table 3 presents a classification to analyse the problems that patients present over the course of the evolution, following the Hoehn & Yahr stages[119] (see annex 1).

Table 3. Classification of patients with PD based on Hoehn & Yahr stages

Classification	Hoehn & Yahr Stages
1. Recently-diagnosed patients	Stage I unilateral affectation
	Stage II bilateral affectation, normal balance

2. Moderately-affected patients	Stage III bilateral affectation with balance alteration
	Stage IV increase in the degree of dependence
3. Severely-affected patients	Stage V, severely affected, requiring wheelchair or bed rest

Recently-diagnosed patients: manifestations

Stage I

- Facial expression normal
- Erect posture
- Possible tremor in an extremity
- Fine motor difficulties
- Rigidity and bradykinesia upon close examination
- Reduced arm movement while walking, slight dragging of feet

Stage II

- Alteration of facial expression
- Reduced blinking
- Slightly bent posture
- Slower execution of the activities of daily life
- Symptoms of depression
- Possibility of side effects of medications

Moderately-affected patients: manifestations

Stages III and IV

- Difficulties walking: shortened steps, difficulty turning
- Balance difficulties: falls, difficulty stopping
- Feeling of fatigue
- Pain
- Communication difficulties
- Symptoms of autonomic dysfunction
- Drug-related symptoms:
  - *On-off* phenomena, with alternating periods during which the symptoms of PD are well controlled (*"on"* periods) with other periods when all of the symptoms reappear (*"off"* periods): fear and insecurity
  - Dyskinesia
  - Behavioural problems: insomnia, hallucinations, confusion

Severely-affected patients: manifestations

Stage V

- Not all patients reach this stage
- Dependants
- Progressive increase in *off* time
- Large part of the time seated or in bed
- Language disorders accentuated
- Development of cramps
- Possibility of bed sores Recurring urinary tract infections
- Progressive dysphagia

5. Treatment and rehabilitation for the persons affected

Unlike other brain diseases, there are several different medical and/or surgical treatments that are effective in the treatment of the symptoms of PD. Currently, rehabilitation (physical therapy, speech therapy, occupational therapy, etc.) are the complements applied to slow the progression of the disease[120].

Each patient requires individualized evaluation at all times, and the treatment possibilities must be adjusted to suit the specific moment and patient.

Treatment of PD can be divided into: pharmacological, surgical, and rehabilitation. This CPG covers the management of pharmacological treatment and rehabilitation.

Pharmacological treatment:

Pharmacological treatment depends on the degree of disability of the patient, and generally is not justified until the symptoms compromise the patient's capacity to work and maintain social relations. Pharmacological treatment is normally initiated at first and requires close supervision to ensure that all of the treatment guidelines are tolerated well and that the proper changes are made to the treatment as the disease progresses. The initial drug is normally levodopa, although there are other alternatives or substitutes that may be used when it loses its efficacy.

Levodopa: is the most effective treatment to improve the symptoms of the disease. This substance is transformed into dopamine in the brain and replaces or substitutes the dopamine that is not produced by the brains of persons with PD.

The effectiveness of levodopa decreases over time. It has been calculated that five years after initiating treatment, a high percentage of patients develop what are known as motor fluctuations, characterised by the alternation *"on"* periods and *"off"* periods.

Over the years, these fluctuations may become more pronounced, which means that the periods of time during which the medication is ineffective become longer and less predictable. This is when the side effects caused by the levodopa appear: mental disorders, increased sex drive, lower blood pressure, digestive alterations...

In addition, administration of levodopa over an extended period of time may facilitate the appearance of excessive abnormal involuntary movements that cannot be controlled by the patient.

Amantadine: sometimes administered when symptoms appear initially, when they are minor, to delay the administration of levodopa. This drug reduces involuntary movements.

Anticholinergics: indicated only in very specific cases and in patients younger than 70 years of age, due to the side effects, which include blurry vision, urine retention, and memory loss. These drugs are effective mainly in the treatment of tremors and rigidity and reduce excessive salivation (sialorrea). However, they are not very effective for relieving clumsiness and slowness of movement.

Dopamine agonists: association with treatment with levodopa in some cases allows the levodopa dosage, and consequently its side effects, to be reduced. These drugs are normally the primary choice in the treatment of PD in patients younger than 65 years of age.

The initiation of treatment with agonists is effective in controlling the symptoms of the disease in the early stages, allows the start of treatment with levodopa to be delayed, and delays, for a time, the appearance of motor fluctuations and involuntary movements.

Apomorphine: this is a powerful dopamine antagonist, which, when administered parenterallly (subcutaneously), takes effect in 20 minutes, although the effects disappear within 2 hours. It can also be administered by a programmable pump, adjusting the hourly dosage and thus minimizing the fluctuations. It does not allow the rest of the drugs to be discontinued, and care must be taken when prescribing it because it could easily worsen pre-existing psychiatric symptoms. Nodes may appear at the point of subcutaneous injection.

Entacapone and tolcapone: administered together with levodopa, they reduce levodopa loss, increasing the amount of levodopa available in the brain. They have been proven effective in decreasing off periods.

Selegiline and rasagiline: selegiline may have more side effects than rasagiline, including insomnia and hallucinations. Recent studies have shown that rasagiline administered early can change the evolution of the disease.

Continuous perfusion of Levadopa/carbidopa intestinal gel (LCIG): this may be an alternative to neurosurgery in patients who are not suitable candidates for this type of surgical intervention, and also in advanced-stage patients with severe motor problems and side effects, when the combination of the available Parkinson's medications have not generated satisfactory results. This is an invasive method in which the medication is administered through a direct connection to the intestine from a programmable pump.

Intraduodenal administration of levodopa makes it possible to keep dopamine levels stable.

The reduction of the variability of levodopa levels in blood reduces motor fluctuations and improves dyskinesia, according to the results of the available clinical trials. It allows better clinical control, administering it as a single drug. It may be very helpful in older patients with psychiatric side effects and alterations of involuntary functions produced by medications that simulate the action of dopamine.

Surgical treatment:

There are some treatment alternatives that are carried out by neurosurgeons, although these do not fall within the scope and objectives of these guidelines, because they have very specific and concrete indications. For more information on this subject, consult the corresponding healthcare professionals.

Rehabilitation treatments:

Physical therapy:

The fundamental objective of physical therapy is to contribute to the achievement of more comfortable and easy mobility in daily activities. To achieve this purpose, strategies have been developed to address and/or overcome the motor difficulties that characterize the disease, and halp patients to remain active to the greatest degree possible.

In addition, physical therapy is aimed at re-educating patients in the movements that are altered or diminished; providing strategies to overcome the difficulties and initiate a movement; improving mobility of the lower limbs that is necessary to carry out the activities of daily life; maintaining muscle tissue in good condition and stimulate blood circulation; re-educating posture, to prevent pain resulting from remaining in incorrect positions; maintaining and/or improving respiratory capacity, which is compromised by rigidity and difficulty of thoracic mobility; maintaining balance and improving coordination.

Occupational Therapy:

The purpose of occupational therapy is to allow the person affected to be as independent and autonomous as possible, to improve and/or maintain their quality of life. In persons with Parkinson's disease, occupational therapy serves a series of very specific functions that are determined by the pathology itself, the stage and evolution of the disease in each subject, and the personal circumstances of the patients.

Also, treatment places emphasis not only on the individual problems and deficiencies, but also on the potential of each person, and is aimed at achieving the following basic objectives, among others: improving and/or maintaining coordination and voluntary activity of the upper limbs, especially the hands; promoting communication of all types (verbal, non-verbal, written) necessary in almost all instrumental activities of daily life (shopping, writing a letter, etc.) strengthening and facilitating the execution of these activities; training in the basic activities of daily life (such as dressing, turning in bed, etc.) so that the person can carry out the activities much more easily; providing advice, when necessary, in regard to different adaptations (such as: putting Velcro on clothing, replacing buttons, thickening handles on toothbrushes and hairbrushes, etc.), modifications in the home (remove rugs, use non-slip mats and boards to enter the bathtub), devices (toilet booster seat, handrails in the bathtub, etc.), support products (mechanisms, devices, etc., which, when used correctly, make it possible to overcome a large number of difficulties and offset disabilities mechanically, and promote personal development and social integration); helping the person with PD and their family members to organize their daily routines, promoting the creation of habits that reinforce autonomy, their rules, occupations, hobbies, etc., in order to continue with the activities their previous activities, or seek alternatives for maintaining quality of life; strengthening cognitive functions (attention, memory, orientation, visual-spatial, perceptual, and executive functions, etc., decreasing bradykinesia); providing information and advice to family members regarding how to assist persons with PD in the activities of daily life.

Speech Therapy:

Treatment is aimed at three main objectives: improving intelligibility of speech, making the person aware of aspects of speech that complicate communication; offering guidelines for the person and caregivers, to facilitate communication with the surrounding social and family

environment, and to improve speech capacity, through systematic and intensive practice of exercises that are aimed at automating control of different aspects involved in speech (breathing, phonation, articulation, and intonation of speech) to improve intelligibility.

In addition it must also: encourage work at home, as well as family collaboration, to support speech therapy sessions in order to promote the transfer of what has been learned to spontaneous language; increase awareness of persons with PD regarding which aspects complicate the process of swallowing in any of its phases, especially in the oral and pharyngeal phases; improve the swallowing process through exercises aimed in improving the oral phase, the learning of postural manoeuvres that facilitate swallowing, as well as adaptations in diet, if necessary, such as the use of thickeners for liquids.

Speech therapy intervention works on the following areas: rehabilitation of postural control; relaxation; respiratory rehabilitation and blowing; therapy to improve muscle function (movements of the face and throat, etc.); rehabilitation in the use and function of the muscles of the face (lips, tongue, and jaw); coordination of breathing and the use of exhalation with speech; rehabilitation of pronunciation and rhythm; rehabilitation of laryngeal functions; prosody rehabilitation (especially intonation); and swallowing.

Psychological:

Psychological treatment is aimed at helping the acceptance of the disease and adaptation to changes; improving mood and management of emotions; improving quality of life; strengthening social and family relations; stimulating autonomy; promoting an active lifestyle; improving self-image and self-esteem; stimulating decision-making; promoting self-control; providing information to the person affected and their families and caregivers, and also caring for the caregivers.

6. Habits and behaviour to prevent complications

Our state of health depends on several determining factors. One of the fundamental determining factors is lifestyle or habits, which include those actions which can be carried out to improve our state of health and prevent complications of the disease.

The following section offers information for persons affected by PD, at three times during day-to-day activities: during the hottest periods, when driving (or carrying out hazardous activities) is required, and on the intake of food.

In regard to the prevention of the effects of high temperatures, it is important to note that some antiparkinson medications may impede the patient's heat loss capacity by limiting sweating, with medications potentially aggravating the exhaustion-dehydration syndrome and heatstroke, as reflected in the information regarding the proper use of the medications in case of heat waves that is published annually.

When taking medication, it is always advisable to read the information sheets of the medications closely. In the case of antiparkinson medications, it should be noted that there are several common characteristics in the labelling of medications in regard to the risks that may be posed to *driving*, which are included in a table prepared by the Spanish Agency for Healthcare Products and Medications (AEMPS)[121]. Normally, all medications that pose problems for driving include the driving pictogram similar to the one shown here (image obtained from the Spanish Agency for Healthcare Products and Medications).

In regard to *food intake*, the Spanish Foundation of Dieticians and Nutritionists proposes an increase in the awareness of the translation of the documents on the descriptors of the consistency or texture of diets and the foods for persons with dysphagia[122].

The texture descriptors describe the types of textures of the diets and foods that are required by persons who have difficulty swallowing and are at risk of choking or aspiration, as is the case of persons affected by PD. The descriptors provide a standard terminology that all healthcare professionals and food providers should use.

Consistencies are textures of foods-diets suitable for persons with dysphagia:

1. Type B texture: thin purée dysphagia diet
2. Type C texture: thick purée dysphagia diet
3. Type D texture: pre-mashed dysphagia diet
4. Type E texture: fork-mashable dysphagia diet.

Descriptors applied to each consistency or texture

	Textures of dysphagia diets			
Descriptors	Type B	Type C	Type D	Type E
Converted to purée				
Mash with a fork before serving				
Requires (little) chewing				
Requires very thick cream or sauce (note 1)				
Takes the shape of the plate			N/A	N/A
Can be moulded			N/A	N/A
Easily poured			N/A	N/A
Spreads out when spilled			N/A	N/A
May be eaten with a fork (does not slip between the tines of the fork)			N/A	N/A
The fork makes a clear permanent pattern in the surface			N/A	N/A
A plastic spoon remains upright when its head is submerged			N/A	N/A
There are two textures (thin-thick)				
Smooth in all senses				
Has lumps (hard, chewy, fibrous, dry, crunchy, or crushable), fibres, skins, pieces of shell, cartilage, pips, seeds etc.				
Requires straining to achieve the texture				
Maintains cohesion in the mouth				
Is wet				
Separation of fluids				
Sticky or rubbery in the mouth				
Additional considerations	Note 2	Note 2, Note 3	Note 4	Note 5

Important: do not offer ice cream or gelatine unless permitted by a speech therapist after a personal evaluation of the patient.

Note 1: very thick sauce or cream means that it DOES take the shape of the plate AND can be moulded, BUT IT CANNOT be poured easily and DOES NOT spread out if spilled. Thinner sauces should only be eaten by patients for whom this has been allowed by the speech therapist.

Note 2: should not be accompanied by any side dish. Before serving and eating, make sure that (a) there are no lumps, crusts, or skins that formed during cooking/heating/waiting; and (b) that the texture has not changed and that none of the liquid has separated.

Note 3: texture type C (breakfast and desserts): thick purée textures made from powdered bases with no loose liquids or lumps are allowed. The texture of cookies – cereals for breakfast are completely softened, dissolved and uniform, and completely soaked with milk. Texture of rice pudding purée.

Note 4: type D texture = pre-mashed (specific food groups): in addition to what was specified above, the following items should be considered for these food groups: (a) meat: must be finely ground (pieces approximately 2 mm). There should be no hard chunks of ground meat. Serve in a very thick sauce (meaning of "very thick" in the previous paragraph). If the purée procedure specified in texture C should be done; (b) fish; must be finely ground and served in a very thick sauce (note 3); (c) fruit; serve mashed and remove any liquids that separate); (d) casserole/stew: must be very thick. It may contain meat, fish, or vegetables if prepared as described and if they are completely mixed; (e) bread: do not offer bread unless allowed by a physical therapist following a personal evaluation of the patient; (f) cereal: texture of very thick purée and with no lumps, and textures of the biscuits-breakfast cereal completely softened, dissolved and uniform with milk completely absorbed. Textures must be very thick, and unless a speech therapist allows thinner textures following a personal assessment of the patient; (g) desserts: texture of very thick yoghurt or very thick fruit cup. Texture of sponge cake served with thick cream. The general texture must be very thick unless a speech therapist allows other thinner textures following a personal evaluation of the patient.

Note 5: type E texture = fork-mashable: before serving and eating, ensure that (a) there are no lumps, crusts, or skins that formed during cooking/heating/waiting; and (b) that the fluids/sauces/creams in or on the food have not changed or separated. In addition to what was specified above, the following items should be considered for these food groups: (a) meat: must be in small pieces or finely ground (pieces approximately 15 mm). There should be no hard chunks of ground meat. Serve in a very thick sauce (note 3); (b) fish must be soft enough to be broken into small pieces with a fork.: Serve in a very thick sauce (meaning of "very thick" in the previous paragraph); (c) fruit: serve mashed and remove any liquid that separates; (d) casserole/stew: must be very thick. It may contain meat, fish, or vegetables if prepared as described and if they are completely mixed; (e) bread: do not offer bread unless allowed by a physical therapist following a personal evaluation of the patient; (f) cereal: texture of very thick purée and with no lumps (particle size 15 mm), and textures of the biscuits-breakfast cereal completely softened, dissolved and uniform with milk completely absorbed. Textures must be very thick, and unless a speech therapist allows thinner textures following a personal assessment of the patient; (g) desserts: texture of very thick yoghurt, with fruit pieces that may be mashed until particles no larger than 15 mm are obtained. Texture of sponge cake served with thick cream. The general texture must be very thick unless a speech therapist allows other thinner textures following a personal evaluation of the patient.

N/A; not applicable.

Also, the book Advice for patients with Parkinson's: the role of diet in Parkinson's, behavioural alterations[123], proposes a series of dietary recommendations to reduce problems of gastrointestinal motility in patients treated with antiparkinson medications::

- Eat slowly
- Eat smaller amounts more frequently over the course of the day
- Consume drinks little by little
- Avoid fried food, fats or very sweet foods
- Avoid orange and grapefruit juice, because they are very acidic and can make nausea worse
- Do not mix hot and cold foods
- Eat food cold or at room temperature to avoid nausea caused by food odours
- Avoid brushing teeth immediately after eating
- Remain seated for approximately 30 minutes after eating
- Do not do intense physical exercise immediately after eating
- If you feel nauseous in the morning, eat some type of salted crackers, provided that you do not have arterial hypertension

7. Entities and organizations to assist patients

The red tulip is the international symbol of PD.

In recent years, the tulip has been adopted as a symbol by many Parkinson's organizations around the world. The European Parkinson's Disease Association (EPDA) adopted the tulip as the symbol for its logo in 1996. The Work Group on Parkinson's disease of the World Health Organization (WHO), later agreed that the logo of the EPDA should be considered to be the international symbol for PD. By using the EPDA's red tulip, you can therefore help to increase Parkinson's awareness and show your support for the people who live with the disease and their families throughout the world.

European Parkinson Disease Association (EPDA)

Represents 45 organizations and defends the rights and needs of more than 1.2 million people with Parkinson's disease and their families. The Association's vision is to permit all persons with Parkinson's in Europe to live full lives, while seeking to promote a cure for the disease. Available at: http://www.epda.eu.com/en/

Spanish Parkinson's Federation (FEP)

The FEP is a non-profit organization, declared to be of public utility, which was created in November of 1996. The FEP currently has 45 associations distributed throughout Spain and with a combined total of more than 11,500 members.

The principal goal of the FEP and the basis of its philosophy is to improve the quality of life of those affected by PD and their families.

To achieve this goal, the FEP works through different projects that cover all of the problems that affect persons with PD.

They have projects related to investigation, training, and information, to leisure aspects, to the environment in nature, to rehabilitation, to support of family members, etc. all of the projects ultimately improve the lives of the patients, either by assisting investigators, training caregivers, offering patients art -related therapies that offer tools to continue their fight with hope, in connection connecting the therapies and families to nature, through reforestation projects...

The following is a modified table with the list of associations related to Parkinson's in Spain. The list with all of the information is available at:

http://www.fedesparkinson.org/index.php?r=site/page&id=21&title=Listado_de_asociaciones&idm=50

Entity name	Website or e-mail
SPANISH PARKINSON'S FEDERATION	http://www.fedesparkinson.org
ASOCIACIÓN ACAPK NERVIÓN-IBAIZABAL	www.parkinsonacapk.org
PARKINSON ALBACETE	http://parkinsonalbacete.blogspot.com.es
Entity name	**Website or e-mail**
PARKINSON ALCORCON	http://www.parkinsonalcorcon.org
PARKINSON ALICANTE	http://parkinsonalicante.es
PARKINSON ARABA	asopara@euskalnet.net
PARKINSON ARAGON	www.parkinsonaragon.com
PARKINSON ASTORGA	www.parkinsonastorgaycomarca.org
PARKINSON ASTURIAS	www.parkinsonasturias.org

PARKINSON ÁVILA	https://sites.google.com/site/parkinsonavila/servicios-yactividades
PARKINSON BAHIA SD CADIZ	www.parkinsonbahiadecadiz.org
PARKINSON BAJO DEBA	deparkel@deparkel.org
PARKINSON BIZKAIA-ASPARBI	http://asparbi.kzcomunidades.net/es/html
PARKINSON BURGOS	www.parkinsonburgos.org
PARKINSON CARTAGENA	parkinsoncartagena@yahoo.es
PARKINSON CASTELLÓN	www.parkinsoncastellon.org
PARKINSON CATALUÑA	www.catparkinson.org
PARKINSON COMARQUES SD TARRAGONA	parkinsonapct@gmail.com
PÁRKINSON ELCHE	www.parkinsonelche.wordpress.com
PARKINSON EXTREMADURA	www.parkinsonextremadura.org
PARKINSON FERROL	https://sites.google.com/site/parkinsonferrol
PARKINSON GALICIA-CORUÑA	http://parkinsongalicia.blogspot.com
PARKINSON GALICIA-BUEU	http://parkinsonbueu.blogspot.com.es
PARKINSON GRANADA	www.parkinsongranada.es
PARKINSON GRAN CANARIA	parkinsongrancanaria@hotmail.com
PARKINSON GUIPUZCOA	www.aspargi.org
PARKINSON L´HOSPITALET I EL BAIX LLOBREGAT	Parkinson_lh_baix@hotmail.com
PARKINSON JOVELLANOS PRINCIPADO SD ASTURIAS	asociacionparkinsonjovellanos@yahoo.es
PARKINSON LA RODA	www.cirenc.org
PÁRKINSON SD LES TERRES SD LLEIDA	www.lleidaparticipa.cat/parkinsonlleida
PARKINSON LORCA	www.parkinson.lorca.es
PARKINSON LUGO	http://www.sergas.es/Microsites/Asociacions/ListadoContidos.aspx?IdPaxina=70511&idasoc=12
PARKINSON MADRID	www.parkinsonmadrid.org
PARKINSON MALAGA	www.parkinsonmalaga.org
PARKINSON MÓSTOLES	parkmostoles@telefonica.net
PARKINSON NAVARRA	www.anapar.org
PARKINSON ON-OFF MURCIA	www.famdif.org/index.php?option=com_content&view=a rticle&id=364:fepamur&Itemid=487
PARKINSON OURENSE	www.aodem.com
PARKINSON SEGOVIA	http://www.segoviaparkinson.org
PARKINSON SEVILLA	www.parkinsonsevilla.org
PARKINSON SORIA	http://www.parkinsonsoria.org/cgi-bin/index.pl
PARKINSON TENERIFE	http://parkinsontenerife.blogspot.com.es
PARKINSON VALENCIA	www.parkinson-valencia.com
PARKINSON VALLADOLID	www.aparval.com
PARKINSON VILLARROBLEDO	http://www.parkinsonvillarrobledo.org
PARKINSON VIGO	www.asociacionparkinsonvigo.es

Social networks:

Social networks and the healthcare 2.0 environment are extremely important as a resource available to persons affected by PD, their families, and caregivers, consisting of "social relations and links between individuals which may provide access to or mobilization of social support for health" (modified definition of social networks from the WHO's Health Promotion Glossary).

These require prior registration and include access to Facebook, Twitter, new service (newsletter), or the Social Parkinson's Project developed by the Spanish Parkinson's Federation. The addresses of these resources are:

- https://www.facebook.com/federacionespanoladeparkinson
- https://twitter.com/ParkinsonFEP
- http://news.fedesparkinson.org/
- http://www.parkinsonpulsaon.es/

The Institute for Social Services and Senior Citizens (IMSERSO) offers a variety of documentation and publications of interest to senior citizens and the elderly who are in dependant situations. In regard to PD, one of the most important publications is the book "La situación de los enfermos afectados por la enfermedad de Parkinson, sus necesidades y sus demandas" ("The situation of patients affected by Parkinson's disease, their needs and their demands"), as part of the Dependence Series Collection of studies[124]. It provides information on the current situation of persons affected by PD and their families, in order to correctly approach the provision of social and healthcare services that respond to their principal demands and needs. It is structured in 5 parts:

- It explains what PD is, its origin, and evolution from a scientific point of view that is clear and simple to understand.
- It analyses the effects of the disease on the person affected at both the physical and psychological level.
- It analyses the healthcare demands and needs generated by the disease, considering the difficulties that accompany the diagnosis of Parkinson's, the need for information of the persons affected, and the needs of the healthcare professionals involved in the treatment.
- It analyses the social needs and demands: the social image of the disease; the different areas of life of the persons affected the home, work and leisure environments; the social protection available; the economic, human, and material resources and assistance; and the role played by associations.
- It presents the conclusions and proposals for action. It is available for consultation at http://www.imserso.es/imserso_01/index.htm

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[1] File URL: http://upload.wikimedia.org/wikipedia/commons/6/6c/Dopamine2.svg Attribution: By Harbin (Own work) [Public domain], via Wikimedia Commons

Annex 3. Glossary

AGREE: *Appraisal of Guidelines for Research & Evaluation*. International collaboration that designed a tool to assess the quality methodology of clinical practice guidelines.

Hallucinations: perceptions in any sensory mode that occur without external sensory stimuli.

Amplitude: the maximum absolute value of a periodically variable quantity. For a sound wave, the maximum variation of the pressure relative to the static conditions (for example, atmospheric pressure). Small variations produce weak (or silent) sounds, while large variations produce strong (or loud) sounds.

Cost-effectiveness analysis: a method of socio-economic analysis that is used to compare alternative interventions, in which the costs are measured in monetary terms and the results are expressed in non-monetary units. It describes the costs for a particular gain or loss of health. E.g.: Reduced mortality, reduced morbidity, etc.

Cost-utility analysis: an economic analysis in which the costs are expressed in monetary units and the benefits in QALY (quality-adjusted life years). The result, expressed as the quotient cost/QALY can be used to compare different interventions.

Sensitivity analysis: a tool for determining the robustness of a mathematical or analytical model that can present a wide range of estimates depending on the values of the independent variables in the trial or that determine whether the variations that occur produce significant changes in the results of the analysis. It can also be used in other types of studies, such as clinical trials or meta-analyses, to see whether the inclusion or exclusion of certain data generates variations in the results.

Articulation: the production of vowels and consonants that use both the movement of parts of the mouth (for example, the tongue and lips) and the fix structure of the mouth (for example, the hard and soft palettes). It does not involve the mouth resonance chamber.

Random assignment / randomization: a method of assigning individuals to groups in such a way that each individual is assigned independently and has the same probability of being assigned to one of the groups.

Bradykinesia: a slowing of the start of voluntary movement with a progressive reduction in the speed and amplitude of repetitive actions.

Cochrane Library: an effectiveness database produced by the Cochrane collaboration, consisting of, among others, the original systematic reviews by this organization (*Cochrane Database of Systematic Reviews* - CDSR).

Freezing of gait: motor blocking while walking, in which the patient attempts to take a step but is unable to do so. This freezing normally occurs when beginning to walk (hesitation when starting / failure to initiate walking) but it may also occur when the patient turns, faces obstacles, or distractions, such as narrow entrances, or during normal walking. Individual episodes of freezing are normally short (lasting seconds) and are not associated with the worsening of parkinsonism of the upper limbs, unlike "*onoff*" fluctuations with which they are frequently confused.

Decibel (dB)**: a unit for expressing the relative difference in power or intensity, normally betw**een acoustic or electrical signals, equal to ten times the common logarithm (in other words, base 10) of the ratio of the two levels.

Swallow: the act of causing or allowing food or any solid or liquid substance to pass from the mouth to the stomach.

Delirium: unshakable false beliefs that cannot be explained by the socio-cultural context of the person.

Dementia: progressive decline in cognitive function due to brain injury or disease beyond what is expected due to normal ageing.

Dysarthria: the collective name of a group of speech conditions that results from disorders in the muscle control mechanisms of speech as a result of damage to the central nervous system. In the case of Parkinson's disease, this includes monotony of tone and volume (dysprosody), reduced articulatory tension, imprecise articulation, variations in speed that result in inappropriate silences as well as sudden bursts of conversation, and agitated respiration with conversation (hypophony), reflecting the patient's difficulty to synchronise language and breathing.

Dyskinesia: involuntary movement with a rotating, twisted appearance, which can affect the limbs, torso, and face, and which occurs as Parkinson's disease progresses. Dyskinesia is one of the motor fluctuations.

Dysphagia: difficulty or inability to swallow.

Dysprosody: abnormal prosody. Loss of the "melody" of expression.

Embase: European (Dutch) database produced by *Excerpta Médic*a with content on clinical medicine, pharmacy, and pharmacology.

Idiopathic Parkinson's disease: a description of the classic Parkinsonian syndrome described by James Parkinson.

Rare disease: any disease whose prevalence is less than 5 cases per 10,000 people in the European Community.

Randomized clinical trial: this is a trial design in which subjects are randomly assigned (by chance) to two groups: one (experimental group) receives the treatment that is being tested, and the other (comparison or control group) receives a standard treatment (or sometimes a placebo). Both groups are tracked to observe any differences in the results. This is how the efficacy of the treatment is measured.

***"on"* and *"off"* states**: after using levodopa for several years, many patients develop fluctuating responses to the medication, which can be divided into *"on"* and *"off"* motor states. *"on"* is used to describe when a person is responding optimally to their medication (mainly a response to levodopa). During *"on"* periods, a person can remain active and carry out the activities of daily life with relative ease, even with less rigidity and fewer tremors. Some individuals may experience involuntary twisting movements as the effect of the medication reaches its peak; this is referred to as "on with dyskinesia". *"Off"* is frequently used to describe the period of time in which a person with Parkinson's disease has more difficulty with movement. Activities such as walking, eating, bathing, and even speaking may be impaired during the *"off"* period and there may be non-motor manifestations such as a more depressed mood or fatigue. Patients most commonly experience *"off"* episodes when their medication is losing its effect, just before receiving the next dose. This is referred to as *"wearing off"* (see the corresponding glossary entry).

Phonation: the mechanism for producing sounds with the vocal cords.

Frequency: the number of complete cycles of a periodic process that occur per unit of time. For sound waves, this is the number of times that the pressure variation cycle occurs in one second. The unit used to measure frequency is the hertz (Hz).

Fundamental frequency: the fundamental frequency is the inverse of the period (T_0); e.g. $F_0 = 1/T_0$. For complex sounds such as speed, F0 normally corresponds to the frequency of the lowest harmonic. It is measured in hertz (Hz). The objective of speech therapy is to increase the fundamental frequency of the discourse of the person with Parkinson's because this leads to improved intelligibility.

Clinical practice guidelines: sets of recommendations based on the systematic review of the evidence and the assessment of the risks and benefits of the different alternatives, in order to optimise the healthcare for patients.

Hertz (Hz): Hertz is the unit of frequency. It is expressed in cycles (sound waves) per second.

Hypophony: reduction in the intensity of the voice, its tone, or timbre.

Orthostatic hypotension: by consensus, this is defined as a drop in systolic blood pressure of at least 20 mm Hg or at least 10 mm Hg in the diastolic pressure during the first three minutes of orthostatism.

Intelligibility: the degree of clarity with which expressions are understood by the average listener. It is influenced by the articulation, rhythm, fluidity, vocal quality, and intensity.

Intensity (of a sound): the power of the sound that is propagated through a unit of area of the sound field in a given direction. For example, the intensity of the sound of a point source that radiates spherical waves and with a particular sound power, will decrease as the distance from the source increases, inversely proportional to the square of the distance (1/distance squared). This is a vector quantity, because it specifies both the magnitude and direction, and is therefore not easily measured directly. Acoustic intensity is expressed in watts per square metre, but can also be expressed in decibels (dB). Acoustic intensity is related to the square of the sound pressure, but the exact ratio depends on the characteristics of the sound field.

Confidence interval: this is the interval within which the true magnitude of the effect (which is never known exactly) lies with a pre-established degree of security or confidence interval. The terms "95% confidence interval" (or "95% confidence limits") are often used. This means that the true value would be found in that interval in 95% of the cases.

Orphan drug: any drug that fulfils the following criteria: used in the treatment, prevention, or diagnosis of a life-threatening disease or a disease that results in chronic disability; the prevalence of the disease in the EU must not have more than 5 out of every 10,000 or it must be unlikely that the marketing of the drug will generate sufficient profit to justify the investment necessary for its development; there is no satisfactory method for diagnosing, preventing, or treating the disease in question, or if a method exists, the medication must be highly beneficial for the persons affected by the disease. Orphan drugs are used with rare diseases.

Medline: database that contains the biomedical research citations and summaries managed by the *U.S. National Library of Medicine*.

Meta-analysis: this is a statistical technique that allows the results of different studies to be integrated into a single estimator, giving more weight to larger studies. It is also used to refer to systematic reviews that use meta-analyses.

Monotonicity: lack of variation of both sonority and tone of the voice.

NICE: *National Institute for Health and Care Excellence*. Independent entity of the British NHS (*National Health Service*). Its role is to provide clinics, patients, and the general public with the best scientific evidence available, mainly in the form of clinical guidelines, as well as recommendations related to public health and healthcare technologies.

Sound pressure level: sound pressure is the variation of the average square root of the tension from the static value (for example, atmospheric pressure). Sound pressure is measured in pascals but can be expressed in decibels (dB).

***Odds Ratio* (OR)**: is a measurement of the efficacy of a treatment. If this is equal to 1, the effect of the treatment is not different from the effect of the control. If the OR is greater (or less)

than 1, the effect of the treatment is greater (or less) than the control. Note that the effect that is being measured may be adverse (e.g. death, disability) or desirable (e.g. stop smoking).

Parkinsonism: a clinical syndrome that includes bradykinesia, along with at least one of the following three characteristics: tremors, rigidity, and postural instability. Parkinsonism is a broader, less specific term than Parkinson's disease, and it is used as a blanket term to describe the clinical profile, without specifying the cause. All patients with Parkinson's disease have parkinsonism (or occasionally monosymptomatic tremors), but not all patients with parkinsonism have Parkinson's disease.

PEDro: *Physiotherapy Evidence Database*. A free database on Evidence-Based Physical Therapy, which includes randomized controlled trials, systematic reviews, and clinical practice guidelines for physical therapy.

Period (T_0): the length of each sound wave (cycle) at the time which is referred to as the period of a waveform. This is equal to 1/frequency.

Prosody: the aspect of spoken language that consists of the correct placement of tone and tension on syllables and words. It is responsible for transmitting the subtle changes of meaning that are independent of the words or grammatical order. In addition to the semantic role, it contributes significantly to the emotional content of speech.

Rehabilitation of cognitive functions: an intervention whose object is to improve cognitive function, applying the repeated practice of cognitive tasks or training in strategies to offset cognitive deficiencies.

Systematic Review (SR): this is a review in which the evidence on a subject has been systematically identified, evaluated, and summarized in accordance with a series of specific criteria. It may or may not include meta-analyses.

Relative Risk (RR): the quotient between the rate of events in the treatment group and in the control group. Its value follows the same interpretation as OR.

Sialorrea: excessive production of saliva, which may cause drooling.

SIGN: *Scottish Intercollegiate Guidelines Network*. A multi-discipline Scottish agency that prepares clinical practice guidelines based on evidence as well as methodological documents on their design.

Sonority: in general, sonority is the subjective impression of the level of a sound. However, in objective sonority can be defined as sonority measured mechanically, based on the intensity, sound pressure level, and decibels. Sonority is sometimes used to refer to a measurement of volume.

Cognitive behavioural therapy or cognitive therapy: this is a psychotherapeutic intervention which focuses predominantly on cognitive restructuring, promotion of a collaborative therapeutic alliance and associated emotional and behavioural through a structured framework. Its working hypothesis is that patterns of thought, so-called cognitive distortions, have adverse effects on the emotions and behaviour and that therefore, their restructuring, by means of psychoeducational interventions and continuous practice, can improve the condition of the patient.

Tone: the perceptual correlate of frequency. Normally, the tone of a complex sound is a function of its fundamental frequency. Equal tone levels are virtually equal at the logarithmic levels in amplitude.

Sleep disorders: these include insomnia, excessive daytime sleepiness, hypersomnia, REM sleep disorder, nocturnal akinesia, restless leg syndrome, and periodic movements of the legs.

Volume: the equivalent of the sonority.

Wearing off **(or end-of-dose deterioration or disappearance of the response to the medication)**: this is one of the motor complications of PD. This is the most frequent and earliest form of clinical fluctuation characterized by the reappearance of motor symptoms before the next dosage of medication. It is normally predictable, and is related to the half-life of the medication, meals, etc. However, in some cases it may appear unpredictably and may begin gradually or suddenly.

Annex 4. Abbreviations

CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
AEMPS - CIMA	Online information centre of the Spanish Agency for Healthcare Products and Medications
AGREE	Appraisal of Guidelines for Research & Evaluation
AIMS	Abnormal involuntary movements scale
TCA	Tricyclic antidepressants
QALY	Quality-adjusted life years
BADS	Behavioural assessment of dysexecutive syndrome
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
RDA	Recommended daily allowance
CDS	Cognitive Difficulties Scale in ADL
CE	Cost effectiveness
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CIND-PD	Cognitive impairment no dementia in PD
Cm	Centimetres
COMPASS-OD	Composite Autonomic Symptom Scale, orthostatic domain
COMT	Catechol-O-methyltransferase
CRD	Centre for Reviews and Dissemination
CS-PFP	Continuous scale-physical functional performance test
HRQoL	Health-related quality of life
WTP	Willingness to pay
dB	Decibel
SD	Standard deviation
D-KEFS	Verbal fluency test form the Delis-Kaplan Executive Function System test battery
DLB	Dementia with Lewy bodies
MD	Mean difference
SMD	Standardised mean difference
WMD	Weighted mean difference
AE	Adverse events (effects)
SAE	Supervised aerobic exercise
CT	Cognitive training
RCT	Randomized control trial
SE	Standard error
MST	Movement strategy training
EEHT	Economic evaluation of health technologies
PST	Progressive strength training
GSDS	General sleep disorder scale
EMA	European Medicines Agency
PD	Parkinson's disease
RE	Respiratory exercises
PRE	Progressive resistance exercises
ESS	Epworth subjective sleepiness scale
SSS	Stanford Sleepiness Scale
EQ-5D	Quality of life scale made up of 5 dimensions
VAS	Visual analogue scale
FBF	Flexibility/Balance/Functioning
FEP	Spanish Parkinson's Federation
FRT	Functional reach test
PS	Product sheet or summary of the characteristics of the product
GDS-15	Geriatric Depression Scale 15 items

GWG	Guideline working group
CPG	Clinical Practice Guidelines
H&Y	Hoehn and Yahr
HADS	Hospital Anxiety and Depression Scale
OH	Orthostatic hypotension
HRSD	Hamilton Rating Scale for Depression
Hz	Hertz
CI95%	95% confidence interval
ICSD-2	International Directive for the Classification of Sleep Disorders.
MAOI-B	Monoamine oxidase inhibitor
BMI	Body mass index
CPI	Consumer price index
SNRI	Serotonin–norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
LCIG	Levodopa-carbidopa intestinal gel
L-dopa	Levodopa (enantiomer L –levorotatory- active)
LSVT	Lee Silverman Voice Treatment
m	Metre
MADRS	Montgomery-Asberg Depression Rating Scale
MDRS	Mattis Dementia Rating Scale
mFC	Modified Fitness Counts
min	Minute
MMSE	Mini-Mental State Examination
NEADL	Nottingham Extended ADL
NICE	National Institute for Health and Care Excellence
Nm	Newton metre (units of moment of force or bending moment or rotation moment)
NPI	Neuropsychiatric inventory
NS	Not significant
NUDS	Northwestern University Disability Scale
OR	Odds ratio
P-A	Penetration-aspiration
PDD	PD with dementia
PDE5	Phosphodiesterase type 5
PDQ-39	Parkinson's Disease Questionnaire
PEDro	Physiotherapy Evidence Database
PEG	Polyethylene glycol
PICO	Patient/Population/Problem-Intervention/Indicator-Comparison Criterion-Outcomes/Results
MP	Mental Practice
ICER	Incremental cost-effectiveness ratio
REM	Rapid eye movement
RHB	Rehabilitation
ROCFT	Rey-Osterrieth Complex Figure Test
RR	Relative risk
RRR	Relative risk reduction
SRs	Systematic reviews
SR	Systematic review
VF	Visual feedback
sc	Subcutaneous
EDS	Excessive Daytime Sleepiness
SDQ	Swallowing Disturbances Questionnaire
sec	Second
SEK	Swedish crowns
SF-36	Short-Form Health Survey con 36-ítems
SIGN	Scottish Intercollegiate Guidelines Network
SIP-68	Sickness Impact Profile with 68 items
ANS	Autonomic nervous system

CNS	Central Nervous System
NHS	National Health System
BP	Blood pressure
CT	Conventional therapy
ICD	Impulse control disorders
OT	Occupational therapy
TOL	Tower of London
DRT	Dopamine replacement therapy
IRT	Intensive rehabilitation treatment
UI	International units
UPDRS	Unified Parkinson's Disease Rating Scale
PO	Per os, administered orally
t/w	Times per week
VAST	Video-assisted swallowing therapy
WBV	Whole body vibration
VO2	Oxygen volume

Annex 5. Disclosure of potential conflicts of interest

The following members of the **preparation** group have declared that they have no conflicts of interests:

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