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Parkinsons Disease: Recent Advancement and Future Aspects

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Abstract: A prevalent neurodegenerative condition known as Parkinson's disease (PD) is characterized by a movement disorder with bradykinesia, rest tremor, rigidity, and postural instability. The majority of contemporary PD treatments are predicated on restoring dopaminergic tone in the striatum; however, there are few effective choices available. These, however, do not change the course of the disease and do not address the dopamine-independent symptoms of PD, such as freezing gait, cognitive impairment, and other non-motor aspects of the condition, which frequently have the biggest effects on quality of life.

Novel therapy approaches are developing as our understanding of Parkinson's disease pathophysiology increases. These include therapies that target PD symptoms while avoiding the unfavorable side effects associated with currently available therapies, as well as therapies that halt pathology, minimize neuronal loss, and moderate disease progression.

This article discusses some promising approaches that are currently being researched in the laboratories or are in the clinical trial phase such as cell based therapies, gene therapy, neuronal therapy, infusion therapy, neuron regeneration and novel drug approaches, which can pose as the future for the treatment of Parkinson's disease.

Keywords: Parkinson's disease, drug repurposing, immunotherapies, gene therapies, neural grafting, neuron regeneration, neural stem cell, transplantation, NTRC-3531-O, non-pharmacological treatment.

I. INTRODUCTION

The name Parkinson disease (PD) honours James Parkinson, whose 1817 monograph "An Essay on the Shaking Palsy" provided a comprehensive account of the clinical characteristics of this ailment. (1) PD is the second most common neurodegenerative disorder, with an average age at onset of about 60 years. An estimated 5 million people throughout the world have PD, with 1 million individuals each in the United States and in Europe with the disorder. PD affects approximately 0.3% of the population and 1% to 2% of those older than 60 years. (2) With the aging of the population and the substantial increase in the number of at-risk individuals older than 60 years, it is anticipated that the prevalence of PD will increase dramatically in the coming decades. (3) Parkinson's disease (PD) is a common neurodegenerative disease characterized by a movement disorder consisting of bradykinesia, rest tremor, and rigidity, along with postural instability, a range of other more-subtle motor features, and many non-motor features. (4) Many of the core motor features result from the loss of a specific population of neurons: the dopaminergic neurons of the substantia nigra pars compacta, which project axons to the striatum (5, 6) As such, most of the current pharmacological treatment approaches for PD aim to restore dopaminergic tone in the striatum. Whilst often effective at improving motor function, current treatments are associated with significant side effects due to delivery of dopamine to extra-striatal regions, variability in their absorption and transit across the blood-brain barrier, and the non-physiological continuous release of dopamine and its effects on the dopamine receptors within the basal ganglia (7, 8). Many features of PD (such as cognitive impairment and autonomic dysfunction) have a mainly non-dopaminergic basis, resulting from neurodegeneration at other sites in the central nervous system as well as the enteric and autonomic nervous systems (6, 9). It is often these features that have the most detrimental impact on the quality of life of patients with PD, yet treatment options remain limited for these elements of disease. Levodopa, the precursor of dopamine, was first developed for the treatment of PD in the 1960s and continues to be the most-effective therapeutic agent for PD in 2020 (10). Since then, more dopaminergic medications have been employed, including dopamine metabolism inhibitors as well as dopamine receptor agonists, but these are generally less well tolerated and less effective. Thus, there is an urgent need for better therapies, including disease-modifying treatments. However, the requirement for relevant preclinical disease models for testing such agents and the lack of robust biomarkers for diagnosing PD and the identification of prodromal disease, which would allow for treatment before significant neuronal loss had occurred, pose barriers to drug discovery. It is on this background that a number of new developments are emerging that may transform the management of PD over the coming years, and we will now discuss those that are in, or soon to be in, clinical trials.

II. TREATMENT STRATEGIES FOR PARKINSON DISEASE

A. Drugs used in treatment of PD

1) Levodopa

Levodopa is a potent dopamine precursor that effectively improves the motor symptoms of PD (229). However, adverse effects such as dyskinesia, nausea, and hallucinations have historically limited its use among older patients with substantial physical impairment (230). The National Institute for Health and Care Excellence (NICE) recommends offering levodopa to patients in the early stages of PD whose motor symptoms impact their quality of life, regardless of age (231). Patients may experience a wearing-off effect and fluctuating efficacy with levodopa, necessitating additional medications (232, 233) or need to discontinue because of adverse events. Anecdotally, levodopa is being used earlier in treatment than in previous years, but possibly at a low dose when used in the beginning stages of the disease.

2) Levodopa-Carbidopa

The combination of levodopa-carbidopa is a mainstay in Parkinson's disease (PD) treatment. Generally, catechol-*O*-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and dopamine agonists are used simultaneously with levodopa to reduce motor fluctuations. Despite use of optimal oral medications, patients progressively develop persistent motor fluctuations such as wearing-off and delayed "On" time characterized by predictable or unpredictable swings from mobility to immobility.(234) Even with optimal oral treatments, dyskinesias are often challenging to manage.(235,236)

Dyskinesias are among the most troublesome symptoms in advanced PD. Approximately 50% of patients present with dyskinesia 4 to 5 years after treatment initiation and approximately 90% after 9 years.(234,237) Dyskinesias are thought to result from pulsatile stimulation of postsynaptic dopaminergic receptors caused by multiple oral levodopa dosing. Multiple oral levodopa doses may cause unstable levodopa levels in plasma and, consequently, unstable dopamine levels in the basal ganglia due to severe neurodegeneration, irregular absorption, unpredictable variability in gastric emptying, and the brief half-life of levodopa. (238-242) Thus, dyskinesias in PD may result from drug therapy, specifically levodopa treatment (243). Dyskinesia treatment options include oral amantadine, continuous subcutaneous apomorphine infusion, and deep brain stimulation (DBS). However, DBS may not be available or suitable for all patients. More treatment options are needed for patients with advanced PD. One option may be continuous levodopa delivery (238,244).

Percutaneous endoscopic gastrostomy with J tube extension (PEG-J) delivers levodopa-carbidopa intestinal gel (LCIG) continuously to the upper intestine with the use of an external pump. Levodopa plasma levels are more consistently maintained with LCIG compared to traditional oral levodopa therapy, which reduces the risk of motor problems including dyskinesia. (245,246)

Various therapeutic strategies may be adopted when starting treatment of Parkinson's disease in an attempt to delay and minimize the long term complications associated with levodopa. One approach is to start treatment with low dose levodopa and, if the efficacy declines, to add a dopamine agonist instead of increasing the levodopa dose.(247) Conversely, treatment may be started with a dopamine agonist or alternative symptomatic agent and low dose levodopa added later if required. Finally, it has been suggested that treatment should be initiated with a combination of low doses of levodopa and a dopamine agonist (248).

Dopamine agonists mimic the endogenous neurotransmitter and act directly on dopamine receptors to produce antiparkinsonian effects. (249) Ergoline and non-ergoline agonists are the two subtypes of dopamine agonists. These two subclasses aim to bind to D2-type dopamine receptors. Bromocriptine, pergolide, lisuride, and cabergoline are ergoline dopamine agonists; ropinirole and pramipexole are non-ergoline agonists. The combination D1 and D2 agonist apomorphine, one of the first dopamine agonists to be shown to alleviate parkinsonian symptoms, must be injected subcutaneously. (250-252)

DA are primarily used in the earlier stages of PD and as adjunct therapies. Ropinirole and pramipexole are also available in extended-release (ER) formulations. Ropinirole ER is more efficacious compared to its immediate-release (IR) formulation [253]. While pramipexole ER would still have the benefits of more convenient dosing, no difference was noted in tolerability compared to the IR formulation (254).

3) COMT Inhibitor

Levodopa, as well as DA itself, is broken down by the widely distributed enzyme catechol-*O*-methyltransferase (COMT). Levodopa is made more readily available by COMT inhibitors, but their effects are not delayed. The current prescription for COMT inhibition is in advanced PD patients who have developed wearing off or "on-off" swings and require additional levodopa medication. [255,256]

However, COMT treatment in the earlier stages of PD may also be worthwhile by preventing or delaying motor complications. COMT inhibition as a new treatment, strategy for PD has been recently comprehensively reviewed. [257,258]

Tolcapone and entacapone have undergone extensive testing as COMT inhibitors thus far. While the use of tolcapone or entacapone frequently reduces or eliminates motor fluctuations such as "off" periods, peak dose dyskinesias might be exacerbated or triggered, necessitating a decrease in levodopa dosage on an individual basis. The patients' quality of life was demonstrated to be enhanced by both medications. Due to suspected liver toxicity, tolcapone was recently taken off the market in the majority of nations. But the precise connection to drug exposure is still unclear. Entacapone must be taken with every levodopa dose because its short 2-hour duration of action necessitates it (or even more frequently). Especially for people being treated with other medications, combinations of levodopa, entacapone, and a decarboxylase inhibitor may be advantageous. It might also be beneficial to use entacapone's long-acting derivatives or sustained-release formulations.

4) MAO Inhibitors

Monoamine oxidase inhibitors are what prevent the monoamine oxidase enzyme from working. Neurotransmitters such as norepinephrine, serotonin, dopamine, and tyramine are broken down by the monoamine oxidase enzyme. The levels of these neurotransmitters are raised by MAOIs, which prevent their breakdown, allowing them to continue to have an effect on the cells that have been damaged by depression. [259]

Monoamine oxidase comes in two varieties: A and B. While MAO B is found in the brain, liver, and platelets, MAO A is mostly found in the placenta, gut, and liver. While tryptamine, phenylethylamine, and methylhistamine are substrates of MAO B, serotonin and noradrenaline are substrates of MAO A. Both MAO A and B metabolise dopamine and tyramine. Safinamide is a reversible and selective MAO B inhibitor while selegiline and rasagiline are irreversible and selective MAO type B inhibitors. [260]

Selegiline and rasagiline are selective MAO-B inhibitors used in early PD as well as those with motor fluctuations, but these are generally weak agents. These drugs reduce the degradation of dopamine thus increasing its CNS concentrations. Selegiline is dosed in the morning and afternoon because it has amphetamine-like metabolites which can cause insomnia. A study which evaluated whether selegiline had neuroprotective effects showed that patients treated with selegiline needed levodopa later than the control group, suggesting disease modification properties [261]. However, the results were confounded by the drug's mild antiparkinsonian and anti-depressant effects [262]. Therefore, it does not have a neuroprotective indication.

Rasagiline has no current role as a disease-modifying treatment.

Safinamide is a newer MAO inhibitor that also blocks voltage-gated sodium channels and calcium channels, reducing glutamate release and transmission [263]. It is given once daily (50-100 mg/day) and increases an "on" time without troublesome dyskinesias [264].

5) Amantidine

Amantidine has been used for a very long time for symptomatic amelioration of PD [267]. However, this symptomatic benefit is of limited value in early PD [268]. Amantidine is often used to treat dyskinesias because of its antiglutamatergic property. It is also thought to block dopamine reuptake, stimulate the release of endogenous stored dopamine, and has a mild anticholinergic effect.

Anticholinergics

Anticholinergics have been used for the treatment of PD even before the advent of levodopa and dopamine agonists. Benztropine and trihexyphenidyl antagonize acetylcholine at muscarinic receptors postsynaptic to striatal interneurons. They are used primarily for the treatment of tremor in PD. There is compelling evidence that the long-term use of anticholinergics in PD contributes to dementia even in younger PD patients [265,266]. Therefore, these medications have limited use in modern clinical practice.

Adenosine A2 receptor antagonist

Istradefylline is an A2A adenosine receptor antagonist that has been approved by the FDA for motor fluctuations. It reduces the excitability of the indirect pathway by modulating GABAergic transmission [269]. It is available in 20 mg and 40 mg formulations and is administered once daily. It has been shown to reduce "off" time by about 0.7 hours compared to placebo [270].

Botulinum Toxin

Botulinum toxin inhibits the release of acetylcholine from the presynaptic terminals by affecting SNARE and SNAP proteins [271]. Currently, four different preparations are FDA approved in the USA, including onabotulinum toxin Incobotulinum toxin A (Xeomin), abobotulinum toxin A (Botox), abobotulinum toxin B, and abobotulinum toxin A (Dysport) (Myobloc). It can be used to treat various symptoms associated with advanced PD. Botulinum toxin injected into the parotid and submandibular glands is beneficial [271,272].

Dystonia can occur in about 30% of patients and may be more likely in younger patients. Dystonia can occur in the “off” state as well as the “on” state. Botulinum toxin can result in improvement of dystonia and has also been shown to be effective for striatal limb deformities [273,274]

Botulinum toxin can be potentially injected for refractory tremor, but its use is often limited due to causation of limb weakness.

III.RECENT ADVANCEMENT

A. Fetal nigral transplantation

Cell-based therapies have been studied based on the notion that transplantation of dopaminergic cells could replace dopamine neurons, which degenerate in PD, and restore dopaminergic function in a more physiologic manner than can be achieved with oral therapies [11] Fetal nigral transplantation has been the best studied of these approaches to date. Numerous laboratory studies have demonstrated that embryonic dopaminergic neurons implanted into the denervated striatum can survive, extend axons, provide organotypic innervations of the striatum, produce dopamine, and provide behavioral benefits in the 6-hydroxydopamine (6-OHDA) rodent and MPTP-monkey. [12] studies have served as the basis for initiating clinical trials in patients with PD. Many transplant variables can influence whether or not implanted cells survive and the likelihood that clinical benefits will ensue.

These include donor age, number of donors, method of storage, type of tissue transplantation, site of implantation, distribution of tissue, the use of immunosuppressants, and the prerequisites for patients. [12] To date, there is no universal agreement on the optimal transplant protocol. Open-label clinical trials using a variety of different transplant regimens produced variable clinical results. Some reported long-term clinical benefits with improvement in motor function during “off ” time, increased “on” time without dyskinesias, and patient entrance requirements, as well as substantially higher striatal FD uptake on PET. [13-16]

B. Infusion Therapies

Infusion therapies offer a nonsurgical means of potentially reversing established motor complications. The treatment is based on the principle that continuous infusion of a dopaminergic agent provides more constant and physiologic activation of striatal dopamine receptors than is accomplished with intermittent administration of the same drug, and thereby reduces the risk of motor complications. Indeed, in all instances where it has been tested, continuous administration of a short-acting, dopaminergic agent is associated with a reduced frequency of motor complications compared with intermittent administration of the same agent. [17,18,19] Continuous infusion of either levodopa or a dopamine agonist (apomorphine and lisuride) has been tested in patients with advanced PD and consistently been reported to reduce the frequency of motor complications. In one prospective study, patients randomized to receive a continuous subcutaneous infusion of lisuride had significant reductions in both “off ” time and dyskinesia compared patients receiving common oral dopaminergic drugs [20].

Benefits persisted throughout the 4-year duration of follow-up. Similar results have been observed with continuous infusion of apomorphine. Dopamine agonists (perhaps with the exception of apomorphine), however, do not provide benefits comparable with levodopa, and it would theoretically be preferable to offer continuous infusion of levodopa. However, levodopa must be maintained at a low pH to maintain stability, and accordingly must be delivered in large volumes, making continuous subcutaneous or intravenous infusion somewhat problematic. Methyl levodopa can be administered in a much smaller volume and can be delivered subcutaneously by an insulin mini-pump or by continuous intrainestinal infusion. One study examined the effect of continuous intrainestinal infusion of methyl levodopa in patients with advanced PD who;had severe motor complications. When they were switched from standard oral formulations of levodopa to continuous infusion of levodopa, they had a marked reduction in both “off ”time and dyskinesia [17]. The Duodopa system uses a gel to reduce the volume that must be administered, and is now being developed for commercial use. Initial studies demonstrated substantial improvement in both “off ” time and dyskinesia, and many patients have continued to experience these advantages after a 4–7 year period of follow-up. [21-23]Double-blind studies to test Duodopa infusion in patients with advanced PD in prospective, double-blind trials are now being organized. [17]

C. Gene Therapies

Gene delivery approaches are also being actively investigated as a possible treatment for PD. In this technology, viruses are used as vectors to introduce the DNA of a desired protein into the genome of cells within a specific brain target. Furthermore, promoters can ensure that the virus vector infects specific brain cells (e.g., TH promoter targets dopamine cells). This sequence can thus potentially result in continuous production of the desired therapeutic protein in the desired target region of the brain. Most human studies have used the adeno-associated virus serotype 2 (AAV-2) as the vector, as AAV-2 does not induce an immune response and permits long-term expression of the transgene.

Three different gene therapy approaches are currently being tested in PD. The first delivers AADC to the striatum to promote the continuous conversion of levodopa to dopamine. This approach has been shown to provide benefits in MPTP monkeys, and is currently being studied in patients with PD.

A second approach used glutamic acid decarboxylase delivered to the STN to promote the formation of GABA, with the intention of inhibiting overactive neuronal firing in this nucleus. An open-label, 12-month trial in 12 patients with PD demonstrated significant improvement in UPDRS scores with no serious adverse effects. [24,25] A third approach involves gene delivery of the trophic factor neurturin to the striatum.

Trophic factors have attracted considerable attention as possible therapies for PD based on their capacity to protect *in vitro* and *in vivo* dopamine neurons from a variety of toxins. Glial-derived neurotrophic factor (GDNF) specifically has been shown to protect SNc dopamine neurons in MPTP monkeys even when administered weeks after the toxin. Although an open-label clinical trial reported that direct infusion of GDNF into the striatum provided significant benefits, these results were not confirmed in a double-blind, placebo-controlled trial. This may relate to point source delivery of the trophic factor with inadequate diffusion of the protein throughout the target region. Gene therapy offers the potential to provide more diffuse distribution of the therapeutic protein through the brain target. In MPTP monkeys, gene delivery of GDNF was diffusely distributed throughout the striatum, and provided motor benefits, restoration of striatal TH staining, and protection of SNc dopamine neurons. Neurturin is a trophic factor in the GDNF family that has been demonstrated to protect and enhance dopaminergic function neurons in both aged and MPTP-lesioned monkeys (figure 26). In these studies, AAV-2-neurturin had an excellent safety profile and was not associated with any toxicity or immune reactivity. In a phase 1, open-label study, AAV-2 was used to deliver neurturin to the striatum of 12 patients with advanced PD. Significant improvement was observed in UPDRS scores during practically defined “off” and “on” time without dyskinesia. On the basis of these pilot results, a double-blind, placebo-controlled study of AAV-2- neurturin was performed. [26-34]

D. Immunotherapies

The pathological hallmark of PD is the presence of abnormal aggregates of α -synuclein¹⁰. The role of α -synuclein in PD is not clear, but it is presumed to play a central pathogenic role. Potential pathogenic mechanisms of α -synuclein include dysfunction of vesicular transport, perturbations in the lysosome–autophagy system, mitochondrial dysfunction, and oxidative stress, for example. [35] Utilizing antibodies to specifically target and destroy extracellular α -synuclein and so stop it from “infecting” nearby cells is one experimental strategy for limiting the spread of the protein. In animal models, approaches for α -synuclein immunisation via passive and active immunisation have been demonstrated to have neuroprotective effects, and now preliminary clinical trial data for humans is beginning to emerge.

Antisense oligonucleotide and ribonucleic acid (RNA) interference techniques to decrease its synthesis are two other strategies to lower levels of α -synuclein, albeit both are still in the preclinical stages of development. [36-38]

A humanized monoclonal antibody targeting the C-terminus of aggregated α -synuclein (prasinezumab or PRX002, Prothena) has been shown to reduce free serum α -synuclein by approximately 97% and to be well tolerated in phase I clinical trials with a phase II trial currently underway (NCT03100149).

Another antibody, BIIB054 (Biogen), targeting the N-terminal portion of α -synuclein reduces the propagation of α -synuclein pathology and improves the motor phenotype in a PD model involving injection of α -synuclein pre-formed fibrils into mice. This antibody has also been found to be well tolerated in humans and is under investigation in a phase II clinical trial (NCT03318523). [39-41]

The company AFFiRiS are approaching this problem in a different way by investigating a range of treatments consisting of α -synuclein fragments or α -synuclein-mimicking epitopes designed to induce an active immune response against α -synuclein, with phase I trials completed (NCT01568099 and NCT02267434). These products have been administered subcutaneously in early trials and seem to be well tolerated. One of these, AFFITOPEPD01A, conveyed a dose-dependent immune response to the peptide itself and to α -synuclein and is now being taken forward to phase II trials.

E. Dopaminergic Neuron Regeneration

Alternatively, the use of astrocytes as the starting cell type for *in vivo* direct reprogramming to obtain functional neurons has been paid extensive attention in recent years due to their ubiquitous distribution in the CNS and their proximity in lineage distance to neurons. [44]

F. Endogenous Regeneration

The discovery that neurogenesis still takes place in the SGZ136 and SVZ137 in the adult brain has instigated intensive research into whether it is possible to rejuvenate the aging or diseased brain by awakening endogenous regenerative capacity. [45] Changes in the proliferation or neurogenesis capability in the SVZ during PD are highly debatable. One study reported a decrease in the number of proliferating precursor cells in the SVZ of PD patients. However, other researchers found no appreciable variations in NSC proliferation between controls, accidental PD cases, and PD patients in the SVZ. [46] Different studies have shown that DA neurogenesis occurs in adults. The earliest evidence was reported by Lie et al., demonstrating that the SN of adult rats contains neural progenitor cells (NPCs) that can differentiate into neurons in vitro but only into glial cells in vivo.[47]

G. Transplantation of Dopamine Secreting Cells

The first cell therapy studies in animal models of PD were performed in late 1970s in rats using fetal rat dopamine-containing neurons as donors with the aim of restoring striatal dopamine levels. [48-49] In the initial transplantation of mesencephalic tissue from rat embryo to rats, further steps included transplantation of mesencephalic dopaminergic neurons, taken from mouse embryos or human fetuses, into dopaminergically denervated striatum of recipient rats or MPTP-monkeys.[50] Among the most promising new experimental approaches developed within the last few years is the intrastriatal transplantation of carotid body (CB) tissue. Autotransplantation of dopaminergic CB cell aggregates has been reported to effect notable histological and functional recovery in parkinsonian rats and MPTP-treated Monkeys. [51,52]

Transplantation of dopamine-secreting cells in advanced PD patients was initiated in the mid 1980's. Despite highly variable clinical outcomes of these studies, with excellent results reported in selected patients but only modest effects in most cases, Clinical trials resulting in higher impact have been those employing adrenal medulla, mesencephalic neurons or carotid body [53] as donor tissues.

The transplantation of adrenal tissue was soon abandoned due to relatively high morbidity/mortality associated with dual (abdominal and cranial) surgery and the development of other therapeutic approaches. On the other hand, transplantation of fetal mesencephalic neurons constitutes a technology that has dominated clinical trials in cell therapy applied to PD patients for the last 15-20 years.[54] The CB is a tissue particularly attractive for antiparkinsonian cell therapy because it combines properties necessary for both dopamine cell replacement and neuroprotection.

The CB contains highly dopaminergic neuron-like glomus cells that express tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of dopamine. [55]

A major advantage of CB with respect to fetal mesencephalic neurons is that the former can be used for autotransplantation since its unilateral surgical thus circumventing most limitations of fetal transplants. Favourable results in preclinical studies encouraged the realization of two pilot phase I/II open test to feasibility, safety and clinical efficacy of autotransplantation in PD.[53] CB based cell therapy is also trying to take advantage of stem cell technology to improve the efficacy of transplantation treatment. A new population of adult CB specific neural progenitors have recently been described within the organ.

These cells are neural crest-derived and able to form neurospheres in vitro. Moreover, progenitors within these neurospheres spontaneously differentiate into dopaminergic glomus cells, which are histologically and functionally similar to those studied in the organ in situ.

However, the CB neurospheres on the amelioration of PD symptoms in animal models of the disease is still under evaluation. CB progenitors are also present in adult and elderly human CB parenchyma and they can form neurospheres in vitro.[56]

H. TDO Inhibition as a Therapeutic Surgery

Age-related α -synuclein toxicity in *Caenorhabditis elegans* has been found to be inhibited by inhibiting the production of the L-tryptophan-catabolizing enzyme tryptophan 2,3-dioxygenase (TDO). A brain-permeable, small molecule TDO inhibitor known as NTRC 3531-0 was created to test TDO inhibition as a potential therapy approach for Parkinson's disease. In cell-based and biochemical studies, this substance effectively suppresses human and mouse TDO. Parallel evaluations were conducted on the structurally different TDO inhibitor LM10. Rotenone-induced motor and cognitive impairment, as well as dopaminergic cell death and neuroinflammation in the substantia nigra, were all ameliorated by both inhibitors. [57] Consistent with this, mice treated with TDO inhibitor showed decreased expression of rotenone-induced glial fibrillary acidic protein, which is a marker of enteric glial cells, and decreased α -synuclein accumulation in the enteric plexus. The available data supports TDO inhibition as a potential therapeutic strategy to decrease motor, cognitive, and gastrointestinal symptoms in Parkinson's disease. [57]

IV. FUTURE DIRECTIONS FOR PD

A. Treatment of Early PD

Symptomatic therapy for the classic motor features found in patients with early PD is usually satisfactory and does not represent a major need at this time. Rather, there remains a need for therapies that provide antiparkinsonian benefits that do not induce motor complications. An early treatment strategy that prevents the development of motor complications would enhance the quality of life of patients with PD and greatly simplify their later management. Much effort has been directed toward achieving this goal. As discussed in detail above, current evidence suggests that motor complications are related, at least in part, to the downstream consequences of non-physiologic, pulsatile stimulation of dopamine receptors. On the basis of these observations, it is hypothesized that the risk of inducing motor complications would be lower with therapies that provide more CDS. (276). It is now clear that starting symptomatic treatment with a long-acting dopamine agonist lowers the risk of motor problems than short-acting medications like levodopa. Even when used in conjunction with a dopamine agonist, levodopa—which raises the risk of motor complications—is eventually required by patients since dopamine agonists' effectiveness is very limited. Therefore, much work has gone into creating dopamine agonists that are more powerful yet cause even less pulsatile stimulation than the currently available long-acting drugs. Transdermal formulations of rotigotine or lisuride, and the extended release formulation of ropinirole, provide relatively stable plasma levels of these drugs and should, therefore, be associated with relatively continuous stimulation of dopamine receptors and a low risk of dyskinesia. However, existing dopamine agonists have very little tendency to induce motor complications, and no additional advantage with respect to dyskinesia has been detected with cabergoline, which has a very long half-life (approximately 48 hours). Furthermore, no dopamine agonist has been shown to prevent the need for levodopa. Therefore, it remains to be determined if new dopamine agonists and new delivery systems for dopamine agonists can provide any additional benefit compared with available agonists. More interest has focused on the possibility that a long-acting formulation of levodopa will reduce dyskinesia associated with the standard short-acting form of the drug.(277)Although it has proven difficult to develop such a formulation, it has been shown that levodopa administered in combination with a COMT inhibitor at 3-hour intervals provides a plasma pharmacokinetic profile that resembles Table 26 Future research directions Treatment of early PD Treatment of dyskinesias and motor fluctuations Interventions that restore function for patients with advanced PD Interventions that treat nondopaminergic features of PD Neuroprotective treatments PD Parkinson disease. *Neurology* 72 (Suppl 4) May 26, 2009 S101 a levodopa infusion, and reduces the risk for motor complications in MPTP monkeys compared with levodopa alone.(278) The STRIDE-PD study failed to show any advantage of administering levodopa in combination with a COMT inhibitor at 3.5 hour intervals. *Neurology* 72 (Suppl 4) May 26, 2009 S101 a levodopa infusion, and reduces the risk for motor complications.

B. Treatment of Dyskinesias and Motor Fluctuations

Levodopa-induced dyskinesia can be an important source of disability for some patients, and perhaps more importantly, limit the utility of dopaminergic drugs to optimally control PD symptomatology. The development of an effective antidyskinetic agent might permit dopaminergic agents to be administered in larger doses and thereby provide better control of parkinsonian motor features without fear of inducing worsened dyskinesia. CDS-based therapies have attracted attention as a treatment to prevent motor complications, but these approaches might also have a role in reversing established motor complications. Improvement in both dyskinesias and “off ” time has been observed with continuous delivery of a dopamine agonist or levodopa.(279,280)However, infusion therapies are not currently approved in the United States (although they are available in some other countries). Continuous subcutaneous infusion of apomorphine and lisuride are currently being pursued for regulatory approval in the United States. It is anticipated that continuous levodopa infusion will provide even greater benefits. Continuous intraintestinal infusion of methyl ester levodopa has been shown to dramatically reduce “off ” time and dyskinesias.(279)Continuous intrajejunal infusion of Duodopa, a specially formulated levodopa gel, is currently being investigated. Furthermore, Duodopa infusion has been found to be superior to optimized combinations of conventional oral and subcutaneous medications in patients with motor fluctuations. Continuous subcutaneous infusion of apomorphine and lisuride are currently being pursued for regulatory approval in the United States. It is anticipated that continuous levodopa infusion will provide even greater benefits. Continuous intraintestinal infusion of methyl ester levodopa has been shown to dramatically reduce “off ” time and dyskinesias.(279)Continuous intrajejunal infusion of Duodopa, a specially formulated levodopa gel, is currently being investigated. Furthermore, Duodopa infusion has been found to be superior to optimized combinations of conventional oral and subcutaneous medications in patients with motor fluctuations. [281]

Continuous infusion of a dopaminergic agent offers an alternative to DBS that avoids the risks associated with intracranial surgery. Such treatments, however, use an infusion system that is cumbersome for both patient and caregiver, and in the case of levodopa, a surgical intervention is also required.

Infusions are also typically only administered during the waking day, and problems of nighttime akinesia and dystonia will have to be addressed. A pharmaceutical therapy would be preferable. The development of more compact infusion systems that use insulin pumps are being pursued.

Several new pharmacologic approaches are currently being investigated as possible treatments for dyskinesia. These include adenosine A2A antagonists, opioid antagonists, 5HT_{2A} agonists, 5HT_{2C} antagonists, CB-1 antagonists, -2 antagonists, atypical neuroleptics, dopamine uptake inhibitors, antagonists of NMDA receptor subunits, selective muscarinic and nicotinic agonists, as well as novel and more traditional dopamine agonists

Adenosine A2A receptors are localized to cholinergic interneurons and cell bodies of D2 receptorbearing striatal output neurons in the indirect pathway,(282)and have the capacity to influence acetylcholine, GABA, and dopamine release. In the dopamine-lesioned state, adenosine A2A antagonists reduce overactivity in D2-bearing striatal neurons that are thought to contribute to dyskinesia.[283] and prevent dyskinesia associated with the introduction of levodopa in the MPTP monkey.(284) The adenosine A2A antagonist KW6002 (istradefylline) has now been tested as add on therapy to levodopa in a 12-week, double-blind, placebo-controlled study in patients with advanced PD with dyskinesias and motor fluctuations.(285) Surprisingly, istradefylline reduced “off ” time by 0.7 hr/d compared with placebo, but did not reduce dyskinesias.

These disappointing results may reflect that in animal models the drug reduced dyskinesia when it was initiated along with levodopa, whereas in the clinical trial the drug was administered only after dyskinesias had already emerged. Other more potent and selective A2A antagonists are being developed, and it is hoped that they will provide antidyskinesia and antiparkinsonian benefits if used in a manner that more closely replicates studies in animal models.

Glutamate receptor antagonists and release inhibitors have also attracted attention as possible antidyskinetic agents. The NMDA receptor antagonists amantadine and dextromethorphan are associated with reduced dyskinesia in MPTP monkeys, and have been reported to improve dyskinesia in PD patients.(286,287,288,289) These drugs are, however, associated with cognitive side effects that limit their utility as a treatment in patients with PD. Rimantadine is the -methyl derivative of amantadine, and has been shown to have motor benefits in PD in an open-label study and to be better tolerated than amantadine.(290,291) It has not yet been studied as a treatment for dyskinesia.

AMPA receptor antagonists are also being studied based on their capacity to block excessive glutamatergic neurotransmission and to reduce dyskinesia in MPTP monkeys. Talampanel has been shown to reduce levodopa-induced dyskinesias in the MPTP-treated monkey model without the toxic effects associated with NMDA receptor antagonists,[292] and is currently being studied in a phase 2 clinical trial. Perampanel is another AMPA receptor antagonist that is also being studied in PD. However, a recently completed, but as yet unpublished, placebocontrolled, double-blind study testing perampanel as an adjunct to levodopa showed no improvement in either “off ” time or dyskinesia compared with placebo.(293)Perampanel was well tolerated with no significant safety issues. Two additional phase 3 studies of perampanel in PD are ongoing.

Striatal opioid binding is reduced in dyskinetic patients with PD patients consistent with the presence of raised enkephalin and dynorphin levels.(294) This suggests that opioid antagonists might be effective in the treatment of dyskinesia. Small clinical trials showed that the opioid antagonist naloxone,(295,296)but not naltrexone,(297,298) had some antidyskinetic effects, but so far this has not been further pursued.

Nicotine has complex interactions with the basal ganglia, and nicotinic cholinergic activity has been shown to regulate dopamine release.(299)In an experimental study in MPTP monkeys, nicotine pretreatment markedly reduced peak and total levodopa-induced dyskinesias.(300) This suggests that either nicotine or nicotine agonists may have a role in the prevention of levodopa dyskinesia. Alpha 2 adrenergic receptor antagonists are also being explored as possible antidyskinetic agents. Activation of -2 adrenergic receptors facilitates movements produced by activation of the direct pathway, and it has been speculated that this might contribute to levodopa-induced dyskinesias.(301)

The -2 adrenergic receptor antagonist fipamezole has been reported to reduce levodopa-induced dyskinesias without counteracting the antiparkinsonian effects of levodopa in the MPTP-lesioned marmoset model of PD.(302)This drug is currently in phase 2 studies. Docosahexaenoic acid (DHA) is an omega-3 essential fatty acid that is found in fish oil. There is some evidence that a reduction in DHA may be associated with lowered serotonin levels in the brain and that this might reduce the risk of dyskinesia. In one experiment, DHA reduced dyskinesia in MPTPtreated parkinsonian monkeys without diminishing the effect of levodopa.(303)These promising results have not yet been tested in clinical trials in patients with PD.Lisuride TTS is currently being tested in phase 2 trials in the United States and Europe, with the goal of reducing levodopa-induced dyskinesias. Despite being ergot-derived, lisuride is devoid of 5-HT(2B) agonistic activity and to date has not been shown to induce fibrotic changes in heart valves as seen with other ergot-derived agonists.(304)

C. Interventions that Treat Non-Dopaminergic Features of PD

The development of nondopaminergic features, such as dementia, postural instability, gait disturbances, and autonomic dysfunction, are among the most disabling aspects of PD for many patients. Yet, we have very little in the way of effective treatment for many of these important problems. Dementia is perhaps the most important source of disability for patients with advanced PD. Cholinesterase inhibitors offer only limited benefit in the treatment of PD-D and DLB.[311,312]

There is some optimism that treatment of patients with PD with MCI will achieve benefits superior to those obtained for patients with MCI in the general aging population, and studies testing this hypothesis are anxiously awaited. Safinamide is the first agent to test the potential of a drug to influence the executive dysfunction that characterizes PD, but the magnitude of benefit seems to be small and may be common to other dopaminergic therapies. Even cholinesterase inhibitors have yet to be tested in patients with PD with executive dysfunction but without frank dementia. Clearly, newer and more effective therapies are required. There are effective treatments for the psychosis that frequently precedes PD-D, and this might represent an interesting population in which to test agents for treatment of early cognitive impairment. Symptomatic therapies exist for some of the features of autonomic dysfunction such as orthostatic hypotension, constipation, and urinary dysfunction, but there are no effective treatments for patients with gait dysfunction and postural instability that does not respond to levodopa. Preliminary data with stimulation of the PPN offers some promise, and is currently being investigated. More insight into the basis of the locomotor defect that occurs in PD might provide new opportunities for novel therapies. The development of therapies to treat effectively or prevent these nondopaminergic features remains one of the major unmet medical needs in the management of PD. To facilitate achieving this goal, an animal model that replicates the nondopaminergic features of the disease would be of enormous value.

D. Surgical interventions that Restore Function in Patients with Advanced PD.

Surgical therapies have now become a part of the routine management of patients with advanced PD who experience disability related to levodopa motor complications that cannot be satisfactorily controlled with currently available medical therapy. Striking benefits, particularly with respect to dyskinesia, were initially observed with pallidotomy. This procedure has largely been replaced by DBS—STN and DBS—GPi, which avoid the need to lesion the brain and thereby avoid side effects associated with bilateral ablative procedures. Both DBS—STN and DBS—GPi seem to provide comparable benefits. Formal studies directly comparing stimulation of these two targets are being performed and their results should be available shortly. DBS—STN is the more widely performed procedure at most centers and may be the more effective, but recent studies suggest that there may be fewer serious adverse effects with DBS—GPi.(310)It should be noted that neither of these procedures have demonstrated improvement of “on” functions beyond what can be achieved with levodopa, and that their primary role is in the management of uncontrolled motor complications. Furthermore, DBS is not a benign procedure, and side effects can occur in relation to the surgical procedure, the stimulation system, stimulation itself, and the periodic need to replace the battery. Future research is focusing on new targets for stimulation such as the PPN for gait dysfunction and a variety of cortical brain targets that might improve psychiatric problems, including depression and compulsive behaviors.

Transplantation strategies have generated considerable enthusiasm based on their potential to achieve physiologic dopamine reinnervation to the striatum without disrupting any component of the basal ganglia system. However, double-blind, controlled trials of fetal nigral transplantation failed to demonstrate significant benefit compared with placebo,(308,309) and transplantation was complicated by a previously undescribed form of dyskinesia that persisted even after the levodopa dose was lowered or stopped (offmedication dyskinesia). Additionally, no benefits of the transplant method have been shown in double-blind studies using foetal porcine nigral cells and retinal pigmented epithelial cells. Although these results are discouraging and have largely halted clinical trials for the present, post-hoc analyses suggest that transplantation of larger numbers of cells distributed more diffusely throughout the striatum, with more prolonged use of immunosuppressants, might lead to improved results in patients who are younger and have milder disease.(307) Stem cell therapies have captured the imagination of researchers and the lay public because of the potential of stem cells to provide an unlimited supply of optimized dopamine neurons. Although preliminary studies show benefits in dopamine-lesioned rodents and monkeys, many obstacles remain to be overcome before clinical trials can be considered. These include determining the type of stem cell to be used, the ideal characteristics of the dopamine nerve cell to be used in transplants, as well as the transplantation procedure.

In addition, it remains to be determined if transplanted cells can survive in adequate numbers, provide benefits superior to what has been achieved with fetal cells, and if stem cell transplantation is associated with a satisfactory safety profile. (306) Furthermore, societal concerns regarding the use of embryonic tissues must be resolved. The use of autologous stem cells has provided some optimism, but results to date are inferior to what can be obtained with ES cells.

Realistically, it does not seem that a cell-based therapy will be available for commercial use in the near term. It is also unreasonable to expect that any of the current dopaminergic cell-based therapies will satisfactorily address the many nondopaminergic aspects of PD.

E. Neuroprotective Treatments.

Perhaps the single most important unmet challenge in the management of PD is the development of a neuroprotective therapy that slows or stops disease progression. Laboratory clues have provided us with many rational approaches to protecting or restoring function to nerve cells that degenerate in PD. Candidate targets include oxidative stress, mitochondrial dysfunction, excitotoxicity, and signals associated with apoptosis.

Proteolytic stress has attracted considerable attention because protein accumulation characterizes PD pathology. This might occur as a consequence of the increased production or impaired clearance of misfolded proteins, and may be diminished by agents that prevent the formation of misfolded proteins or promote their clearance through the proteasomal or autophagy system.

Genetic studies lend considerable support for the possibility that protein and/or mitochondrial abnormalities play a key role in cell death in PD, and thus present additional targets for novel drugs. Recent studies have also focused attention on the potential of calcium channel blockers to provide neuroprotection in PD. They demonstrate that dopamine neurons have an unusual reliance on L-type Ca(v)1.3 calcium channels to drive their pacing, which increases with age and makes them vulnerable to neurodegeneration. (305) Blocking these channels induces a reversion of these neurons to a more juvenile form of pacemaking and protects them in both in vitro and in vivo models of PD. This provides another exciting new target for development of a neuroprotective drug.

V. CONCLUSIONS

On the above studies and approaches the conclusion of this review article is that the new approaches are very efficient and effective as well in the Parkinson disease as compared to the long-term treatment management by drugs used in earlier. Future aspects are bright belief for patients that are suffers from pd. This review is a promising approach to every suffered patient of pd.

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