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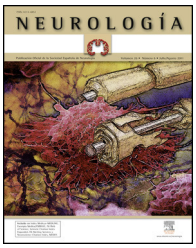

CONSENSUS STATEMENT

Advanced Parkinson's disease: Clinical characteristics and treatment. Part II☆

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KEYWORDS
Advanced Parkinson's disease;
Deep brain stimulation;

Abstract
Introduction: Many patients who have had Parkinson's disease (PD) for several years will present severe motor fluctuations and dyskinesias which require more aggressive therapies. The different approaches which are now available include deep brain stimulation of the subthalamic nucleus or medial globus pallidus, subcutaneous infusion of apomorphine, and intestinal infusion of levodopa—carbidopa.
Objective: To define the indications and results for the 3 available therapies for advanced PD.

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Subcutaneous apomorphine infusion;
Intestinal levodopa—carbidopa infusion

Development: Exhaustive review of the literature concerning the indications and results of deep brain stimulation, subcutaneous apomorphine infusion and duodenal infusion of levodopa/carbidopa gel to treat patients with advanced Parkinson disease.
Conclusions: Although numerous studies have confirmed the efficacy of the 3 different therapies in advanced PD, there are no comparative studies that would allow us to define the best candidate for each technique.

PALABRAS CLAVE
Enfermedad de Parkinson avanzada;
Estimulación cerebral profunda;
Infusión de apomorfina;
Infusión intestinal de levodopa-carbidopa

Enfermedad de Parkinson avanzada. Características clínicas y tratamiento. Parte II

Resumen
Introducción: Muchos de los pacientes con enfermedad de Parkinson (EP) presentan al cabo de varios años fluctuaciones y discinesias graves que requieren de terapias algo más agresivas como la estimulación cerebral profunda del núcleo subtalámico o globo pálido medial, la infusión continua de apomorfina y la infusión intestinal continua de levodopa-carbidopa.
Objetivo: Establecer las indicaciones y resultados de las 3 técnicas disponibles en la actualidad para el tratamiento de la EP avanzada.
Desarrollo: Revisión exhaustiva de los datos publicados en la literatura sobre las indicaciones y resultados de la estimulación cerebral profunda del núcleo subtalámico, infusión subcutánea de apomorfina e infusión intestinal continua de levodopa-carbidopa en pacientes con EP avanzada.
Conclusiones: Aunque existen numerosos estudios que han descrito la eficacia de cada una de estas 3 técnicas, faltan estudios comparativos que permitan definir el candidato ideal para cada una de las técnicas.

Introduction

Available treatments for Parkinson's disease (PD) lessen patients' symptoms considerably in addition to improving quality of life parameters over 5 to 8 years. However, at the end of this period, most patients develop neuropsychiatric complications and motor complications (fluctuations and dyskinesia). In some cases, they may also present significant cognitive impairment that is difficult to manage clinically. At this point, it will be necessary to resort to different treatment strategies; these alternatives are usually effective, although more aggressive than conventional therapy. It is therefore necessary to understand the clinical characteristics defining patients with advanced PD who would be good candidates for certain types of treatment. This article reviews indications for the different therapeutic measures that have been developed for advanced PD.

Treatment for advanced Parkinson's disease

Conventional antiparkinson drugs in advanced Parkinson's disease

In the last few decades, treatment for Parkinson's disease has been a success on par with that of diabetes treatments.[1] However, none of the currently available treatments has been able to modify the natural course of PD. In patients undergoing treatment, PD follows a variable neurodegenerative course that is often unpredictable.[2–5] About 10 years after disease onset (or earlier in some cases) most patients will present significant functional disability, including cognitive decline. This pattern has not changed over the years.[3–5] Treatment for initial or uncomplicated PD is relatively easy, and recent clinical guidelines indicating treatment protocols are available.[6] However, treatment for advanced PD remains a topic for debate, mainly because no consensus has been reached regarding the definition of advanced PD.[2,3] In any case, if we were arbitrarily to adopt the very conservative stance that advanced PD is characterised by the presence of motor complications (and others), and then more than 80% of all patients would fit this description after a decade with the disease.[5]

Conventional treatments

Our aim in this review is to assess conventional treatment for advanced PD.

Levodopa After more than 40 years, levodopa is still the fundamental drug for treating PD. The effectiveness of levodopa has been confirmed by several classic studies,[7–12] and the drug is effective for treating both early and advanced PD. It is interesting to note that the first levodopa trials (with or without enzyme inhibitors) were performed in *de novo* patients with severe PD, and results were unmistakeable.[8–12] Although most of the patients with severe disability registered significant improvement, they also rapidly developed complications. The advent of levodopa treatment resulted in improved quality of life and better survival times for parkinsonian patients.[11]

Dopaminergic agonists Currently available non-ergoline dopamine agonists (ropinirole, pramipexole, rotigotine) are effective for initial PD in monotherapy and also for PD with motor fluctuations when used with levodopa.[6] The mean improvement in daily 'off' time is approximately 2 hours. Strangely enough, this result shows no significant variations across numerous studies with dopamine agonists.[13–22] It seems that currently available oral/transdermal dopamine agonists have a therapeutic ceiling. Dopamine agonists act on motor manifestations of the disease, with robust evidence also confirming that they effectively decrease non-motor symptoms. For example, a recent study shows that rotigotine improves night-time sleep and depression in PD patients. In addition, this transdermally delivered drug seems to be especially useful for certain typical manifestations of advanced PD including atonic seizures, as well as during perioperative periods when the patient's oral intake is compromised.[23,24] Delayed-release oral dopamine agonists (ropinirole and pramipexole) are comparable to standard-release drugs in terms of efficacy. However, their simpler dosages guarantee better treatment compliance.[14–16,19] In any case, scientific evidence underlines that available non-ergoline dopaminergic agonists (ropinirole, pramipexole, rotigotine) are effective treatments for PD with motor fluctuations. None of the agonists has been shown to be better overall than another.

Rasagiline Although there is a tendency to associate rasagiline use with initial treatment for PD, we cannot overlook the fact that this drug has also produced good results in controlled trials in patients with advanced PD.[25,26] Rasagiline is able to reduce 'off' time by a little less than 2 hours, and its efficacy resembles that of entacapone. A meta-analysis from the LARGO study seems to indicate better results for rasagiline than for entacapone on some parameters in advanced PD (gait and postural stability).[25]

Catechol-O-methyltransferase inhibitors The catechol-O-methyltransferase (COMT) inhibitors entacapone and tolcapone have also been shown to be effective as treatment for PD with motor fluctuations. Entacapone reduces 'off' time by approximately 1.5 hours daily.[27,28] Tolcapone is a more potent drug with a more pronounced reduction in 'off' time[29,30] and its effect resembles that of pergolide. Generally speaking, tolcapone has been shown to be superior to entacapone.[31] This is probably due to tolcapone's more complete central and peripheral inhibition of the enzyme. While tolcapone is an excellent drug in many respects, one disadvantage is that patients taking it will require routine analyses to check for liver toxicity.

Considering currently available drugs administered by oral or transdermal routes as adjuvant treatment to levodopa, dopaminergic agonists are probably more effective as a group than enzyme inhibitors (MAO and COMT).[32] Tolcapone also seems to be more effective than entacapone, although it should be used cautiously, as indicated above.

Apomorphine Apomorphine possesses unique characteristics that set it apart from other dopaminergic agonists.[33] As its plasma half-life is very short and the drug is metabolised quickly and extensively, it cannot be delivered by the oral route. Apomorphine delivery may be subcutaneous, intranasal, sublingual, or rectal, to name a few; at present, intermittent subcutaneous delivery is the most well-known route, although it is infrequently used.[33] Subcutaneously injected apomorphine is yet another breakthrough in advanced PD treatment. It is used as a quick and predictable means of managing 'off' periods.[34,35] The drug's greatest drawback is that it can only be used as rescue treatment due to its limited active time (less than 90 minutes). Each patient's minimum effective dose must also be established, which requires time and dedication.

Apomorphine is an excellent drug which nonetheless has seen little use. This may be due to the minor technical complications involved and because it requires more time and skill from the patient.

New treatments for advanced Parkinson's disease New treatment approaches in advanced PD focus on the search for non-dopaminergic strategies permitting control or elimination of motor symptoms or providing a more physiological dopaminergic stimulus. Researchers have studied NMDA glutamate receptor antagonists selective for the NR2B subunit, and non-competitive AMPA receptor antagonists such as talampanel (NCT00036296). Other drugs that act on 5-HT1A and 5-HT2A receptors seem to be effective for dyskinesia control. Researchers have also studied the effect of α2 adrenergic receptor antagonists including JP-1730 (NCT00040209). Adenosine A2 receptor antagonists like preladenant increase dopaminergic activity in D2 receptors, which results in attenuation of parkinsonian symptoms (study NCT01155466). While dopamine reuptake inhibitors have been shown to be ineffective in patients with advanced PD, new dopamine agonist drugs are in the experimental phase of development. Another treatment under study for use in PD patients is transcranial stimulation.

Conventional treatment indications in patients with advanced Parkinson's disease

There are no guidelines to explain or resolve current problems. These include motor symptoms that have not responded to multiple treatments intended to control them, significant freezing episodes that limit daily activities, and non-motor complications, including 'off-time' anxiety attacks that negatively impact both the patient and family members. At this point, the vast majority of PD patients are already taking levodopa and a dopaminergic agonist at optimal (usually maximum) doses. Treatment is also likely to include a COMT inhibitor either with or without levodopa, and patients will probably continue taking rasagiline. Many will already be using pen-injected apomorphine.

While conventional pharmacological treatments deliver limited results, there are a few general rules that may be useful for managing patients with advanced PD.

Increasing the dosage of a dopaminergic agonist already in use is one option, but in practice, patients are likely to already be taking full doses of rotigotine, ropinirole, or pramipexole. Using faster dose titration or larger-than-normal doses of a dopaminergic agonist has had favourable results in some isolated cases of patients with advanced

PD.[36] Nevertheless, augmenting the dose of dopaminergic agonists tends not to be effective because all these drugs are likely to have a ceiling effect. Moreover, any small increases in efficacy are always accompanied by a significant increase in adverse effects.[37] Substituting one dopaminergic agonist for another also seems to be of little use in general, since none of them has been shown to be the best overall.[32] Combining the agonists, as Stocchi et al. suggests,[38] does not have a solid scientific basis, and its effectiveness in clinical practice has not been proved except in anecdotal cases.

Patients with advanced PD often experience a combination of motor and non-motor complications. In addition to motor fluctuations, most will also present some degree of cognitive decline, more or less disruptive behavioural disorders, sleep disorders, pain, and a long list of other symptoms. In cases of advanced PD with multiple motor and non-motor complications, doctors should assess the possibility of *simplifying* the overall treatment rather than adding to it.[39] At times, reducing and simplifying drug regimens will at the very least reduce their adverse effects (drowsiness, confusion, agitation, hallucinations, etc.). Kurlan's observation of is useful for patients with very advanced PD accompanied by significant cognitive impairment.[39]

Doctors have known for years that levodopa solutions may be an option for certain patients with advanced PD whose main problem is marked delay of the digestive process. Digestive system impairment is typical in PD,[2] which may explain the extreme latency of the drug effect observed in some patients ('delayed on'). Levodopa solutions let the drug pass through the pylorus easily and promote quicker absorption.[40–43] These solutions are easy to prepare. First, 10 levodopa/carbidopa tablets (100/25 mg) or 5 levodopa/benserazide hydrochloride tablets (200/50 mg) are ground together with the addition of 1 litre of water and 1 vitamin C tablet. The solution must be preserved in an opaque container or a flask wrapped in dark-coloured paper to avoid the oxidising effect of light. Once the tablets are well dissolved, dosage can be calculated easily by dividing the total amount of levodopa into 8 to 10 doses (the normal dose is usually increased by 10%–20%). This results in a mean dose of 80 to 100 millilitres of solution every 60 to 90 minutes. This regimen is somewhat cumbersome, but it allows some patients to maintain a reasonable level of motor ability throughout the day.

Another option for patients with very advanced PD and variable response to medication may be to take a classic 'break from levodopa' and temporarily substitute the drug with amantadine infusion. Amantadine infusion is not available in Spain, but it seems to be a good option as rescue treatment.[44]

In summary, although conventional treatment is highly effective in initial and intermediate stages of PD, it shows its limitations as the years go by. Many patients with advanced PD require a change in treatment approach, which may involve aggressive techniques including apomorphine infusion, continuous levodopa/carbidopa intestinal infusion, or deep brain stimulation. From a therapeutic viewpoint, PD is clearly considered both a medical and a surgical disease.

Conclusions and recommendations
(Based on the SEN's 2009–2010 clinical practice guidelines for Parkinson's disease)

1. Levodopa is the most effective drug for controlling motor symptoms of PD, and it is effective in both initial and advanced stages.
2. Motor fluctuations and dyskinesias are managed with levodopa through a process of identifying and developing a pharmacokinetic interpretation of the predominant problem. Absorption is subsequently optimised (gastric emptying), and the dosage is adjusted by changing dose amount or frequency. Levodopa transport can be improved by adhering to a low-protein diet.
3. Currently available non-ergoline dopaminergic agonists (ropinirole, pramipexole, and rotigotine) are effective for decreasing 'off' periods in patients with PD and motor fluctuations.
4. Subcutaneously injected apomorphine effectively reduces 'off' period duration in patients with advanced PD.
5. Rasagiline is effective as adjuvant treatment to levodopa in patients with mild to moderate motor complications. Its efficacy is greater than a placebo's and similar to that of entacapone.
6. Entacapone in association with levodopa is effective treatment for advanced PD. It may reduce 'off' time more effectively than levodopa monotherapy (or placebo), and it can be used in non-elderly patients with advanced PD whether or not they experience motor fluctuations.
7. Tolcapone is effective in PD with motor fluctuations and allows use of lower levodopa doses. However, since it causes liver toxicity, it should only be considered for patients with PD and drug-resistant fluctuations, or those who are not candidates for other adjuvant treatments.
8. Amantadine is effective in PD, whether as monotherapy or as an adjuvant treatment. It is able to lessen levodopa-related dyskinesias.

Treatment for cognitive and neuropsychiatric symptoms in advanced Parkinson's disease

Dementia, depression, and psychosis are the most frequent problems in advanced stages of PD. Other neuropsychiatric changes, such as impulse control disorders, anxiety, and apathy, may also be present, and interest in these entities is growing.[45–47] There have been advances in treating these symptoms, but benefits are usually suboptimal.[46] In this chapter, we will review the scientific evidence regarding treatment for these conditions and list some treatment recommendations for normal clinical practice.

Cognitive impairment and dementia

Cognitive impairment in PD ranges from subtle and early deficits (bradyphrenia, difficulty finding words, or mild planning trouble) to developing full-blown dementia. Dementia prevalence in PD is approximately 30%, with an annual incidence approaching 10%.[48] The mean time after which a patient with PD will develop dementia is approximately

10 years.[49] The presence of dementia at disease onset may lead us to suspect dementia due to Lewy bodies or another type of degenerative parkinsonism.[50] The most important risk factors for dementia development include old age, PD severity, postural instability and changes in gait, and baseline mild cognitive impairment.[51,52] The current criteria for dementia associated with PD include the Queen Square Brain Bank criteria for PD and cognitive and functional impairment characterised by changes in at least 2 of the following 4 areas: attention, executive functions, memory, and visuospatial functions.[53] The neuropathological and neurochemical substrate is heterogeneous, although a cortical cholinergic deficit is typical.[53,54]

Treatment for dementia associated with Parkinson's disease

Cholinesterase inhibitors are fundamental for treating dementia associated with PD. A Cochrane Review concluded that these drugs generate significant benefits in 15% of all patients. At present, rivastigmine is the only drug in this group with sufficient clinical evidence to recommend its use.[55,56] A double-blind randomised study of 514 patients with PD and dementia showed significant improvement in both primary and secondary variables. The most frequent adverse effects were nausea, vomiting, and dizziness, which were more common in the rivastigmine group. Some patients treated with rivastigmine experienced changes in tremor, but no statistically significant differences were found between the groups.[55,56] Three double-blind randomised studies have been completed to evaluate the effectiveness of donepezil. All 3 featured small patient samples and results were contradictory. One of them showed a low but significant level of effectiveness, another reported no improvement in the study's primary variable, and the third showed a negative result.[55,57–59] Galantamine was shown to be more effective than placebo in a trial that was randomised but not blinded, meaning that its quality was insufficient.[55,60]

Three clinical trials have examined memantine (an NMDA receptor antagonist) for its efficacy in cases of dementia associated with PD. Two trials also included patients with MCI. Two of these studies yielded negative results, with the third delivering positive results. Since results were contradictory, evidence is insufficient to recommend use of memantine for dementia associated with PD.[55,61]

Conclusions and recommendations

1. The first step to take in cases of PD with cognitive impairment is to discontinue all drugs that may provoke cognitive changes, especially anticholinergic drugs. Doctors should also withdraw tricyclic antidepressants, amantadine, and MAO inhibitors; reduce or suspend dopaminergic agonists (especially if the patient also experiences hallucinations); and adjust the levodopa dose according to the patient's needs.
2. Rivastigmine is the only drug approved in Spain for treatment of dementia associated with PD. It is available in either an oral formulation (initial dose of 1.5 mg/12 h progressively increased to 6 mg/12 h) or a transdermal formulation (initial dose of 4.6 mg increased to 9.5 mg/24 h). The most frequent adverse effects are gastrointestinal problems, which can be reduced considerably by choosing the transdermal route. Apart from eliciting a distinct improvement in cognitive decline, rivastigmine has also been shown to decrease hallucinations.

Psychosis and hallucinations

Psychosis and hallucinations affect approximately one third of PD patients.[62,63] They frequently result from antiparkinson drugs and are usually associated with cognitive decline. Early manifestation of these symptoms should lead us to suspect MCI.[50] Their clinical spectrum ranges from visions or visual hallucinations with preserved insight to delusions and hallucinatory psychoses. Hallucinations are usually visual and well-defined, featuring complex images or concrete situations. In addition, patients often report seeing shadows or feeling presences behind or near them.[63,64]

Treatment for psychosis and hallucinations in Parkinson's disease

The drugs most frequently employed for treating psychosis in PD are the atypical neuroleptics quetiapine and clozapine. According to several controlled studies, clozapine has been shown to be effective in treating psychotic symptoms.[55] The studies performed to date suggest that quetiapine is probably another effective treatment, although some results are contradictory and current clinical evidence is not sufficient to recommend it. Two (partially blind) clinical trials comparing quetiapine and clozapine[65,66] confirmed that both antipsychotic drugs were effective, with one study showing clozapine to be slightly more effective. Other studies evaluating the efficacy of quetiapine compared to a placebo did not report positive results. While clozapine has not been linked to motor symptom exacerbation, up to a third of patients treated with quetiapine experience increased parkinsonian symptoms.[67] The most common side effects are sedation and hypotension. Furthermore, clozapine is associated with a low but serious risk of agranulocytosis (0.385), so patients treated with this drug require routine blood tests. Haematological changes reverse after treatment has been withdrawn.[68] Neuroleptic malignant syndrome is also a risk, and these drugs should therefore be discontinued gradually. Required doses in patients with PD are lower than those for patients with schizophrenia. Other atypical drugs, such as olanzapine or typical antipsychotic agents, are not recommended because they exacerbate parkinsonism.[46,55]

Conclusions and recommendations

1. In patients with acute psychosis in addition to PD, doctors must first rule out intercurrent medical processes (urinary infections, dehydration) and adverse drug effects (caused by dopaminergic or anticholinergic drugs, amantadine, opiates, benzodiazepines, etc.).[69]

   Benign' hallucinations, those that are stable and not disturbing, indicate a high risk of progression to more florid symptoms and should therefore be treated.[70]
2. The first step in treatment is examining the patient's medication and discontinuing any drugs that may induce psychosis. Antiparkinson drugs should be limited,

whenever possible, to levodopa, and other drugs should be withdrawn in the following order: anticholinergics, amantadine, selegiline and rasagiline, dopaminergic agonists, and COMT inhibitors. As a last step, the levodopa dose should be reduced to a minimum.[71]

3. If psychotic symptoms persist despite these measures, we recommend treatment with quetiapine or clozapine.[55] In normal practice, quetiapine is used as the initial treatment because of the risk of agranulocytosis associated with clozapine. Clinical manifestations of delusions or paranoia are more serious than hallucinations and will require more aggressive treatment. Clozapine displays faster onset of action than quetiapine, and it is therefore regarded as the first choice for severe cases. The initial dose of quetiapine is 25 mg and the dose is gradually scaled up to reach 100 or 150 mg. Clozapine is typically started at doses of 12.5 mg and progressively increased to between 50 and 75 mg. Patients taking this drug require regular blood tests.[55]
4. The last therapeutic step would be to consider using rivastigmine, which is a first-choice option for patients with hallucinations and dementia.[72]

Depression, anxiety, and apathy

Depression is one of the most common non-motor symptoms in PD, with a mean prevalence of approximately 40%.[73] Compared to patients with primary depression, patients with PD feel less guilt and are less likely to experience self-destructive or suicidal thoughts.[74] Up to 30% of patients have symptoms of depression before motor problems begin.[46,75] Anxiety and apathy are also common.[47] Anxiety (general anxiety disorder, panic attacks, social phobia) may be associated with onset of 'off' periods, and it tends to coexist with depression.[76] Apathy, which generally appears in conjunction with depression and cognitive impairment, may also present without either of those factors.[77]

Treating depression associated with Parkinson's disease

Studies in animal models suggest that dopaminergic agonists (with affinity for D2 or D3 receptor subtypes) may have an intrinsic antidepressant effect. Pramipexole is the only agonist found by 3 randomised clinical trials to be clinically effective for controlling depressive symptoms.[78]

Selective serotonin reuptake inhibitors (SSRIs) and TCAs are the drugs most frequently used to treat primary depression. Controlled studies of TCAs are scarce, and those that do exist feature small patient samples. Current scientific evidence suggests that nortriptyline[79] and desipramine[80] are probably effective for treating depression in PD. Two studies showed that amitriptyline was effective compared to SSRIs, but as they were not controlled by placebo, evidence is currently insufficient.[81] The most common adverse effects — dry mouth, constipation, and hyperhidrosis — are typical of antimuscarinic drugs. TCAs should be used with caution in patients with a history of urinary retention, narrow-angle glaucoma, or cardiovascular problems. We must also be aware that these drugs may cause sedation and induce psychosis and cognitive decline in patients with dementia. SSRIs are the drugs most frequently used to treat primary depression. Sertraline[79] and fluoxetine have delivered positive results in several studies, while those for citalopram have been contradictory.[81] The current guidelines hold that while SSRIs are probably effective, evidence is not sufficient to recommend that they be used in depression associated with PD. The adverse effect profile is better for SSRIs than for TCAs, but we must be mindful of the fact that they may exacerbate parkinsonian symptoms, especially tremor.[82] There is also a slight risk of serotinergic syndrome if the drugs are used concomitantly with MAO-B inhibitors (selegiline and rasagiline).[83] Elderly patients will present a risk of hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion.[84] At present, studies are insufficient to recommend use of new antidepressant drugs that act on different systems (serotonergic and noradrenergic or dopaminergic, as in the case of bupropion). Other studies have evaluated the efficacy of omega-3 fatty acids, transcranial magnetic stimulation, and electroconvulsive therapy. Current evidence is insufficient to recommend any of these treatments.[55]

Treating anxiety and apathy associated with Parkinson's disease

One study compared immediate-release levodopa to sustained-release levodopa to test each drug's effect on anxiety associated with PD. Anxiety lessened with the immediate-release formulation, and this improvement was positively correlated to the improvement in motor function.[85]

To date, no controlled studies have evaluated the effectiveness of anxiolytic drugs on anxiety associated with PD. Nevertheless, they are routinely employed in PD based on experience with these drugs in primary anxiety and the fact that they are widely used. Studies report that antidepressants are beneficial in cases of anxiety.[86] No studies have evaluated treating apathy in PD either. One observational study found that apathy caused by stimulation of the subthalamic nucleus (STN) responded to dopaminergic agonists.[87]

Conclusions and recommendations

1. There are 2 lines of action in the pharmacological management of depression: dopaminergic drugs and traditional antidepressants. Mood swings and anxiety attacks seem to be related to 'wearing off' episodes and poor motor control, and therefore one course of action is to optimise the patient's motor function.[73]
2. Antidepressants are indicated if symptoms continue after that step has been taken. Based on experience with SSRIs in primary depression and the fact that these drugs have a more favourable adverse effect profile, SSRIs are considered the first line of treatment for depression. Nortriptyline or amitriptyline may be used in cases that are refractory to treatment.
3. In patients with anxiety, doctors must examine the relationship between episodes, 'off' periods, and underlying depression.
4. Doctors of apathetic patients must rule out depression and consider increasing the dopaminergic agonist dosage.

Impulse control disorder

There has been increasing interest in impulse control disorders (ICDs) in PD in recent years. ICDs occur in about 13.6% of all patients with PD, compared to rates between 0.3% and 1.3% in the general population. The 4 most common ICDs are compulsive spending, pathological gambling, compulsive sexual behaviour, and compulsive eating. Nearly 4% of all PD patients are affected by 2 or more of these disorders. Using dopaminergic agonists increases the risk of suffering ICDs by a factor of 2 to 3.5. There are no differences between pramipexole and ropinirole, and no direct relationship has been found between the disorder and the dosage of the agonist. On this basis, it is considered a drug class effect.[88]

Other ICDs or behaviours with obsessive-compulsive traits include dopaminergic dysregulation syndrome (DDS, compulsive consumption of dopaminergic drugs in which a patient increases both dose amounts and frequencies at the expense of exacerbating motor fluctuations and dyskinesias) and punding (repetitive manipulation, organisation, and classification of common items (folding pieces of paper repeatedly, collecting and arranging objects such as buttons or watches). Patients derive a sense of relaxation from these activities and experience irritation and distress when they are unable to complete them. DDS is fundamentally linked to high and frequent doses of levodopa, while punding has been linked to use of dopaminergic agonists as well as to high doses of levodopa.[88]

Treating impulse control disorder in Parkinson's disease

Scientific evidence is currently insufficient to recommend a specific approach to ICDs. Observational studies show that they resolve partially or completely when treatment with dopaminergic agonists is decreased or discontinued.[89] A double-blind, randomised crossover study demonstrated that amantadine improved pathological gambling behaviour.[90] A subsequent study, however, found the opposite to be the case.[91] Deep brain stimulation of the subthalamic nucleus allows patients to experience a good level of motor control while offering the possibility of reducing their dopaminergic drug dosage. Nevertheless, the role of DBS in ICD management is controversial, since studies have described both favourable and unfavourable results. A recent prospective study demonstrated that the drastic reduction of dopaminergic drugs made possible by DBS of the STN was associated with ICD resolution.[92] SSRI drugs, including clomipramine, have not been shown to be beneficial. Atypical antipsychotic drugs and psychotherapy have also been used, with no promising results.

Conclusions and recommendations

1. Patients (and their families) must be informed about the possibility of developing ICDs as soon as they begin treatment with dopaminergic drugs, and every time their doses are increased. Patients tend not to recognise the disorder, so close observation by carers and doctors is crucial.
2. Once the disorder has been detected, doctors should slowly reduce the dose of dopaminergic agonists and even withdraw them completely if necessary. Observing patients closely is fundamental because of their risk of developing dopamine agonist withdrawal syndrome.[93] Maintaining optimal motor control will require raising the levodopa dosage or evaluating other treatment options including DBS or continuous intestinal infusion of levodopa/carbidopa.
3. Another possibility would be to prescribe amantadine, exercising caution.
4. When symptoms are refractory, we recommend working closely with psychiatrists, considering treatment with quetiapine, clozapine, or psychotherapy, and taking such legal measures as are necessary.
5. In DDS cases, levodopa abuse must be prevented by reducing the patient's doses and dose frequency. Patients often do not comply with these recommendations, so limiting their access to medications may also be necessary.
6. High doses of SSRIs lessen obsessive ideation and may be useful for patients with compulsive eating disorders.
7. Treatment with antiandrogens may also be useful in severe cases of hypersexuality.

Surgical treatment for advanced Parkinson's disease: deep brain stimulation

DBS is a widely used treatment for advanced PD. The main benefits and limitations of this technique are listed below.

Clinical efficacy

Motor symptoms Control over motor symptoms is the main treatment objective in patients with PD. Several studies have been published in the medical literature over the last 10 years that examine the efficacy of DBS to the subthalamic nucleus (STN) and the internal globus pallidus (GPi) as treatment for PD. Although studies observed improved motor symptoms after STN DBS, symptoms gradually returned.[94] No studies have specifically evaluated the reappearance of PD motor symptoms after DBS to the GPi, but data from studies in this area suggest that this does occur.[95,96]

Initial studies showed that DBS effectively reduces 'off' times in patients with advanced PD[97] in addition to decreasing dyskinesias associated with chronic levodopa treatment.[98] These studies also indicated that most patients required further drug treatment after DBS, although medium-term studies showed that the required equivalent dose of levodopa after STN DBS decreased by a mean of 55.9%,[99] with reductions of up to 63%.[100]

A German multi-centre study compared the effectiveness of STN DBS with best medical treatment in patients younger than 75 with severe motor complications of PD.[101] The study found that DBS was more effective for controlling PD motor symptoms than the medical treatment.

A multi-centre study from the United States compared the efficacy of GPi and STN DBS to that of best medical treatment. This is the largest series studied to date. This study showed that dyskinesias and principal motor symptoms in PD (tremor, rigidity, and bradykinesia) improved in patients fitted with a neurostimulator.[102] Other studies have delivered similar results.[103,104] In a meta-analysis of 38 short-term studies of centres in an array of

countries, STN DBS was shown to improve rigidity in 63% of the patients and bradykinesia in 52%. When dopaminergic treatment is added concomitantly, these percentages reach 73% and 69% respectively.[105] Randomised multi-centre prospective studies have shown that with regard to PD-linked rigidity and bradykinesia, there are no significant differences in the clinical efficacy of STN DBS and GPi DBS.[106] Studies have reported that GPi DBS also reduces rigidity and bradykinesia as well as STN DBS at 1 to 2 years post-implantation.[96,107]

DBS treatment for PD-associated tremor has been applied to different nuclei. Current targets of choice are the STN,[100] GPi,[108] and the ventral intermediate nucleus.[109]

DBS generally exerts a positive effect on the principal motor symptoms in PD (tremor, rigidity, and bradykinesia), with decreases in dyskinesia ranging from 70% to 90% and a reduction in 'off' periods of 10% to 90%.[96,100,101,104,110,111] Nevertheless, its effects on postural instability and gait are much more variable. A meta-analysis showed that one year after surgery, STN DBS decreased postural instability and short term difficulty walking, with similar results to those delivered by preoperative medical treatment.[112] Another short-term study observed that after STN DBS, medical treatment had an additive effect on postural stability and control over gait.[113] However, some patients may show poor or absent improvement after STN DBS, even in the short term.[110,112]

Over the long term, axial symptoms intensify despite STN stimulation.[100,114] At 5 years after surgery, between 15% and 40% of the patients report walking difficulties that respond poorly to STN DBS.[115] The long-term efficacy of GPi DBS is not as well-documented. Some findings suggest that GPi DBS is less effective for controlling axial symptoms,[103] but a recent meta-analysis reveals that symptoms of postural instability and difficulty walking will improve initially after DBS, whether to the STN or the GPi. These symptoms will then gradually return to pre-surgical levels within 2 years of surgery in the case of STN, but not for GPi.[116] Exacerbation of axial symptoms after surgery has been observed in patients over 70, especially those who already presented gait changes prior to surgery.[117]

Studies with long-term follow up therefore show that postural instability and gait improve after DBS with respect to the baseline 'off' period levels. Nevertheless, scores for these symptoms on the UPDRS motor scale are significantly poorer than those of a medicated patient during 'on' periods. This finding has been interpreted as a manifestation of disease progression which often signals the appearance of symptoms that do not respond correctly to levodopa.[100]

On the other hand, some studies suggest that DBS to the pedunculopontine nucleus (PPN) is beneficial to motor symptoms, especially gait and balance, even though inter-individual variability is considerable.[110,118] Taking this into account, some authors state that PPN DBS at low frequencies (10—25 Hz) may be used in patients with PD and severe axial symptoms that do not respond to pharmacological treatment.[118]

In summary, although there is evidence that gait and balance improve after DBS compared to the unmedicated baseline condition, the degree of improvement may be insufficient, or less than that provided by levodopa. This is especially true in certain groups of patients, such as the elderly, patients with axial symptoms prior to surgery, or those with an incomplete response to pharmacological treatment.

Non-motor symptoms Non-motor symptoms of PD have different clinical manifestations and include cognitive dysfunction, mood swings, hyposmia, autonomic dysfunction, and sleep disorders. These characteristics are often more disabling and resistant to treatment than motor symptoms, and they have a marked effect on the patient's quality of life.[119]

Psychiatric symptoms

The literature contains contradictory results regarding the effect of DBS on psychiatric symptoms in PD.[102,120,121] On the one hand, the largest prospective series do not find significant differences between baseline and postoperative situations with regard to scores on scales measuring psychiatric symptoms. They do report positive effects for anxiety. On the other hand, there are numerous articles on small patient series that point to temporary or permanent effects on mood among patients treated with DBS. Retrospective series have documented increased suicidal tendencies among patients after implantation.[122] Postoperative changes in mood may appear after the electrodes are implanted, and they may be acute and transient or chronic and persistent.[123,124] A retrospective study examined the percentage of suicides after STN DBS in a large series of PD patients and found a 9% rate of suicide attempts, with 45% of those attempts being successful.[122] The number of suicides was higher during the first year after surgery than at any other time. A number of factors (postoperative depression, absent partner, prior history of impulse control disorder or compulsive drug use) were associated with risk of attempted suicide. Social and cultural factors may also play a part in a patient's risk of attempted suicide.[125]

It has been reported that up to 25% of patients undergoing DBS experience apathy. This symptom has been linked to insufficient levels of dopamine after DBS, which leads to deactivation of dopamine receptors in the mesocortical and mesolimbic receptors.[87]

Up to 13% of patients with PD develop an ICD while receiving pharmacological treatment.[88] The effects of DBS on this disorder are contradictory. In most studies, impulse control disorders improved significantly following STN DBS.[126—128] This improvement might be due to the reduction in the levodopa dose, which would decrease stimulation of the mesolimbic dopaminergic circuits.[127] It could also be due to direct inhibition of ascending dopaminergic and serotonergic pathways involved in the reward phenomenon.[128] Nevertheless, some studies show that impulse control disorders have developed after STN DBS in PD patients despite decreases to their levodopa doses.[129] The effects of GPi DBS on ICD have yet to be determined. Postoperative levels of hypersexuality in 2 patients who underwent surgery remained the same as before.[128]

We should stress that most of these studies excluded patients with marked psychiatric problems, and results in the literature could therefore be biased against situations found in normal clinical practice.

In any case, the studies described here show that patients require a specialised psychiatric evaluation before surgery. This step will help identify factors that may indicate tendencies toward developing depressive symptoms, suicidal thoughts, or impulsive behaviours, which in turn lets us determine if surgery is the right choice. Patients at risk should also be subject to close postoperative monitoring. A weighted evaluation of psychoactive medications administered before and after the operation is also fundamental.

Cognitive symptoms

A number of studies have analysed the effects of DBS on cognitive functions.[102,103,130–135] Most have concluded that STN DBS may change areas related to the executive functions and semantic and phonological verbal fluency[136,137] without significantly affecting higher cognitive functions across the board.[138] Changes in verbal fluency and in certain executive functions have been shown to remain constant after 8 years of postoperative follow-up.[139] Comparison of the cognitive effects of DBS to the STN and GPi revealed no differences except for the effects on verbal fluency,[140] as stated above. These changes were more common with STN stimulation than with GPi stimulation.[141] This being the case, DBS seems to be a relatively safe technique over the short- and medium terms. It preserves cognitive function in patients with PD who meet inclusion criteria for surgery.[142] Typical cases for exclusion would be patients with mild to severe cognitive impairment and dementia, among others. Neuropsychological findings from patients evaluated 9 years after STN DBS showed that 29% developed significant cognitive impairment during the follow-up time.[143] This is consistent with the disease's natural history. There are no formal studies evaluating long-term effects of DBS on cognition in patients with PD.

Quality of life In the study mentioned above,[101] neurostimulation had a larger impact on baseline condition than medication alone over a 6-month period. Results measured using a quality of life scale (PDQ-39) showed particularly marked improvement in the areas of mobility, activities of daily living, emotional well-being, stigma, and discomfort.

The study from the United States demonstrated a significant improvement in quality of life parameters among PD patients treated with STN DBS.[102] This randomised, controlled multi-centre study confirmed earlier studies that had shown that DBS performs better than the best medical treatment for increasing motor function and quality of life in patients with advanced PD and poorly controlled motor complications. Nevertheless, benefits of the treatment must be weighed against its potential risks. The study showed a significantly higher rate of adverse events in the group treated with DBS. Patients who underwent DBS also showed slightly poorer cognitive performance in addition to adverse behavioural and psychiatric effects including depression, confusion, and anxiety. Based on the above, it is important to evaluate each patient's risks associated with DBS on a case-by-case basis.

Safety

The most severe adverse events were more frequently associated with neurostimulation than with medication only (13% vs 4%), including a case of intracerebral haemorrhage that caused the patient's death.[101] A retrospective analysis of complications in 180 patients who underwent bilateral DBS of the STN detected surgery-related complications (intracerebral haemorrhage, chronic subdural haematoma, intracerebral infections, and skin erosions) and treatment-related complications (apraxia of lid opening, refractory dyskinesia/dystonia, dysarthria, and neuropsychiatric symptoms).[144,145] Adverse effects in most of these cases are mild and transient, but the low percentages of morbidity and mortality associated with DBS must be taken into account. In addition to the risk of infection and haemorrhage as intraoperative complications, postoperative complications such as deep vein thrombosis or pulmonary embolism may also affect patients who remain immobilised for long periods of time. Local infections in the surgical area near sutures may also arise. Infections are more frequent in the subclavicular or abdominal area where the impulse generator is implanted. Seromas or accumulations of fluid may also be observed in the surgical pocket containing the neurostimulator. One study investigated mortality associated with this procedure in 171 consecutive patients with PD.[146] Their mean age was 57 years and mean disease progression time was 13 years. The mean follow-up period was 41 months. Sixteen patients died within 8 to 83 months of surgery. The mortality rate is no different from the rate in a population of PD patients who did not undergo surgical treatment.

The most frequent complications having to do with implanted devices are migration of cables, infection, and malfunction of certain components. In general, affected patients require further operations to treat such complications.

Patient profile

Some studies have focused on detecting findings that may predict a patient's progress after DBS.[101,102,104,111,147] Baseline response to levodopa has traditionally been considered the most relevant predictive factor.[148] Examining multiple analyses reveals that age is an important predictor of a favourable clinical result. Observations of patients older than 70 indicate that they may experience a decline in multiple clinical areas after DBS, especially with regard to axial symptoms. The risk of developing dementia is also higher among elderly patients.[117] On the other hand, results from the U.S. multicentre study[102] do not support this hypothesis, given that 25% of the patients included in the study were older than 70 and their benefits from DBS resembled those in younger patients. Quality of life also showed the same degree of improvement in both patient groups. Furthermore, this study reported no significant differences between patients older than and younger than 70 with regard to occurrence of severe adverse effects.

It has also been suggested that elderly parkinsonian patients have an increased risk of developing brain haemorrhage, which is a leading cause of mortality associated with surgical PD treatment.[144] However, a retrospective study of a large patient sample did not find significant differences in the incidence rate of severe complications in the immediate postoperative period.[149] Regarding disease progression time and surgery, good surgical results have

been reported in a group of patients with histories of PD exceeding 15 years.[111] Nevertheless, risk of dementia seems to be higher among patients at more advanced stages of the disease.[147]

In light of the above, it may be wise to recommend DBS before the disease elicits signs of cognitive impairment or axial symptoms that respond poorly to levodopa. These symptoms are often more prevalent in patients older than 70 years.[150]

Conclusions and recommendations

Conclusions Based on results from the studies we analysed, the conclusion is that DBS is a useful technique for treating motor symptoms in PD. It effectively reduces 'off' periods and dyskinesia, permits use of lower doses of antiparkinson drugs, and improves quality of life in patients with advanced PD. The technique, which is not without its risks, is linked to a higher frequency of severe adverse events than is the case for conventional drug treatment. All of these factors should be weighed when determining the ideal treatment for each patient.

Recommendations

1. There are specific indications for DBS, including tremor refractory to levodopa treatment.
2. DBS is very useful in treating levodopa-induced dyskinesias.
3. Patients older than 70 are likely to experience higher risks and fewer benefits from DBS, but this claim is controversial and has not been clearly demonstrated.
4. The baseline response to levodopa is the best predictor of short-and medium-term response to DBS, but this is not true over the long term.
5. There are no formal psychiatric contraindications for DBS except for severe depression and active psychotic episodes.
6. Patients who had experienced psychiatric disturbances prior to DBS intervention must be monitored closely.
7. Some patients experience exacerbation of dysarthria following DBS.
8. Gait disorders, freezing of gait, and falls are relatively frequent in some patients who have undergone DBS, which points to a need for better candidate selection for this treatment.

Treatment for advanced Parkinson's disease using continuous apomorphine infusion

Subcutaneous infusion of apomorphine is an accepted therapy for advanced PD. It may also be the treatment requiring the least amount of training for the neurologist, and it is very effective in most cases.

Apomorphine is a dopaminergic agonist with a similar drug potency to that of levodopa. This subcutaneously administered drug has a rapid onset of action and a short duration of between 60 and 90 minutes, although its plasma half-life is somewhat lower at about 40 minutes. It acts primarily on D2 dopaminergic receptors, and to a lesser extent, on D1 receptors.[151] The threshold dose of apomorphine to produce a motor response varies greatly between individuals.

Clinical efficacy

Motor symptoms Continuous apomorphine infusion has been shown to be effective by numerous retrospective and open prospective studies, whether as monotherapy or used concomitantly with levodopa.[152–165]

Authors of most of these studies have observed that improvements in dyskinesias vary. Nevertheless, if we focus on those studies with the most marked improvements, we find that all achieved or aimed for what these studies call apomorphine monotherapy (apomorphine infusion with no concomitant medication and a dose of levodopa or apomorphine bolus in the morning with levodopa taken at night)[155,160] or a minimum daily dose of levodopa.[161,163] The rest of the studies[153,162] and the Spanish study,[165] show a less pronounced decrease in dyskinesias. This was probably due to maintaining concomitant oral antiparkinson drugs in these cases.

The study by Manson et al.[160] compares the reduction in dyskinesias observed in patients treated in monotherapy (apomorphine infusion with no concomitant medication and a dose of levodopa or an apomorphine bolus with a dose of levodopa nightly) with that observed in patients on polytherapy. The authors found a very significant difference that favoured patients on monotherapy (dyskinesia decrease of 60% vs 30%). This study also supports attempting use of monotherapy in patients who are mainly affected by dyskinesias. Reducing concomitant medications is not as important when motor fluctuations constitute the chief problem. This concurs with the Spanish retrospective study[165] which demonstrated a decrease in 'off' time of nearly 80% with a less marked reduction in dyskinesia. To offer further comments on dyskinesias by type, the study by Kanovsky et al.[159] included patients with numerous levodopa-induced dyskinesias: peak-dose dyskinesias, 'wearing off' dyskinesias, biphasic dyskinesias, and dyskinesias during 'off' times. In this study, subcutaneous apomorphine infusion was combined with levodopa. Treatment elicited improvements for all types of dyskinesia, and the improvements continued over the 24-month study period.

Apomorphine is able to reduce 'off' time in patients with advanced PD. For example, Stibe et al. observed a mean decrease in 'off' time of 6.3 hours, which improved 'on-off' oscillations in PD patients.[156] Chaudhuri et al. reported an 85% reduction in 'off' time among their patients.[161]

Non-motor symptoms Most clinical studies of apomorphine did not include an analysis of non-motor symptoms in PD. A recent study[166] includes an analysis of these symptoms and reveals a considerable improvement in non-motor symptoms with respect to the situation prior to apomorphine treatment. The improvement was measured using the Non-Motor Symptoms Scale. Improvement was significant for all domains on the scale except sexual health (cardiovascular, sleep, mood/cognition, perception, attention, gastrointestinal and urinary symptoms, miscellaneous).[166]

Neuropsychiatric symptoms

Apomorphine is a dopaminergic agonist, and as such, it may provoke neuropsychiatric problems (sedation, confusion, visual hallucinations, and psychosis). However, the incidence of these problems is lower for apomorphine than for other oral dopaminergic agonists[151] and frequency also tends to be low.[151,152,154,159]

Hallucinations and psychosis

There have been numerous studies of starting apomorphine infusion treatment in patients with a history of hallucinations[131,161,165,167,168] which were likely secondary to or aggravated by excess of oral antiparkinson drugs.

The study by Chaudhuri et al.[161] reported no adverse psychiatric reactions, even in patients with a history of hallucinations. The Ellis et al. study[167,168] pointed to improvement in the hallucinations previously induced by oral medication when patients began apomorphine infusion therapy. The Sharma et al. study[168] found 15% to 34% decreases in hallucination frequency among patients on apomorphine infusion therapy.

In a study carried out in Spain,[165] 22 of the 82 patients presented hallucinations before being treated (13 mild cases, 8 moderate, and 1 severe). Differences after treatment were not significant: 10 mild and 5 moderate cases with no severe cases.

Stibe at al.[156] did not report psychosis among the cases treated with apomorphine infusion in their study, even though it included 3 patients with past psychotic reactions. The study by Manson et al.[160] indicated that neuropsychiatric symptoms improved, and it also included patients with a history of psychosis. Lastly, Ellis et al.[167] cite a patient with a history of psychotic episodes who improved with apomorphine infusion therapy.

Depression

The percentage of patients affected by both depression and PD is quite high. This symptom is also linked to a poorer prognosis for PD. We must also consider the fact that little evidence is available on this topic.

The study by Manson et al.[160] reports improvement for most patients with neuropsychiatric disorders, especially symptoms of depression. On the other hand, Morgante et al.[163] observed improved mood among patients after 1 and 2 years of follow-up, probably because apomorphine may induce a state of euphoria.

Cognitive symptoms

Patients with cognitive disorders are also difficult to manage. The literature provides little evidence of what effect continuous apomorphine infusion may have on this symptom. A Spanish retrospective study[165] included 82 patients, of whom 27 had a cognitive disorder (19 mild, 7 moderate, 1 severe) before being treated with apomorphine infusion. After treatment, patients experienced a decline that was not statistically significant and may have been caused by the natural course of PD. The study only documents 8 cases of mild delirium, 5 moderate cases, and 1 severe case.

On the other hand, some publications cite no cognitive changes (according to the MMSE) in patients treated with subcutaneous apomorphine infusion and evaluated at the 6-month, 1-year, 2-year, and 40-month marks.[131,163,164,169]

Quality of life One published study points to changes in quality of life among patients treated with continuous apomorphine infusion.[166] The study demonstrates a significant degree of improvement on the PDQ-8 scale in 17 patients treated with continuous apomorphine infusion. Furthermore, patient quality of life during follow-up was better than that in a control group whose PD was treated with oral medication.[166]

Patient profile

Patients included in these studies responded well to levodopa[155] and exhibited dyskinesias (levodopa-induced,[155,158] peak dose,[10] and biphasic dyskinesias,[153] and dyskinesias during 'on' and 'off' periods).[154,159] Symptoms in some cases were described as severe and incapacitating.[155] One of the inclusion criteria for patients in this study was presence of moderate to severe motor fluctuations despite optimised oral treatment.[152,153,155–165] For patients in these studies, the most frequent motor fluctuations were 'wearing off'[153] and 'on-off' episodes.[152–154,156] Studies also included patients with severe 'off' foot dystonia,[154] a history of hallucinations,[156,165] confusion caused by the previous oral drug,[156] or cognitive impairment,[165] as well as patients who were not candidates for surgery or who experienced no improvements with this treatment, and cases from centres that do not offer surgical options for PD.[165]

The mean age of patients in these studies[152–164] is about 60 (51–65 years) but patients as old as 85 were also included. There is no clear age limit for starting treatment with continuous infusion of apomorphine, but treatment should be used cautiously in elderly individuals. Mean disease duration in these studies was 14 years, and mean Hoehn and Yahr stage was 4 (interval 3–5). These figures generally indicate that treatment was started too late, given that some patients were already at stage 5 of the disease. If we examine the 'off' time and percentage of waking hours in 'off' we also see considerable variability. Some patients have 'off' times lasting 9 to 10 hours daily,[152,154,156] that is, half of their waking hours,[158,159,162] while others experience no more than 3 hours of 'off' time daily.

Unlike STN DBS, for which standard indications have been established, there are no consensus criteria for using continuous infusion of apomorphine. The following indications may serve as guidelines for using this drug:

Indications

1. Patients with confirmed PD and a demonstrated response to levodopa.
2. Unmistakeable positive response to the apomorphine test.
3. Patient or caregiver cooperation.
4. Ability to understand the technique, objectives, and side effects.
5. Patients who do not meet criteria for DBS because of their age or cognitive function may be included.
6. No age limits have been established.
7. Moderate cognitive impairment is not a contraindication.
8. Balance disorders during 'on' times are not a contraindication.
9. Treatment does not improve freezing of gait during 'on' times, but it may be used in patients with FOG to relieve other 'off' period symptoms (drowsiness or pain, for example, may respond remarkably well).

Contraindications

1. Patients with PD and hypoventilation, dementia, psychotic disorders, liver failure, allergies, or those younger than 18.[170]

2. The following patients are candidates for subcutaneous apomorphine infusion, although we recommend starting treatment with caution: patients with PD and kidney, pulmonary, or cardiovascular disease; those with a predisposition to nausea and vomiting; elderly patients; patients with a history of orthostatic hypotension; those taking vasoactive drugs (antihypertensives); patients with arrhythmias; and those with neuropsychiatric disorders.[170]

Safety

Since apomorphine is a dopaminergic drug, it often produces typical adverse effects, such as autonomic dysfunctions (nausea, dizziness, orthostatic hypotension, bradycardia), motor symptoms (dyskinesias), or psychiatric symptoms (behaviour disorder, hallucinatory-delirious syndrome).[151,154]

As patients may experience occasional haemolytic anaemia,[151,154] a direct Coombs test is recommended every 6 months. Patients are rarely allergic to this drug.

Subcutaneous nodules are the most frequent complication. While nodules are normally painless, they may result in panniculitis if they become generalised.

The most effective means of controlling nodules are as follows: 1) strict hygiene, 2) not reusing disposable material, 3) using 25G 20 mm butterfly needles with 30 cm tubing and a luer lock connector (screw top), 4) placing needle horizontally with deep penetration at a 45° angle and attaching the butterfly to the body, 5) rotating injection sites and avoiding the periumbilical area, 6) using silicone patches, and 7), applying ultrasound to any nodules that may appear.

Conclusions and recommendations

Conclusions Subcutaneous infusion of apomorphine is indicated for treating advanced PD. If this treatment has been chosen, it should not be delayed once PD has reached the advanced stage. The dopaminergic symptoms it improves may be either motor (wearing off, delayed on, dose failure, random on/off oscillations, off dystonia) or non-motor (swallowing disorders, pain, urinary disorders, and anxiety/panic).

Recommendations

1. There is no need for patients to have used pen injectors before starting this treatment. This is merely an administrative requirement.
2. To start treatment, the patient's result on the apomorphine test has to be positive with no significant adverse effects.
3. The patient requires a minimum of 5 days of domperidone treatment to limit adverse effects before starting apomorphine.
4. There is no established age limit. However, the probability of adverse effects increases with age.
5. The drug can be used with caution in patients with mild or moderate cognitive impairment. It is not indicated in patients with dementia and should also be avoided in cases of severe dyskinesias. It may be used in patients with mild or moderate dyskinesias as long as the response is monitored closely.[151,155]
6. Unlike STN DBS, this treatment can be used in patients with balance alterations or freezing of gait during 'on' periods. While those symptoms will not improve, there are other symptoms that do respond to dopaminergic treatment. Even patients with considerable functional disability may experience marked improvement in sleep disorders and pain, 2 symptoms that may be incapacitating.
7. The patient and the patient's family or carer must cooperate if this treatment is to be used correctly. They must understand the objectives, the anticipated benefits, and the possible complications that may arise and how they might be resolved.

Treatment for advanced Parkinson's disease using continuous intestinal levodopa/carbidopa infusion

More than 2 decades ago, many researchers discovered that the motor fluctuations in advanced PD could be controlled using intestinal infusions of levodopa and that dyskinesias could also be treated to a lesser extent. Although studies showed that a consistent supply of levodopa would be a key factor for preventing motor fluctuations, these researchers did not have a system enabling constant delivery of levodopa by means of an external device. At a later date, Kurlan et al.[171] showed that the same beneficial effect could be achieved by administering levodopa by the intrajejunal route. These 2 findings were the basis for developing CIILC, the new treatment for advanced PD.

Continuous intestinal infusion of levodopa/carbidopa (CIILC) eliminates the erratic gastric emptying seen with levodopa by achieving constant intestinal absorption of the drug. It also reduces the variability of the levodopa plasma concentration.[172] This ensures a stable flow of dopamine to the patient's striatum, which results in increased 'on' time.

Clinical efficacy

Motor symptoms Several published studies have clearly demonstrated that CIILC is effective for controlling motor fluctuations in patients with PD. Results of this treatment for dyskinesia control are more varied. There are 3 randomised level I trials comparing CIILC to oral levodopa therapy.[173] Researchers recently presented results from a randomised, double-blind, double-dummy trial comparing CIILC to oral levodopa in the areas of efficacy, tolerability, and safety.[174,175]

The study by Kurth et al.[176] is a double-blind, placebo-controlled crossover clinical trial comparing oral and duodenal levodopa treatments in 10 patients with PD and motor fluctuations. The levodopa infusion elicited both significant increases in daily 'on' time and significant decreases in daily 'off' time. The Nyholm et al. study[177] is a randomised crossover trial in 12 patients in which the authors compared nasointestinal CIILC to oral route, sustained-release levodopa/carbidopa tablets. The analysis showed that CIILC treatment was associated

with significantly more 'on' time and less 'off' time and dyskinesias than was oral treatment. Randomized Efficacy and Quality of Life Trial[178] is a multi-centre randomised crossover study designed to evaluate efficacy and quality of life associated with CIILC monotherapy. Results showed that CIILC was significantly more effective than optimised oral treatment. Authors reported increased 'on' time with a mean gain of 4.5 hours. Moderate to severe parkinsonian episodes nearly disappeared. Infusion was significantly more effective than oral treatment for limiting 'off' time, but no significant changes were observed for dyskinesias. Furthermore, results from the randomised, double-blind, double-dummy study[174,175] show significant increases in 'on' time (+4.11 h) and decreases in 'off' time (−4.04 h) with respect to the patient's baseline condition.

Several observational studies (of more than 240 patients) have systematically demonstrated that CIILC effectively controls motor fluctuations and improves other efficacy parameters, including UPDRS and quality of life scores, compared to the conventional treatments used before.[179–187]

Of the crossover studies, only the study by Nyholm et al.[177] describes better control over dyskinesias for CIILC than for oral treatment. The other studies did not find any significant changes. Observational studies revealed varying degrees of improvement for disabling dyskinesias, depending on how those dyskinesias were measured.

Non-motor symptoms Several clinical studies have evaluated the effect of CIILC treatment on non-motor symptoms of advanced PD.

The prospective observational study by Honig et al.[185] found a significant increase on the Non-Motor Symptoms Scale total in patients treated with CIILC. Areas showing significant improvements were as follows: cardiovascular symptoms, sleep/fatigue, attention/memory, gastrointestinal tract, urinary symptoms, and miscellaneous (including pain, weight loss, and excessive sweating). The mood/cognition, perceptual problems/hallucinations, and sexual function sections showed improvements that were not statistically significant. Researchers specifically evaluated sleep in 13 of the 22 patients using the Parkinson's disease sleep scale and found a significant improvement. One retrospective study[187] describes improved non-motor symptoms in 83% of the patient sample. Another retrospective study of 91 patients has also described improvements for more specific non-motor symptoms including pain, dysphagia, and dysarthria.[188] A recent study showed that 24-hour infusion was a viable means of controlling night-time symptoms in selected cases.[189,190]

Other studies describe psychiatric symptoms. The observational study by Eggert et al.[182] indicates that 6 of the 7 patients who had psychiatric symptoms (psychosis) before treatment remained stable with no recurrences or exacerbations. There have also been cases in which cognitive function and MMSE scores improved with CIILC treatment.[191] Nevertheless, the effect of CIILC on cognitive treatment and psychiatric symptoms must be evaluated prospectively in clinical trials that include these symptoms as efficacy variables.

Quality of life Multiple clinical trials and publications have reported an improvement in quality of life associated with CIILC treatment.[175,178,181,184,185,187,192–194] Other observational studies also report sustained improvement in quality of life over 14 and 18 months with significantly lower scores on PDQ-39 and better functional ability as measured by the Schwab & England scale and the Activities of Daily Living scale.[184,187]

The reduction in burden and stress for the carers of advanced PD patients was assessed in a recently published article. This observational study describes a significant decrease in the scores on the Zarit Caregiver Burden Interview and Caregiver Strain Index. These scales correlate significantly with improvements in quality of life for the patients.[195]

Safety

Adverse effects of levodopa Estimates indicate that more than 3200 patients have been treated with CIILC to date.[196]

The review by Nyholm et al.[197] included 65 patients treated with CIILC between 1991 and 2002 with a mean treatment duration of 3.7 years and a maximum of 10.7 years. The review showed that CIILC's drug safety profile resembled that of oral levodopa. Dyskinesias were listed as the most common adverse effect at treatment onset and after 1 year of follow-up. They also listed the following adverse drug events: psychiatric disorders including anxiety, depression, hallucinations, and confusion; and disorders associated with PD, such as dystonia and freezing of gait. The 7 recorded deaths were not related to treatment. There are also published cases of biphasic dyskinesias (end-of-dose dyskinesias) that are refractory. Some have led to CIILC treatment being discontinued.[184,198]

Some authors cite low rates of psychiatric complications after starting CIILC, even in patients with very advanced PD and cognitive impairment or a history of psychosis associated with dopaminergic drugs,[182] and even when equivalent doses of CIILC exceed doses used in oral combination therapy.[188] This finding may have to do with the fact that CIILC is used in monotherapy, meaning that dopaminergic agonists or other antiparkinson drugs associated with the appearance of psychiatric complications may be discontinued.[198]

A possible complication of treatment with CIILC is development of peripheral polyneuropathy.[186,199–202] This condition has been described in patients on long-term treatment with high doses of oral levodopa, and it may be associated with increased levels of homocysteine and decreased cobalamin metabolism.[203] Polyneuropathy has been described in some patients treated with CIILC, and while its cause is still unclear, most patients improve upon being treated with cyanocobalamin supplements. There is a published case of a patient experiencing severe depression and suicidal thoughts who did commit suicide while being treated with CIILC.[204]

Adverse effects of the infusion system Infusion system complications are the most common adverse effects of this treatment. They may be related to PEG or

percutaneous endoscopic gastrostomy, (duodenal ulcer, granuloma, abdominal pain, stoma infection) or to the infusion device (broken external connectors, migration of the internal line or line kinking that may result in the line having to be moved or replaced, or damage to the perfusion pump). Granuloma and complications related to the device are the most frequently observed problems, and Nyholm et al. detected them in 69% of the patients they reviewed.[205] A similar percentage (63%) is cited in a retrospective study that aimed to assess drug safety and tolerance in a sample of 91 patients who began CIILC treatment between 2003 and 2007.[188] These complications result in frequent visits to the doctor and numerous radiology and endoscopic studies. Although such complications are easy to manage, there are published cases of complications involving PEG and a duodenal tube.[206]

The cited frequency of peritonitis after a PEG procedure is 4.3%.[188] This complication has resulted in treatment being discontinued in 1 case only. Prophylactic antibiotics are recommended after PEG to prevent peristomal infections.[207,208] At present, most protocols for using CIILC cite this recommendation.

Patient profile

The most recent version of the Spanish Society of Neurology's official guidelines for diagnosing and treating Parkinson's disease (2009)[6] includes only a single recommendation for either CIILC or apomorphine infusion in patients with advanced PD and motor fluctuations. However, it does specify indications and contraindications for DBS.

While descriptions of candidates for each of the 3 types of treatment are similar, no studies have directly measured the safety and efficacy of all 3 treatments. For this reason, the criteria for indicating which treatment alternative is best for which patient have not been established.

Some authors state that surgery has clear contraindications while CIILC is available to a wide variety of patients with advanced PD. Specifically, old age, mild to moderate cognitive impairment, psychosis or depression, and anxiety do not contraindicate CIILC therapy.[209]

The consensus guidelines for CIILC use published in 2008 by the Danish Movement Disorder Society and the Swedish Movement Disorder Society state the following: CIILC is recommended for patients with advanced PD and motor complications who continue to present severe symptoms needing advanced treatment despite optimised oral or transdermal therapy. These guidelines suggest that CIILC be considered for the following specific situations or groups: 1) patients experiencing long and/or frequent 'off' periods or severe dyskinesias despite optimal oral treatment; 2) patients for whom DBS or apomorphine infusion are contraindicated, ineffective, or inappropriate; 3) elderly patients, since there are no age limits for CIILC; 4) and patients with severe sleep disorders despite oral treatment who might benefit from 24-hour treatment with CIILC. Severe dementia was considered a relative contraindication, while moderate or mild dementia were not.[210]

Treatment with CIILC may also benefit some patients with a wide array of motor complications, including freezing of gait, festinating gait, or 'off' period dystonias, but its efficacy in these areas is not yet fully demonstrated.

Axial symptoms such as altered balance, dysphagia, and freezing of gait do not appear to respond well to CIILC, although further studies are needed to analyse these variables systematically.

Conclusions and recommendations

Conclusions Based on results published in the literature, CIILC is effective for controlling motor fluctuations in patients with advanced PD. It significantly reduces 'off' time, and this decrease remains stable over the long term.

While the number of randomised studies supporting these results is still low, we can state that CIILC probably reduces incapacitating dyskinesias. The total time a patient experiences dyskinesia tends to decrease or remain stable. This probably occurs in conjunction with longer 'on' times with mild or moderate dyskinesias that are well-tolerated and often underestimated. Except for a minority of patients for whom dyskinesia is the most prominent symptom, patients maintain good long-term control over symptoms.

Published data indicate that treatment with CIILC improved some of the non-motor symptoms in advanced PD, especially those associated with 'off' periods.

In patients with advanced PD, CIILC increases quality of life globally and continuously over time. Improvements are especially noteworthy in the areas of mobility and activities of daily living. The treatment probably also contributes to increasing emotional well-being and reducing discomfort.

Furthermore, the potential lessening of carer burden is a substantial advantage, considering that most patients undergoing CIILC require some degree of supervision.

The studies we revised indicate that the CIILC's adverse effect profile seems similar to that of oral treatment, and that CIILC presents the potential advantages associated with monotherapy. CIILC is generally well-tolerated despite the complications associated with the infusion device.

Recommendations

1. Generally speaking, CIILC is recommended for treating complicated advanced PD with motor fluctuations and dyskinesias that are responsible for major functional impairment and that do not respond correctly to conventional treatment.
2. There is no set age limit for this therapy.
3. In patients with advanced PD and psychiatric symptoms, psychosis is not a contraindication, particularly in cases in which psychosis is related to use of dopaminergic drugs.
4. Regarding patients with advanced PD and cognitive complications, advanced dementia is a contraindication while mild to moderate cognitive impairment may not be. In these cases, carer assistance will be necessary.

5. Although CIILC's main indications do not include controlling non-motor symptoms and sleep disorders, the treatment can be used in certain cases.
6. The presence of axial symptoms, including balance impairment, dysphagia, freezing of gait, and intense dyskinesias, does not necessarily indicate CIILC, and patients' response to treatment may be variable.
7. Most patients undergoing this treatment require some degree of care or supervision.
8. We recommend changing the infusion device every 18 to 24 months to prevent potential complications that become more frequent as devices age.
9. We also recommend forming a multidisciplinary team that includes an experienced endoscopy provider and a nurse specialised in PD for proper management and follow-up on complications.
10. Results from CIILC treatment may be improved by selecting patients well according to age, lack of psychiatric or cognitive complications, and good functional ability in 'on' times prior to the intervention.

Non-pharmacological treatments for advanced Parkinson's disease

Treating advanced PD will probably require input from physical, speech, and occupational therapists.[211–213] However, these resources tend to be indicated infrequently or late, if at all. Patients with PD may benefit from treatments spanning a wide range of healthcare disciplines. The purpose of such treatments is to increase independence and improve well-being. Non-pharmacological treatments include physiotherapy, occupational therapy, speech and dysphagia therapy, and others. Both the treatments and the professionals providing them vary considerably. Furthermore, means of measuring progress are even more diverse, and on occasions it may be difficult to gauge and ascertain whether the PD patient has experienced any significant changes. Lastly, studies in these areas typically do not mention the patient's drug treatment (not to mention dosages). They do tend to indicate what therapy was provided to patients during 'on' periods.[211–214]

Physiotherapy

Physiotherapy includes stretching, walking, and using conventional exercise machines, especially treadmills. Its purpose is to maximise the patient's functional and social abilities. For patients with chronic diseases like PD, physiotherapy is generally considered an active and continuous treatment programme that should be personalised and revised periodically. Physiotherapy includes both patient education and following up on activities intended to maximise the patient's aptitudes and abilities, such as specific exercises for improving mobility and preventing falls in PD, and exercises intended to improve respiratory function or reduce pain. The principles behind physiotherapy are applying a customised plan of specific activities, using reliable and practical assessment instruments that identify and follow up on treatment priorities, identifying impairment and the right intervention for treating it, using therapies aimed at restoring or compensating for lost function, and fostering patient and carer participation in the decision-making process and in management strategies.

How effective is physiotherapy compared to standard treatment for patients with PD? We located 9 studies[215–223] including a total of 271 patients. One of these is a substudy[223] of another in the group.[218] Since their methods vary greatly and assessment data are presented in questionable ways at best, reaching clear conclusions is a difficult task. In studies employing timed walking tests to assess mobility, patients improved with a routine of stretching and walking on a treadmill during three 40-minute sessions during 8 weeks[216] or 6 weeks.[217] Another study used similar exercises on a level and downward-sloping treadmill, and while its results were significant, effects had vanished 4 weeks after sessions ended.[221] Another study[223] showed no improvement in the distance covered by the patient in 2 minutes, but the study has little value because of lost data. The same study is based on a more ambitious project[218] evaluating 3 groups of patients: 1 control group and 2 patient groups engaging in intense or moderate exercise. The main variable, which was the PDQ-39 score, improved significantly in the treatment groups. Beneficial effects remained 6 months after treatment, and they were most apparent on the communication and mobility subscales. Another study assessed 60 patients divided into 3 groups. The first group performed a wide range of vigorous exercises; the second did Nordic walking and similar exercises (16 sessions in 4 weeks), and the third received instructions to do hour-long exercise sessions at home. These exercises were also performed by the other 2 groups.[219] According to video assessments, there were significant improvements in the UPDRS-II score for all 3 groups. Three studies focused on falling and freezing of gait. In a study of 142 patients during a 6-month period, patients were instructed to perform unspecified exercises at home. Instructions were reinforced by telephone calls and home visits by specialised nurses.[215] While the number of falls remained unchanged, near-falls decreased. In another study of 48 patients over 6 months, exercises also had no effect on the number of falls, but they did improve the score on the Freezing of Gait questionnaire.[220] Lastly, we find the Goodwin et al. study[222] of 130 patients with PD who had fallen at least twice in the past year. Half were treated with physiotherapy over 10 weeks to improve their strength and balance. Once again, there were no differences in the number of falls (the main variable), but there were differences in secondary variables.

Conclusions and recommendations

1. Data show that physiotherapy has a positive effect as adjuvant treatment for PD. Since the quality of these studies is low overall, new studies are needed to confirm their findings. It would be useful to know which types of physiotherapy interventions are effective in the different stages of the disease. In addition to this evidence, diverse expert groups advocate physiotherapy for patients with PD.[211]

2. Physiotherapy should be made available to people with PD, and its objectives must be the following:
   - Rehabilitating gait and improving balance and flexibility.
   - Improving aerobic capacity.
   - Improving 'start hesitation'
   - Improving functional independence, including mobility and activities of daily living.
   - Providing expert advice regarding safety in the home.

Occupational therapy

The main goal of occupational therapy is to enable patients to participate in routine activities. Referral to an occupational therapist may let patients with PD improve their abilities, prolong independence as much as possible, and develop their own strategies for facing new challenges.

The principles of occupational therapy are as follows: 1) Early intervention to establish a good rapport and discontinue activities or functions that have been limited or lost, developing good strategies to compensate for losses when necessary. 2) Treatment focusing on the patient and caregivers. 3) Aiming for specific objectives and ensuring that they are met. 4) Using a wide range of interventions to address physical and psychosocial challenges and increase the patient's involvement in such activities of daily living as personal care, mobility, transfers, domestic tasks, and family, work, and leisure activities. Since this therapeutic process is personalised, it provides counselling, training, cognitive, and sensory strategies for problem-solving, and equipment and devices allowing patients to adapt to their surroundings.

How effective is occupational therapy for PD management compared to standard medical treatment?

The Cochrane review[212] found 2 parallel-group randomised trials containing a total of 84 subjects ($n = 64$ and $n = 20$).[224,225] There were no significant differences in methodology between the studies. In 1 study, patients received 20 hours of treatment over 5 weeks with a year of follow-up; in the other, they received 12 hours of treatment during a month with no follow-up. Only the first study demonstrated positive effects at the 1-year mark, i.e. better scores on the Barthel index and Activities of Daily Living scale. In addition to its methodological limitations, one study was only published as an abstract.[225] The review concludes that considering the methodological shortcomings of the trials, and their small patient samples, evidence is not sufficient to support occupational therapy as an effective treatment in patients with PD. However, it does support the benefits offered by several aspects of this treatment, especially regarding the assistance and adaptations provided so that people with PD are able to prolong their functional independence. Evidence is based on improvements in daily living activities in the experimental group and the decline in the control group at the 1-year mark in a single study.[224] Further trials are needed to assess the role played by different factors in occupational therapy.

We located 11 studies published since 2007. One study, which has already been mentioned, evaluates a combination of physiotherapy and occupational therapy; assessing the treatments separately is not possible.[218] The others focus on using cueing or sensory training to improve gait in PD.[226–234] Two of them[227,228] are substudies of the RESCUE trial,[226] the most ambitious of the studies we reviewed; the study by Lim et al.[229] is similar to RESCUE. Viewing these studies as a whole, there are either no differences between the experimental and control groups, or else differences are very small and do not persist over time. It seems that using cues and sensory training may improve gait, but the effect is not sustained. This indicates that the treatment either has a ceiling effect, or that it should be continued on a long-term basis, which is a more likely interpretation.

Conclusions and recommendations

According to the NICE[211] guidelines, occupational therapy should be made available to patients with PD. Therapy should stress the following aspects:

1. Maintaining workplace and family roles and the ability to engage in domestic tasks and leisure activities.
2. Improving and maintaining transfers and mobility.
3. Improving personal care and such tasks as eating, dressing, and washing oneself.
4. Modifying the patient's surroundings for better safety and motor function.
5. Using cognitive function to focus attention in order to improve gait, overcome freezing of gait, and prevent falls.

The American Academy of Neurology lists the following types of physical therapy as being useful in PD: multidisciplinary rehabilitation with standard physiotherapy and occupational therapy; treadmill training; using visual, auditory, and tactile signals; and music therapy. While functional improvements gained through these interventions are slight and their benefits are limited to the treatment period, many patients enjoy a long-term increase in self-confidence and better control over their bodies.[235] Keus et al.[236] proposed 6 key areas for physiotherapy: transfers, posture, reaching and grasping, balance, gait, and physical capacity. Using evidence from 2 or more controlled clinical trials as a their criterion, they also identified 4 effective intervention methods: cueing strategies to improve gait, cognitive movement strategies for better transfers, specific exercises for improving balance, and training joint mobility and muscle strength to increase physical capacity.

The Royal Dutch Society for Physical Therapy published clinical practice guidelines for PD that list 6 indications for referring a patient to physiotherapy.[237] 1) Limits on activity or impairments affecting any of the following: transfers, posture, reaching and grasping, balance and gait; 2) decreased physical capacity; 3) increased risk of falls or fear of falling; 4) increased risk of pressure sores; 5) limitations secondary to neck and shoulder rigidity; and 6) needing information about consequences of PD, especially its effects on posture or movement. These guidelines also state that the duration and frequency

of physiotherapy sessions will depend on the patient's individual requirements. If the patient achieves an activity's proposed goals, or does not experience the benefits that were expected at onset, then that particular therapeutic activity will be dropped from that patient's list of rehabilitation exercises. Likewise, if the physiotherapist finds the patient capable of reaching the established goals alone, therapy may continue without the professional's direct supervision if the referring doctor agrees. These guidelines recommend a therapy duration of at least 4 weeks to decrease limitations on daily life activities (especially those in the home) and 8 weeks of exercise to improve physical capacity. The patient will need weekly check-ups to adjust the prescribed treatment programme.

Other techniques

A number of published studies have compared different types of exercises and activities ranging from tai chi[238] and qigong/chi-kung[239,240] to ballroom dancing[241,242] or acupuncture.[243] One crossover study comparing qigong to aerobic exercise (cycling), found no differences between groups performing each exercise.[239] In the other study comparing a qigong group to a control group, initial differences disappeared over time.[240] The study that compares a tai chi group to a control group with no treatment[238] cites favourable results for the tai chi group as measured by the motor section of the UPDRS and the Berg Balance scale. Nevertheless, it seems that these differences may already have been present at the baseline visit. In a recent study, 195 patients with PD were randomly placed in 3 groups to do tai chi, resistance training, or stretching exercises.[244] The main study variable was change on a stability test scored from 0 to 100%; secondary variables were gait measurements, the Timed Up and Go test, UPDRS score, and number of falls. The tai chi group showed better results than other groups on the stability test. Its results for all secondary variables were better than the stretching group's results only. The acupuncture study is somewhat unusual. It compares 4 groups receiving the following: acupuncture plus an unspecified herbal drink, acupuncture only, the herbal drink only, and a control group. No differences were observed.[243] Lee et al. completed a systematic review of acupuncture in PD[245] and found that the quality of the trials was too low for the review to reach firm conclusions. To all practical effects, acupuncture should be considered a treatment which is still under study in PD. A ballroom dancing study compared patients dancing tango alone or with a partner and found no differences, although baseline balance scores improved in both groups.[241] Another study found no significant differences between patients dancing tango or foxtrot, although both dancing groups differed from the control group and study parameters showed more improvement in the tango group.[242]

Speech therapy

Dysarthria is common in PD, and it tends to worsen as the disease progresses. It is characterised by monotonous speech tone and volume (dysprosody), native accent loss, imprecise articulation, speech variations that produce inappropriate pauses or hurried speech, and a breathy tone (hypophonia). All of these symptoms reflect the patient's difficulty coordinating speech and breathing. Many of these traits are attributed to bradykinesia and rigidity. Two studies, published a decade ago, aimed to improve vocal volume using strategies that included Lee Silverman Voice Therapy, a course of treatment specifically developed for patients with PD.[246,247] Despite having some methodology flaws and a small patient sample, the study demonstrated significant differences that could still be observed 2 years after treatment had ended.[247] As a result, the Cochrane review,[248] the NICE guidelines,[211] and more recent reviews[212,249] all recommend this programme as speech therapy in PD. In any case, each of these reviews highlights the poor quality of the evidence and the need for further research in this area. Other considerations in the area of speech and language therapy for patients with PD include the following: teaching strategies for optimising intelligibility; ensuring effective communication as the disease progresses; and assessing swallowing efficiency and safety to minimise the risk of choking.

Dysphagia

One study compares a group engaging in daily 20-minute sessions over 4 weeks intended to increase expiratory muscle strength to a control group practising a sham technique.[214] Researchers examined the swallowing safety scale and the videofluoroscopy results and found significant differences between the groups. This study supports using the technique to manage dysphagia in PD.

Nursing care

The role of nursing staff at both primary care and specialist care levels is not limited to medical care, but also covers help with communication, support for the patient and carer, management of symptoms and medications, and education at different care levels. In general, these professionals provide patients and carers with counselling and training in various aspects of the disease, and monitor patients' quality of life. Other activities address patients' physical problems (decreased mobility, impaired verbal communication or swallowing, pressure sore care, managing bowel and urinary incontinence, and self-care) or psychological problems (depression, anxiety, fear, cognitive decline, coping, and family support). Lastly, other interventions have to do with social or family problems (contact with family, home visits, etc.).[211]

Palliative care

The World Health Organization defines palliative care as the approach that improves quality of life for patients and families facing the problems associated with life-threatening illnesses. Its measures focus on the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other physical, psychosocial, or spiritual problems.[213] Palliative care includes palliative management of motor and non-motor complications by identifying, evaluating, and tending to physical, psychological, spiritual, and social needs in the context of end-of-life care. It requires cooperation among professionals representing all of the disciplines involved. Prognosis-indicating guidelines help

identify those patients who are reaching the end-of-life stage.[250] Some of the criteria suggesting that a patient with PD may begin to need palliative care are as follows[211]:

- Lack of response to medication.
- Decreased independence and needing help for activities of daily living.
- Lack of predictability for 'off' periods.
- Presence of dysphagia, stability problems, freezing of gait, and falls.
- Severe dementia.

Palliative interventions should also be designed to meet needs that go beyond medical care, including patient safety, concerns about dependence, and the material and moral issues that affect transcendent decisions in this stage of life.[251–254]

In the final stages of the disease, specific objectives for caring for patients with PD include the following:

- Relieving the patient's symptoms and the patient's and carer's distress.
- Preserving the patient's remaining dignity and functions despite the advanced stage of disease.
- Preventing treatment-related complications.

Palliative care programmes may offer carers support and training and they are intended to prevent caregiver syndrome.

Applicability of non-pharmacological treatments in our setting

The Spanish national health system's list of services does not include continuous rehabilitation for chronic illnesses (although there are a few exceptions). In general terms, non-pharmacological treatment for PD is not provided by the public health system. Patients must resort to patient associations or private organisations. Doctors may recommend adhering to a healthy diet and engaging in physical exercise. They can also provide aids to mobility such as walking canes, walking frames, or wheelchairs and anti-decubitus mattresses for patients in advanced stages. Assistance from a trained nurse is rarely available. However, this is also the case even in neurology departments specialising in care for patients with movement disorders. Social workers and assistants can provide day care and home modifications, in addition to filling out claims for disability and dependency status. Palliative care is normally available to a large majority of the population. It is typically excellent and reaches patients in moments of pronounced distress as they reach the final stage of PD.

Conclusions and recommendations

1. Non-pharmacological treatments may improve quality of life for patients with PD. Despite the fact that good-quality evidence is not available, we recommend physiotherapy and occupational therapy to improve the following:
   - Balance and flexibility
   - Mobility
   - Starting movement
   - Functional independence
   - Awareness about safety in the home
2. Tai chi may increase balance in PD patients.
3. The Lee Silverman Voice Therapy technique is helpful for patients with PD.
4. Treatment designed to improve respiratory muscle strength reduces dysphagia in PD patients.
5. Nurses specialising in PD care and palliative care programmes may offer valuable support to the patient and those close to him or her.
6. Lastly, to determine which treatments are the most appropriate, doctors need additional good-quality studies that take into account the natural fluctuations present in advanced PD.

Conflicts of interest

The authors have no conflicts of interest to declare.

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