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Newer and Emerging Treatment Modalities in Parkinson's Disease.

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Abstract : Over the last two decades enormous progress has been made in the treatment of Parkinson's disease (PD). As a result of recent advances promising therapy are emerging. Although levodopa is the main stay of treatment in PD, yet it is associated with significant complications like "wearing off" effect, motor fluctuations and dyskinesia. Newer drugs are primarily aimed at addressing the complications of levodopa therapy and to explore the newer targets in management of PD. Novel medications that provide symptomatic relief remain under demand. Although in this review, we intend to focus on newer and emerging therapies it should be remembered that newer treatment are not necessarily better than the conventional treatment and treatment options must be individualized.

INTRODUCTION

Parkinson's disease (PD) is a commonly encountered neurodegenerative disorder, characterised clinically by bradykinesia, resting tremor and rigidity, and postural instability¹. Although the exact cause is not known, loss of dopamine secreting neurons within the substantia nigra (SN) and presence of Lewy bodies are major pathologic finding in patients with PD. Since its introduction in 1968², levodopa has remained the most efficacious treatment of PD, however about 50% patients using it for more than 5 year experience different motor complications like 'wearing off',

'dyskinesia' and 'on-off' phenomenon³. Levodopa therapy aims at only dopamine deficiency although other neuronal targets such as acetylcholine, glutamate, and N-methyl-D-aspartic acid may be important and pharmacotherapy aimed at these targets may be the future of treatment of PD. Over the last two decades a diverse group of drugs have been in use for management of motor and non-motor symptoms of PD. In this review, we intend to focus on the newer and emerging treatment strategies for PD.

DOPAMINERGIC STIMULATION

Under normal circumstances, the steady state of firing of dopaminergic neurons in the substantia nigra pars compacta (SNc) maintains striatal dopamine at a fairly constant level, providing continuous stimulation of striatal dopamine receptors^{4,5}. In PD, with the progressive loss of dopamine secreting neurons in the SNc, striatal

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dopamine levels become increasingly dependent on the availability of peripherally administered levodopa⁶. The half-life of immediate release levodopa is 1-3 hours which can be modestly increased by use of peripheral catechol-O-methyltransferase (COMT) inhibitors like entacapone or tolcapone. This non-physiologic stimulation of dopaminergic neurons has been implicated as the basis for the motor fluctuations seen with chronic levodopa therapy. A potential method to address the troublesome motor fluctuations and dyskinesia is to provide dopamine in a continuous manner, thus avoiding fluctuations in dopamine levels that are associated with intermittent oral dosing. This has been substantiated by studies which have shown that continuous infusion of levodopa reduced 'off time', dyskinesia, and motor fluctuations in patients with advanced PD^{7,8}.

CONTINUOUS DOPAMINERGIC STIMULATION (CDS)

Continuous dopaminergic stimulation can be achieved through several ways like continuous enteral infusion of levodopa, sustained-release levodopa, increased frequency of dosing, and use of catechol-O-methyl-transferase (COMT) inhibitors.

CDS WITH FREQUENT DOSING AND COMT INHIBITORS

The Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD), a double blind study comparing the risk of developing dyskinesia in PD patients initiated on the combination of levodopa/carbidopa/entacapone (LCE) versus levodopa/carbidopa (LC) administered 4 times daily⁹. Subjects treated with LCE demonstrated a shorter time to onset of dyskinesia and increased frequency of dyskinesias compared to those treated with standard LC in spite of extended elimination half-life and plasma area under the curve of levodopa associated with LCE. The authors of the trial speculated that the goal of continuous dopaminergic stimulation may not have been achieved with the chosen dosing frequency.

DUODENAL LEVODOPA

Studies have shown that Intravenous and enteral levodopa have a more predictable motor control and reduced fluctuations when compared to oral therapy. This has led to development of Duodopa, which is a concentrated levodopa/carbidopa formulation intended for long term enteral infusion therapy. It is placed directly in to the duodenum via a transabdominal port. Clinical trials have proven the safety and efficacy of this method with improvement in the motor scores and quality of life, by providing a more consistent plasma levodopa levels¹⁰. This therapy is now considered for viable treatment alternative for patients with advanced PD. It was approved by the FDA in 2000 as an orphan drug and continues to be evaluated for clinical use.

LEVODOPA FORMULATIONS

After oral ingestion, Levodopa is actively transported in the duodenum by a specific, large neutral l-amino acid carrier. However, high percentage of patients with PD have erratic gastric emptying which hampers the availability of levodopa at duodenum which subsequently leads to fluctuations in the plasma concentrations which may lead to motor fluctuations in advanced disease. Newer levodopa formulations are currently under trial to address this issue.

Newer levodopa formulations:

- 1) Melevodopa – It is methyl ester of levodopa. It is used in tablet form as an effervescent prodrug with about 250 times higher water solubility, which allows faster and more consistent absorption and a more rapid onset of action. This is more helpful for the treatment of motor fluctuations¹¹.
- 2) XP21279- It is a levodopa prodrug which is designed for active transportation throughout the entire gastrointestinal tract. It is currently under phase II trial in PD patients with frequent motor fluctuations¹².
- 3) IPX066- It is an experimental extended-release carbidopa-levodopa formulation designed to produce quick and sustained concentrations of levodopa with the goal of improved and more reliable control of PD symptoms. In a recent phase III trial it has showed improved efficacy in achieving lower "off" time and longer "on" time in comparison to patient with Carbidopa + Levodopa with Entacapone¹³.
- 4) CVT-301 – This is a novel, Intranasal levodopa formulation which aims at providing relief from the "off" period in PD patients. It is currently under phase II trial.

ADENOSINE A2A ANTAGONIST

Among the non-dopaminergic therapies Adenosine A2A antagonist seems to be promising in treatment of PD. The A2A subtype of adenosine receptors are concentrated on α -aminobutyric acid (GABA) containing medium spiny neurons of the indirect pathway that project from the striatum to the globus pallidus externa¹⁴. Antagonism of these adenosine A2A receptors facilitates intrastriatal GABA release, reducing striatopallidal neuronal overactivity which in turn helps to increase indirect inhibitory output from the striatum to the globus pallidus, thus restoring balance between the basal ganglia output pathways¹⁵. The different Adenosine A2A antagonist that are under phase I and II trials are Istradefylline, Preladenant, ST-1535, SYN-115.

MONOAMINE OXIDASE B INHIBITORS

Monoamine Oxidase B Inhibitors are receiving renewed attention based on trials which revealed a possible disease-modifying and neuroprotective effect of rasagiline in animal models of PD. In a double blind, parallel- group, randomized, delayed start clinical trial by Parkinson Study Group in 2004, patients treated with rasagiline early in the course of disease were found to show less functional decline in form of UPDRS score after 12 months than those in whom rasagiline was started late¹⁶. The Attenuation of Disease Progression with Rasagiline Once-daily (ADAGIO) study in 2009, was a double-blind, placebo-controlled, delayed-start trial which was designed to evaluate the effect of rasagiline on the rate of progression of PD in patients over 72 weeks¹⁷. Subjects randomized to early lower dose (1 mg/day) treatment showed a sustained slower rate of progression and significant improvement in the change in total UPDRS score compared to those delayed to treatment. Although those randomized to early higher dose (2 mg/day) did show a slower rate of progression compared to those delayed to treatment, the change in total UPDRS did not differ significantly. These confounding results suggested a disease-modifying effect for lower dose Rasagiline, although the same conclusion could not be drawn for higher dose. Rasagiline remains a useful treatment in both early and moderate PD, but its neuroprotective properties continue to be the subject of much debate¹⁸.

Safinamide: It is an amino amide derivative, acts as a highly selective,

reversible inhibitor of MAO-b, reduces the uptake of dopamine, blocks voltage dependent Na⁺/Ca²⁺ channels and inhibits glutamate release¹⁹. A study by F Stocchi et al in 2004, revealed in early PD patients when safinamide was added to those on dopamine agonist monotherapy was associated with improved motor UPDRS scores²⁰. A recent Phase III, multicenter, double-blind, placebo-controlled, parallel-group study by R Borghain et al evaluated the efficacy of Safinamide as add-on to L-dopa in treatment of patient with PD with motor fluctuations. The authors reported that addition of safinamide 50mg/day or 100mg/day to L-Dopa in patients with PD with motor fluctuations significantly increased total 'on' time with no or troublesome dyskinesia and decreased 'off' time.

DOPAMINE AGONIST

The onset of levodopa induced complication may be related to the duration of treatment. This is the main reason for which many expert recommend delaying levodopa therapy until the symptoms clearly begin to interfere with the patient's normal day to day activities. In order to delay the onset of levodopa induced complications many expert recommend using a Dopamine agonist (DA) as initial and early form of dopaminergic therapy.

DA exert their pharmacological effect by directly activating dopamine receptors, bypassing the pre-synaptic synthesis of DA. Experimental and clinical studies have demonstrated that activation of D2 receptor is important for the beneficial effects of DA, but concurrent D1 and D2 stimulations are required to produce optimal physiological and behavioural effects. In contrast to older DA agonists (Bromocriptine and pergolide), pramipexole and ropinirole are non-ergot derivatives and have better side effect profile.

In the Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) study,²¹ patients were randomized to initial treatment with either levodopa or pramipexole and followed for up to 4 years. There was a significant reduction in transporter loss at each time point over the 46 months in the pramipexole group in comparison to levodopa group. Similar results were seen in the Ropinirole as Early Therapy versus L-dopa Positron Emission Tomography (REAL-PET) study²².

The PRamipexole On Underlying Disease (PROUD) study aimed at examining the disease modification effect of pramipexole, compared immediate treatment with delayed treatment of pramipexole. However, it failed to demonstrate any significant difference in UPDRS between the two groups²³. Both ropinirole and pramipexole have been approved as once daily prolonged-release formulations, providing important additions to the treatment options in both early and advanced PD. Both immediate and prolonged release formulations have shown similar efficacy in treating motor symptoms and tolerability in different comparative studies.

The most frequent limiting factor for in use of DA is development of Impulse Control Disorders (ICD) like pathological gambling, compulsive sexual behaviour, compulsive buying and binge or compulsive eating. About 17% of PD patients with DA have been reported to have ICDs²⁴. The DOMINION study involving 3000 PD patients treated with at least one PD medication for at least 1 year, showed a 2 to 3.5 fold increase risk in ICD associated with DA treatment²⁵. Patients treated with higher dose of Levodopa also experience ICD. Amantadine has been found to be effective in treatment of pathological gambling. The anti-glutamatergic action of amantadine has been attributed for this.

SUBCUTANEOUS APOMORPHINE

Apomorphine is a non-ergot derivative directly acting dopamine receptor agonist. It has high affinity for D4 receptors and lower affinity for D2, D3, D5 and lowest affinity for D1 like receptors. Subcutaneous apomorphine provides rapid and effective relief of 'off' episodes and has been used as a rescue therapy in advanced PD. The effect begins within 20min of administration and lasts for about 100 minutes. Usual therapeutic rescue doses are 2-6mg. The side effects associated with apomorphine are nausea, orthostatic hypotension and psychiatric complications.

TRANSDERMAL ROTIGOTINE

Rotigotine is a non-ergot, D3, D2, D1 dopamine receptor agonist. Transdermal rotigotine patch is a unique delivery system which allows continuous, once daily administration and hence ensures better patient compliance. It provides a constant rate of delivery of rotigotine over 24 hours ensuring more continuous plasma concentration than compared to the oral formulations. Rotigotine transdermal patch is well tolerated at doses up to 6mg/24hour. Most common side effects are high incidence of local reaction, nausea and somnolence.

SURGICAL THERAPY

Deep Brain Stimulation (DBS)

DBS is now the preferred surgical procedure for treatment of advanced PD and is very effective in treating the motor disability and improving quality of life in PD patients with severe motor fluctuations than best medical therapy. Using microelectrode recording, electrophysiological exploration of the target structure is undertaken under local or general anaesthesia. Local anaesthesia allows the advantage of intraoperative testing of effects of DBS and more precise localization. Once the optimal target is found, the electrode is then replaced by a chronic lead which is then fixed to a pulse generator implanted under the skin, typically in subclavicular area.

The most common target for DBS in PD is the Sub thalamic Nucleus (STN). However in patients with severe dyskinesia Globus pallidus internus (GPi) have been considered as a target. In a randomized trial comparing these two targets involving 299 idiopathic PD patients, no significant difference in motor function was noted in between two groups after 24 months. However those in subthalamic group showed a significant worsening in depression and visuomotor speed while those in pallidal group required more dopaminergic medications. Both the group were comparable in the quality of life measures²⁴.

Advanced PD with recurrent falls and gait freezing are not well maintained with pharmacotherapy or DBS targets. Stimulation of the pedunculopontine nucleus (PPN) has been explored as a target to maintain the postural instability in advanced PD, however outcome have been mixed.

Patients eligible for DBS are those with clinically diagnosed Idiopathic PD experiencing disabling motor fluctuations, in absence of dementia, and remain responsive to levodopa therapy. Currently mean disease duration is 14 years before STN-DBS is performed and overall less than 5% of PD patients fulfil the eligibility criteria. There is emerging interest that DBS is neuroprotective. This has led to consideration of Early DBS in patients with PD. Currently phase III trials are underway to evaluate the effect of DBS in Early PD.