Treatment in late Parkinson's disease

It is almost 200 years since James Parkinson described the major symptoms of idiopathic Parkinson's disease (IPD). Since then, our treatment armamentarium has slowly increased, providing effective treatment to many patients, but the management of the late stage of the disease is still a huge challenge. Levodopa is the most effective pharmacological treatment available for IPD.[1] In late stages of the disease, however, it is difficult to maintain a stable therapeutic response with pharmacological therapy. Motor complications such as wearing off fluctuations[2] and dyskinesias[3] develop with increasing frequency in patients after 5–6 years of dopaminergic therapy.

Pharmacological Therapy

Motor complications are often managed in the initial stages with adjustment in levodopa dosage. Motor off time can be reduced by the addition of various dopaminergic agonists including pergolide, pramipexole, ropinirole, cabergoline, and drugs such as monoamine oxidase (MAO) inhibitors (rasagiline) and catechol-O-methyl transferase (COMT) inhibitors (entacapone).[4] A recent Cochrane review demonstrated that all the three groups of adjuvant drugs – dopaminergic agonists, MAO-B inhibitors (MAOBI) and COMT inhibitors (COMTI) – reduced off time, levodopa dose, and improved Unified Parkinson Disease Rating Scale (UPDRS) scores in Parkinson's disease (PD) patients with motor complications but at the cost of increased dyskinesias and numerous other side effects. In the same review, indirect comparisons suggested that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy. However, there is lack of direct evidence and head to head comparison trials between these drugs.[5]

Management of troublesome dyskinesias is a major challenge in late stages of the disease. Studies have shown that dyskinesias occur in about 50% of elderly and almost 100% of younger patients under the age of 40 years after 6 years of levodopa therapy.[6]

The exact pathophysiology of dyskinesias is still not clear. As fluctuations in the dopamine levels may contribute to the appearance of dyskinesias, reducing the dose and increasing the frequency of levodopa, addition of MAOBI or COMTI and addition of dopaminergic agonists can be tried in the initial phases. There is strong evidence that initial therapy with dopamine agonists in early stages of the disease results in delay in the appearance of dyskinesias compared to that with levodopa.[7,8] However, once levodopa treatment is initiated, alone or in addition to dopaminergic agonists, the time duration from the onset of levodopa therapy to occurrence of dyskinesias was the same in both groups. Similarly, addition of entacapone to levodopa/carbidopa theoretically should cause less dyskinesias, but the evidence is still lacking. A recent review and guidelines by AAN identified amantadine as a safe and effective pharmacological therapeutic agent for dyskinesias.[4] Various studies have shown that amantadine significantly reduces dyskinesias by about 50%. However, there are still confounding results on whether the antidyskinetic effect of amantadine wears off after a year or there is a long-standing effect.[9-11] Though clozapine has also shown reduction in dyskinesias, the side effect profile, especially the occurrence of agranulocytosis, restricts its usage.[4] Thus, in late stage of PD, there is limited efficacy of medical therapy.

Surgical Therapy

The recent progress in functional neurosurgery probably marks the second most important therapeutic advance in PD after the introduction of levodopa. In the last 15 years, there have been many Class III and Class IV studies suggesting the effectiveness of deep brain stimulation (DBS).[4] With the results of the recently concluded two large-scale randomized clinical trials involving 156 patients with PD[12] and 255 patients with PD[13] with severe motor complications, the evidence has become more robust. DBS is more effective than the best medical therapy in improving "on" time without troubling dyskinesias by 4.6 h/day, motor function in 71% compared to 36% in medical therapy, and quality of life at 6 months after surgery.[13] There was, however, an increased risk of side effects related to the procedure.[13] Thus, while DBS is the most effective therapy in patients with motor complications, it is important to select the correct patients who are eligible for the procedure.[14]

PD patients with at least 5 years disease duration, UPDRS-III off score of 30 or more, H and Y score of ≤3, significant response to syndopa with troublesome dyskinesias and normal cognition are eligible for DBS.[14] Best results have been reported in patients with advanced PD with at least 5 years of disease duration and (a) excellent levodopa response, (b) younger age, (c) no or few axial non-levodopa responsive motor symptoms, (d) no or very mild cognitive impairment, and (e) absence of or well-controlled psychiatric disease.[15] Unfortunately, these stringent criteria imply that only a small percentage of PD patients are eligible for DBS.[16]

Various sites have been proposed but the effect is maximally seen with stimulation of bilateral subthalamic nucleus (STN) and globus pallidum interna (GPi) for most features of IPD. Similar benefits for both STN and GPi DBS have been reported in only a few randomized studies.[17] The recent co-op study addressed this issue.[18] Two hundred ninety-nine patients with PD were randomized to STN or GPi DBS with the primary outcome of UPDRS-III assessed in a blinded manner. Similar

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improvements were found at 2-year follow-up for both surgical sites. Dopaminergic medication was decreased more for the STN group but visuomotor processing speed declined less after GPi DBS. Furthermore, subjects who had GPi DBS showed improvement in depression, whereas subjects who had STN DBS worsened. Taken together, both STN and GPi DBS improve motor function, but the target selection should be individualized considering the differences in nonmotor outcomes.[18] Various complications can occur with DBS, including risk of intracranial hemorrhage (<2%), lead fracture and migration and hardware infection, but the rates have come down markedly with improvement in technology and operative procedures.

Ablative Surgery

Although thalamotomy and pallidotomy have largely been abandoned and replaced by DBS, ablative therapies may yet have a role in certain patients such as those with an increased risk of infection or a history of recurrent infection of their DBS systems, economic reasons and in patients with predominantly unilateral symptoms. Ablative surgeries are not preferred because of significant side effects including dysphagia, dysarthria and cognitive deficits. Disadvantages of ablative surgery include mistargeted lesions with permanent neurological deficits and suboptimal and unilateral benefits even in well-targeted approach.[19-21]

Newer Treatment Modalities

Continuous dopaminergic stimulation

Intrajejunal constant-rate infusions of levodopa are a newer therapeutic option to provide a constant dopaminergic level in the blood. Studies have shown that with this approach, motor fluctuations, and particularly, the intractable dyskinesias of patients with advanced PD are substantially reversed even as the total daily levodopa dose and corresponding "on" time are increased. The carboxymethylcellulose formulation of levodopa, provided in a gel formulation (duodopa) at a concentration of 20 mg/mL and delivered through an intrajejunal pump system, is approved in most countries of Europe.[22,23] Studies are being conducted to further validate the results of this procedure and look at its technical liabilities for long-term therapy (e.g., potential percutaneous gastrostomy infections, dislocation, kinking and occlusion of catheters, high cost) to assess the overall efficacy.

Similarly, mini pumps with continuous subcutaneous delivery of the dopamine agonist apomorphine have been shown to reverse fluctuations and dyskinesias.[24]

Newer molecules like glutamate receptor antagonists (that reduce D1 output), cannabinoid receptor antagonists, a2-adrenergic receptor antagonists (that inhibit GPe), adenosine A2A-receptor antagonist, and 5-HT1A-receptor agonists are being evaluated for reducing dyskinesias.[25]

Conclusions

Late stages of PD are characterized by the development of motor complications including wearing off and dyskinesias.

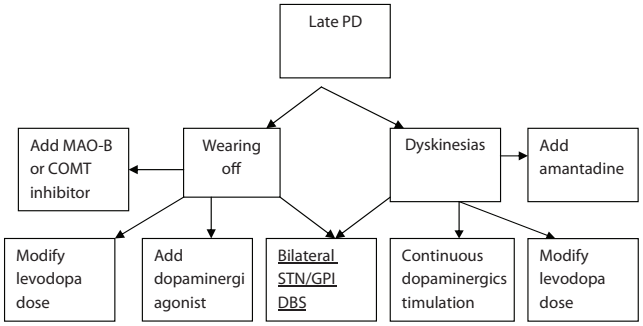

Figure 1: Algorithm for management of late stage PD

Although few patients improve with modifications in levodopa dosage and addition of dopaminergic agonists, MAOBI and COMTI, many develop troublesome dyskinesias. Best therapy available is bilateral DBS of STN or GPi. Continuous dopaminergic stimulation with duodopa or apomorphine may be considered [Figure 1].

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