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Treatment of advanced Parkinson's disease

Juan C. Giugni, M.D and **Michael S. Okun, M.D.**
Departments of Neurology and Neurosurgery, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, FL

Abstract

Purpose of the review—Later stage Parkinson's disease (PD), sometimes referred to as advanced disease, has been characterized by motor complication, as well as by the potential emergence non-levodopa responsive motor and non-motor symptoms. The management of advanced stage PD can be complex. This review summarizes the currently available treatment strategies for addressing advanced PD.

Recent findings—We will discuss the latest pharmacological strategies (e.g. inhibitors of dopamine-metabolizing enzymes, dopamine agonists and extended release dopamine formulations) for addressing motor dysfunction. We will summarize the risks and benefits of current invasive treatments. Finally, we will address the current evidence supporting the treatment of non-motor symptoms in the advanced PD patient. We will conclude by detailing the potential non-pharmacological and multidisciplinary approaches for advanced stage PD.

Summary—The optimization of levodopa is in most cases the most powerful therapeutic option available, however medication optimization requires an advanced understanding of PD. Failure of conventional pharmacotherapy, should precipitate a discussion of the potential risks and benefits of more invasive treatments. Currently, there are no comparative studies of invasive treatment. Among the invasive treatments, deep brain stimulation has the largest amount of existing evidence, but also has the highest individual per patient risk. Non-motor symptoms will affect quality of life more than the motor PD symptoms, and these non-motor symptoms should be aggressively treated. Many advanced PD patients will likely benefit from multi- and interdisciplinary PD teams with multiple professionals collaborating to develop a collective and tailored strategy for an individual patient.

Corresponding Author: Michael S. Okun, M.D., 3450 Hull Road, Gainesville, FL 32607, 352-294-5400, FAX 352-273-5575, okun@neurology.ufl.edu.

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Keywords

Parkinson's; deep brain stimulation; medications; behavioral; selection criteria

Introduction

Despite the availability of medical and surgical treatments that improve PD motor symptoms, the disease will in the majority of sufferers lead to progressive disability (1). Progression in later stages is characterized by motor complications inclusive of fluctuations and dyskinesia (2). As PD progresses there is an emergence of a symptom constellation that may be non-responsive to levodopa. This resistant symptom complex includes postural instability and falls, speech and swallowing difficulties, and non-motor symptoms (NMS) (3).

Hoehn and Yahr suggested that the mean time of PD progression to disability was seven years in the pre-levodopa era (4). However in the post-levodopa era, the mean time from disease onset to wheelchair-dependence was fourteen years (5). PD progression has been universally associated with increased disability and a diminished quality of life (QoL) (6–8).

Advanced PD is commonly defined by clinicians as stage 4 and 5 on the Hoehn and Yahr scale (4). Other authors have suggested as an alternative definition that the onset of motor complications is a more reasonable description of advanced disease (6, 9, 10). Additionally, the older definition does not differentiate PD patients who develop levodopa resistant symptoms, and those who become highly dependent on caregivers (11). In this paper we will define advanced PD as the onset of motor complications, despite aggressive pharmacological and behavioral management. We will not exclude patients with NMS and/or levodopa resistant symptoms. We will present an evidence-based review of current treatment options for the management of motor and non-motor complications of advanced PD. (Figure 1)

Treatment of motor complications

There are several potential mechanisms involved in the development of motor complications. These mechanisms collectively lead to a narrow therapeutic window where low plasma and striatal levels of dopaminergic drugs will lead to OFF periods, and high levels will lead to an increase in peak-dose dyskinesia. It has been estimated that motor complications accrue in 10% of PD patients per year, and have an estimated 50% occurrence by five years of disease (12). Other motor signs and symptoms may emerge including gait and postural abnormalities and these increase the risk of falling, dysphagia, dysarthria, and cognitive problems.

Non-invasive treatment for advanced PD

Non-invasive treatment of advanced PD should focus on the optimization of dopaminergic therapy inclusive of factors such as absorption, timing, dosage(s), and pharmacokinetic and delivery changes. Absorption of levodopa can be delayed by amino acids present in large

protein containing meals (13) and can be improved by administration one half to one hour before meals. Fractionating the levodopa dosage and changing the time intervals between dosages can be useful (14). These options may impact compliance and ultimately effectiveness (15, 16) though failure to do so may also impact therapeutic benefit. Another therapeutic option is to utilize a controlled release formulation. Several clinical trials have failed to reveal a significant reduction in OFF time or an increase in ON time compared to immediate release formulations (17, 18). However a recent phase 3 trial comparing IPX066, an oral extended release formulation of carbidopa levodopa, versus immediate release carbidopa levodopa, has shown promising results with a reduction of over one hour of OFF time compared to standard release formulations ($p<0.0001$) (19**). Since this drug has yet to be released onto the market, it remains unknown whether it can be effective in cases of severe dyskinesia, and whether it can aid in reducing the total number of pills taken in a day.

According to the Movement Disorder Society (MDS) recommendations, rasagiline 1 mg daily as an adjunct to levodopa can be clinically useful for motor fluctuations (20). This recommendation drew its genesis from two clinical trials: PRESTO (21) and LARGO (22). These studies revealed that adding rasagiline 0.5 and 1 mg to levodopa-carbidopa/levodopa-benserazide (LC/LB) reduced OFF time and increased ON time in PD patients with motor fluctuations. In the post-hoc analyses of the PRESTO and LARGO studies (23), rasagiline seemed to improve the cardinal PD motor symptoms and to significantly reduce daily OFF time when used as a first line adjunctive therapy for PD patients with mild motor fluctuations. Rasagiline has a reasonable side effect profile (24). Early studies of the generic drug selegiline by the Parkinson Study group, have revealed similar very mild symptomatic improvements in PD motor symptoms and wearing off (25).

Adjunctive entacapone added to LC/LB treatment in patients with moderate and severe PD has been shown to reduce the dose and the frequency of the administration of levodopa, and this strategy has led in many patients to an increase in ON time, and a reduction of OFF time (26). Entacapone was observed to be effective as compared to LC in PD patients with mild motor fluctuations (27). There has however, been a consistent increase in dyskinesia(s) reported in patients taking catechol-O-methyltransferase inhibitors (28). In a prospective double-blind trial, the STRIDE-PD study, the authors compared the risk of developing dyskinesia in PD patients to initiated LC and levodopa/carbidopa/entacapone (LCE) treatment (29). 373 patients in the LCE group and 372 in the LC group were randomized. After 134 weeks, patients receiving LCE had a shorter time to onset dyskinesia with no significant difference in time to wearing off or to motor score. By contrast, the results showed in the FIRST-STEP study where the authors did not observe a difference in motor fluctuations and dyskinesia after randomizing 423 patients in a double-blind study comparing LCE and LC in early PD patients (30). The results of the STRIDE-PD study were sobering (i.e. dyskinesia induction), but also very helpful in instilling a sense of caution when using COMT inhibitors (29). Additionally in the STRIDE-PD study there was an increase in acute myocardial infarction (29), though in more recent studies it was not associated with entacapone (entacapone-treated PD patients) (31).

Long-acting dopamine agonists (DAs) that can be administered once a day have become more popular with patients (32), however in practice sometimes even these formulations

need to be administered more than once a day (33). The idea of an extended release agonist fits well with the continuous dopaminergic stimulation hypothesis. This hypothesis would support the notion that an extended release formulation would result in less plasma fluctuations, and thus less motor complications (34). This theory has been challenged by many experts (35), and has yet to be completely proven.

Extended versus immediate release pramipexole versus a placebo were compared in PD motor fluctuaters (518 patients were enrolled). Both DA formulations significantly improved UPDRS scores and OFF time when compared to placebo ($p<0.0001$ and $p<0.0001$), however there was no significant difference in efficacy, tolerability and safety between groups (36).

The PREPARED study compared ropinirole prolonged release (PR) versus immediate release (IR). It enrolled 343 advanced PD patients, 174 in the PR group and 169 in the IR group. There were 251 patients who completed the study. The primary endpoint was the proportion of patient maintaining ≥20% reduction in OFF time from baseline to week 24. There was a 66% improvement in the PR group, and a 51% improvement in IR group, and this improvement was maintained. There was a ≥20% reduction in OFF time from baseline ($p<0.009$). However, the mean dosage at the end of the study was 18.6 mg/d and 10.4 mg/d respectively (37).

The PREFER trial and the CLEOPATRA-PD study collectively, revealed that rotigotine was superior to placebo in decreasing OFF time (38, 39), and was non-inferior to pramipexole (39). In the CLEOPATRA-PD study 506 patients were randomized to receive rotigotine (n=204), Pramipexole (n=201) and placebo (n=101), after 6 months the absolute change in off time from baseline compared to placebo were −1.58 hs ($p<0.001$) and −1.94 ($p<0.001$) for rotigotine and pramipexole respectively (39). When rotigotine was added to levodopa in another study it revealed significant improvements in nocturnal sleep disturbances, and in early morning motor symptoms (40). In the open-label extensions of the PREFER (SP715) and CLEOPATRA-PD (SP516) trials, 395 patients in SP516 and 256 in SP715 were randomized and it was shown that adjunctive rotigotine treatment in advanced PD patients was efficacious and had a reasonable safety profile at 6 years of follow-up (41*). Rotigitine has a similar side effect profile to other agonists, however it can also result in application related skin reactions (42).

Clinicians should be aware of the dangers of using DAs in the setting of dementia, hallucinations, autonomic dysfunction and sleep disorders. Impulse control disorder (ICD) is another possible side effect of all DAs (43). A recent study evaluated ICD in 223 PD patients taking DAs. The results revealed that 42% of patients treated with an oral DA developed ICD versus 19% treated with transdermal rotigotine ($p<0.01$) (44). These results are interesting as they point to a decrease in unwanted side effects when PD patients receive DAs. Since this research hasn't been replicated, it's unclear if clinicians should choose rotigotine over others in order to avoid these side effects when treating PD patients.

Istradefylline, a selective adenosine A_{2A} receptor antagonist, was shown to result in a significant reduction in OFF time when employed as an adjunctive therapy in an advanced

PD cohort (45–47). In a randomized placebo-controlled trial including 373 advanced PD patients, istradefylline 20 and 40 mg/day significantly reduced OFF time (0.99 hours and 0.96 hours with $p<0.003$ and $p<0.003$ respectively). Induction of dyskinesia was the most common side effect (48*). Istradefylline failed to achieve FDA approval, but it is currently approved and used in Japan. Istradefylline and several other adenosine A_{2A} receptor antagonists are currently under trial in the US.

Medical management of dyskinesias

Dyskinesia has a reported incidence in levodopa treated patients of 59% at 10 years, though only 12% reported dyskinesia as troublesome and difficult to manage (49). The most common approach to address dyskinesia is to lower the dose of levodopa, and to shorten the time intervals between dosages.

Currently amantadine, an N-methyl-d-aspartate (NMDA) antagonist can be administered at a dose of 100–400 mg/day. Amantadine is the only drug that has been shown to be clearly and directly useful to suppress levodopa-induced dyskinesia (LID) (20, 50).

However other drugs and new treatment targets are under investigation for the treatment of dyskinesia (51). A 13-week, double-blind placebo controlled study evaluated the efficacy and safety of AFQ056, a selective metabotropic glutamate receptor 5 antagonist (mGluR). This study of 98 patients revealed that the antidyskinetic efficacy showed promise when examining the response fluctuation item of the UPDRS IV (item 32). This finding was demonstrated with the 50 and 200mg dosages ($p<0.003$ and $p<0.005$ respectively) (52*). Currently, clinicians should be aware that the addition of amantadine to frail elderly advanced patients may possibly result in confusion, hallucinations, and worsening of symptoms.

Invasive treatment options to treat motor complications

There are circumstances when therapeutic management using oral medication will not adequately address motor complications. In this setting patients may benefit from one of three invasive options: 1- continuous subcutaneous apomorphine infusion, 2- continuous duodenal levodopa carbidopa pump, or 3- deep brain stimulation (DBS). Currently there are no large studies comparing and contrasting the procedures. DBS treatment currently has the highest level of evidence (with the most randomized controlled studies). The decision to employ any of the therapies should be made only after employing a multidisciplinary team that has carefully examined and weigh relative risks and benefits of each therapy (53).

Apomorphine

Apomorphine is D1/D2 DA. Because apomorphine has a rapid onset of action, it is effective in addressing OFF periods through the implementation of rescue injections (54). Apomorphine is also available as a continuous infusion treatment, and several trials suggest it is effective in treating motor symptoms (55–57) and some non-motor advanced PD symptoms (58).

Duodopa

Levodopa carbidopa intestinal gel (LCIG) can be delivered directly to the proximal jejunum via a percutaneous endoscopic gastrojejunostomy (PEG-J) tube connected to a portable infusion pump (53) (Figure 2). This pump therapy can be used to avoid erratic gastric emptying and to improve intestinal absorption (59). Several studies have observed that LCIG is an effective treatment for improving motor fluctuations and quality of life scores when compared to conventional therapy (60–62). In a recent placebo controlled parallel group study including 71 patients with advanced PD, 66 patients completed the trial. There were 35 patients randomly allocated to treatment with LCIG plus oral placebo, and 31 were randomly allocated to treatment with immediate release oral levodopa carbidopa plus placebo intestinal gel. At the end of 12 weeks of treatment with levodopa carbidopa intestinal gel, the infusion showed a significant reduction in OFF time of −4.04 h/day compared with treatment with immediate release oral levodopa carbidopa plus placebo intestinal gel (2.14 h/day $p<0.0015$). This improvement was also observed in ON time without troublesome dyskinesia ($p<0.0059$), and in ON time without dyskinesia ($p<0.0142$). Similar to the other studies, 95% of patients in the levodopa carbidopa intestinal gel group had an AE, and 14% of them an SAE. Interestingly 100% in the placebo group had AEs, and 21% had an SAE. Most of the complications of the pump therapy were associated with the percutaneous gastrojejunostomy (63**). Though available in 43 countries this therapy is not currently available in the US.

Deep brain stimulation (DBS)

DBS is functional neurosurgical technique that can be employed to treat motor fluctuations, dyskinesia, and tremor. There have been three recent randomized controlled clinical trials comparing GPi and/or STN versus best medical management for advanced PD. These trials have provided support for the notion that in many fluctuating patients, DBS is superior to medication therapy, and may also enhance quality of life (64–66) (Table 1). In the German Parkinson Study Group trial (64) after 6 months of bilateral STN DBS therapy there was a significant improvement in both motor function and quality of life. Similarly in the CSP 468 Veteran's Administration Study Group (65), a total of 255 patients were enrolled and randomized to STN or GPi DBS. There was also a best medical therapy group. After 6 months, the DBS group revealed a mean of 4.6 hours/day of on time without troublesome dyskinesia as compared with 0 hours in the best medical therapy group ($p<0.001$), and motor outcomes were similar for STN and GPi. The PD SURG Collaborative Study Group (66) included 366 patients in the United Kingdom and it reported an improved in quality of life (PDQ-39) of 5.0 points in the DBS group and 0.3 points in the medical treatment group over a 1-year follow up period ($p<0.001$).

There are however, important decisions for clinicians considering DBS therapy including the most appropriate target for an individual patient (STN vs. GPi). Several trials have compared both targets and had similar motor results (67–70). Depressive symptoms may have been less frequent in GPi patients (71*). Appropriate patient selection is the most critical factor for successful DBS, and this selection process can be best accomplished through the use of an interdisciplinary team (72, 73).

It is important to recognize that in advanced PD, symptoms unresponsive to levodopa such as cognitive impairment, gait instability, mood disorders, speech impairment and autonomic dysfunction are unlikely to improve with DBS, and could even worsen (74, 75). There is a search for other targets to address levodopa resistant symptoms, and the most information available has been on the use of pedunculopontine nucleus and SNr stimulation which may improve gait and balance (76, 77) in some patients, though their use is still limited to research. Not all experts agree that PPN stimulation is an effective way to treat gait and balance, and some of the issues may be due to lead location relative to the appropriate fibers and connections (78), and due to the technique of applying stimulation (parameters and schedule).

Treatment of balance and gait disorders

Despite many treatments available for advanced PD, the management of postural instability and gait disorders have yet to be fully elucidated. Trials of apomorphine continuous infusion and LCIG have reported some improvement in gait and postural problems (56, 60), but not beyond what can be achieved with medication therapy. Physical, occupational and exercise therapy can all be helpful in the symptomatic treatment of advanced PD (79). Both tai chi and resistance exercises have been shown to reduce the risk of falling (80).

Treatment of non-motor symptoms

Despite the recognition of NMS and the impact of NMS on quality of life, treatment is still not completely established for many of the symptoms (81). The first step in the treatment of NMS, following a search for a secondary cause. Some clinicians discontinue many medications but it should be appreciated that this approach may potentially worsen motor symptoms, so caution should be exercised, and carefully monitoring sought (82)

Dementia

Currently, rivastigmine, a cholinesterase inhibitor, is the only FDA approved medication for the treatment of mild to moderate PDD, and rivastigmine is the only agent with efficacy data in PDD (81, 83). In a double-blind randomized study of 541 patients with PDD (MMSE 10–24), a significant improvement in dementia was seen at 24-weeks (83). This improvement in PDD was maintained in the extension of this trial, which was a long-term treatment study (up to 48 weeks) (84). In a 76-week randomized open label study of rivastigmine 12 md/d capsules and 9.5 mg/24h patch, 583 patients were randomized (85). The incidence of AEs due to worsening of PD was 36.1% in the capsule group with tremor the most frequently reported (24.5 %; 95 % CI). In the patch group AEs due to worsening of PD were 31.9%, however tremor was reported in 9.7% (95 % CI). In both groups there was a 2.1 point worsening on the UPDRS-III motor scale. The efficacy was comparable to results in previous trials (83, 84). Donepezil, galantamine and memantine have been evaluated for the treatment of PDD in different trials (86–88), but their efficacy has not been clearly demonstrated (81).

Psychosis and hallucinations

Clozapine is the only antipsychotic drug that has revealed efficacy for the treatment of PD psychosis across clinical trials (81), however the risk of agranulocytosis and the need for frequent blood draws has limited its use. Quetiapine is safer than clozapine, however studies have revealed that it is much weaker when employed for the treatment of PD psychosis (81). Pimavanserin, a select serotonin 5-HT2A inverse agonist, has shown evidence of benefits and tolerability in treating PD psychosis and it does not block dopamine receptors, and thus does not worsen PD (89, 90). In a 6-week randomized, double-blind, placebo-controlled trial in 199 patients, the safety and efficacy of pimavenserin was assessed. The patients in the pimavenserin group showed a decrease of 5.79 points in the mean PD-adapted scale for assessment of positive symptoms (SAPS-PD) as compared with 2.73 for the placebo group ($p=0.001$). Additionally, patients in the pimavenserin group had greater improvement on the clinical global impression scale and the caregiver burden scale. Pimavenserin was well tolerated with no worsening of motor function (90**)

Depression, anxiety and apathy

Currently, tricyclic antidepressants (TCA's) may be the best choice to treat depression in PD, followed by serotonin reuptake inhibitors (SSRI's), and in some cases dopaminergic therapy (91) Cognitive behavioral therapy (CBT) appears to be a promising treatment. (92). Most experts in the field use traditional SSRI's, SNRI's or a TCA and will follow the PD patient closely in 4–6 weeks, and adjust therapy as needed. In exceptionally severe cases, transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT) is used. No established treatment for apathy is available. Methylphenidate, levodopa, selegiline and antidepressants have been suggested to be useful (93, 94). In a small double-bind, randomized trial, rivastigmine 9.5 mg/day transdermal patch improved the Lille Apathy Rating Scale (LARS) from −11.5 at baseline to −20 after treatment and the improvement exceeded placebo ($p=0.031$) (95). There was also improvement in the instrumental activity of daily living scale, and caregiver burden, but not the quality of life. Though there is a lack of literature on the subject many experts use a DA for severe apathy, but do so with an abundance of caution for impulsive behaviors.

Autonomic Failure

The first step to treat orthostatic hypotension (OH) should be non-pharmacologic methods, such as elastic stockings/abdominal compression bands, fragmentation of meals, increased water and salt intake, avoidance of alcohol consumption, night time head-up-tilt, and physical counter-maneuvers (96). OH is often accompanied by supine hypertension, therefore the treatment should aim at minimizing OH without exacerbating supine hypertension. Fludrocortisone and midodrine are commonly used to treat OH, but could worsen supine hypertension (97). Interim exploratory analysis of 51 PD patients with OH enrolled in a phase 3 study of droxidopa (L-threo-3,4-dihydroxyphenylserine) (98), failed to show benefit with droxidopa as compared to placebo. The study was stopped, though recently a new study has been exploring the potential of this drug in OH. The FDA has

recently approved droxidopa for treatment of neurogenic OH, but it is still unclear how effective this therapy will be in clinical practice.

Sleep disorders

Clonazepam and melatonin are commonly used to treat REM sleep behavior disorder (RBD), and both are well tolerated (99, 100), but there is a worry that clonazepam may contribute to cognitive issues and falling, and that melatonin will be ineffective. Modafinil is an option to treat excessive daytime sleepiness, but evidence has not supported its use (81). Cognitive behavior therapy with bright light therapy or doxepin 10 mg/day substantially improved insomnia in PD in a recent small randomized study (101). For advanced PD most practitioners use sleep hygiene, and/or a light dose of a benzodiazepine particularly for RBD. If these therapies are not effective, most experts proceed rapidly to a sleep study.

Pain

Pain will occasionally respond to optimization of dopaminergic treatment (102). Dystonic focal pain may respond to botulinum toxin injections (103). Other treatments including NSAIDs, opiates, antidepressants, and rTMS have all been found effective in PD pain (104). Clinicians should be aware that prescribing narcotics could increase fall risk, aggravate constipation, and could worsen PD symptoms.

Non-pharmacological treatment in advanced PD

Non-pharmacological treatments inclusive of physical therapy, occupational therapy, speech therapy, swallowing therapy, and counseling psychology may all be very helpful in PD. Many patients with advanced PD will benefit from integration of these interdisciplinary therapies when appropriate (20, 105–108).

Conclusion

Despite recent new therapies and a better understanding of PD, the disease will ultimately lead to progressive disability in most sufferers. In advanced PD, optimization of dopaminergics is a powerful therapeutic option. In select cases, advanced PD patients will benefit from invasive treatments. DBS has the highest level of evidence for invasive treatments, however results of LCIG trials should make this option a possibility for some sufferers. The management of levodopa resistant PD symptoms, as well non-motor symptoms, can affect quality of life more than the management of typical motor symptoms. Interdisciplinary therapy inclusive of physical therapy, occupational therapy, speech therapy, swallowing therapy and counseling psychology may be helpful in advanced PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Levodopa optimization is critical in the management of advanced PD and should include attention to absorption, timing, and dosages. Other pharmacological optimization strategies include the addition of a MAO-B inhibitor, a COMT inhibitor, a DA, and/or an extended-release levodopa formulation.
- Amantadine has been shown useful to suppress dyskinesia.
- DBS, LCIG and apomorphine continuous infusion treatment can be used in appropriately screened and selected PD patients. Currently DBS treatment has the highest level of evidence.
- Axial symptoms and NMS are considered hallmarks of advanced PD, and can be important predictors of an impaired quality of life. Treatment of depression should be aggressively pursued.
- Non-pharmacological treatments inclusive of physical therapy, occupational therapy, speech therapy, swallowing therapy and counseling psychology are all very helpful in the treatment of advanced PD.

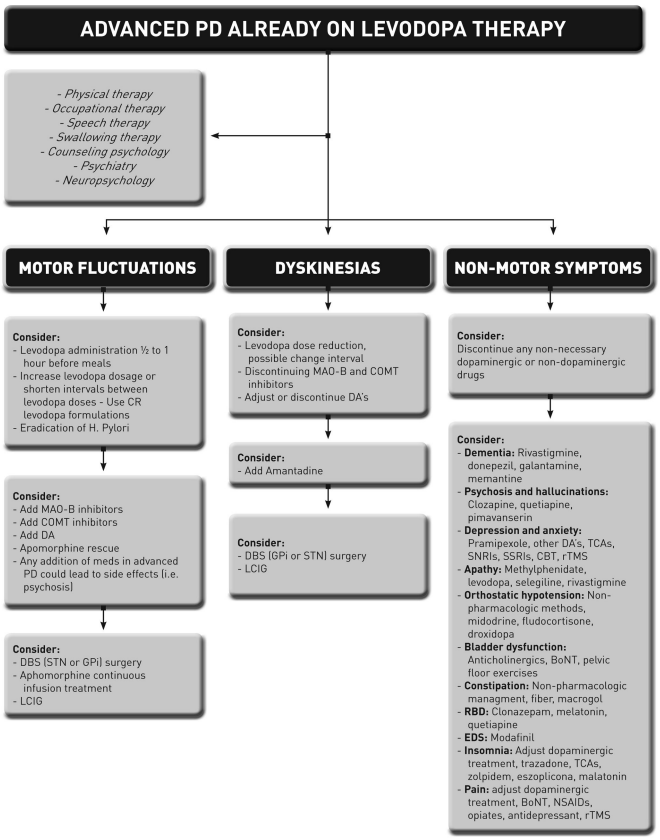

Figure 1. Suggested guideline for the management of advanced PD

H. Pylori, Helicobacter pylori; CR, controlled release; MAO-B, monoamine oxidase-B; COMT, catechol-O-methyltransferase; DA, dopamine agonist; DBS, deep brain stimulation; STN, subthalamic nucleus; GPi globus pallidus interna; LCIG, levodopa carbidopa intestinal gel; TCAs, tricyclic antidepressant; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, serotonin reuptake inhibitors; CBT, cognitive behavioral therapy; rTMS, repetitive transcranial magnetic stimulation; RBD, REM sleep behavior disorder; EDS, excessive daytime sleepiness; BoNT, botulinum toxin; NSAIDs, non-steroidal anti-inflammatory drug.

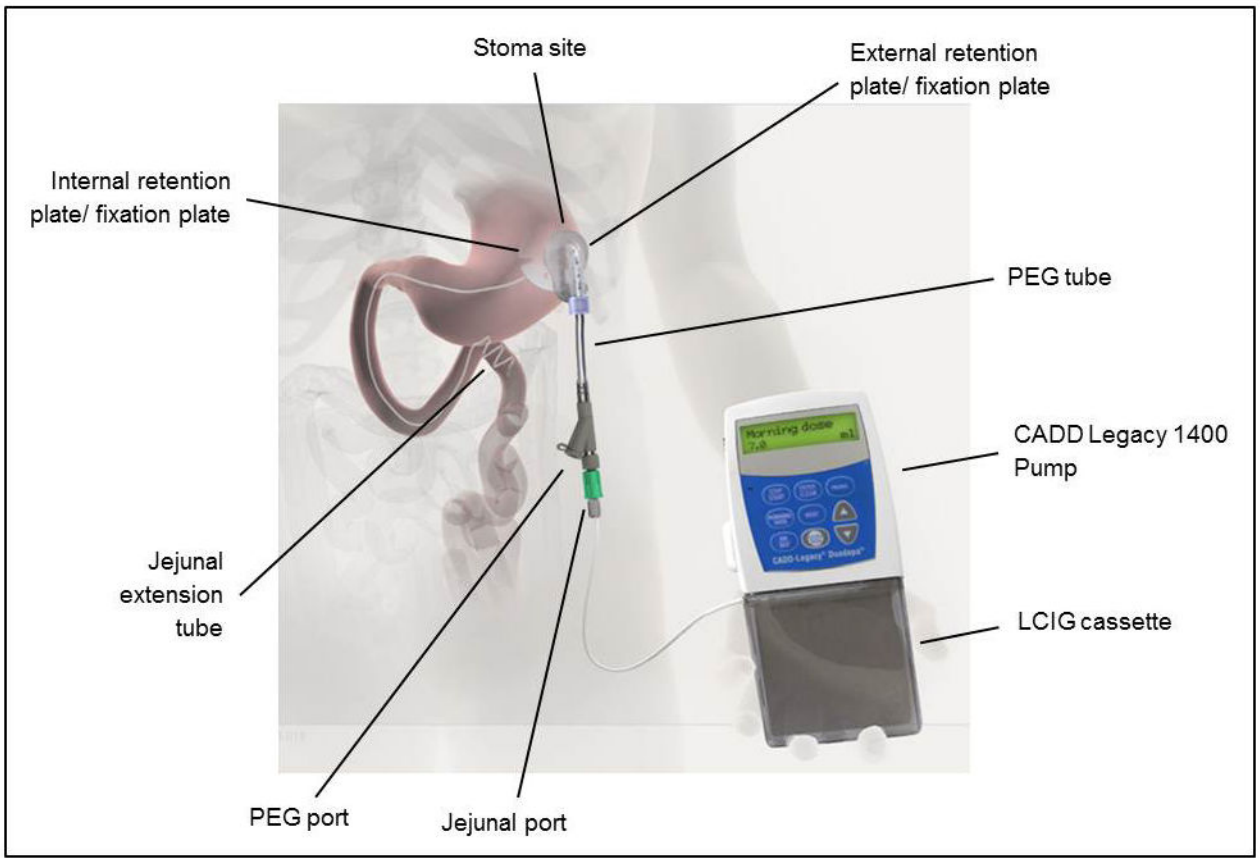

Figure 2. Levodopa carbidopa intestinal gel delivered system

Reproduced with permission from, Olanow CW, Kieburtz K, Odin P, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet neurology. 2014;13(2):141–9. (63)

Table 1

DBS randomized controlled clinical trials for advanced PD

Adapted and updated with authorization of the authors from Martinez Ramirez D and Okun MS. Gerontology, 2014 (73).

Patients Features	German Study Group; 2006 (64)		CSP 468 Study Group; 2009 (65)		PD SURG Collaborative Group; 2010 (66)	
	NE (n=78)	BMT (n=78)	NE (n=121)	BMT (n=134)	NE (n=183)	BMT (n=183)
Age, yr	60.5±7.4	60.8±7.8	62.4±8.8	62.3±9	59 (37–79)	59 (36–75)
Sex						
Male, n (%)	50 (64)	50 (64)	98 (81)	110 (82.1)	125 (68)	135 (74)
Female, n (%)	28 (36)	28 (36)	23 (19)	24 (17.9)	58 (32)	48 (26)
Disease duration, yr	-	-	12.4±5.8	12.4±5.8	11.5 (2–32)	11.2 (2–30)
Years taking	13.0±5.8	13.8±5.6	10.8 (5.4)	12.6 (5.6)*	-	-
LD						
HY, n (%)			3.4 (0.9)	3.3 (0.8)		
≤ 2	1 (1)	4 (6)			12 (7)	11 (6)
2.5	10 (13)	6 (8)			19 (11)	29 (16)
3	17 (22)	13 (17)			65 (38)	59 (34
4	40 (51)	41 (53)			54 (32)	55 (31)
5	10 (13)	14 (18)			19 (11)	22 (13)
DBS target	Bilateral STN	-	Bilateral STN or GPi	-	STN or GPi; stimulation or lesion	-
Primary outcome	PDQ-39 UPDRS III		Time spent in on state without troubling dyskinesia		PDQ-39	
Results	PDQ-39 25% and UPDRS III 41% improvement*	No change in PDQ-39 and UPDRS III from baseline	4.6 h/day*	0 h/day	Main change −5.0 points*	Main change −0.3 points
SAE**	10*	3	82	19	25	14
Died	3	1	2	-	2	1

*Statistical significance

**Numbers of SAE

NE, neuroestimulation; BMT, best medical treatment; LD, levodopa; HY, Hoehn and Yahr; DBS, deep brain stimulation, STN, subthalamic nucleus; GPi, globus pallidus; PDQ-39, Parkinson's disease questionnaire; UPDRS III, unified Parkinson's disease rating scale part III; SAE, serious adverse events.

Adapted from Martinez-Ramirez D, Okun MS. Rationale and clinical pearls for primary care doctors referring patients for deep brain stimulation. Gerontology. 2014;60(1):38–48. (73)